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by

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certifies that this is the approved version of the following dissertation:

Applications of Ring-Closing Metathesis Reactions to the Total Syntheses of (+)-Anatoxin-a and 8-*epi*-Xanthatin and Progress Toward the Total Synthesis of (+)-Pinnamine

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by

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Applications of Ring-Closing Metathesis Reactions to the Total Syntheses of (+)-Anatoxin-a and 8-*epi*-Xanthatin and Progress Toward the Total Synthesis of (+)-Pinnamine

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The application of ring-closing enyne metathesis (RCEYM) reactions to the preparation of biologically active natural products has been described. During the course of the studies toward the assembly of the potent nicotinic acetylcholine receptor agonists (+)-anatoxin-a and (+)-pinnamine, several new methods were developed to obtain suitable metathesis precursors. A method to prepare α-branched enones bearing a high degree of functional group diversity was accomplished from carboxylic acid precursors using a new titanium-mediated Peterson olefination sequence, and a new catalytic diastereoselective method for the preparation of *cis*-2,5-disubstituted pyrrolidines bearing unsaturated moieties was discovered. The application of these methods to the total synthesis of (+)-anatoxin-a constituting the first application of a RCM approach to the azabicyclo[4.2.1]nonane skeleton is described. Studies directed toward the total synthesis of the related alkaloid (+)-pinnamine are also discussed.

In a related effort, the first total synthesis of the cytotoxic farnesyltransferase inhibitor 8-*epi*-xanthatin was achieved. The total synthesis featured a palladium-catalyzed carbonylation-lactonization sequence to prepare an α-methylene lactone bearing enyne moieties. A subsequent domino RCEYM-cross metathesis between this enyne and methyl vinyl ketone produced the fully functionalized pseudoguaianolide skeleton and completed the total synthesis. Additionally, a new chiral *N*-enoyloxazolidininone bearing a dinaphthylmethyl group was prepared and utilized as a substrate to explore the addition reactions of aluminum acetylides to imides.

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CHAPTER 1: ALKALOID NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

1.1 INTRODUCTION

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated cation channels responsible for the transmission of neuronal impulses over the synaptic cleft between two consecutive nerve cells. The nAChRs are found within the neuronal (brain) and peripheral (muscular ganglia) tissues of vertebrate organisms and are essential for the normal operation of the central nervous system. It is, however, the complex mechanism by which neurotransmission is achieved at the neuronal nAChRs that has attracted the greatest degree of attention within the scientific and medical communities. This interest is largely due to the poor understanding of the pathways by which neurotransmission proceeds and the importance of these pathways in the context of neuronal development, cognitive processing, and reward.[1] An improved understanding of the mode of action and structural characteristics of the neuronal nAChRs has facilitated an effort to discover exogenous ligands that can serve as therapeutic modulators of neurological disorders in which the normal acetylcholine-mediated neuronal signaling pathways are obstructed or absent. Such disorders include Parkinson's disease, Alzheimer's disease, Tourette's syndrome, schizophrenia, and nociception.[2,3]

1.2 NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR SUBTYPES

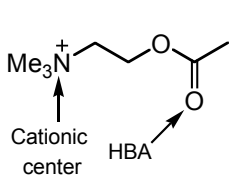
The neuronal nAChRs are membrane-bound pentameric ligand-gated cation channels comprised of a large variety of subunits.[4] These receptors of the central and peripheral nervous system are comprised primarily of various combinations of the eleven α (α2–10) and β (β2–4) subunits to provide a large degree of heterogeneity between receptor subtypes.[5] The structural diversity of the receptor subtypes has been confirmed by the preferential binding of specific radiolabelled exogenous ligands to one receptor subtype in preference to another, thereby indicating the existence of discrete structural features within the binding pockets of the receptors that allow for the selective binding of a particular ligand. It is this specificity that has prompted the search for receptor-selective, non-lethal ligand development as a means of targeting specific neurological disorders governed by the action of a particular receptor subtype.

Although still somewhat in its infancy, the rational design of receptor-selective ligands has focused on the most widespread subtypes in the vertebrate CNS and hence best understood. These include the $\alpha4\beta2^*$, $\alpha3\beta4^*$, and $\alpha7$ subtypes. Of these subtypes, the neuronal $\alpha4\beta2^*$ and homopentameric $\alpha7$ nAChRs are the major subtypes found in the brain.[6,7] The $\alpha3\beta4^*$ subtype is the major receptor of the peripheral nervous system and is typically screened in conjunction with the two aforementioned nAChRs as a measure of the selectivity a ligand exhibits for the receptors of the peripheral CNS versus those of the brain.[8] The $\alpha3\beta4^*$ nAChRs are generally responsible for many of the toxic side-effects associated with depolarization of the synaptic junctions of the peripheral nervous system by high-affinity binding of exogenous toxins.[4]

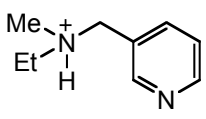
One important feature of the nAChRs is the stereospecificity of their binding pockets. It has been shown that the receptors discriminate between ligands with rigid molecular architectures on the basis of their stereochemical topology, resulting in most cases in one enantiomer of ligand serves as a high-affinity binder while the other enantiomer exhibits little or no binding whatsoever. This will become a defining feature of successful exogenous ligand design that will be addressed during subsequent sections pertaining to specific known high-affinity nAChR ligands.

1.3 NEURONAL nAChR LIGAND CLASSES

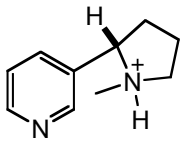
Extensive structure-activity relationship (SAR) studies in conjunction with molecular modeling and computational methods have revealed the importance of a π-cation interaction between the ligand and aromatic amino acid residues within the binding pocket of the nAChRs and the incorporation of a hydrogen-bond acceptor (HBA) system in the ligand. These features have been deemed critical for high-affinity binding.[5] On the basis of these crucial structural elements, the non-peptidic ligands of the nAChRs can be divided into five distinct categories. The first category (Class A) represents those ligands in which the cationic center and HBA moieties are both acyclic as in the case of acetylcholine (**1**). The second category of ligand (Class B) defines ligands in which the cationic center is acyclic and the HBA site is cyclic. Class C contains ligands in which both the cationic center and HBA motifs are contained in separate non-fused rings. Class D is comprised of ligands with a cyclic cationic center and an acyclic HBA. The final class (Class E) is populated by compounds in which the cationic centers and HBA sites are both contained within fused poly- or spirocyclic ring systems. Representative examples of each ligand category are provided below as their ammonium salts.



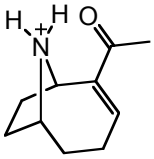
acetylcholine (**1**)
Class A



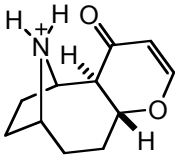
2
Class B



nicotine (**3**)
Class C

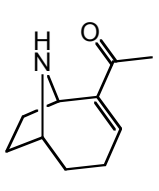


anatoxin-a (**4**)
Class D

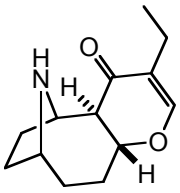


pinnamine (**5**)
Class E

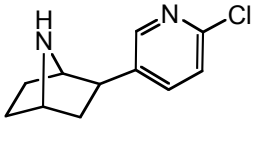
Although a great deal of research has been invested in the discovery of potent and receptor-selective ligands from each structural class, the discovery and biological evaluation of several lethal, naturally occurring bridged azabicyclic neurotoxins from classes D-E have sparked the interest of the synthetic and medicinal chemistry communities. The rigid azabicyclic structures of epibatidine (**6**), ferruginine (**7**), anatoxin-a (**4**), and pinnamine (**5**) provide a unique combination of hydrophobicity, electronics, and steric bulk that affords compounds with high binding affinities for the $\alpha 4\beta 2^*$ receptors.



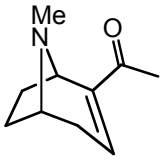
4



5



6



7

In addition, the azabicyclic scaffolds provide multiple sites for structural modification thereby increasing the potential for SAR based drug design. Though

themselves lethal, the potent biological activity imparted by the azabicyclic skeletons of these alkaloids has resulted in their emergence as lead structures for the development of non-lethal and receptor-selective therapeutics. As a result, these toxins have become the focus of a vast majority of the medicinal strategies directed toward the treatment of various neurological disorders.

1.4 EPIBATIDINE

1.4.1 Background

Epibatidine (**6**) is an alkaloidal toxin isolated from the Ecuadorian poison dart frog *Epipedobates tricolor*.[9] This toxin was the first naturally occurring compound discovered with the azabicyclo[2.2.1]heptane skeleton. Examination of the biological activity of **6** revealed it to be a powerful analgesic, approximately 200 times more potent than morphine. Surprisingly, **6** exhibited a 9000-fold less potent binding affinity for opioid receptors compared to morphine, indicating a nonopioid mode of action.[9] In addition, it was found that both (+)-**6** and (–)-**6** are equipotent nAChR agonists with binding affinities in the subpicomolar range.[10] As mentioned earlier, the nAChRs typically demonstrate a preference for the selective binding of a particular stereoisomer of a ligand. It is believed that either enantiomer of **6** can efficiently bind to the nAChRs due to the ability of the less sterically demanding and less dissymmetric azabicyclo[2.2.1]heptane nucleus to accommodate the binding pockets compared to the additional ring-expanded and more dissymmetric azabicycles mentioned earlier.[4] The potency of either enantiomer of **6** coupled with the uncertainty pertaining to its mode of action prompted a flurry of synthetic endeavors aimed at the preparation of **6** and analogs that would be used to probe its unique analgesic properties.

Several reviews detailing alternative approaches to this azabicyclic core and to **6** are reported in the literature.[11] Hence, only the most efficient and divergent approaches to the synthesis of **6** and related analogs will be presented.

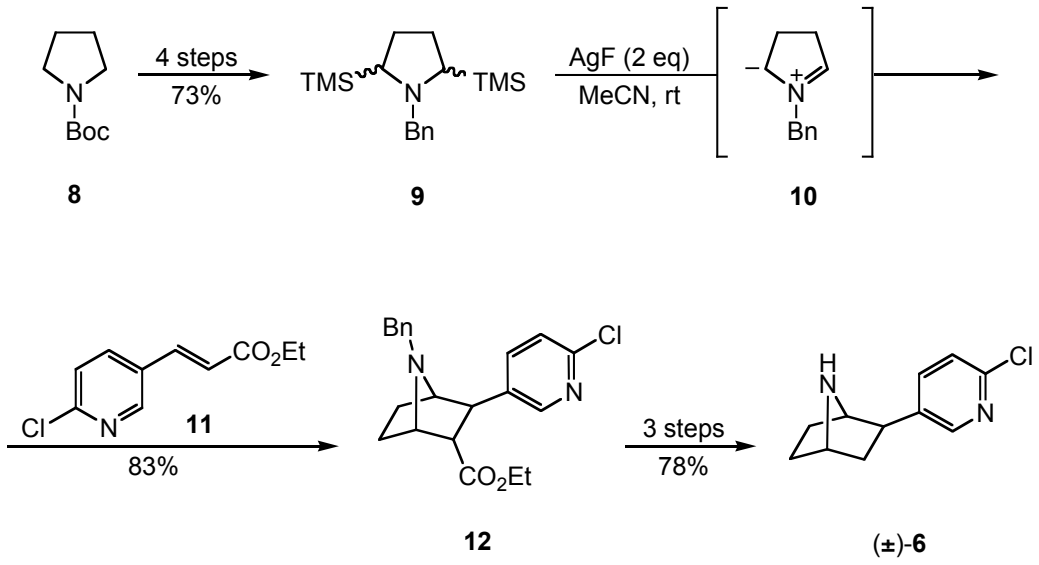
1.4.2 Pandey 1994: [3+2]-Dipolar Cycloaddition

The majority of the syntheses of **6** to date have utilized one of two general approaches. The first of these relies on an intramolecular transannular nucleophilic displacement of a suitable leaving group by a substituted cyclohexyl amine to form the azabicycle. Alternatively, a Diels-Alder cycloaddition between a pyrrole and an activated alkyne has commonly been used to produce the requisite azabicyclo[2.2.1]heptane skeleton.

In a conceptually different approach, Pandey and coworkers highlighted the utility of a previously disclosed azomethine ylide [3+2] cycloaddition for constructing azabicyclo[m.n.1]alkanes in an efficient synthesis of (±)-**6**.[12] The synthesis began with the four-step conversion of *N*-Boc pyrrolidine (**8**) into the disilylated cycloaddition precursor **9** following standard procedures (Scheme 1). Exposure of **9** to a stoichiometric quantity of AgF generated the transient, non-stabilized azomethine ylide **10**, which subsequently underwent a [3+2] cycloaddition with the unsaturated ester **11** to afford **12** in 83% yield with complete *exo*-selectivity for the 2-chloropyridyl group. An additional three operations afforded (±)-**6** in a total of eight chemical operations and in 47% overall yield. In addition to providing a rapid protocol for the assembly of the azabicyclo[2.2.1]heptane skeleton, Pandey's approach may be utilized to prepare analogs for biological evaluation by modification of the substituents contained within the dipolarophile **11**. However, two apparent drawbacks to the synthesis are evident. First, generation of the azomethine ylide requires stoichiometric quantities of the expensive reagent AgF. Secondly, the potential for obtaining undesired *endo*-*exo* mixtures from the

cycloaddition step is likely to increase for dipolarophiles containing substituents smaller than the chloropyridyl ring.

Scheme 1

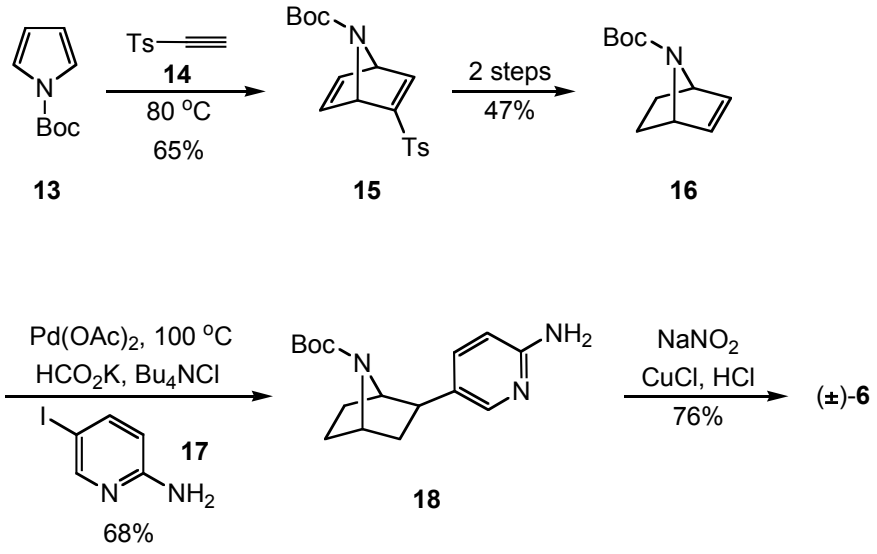


1.4.3 Carroll 1998: [4+2]-Cycloaddition

In one of the shortest syntheses of (±)-**6** to date, Carroll and coworkers adopted a Diels-Alder approach for the preparation of the azabicyclic core. Although not the first or last to employ this strategy, Carroll has reported multiple iterations of the [4+2] cycloaddition approach originally disclosed by Shen,[13] resulting in a highly streamlined protocol in which many of the limiting features of the previous syntheses have been resolved (Scheme 2).[14] The key Diels-Alder cycloaddition reaction between the tosylacetylene **14** and *N*-Boc pyrrole (**13**) proceeded in moderate yield to deliver **15**. Two additional transformations afforded the azabicyclic alkene **16**. An *exo*-selective Heck arylation with 2-amino-5-iodopyridine (**17**) provided **18**. A final diazotization step in the presence of copper(I) chloride (CuCl) resulted in the concomitant formation of the 2-chloropyridyl moiety and removal of the *t*-butyl carbamate (Boc)-protecting group.

Carroll's synthesis of (±)-**6** proceeded in 16% yield over five chemical operations. The synthesis is amenable to analog preparation at both the stage of the Heck arylation reaction, through the choice of various aromatic coupling partners and during the diazotization protocol in which the intermediate diazo species may be transformed into a variety of additional functional groups using standard methods. Additionally, Carroll has shown that this route is amenable to the preparation of gram-scale quantities of (±)-**6**. The major limitation to this protocol is the low yielding transformation of **15** to **16**.

Scheme 2

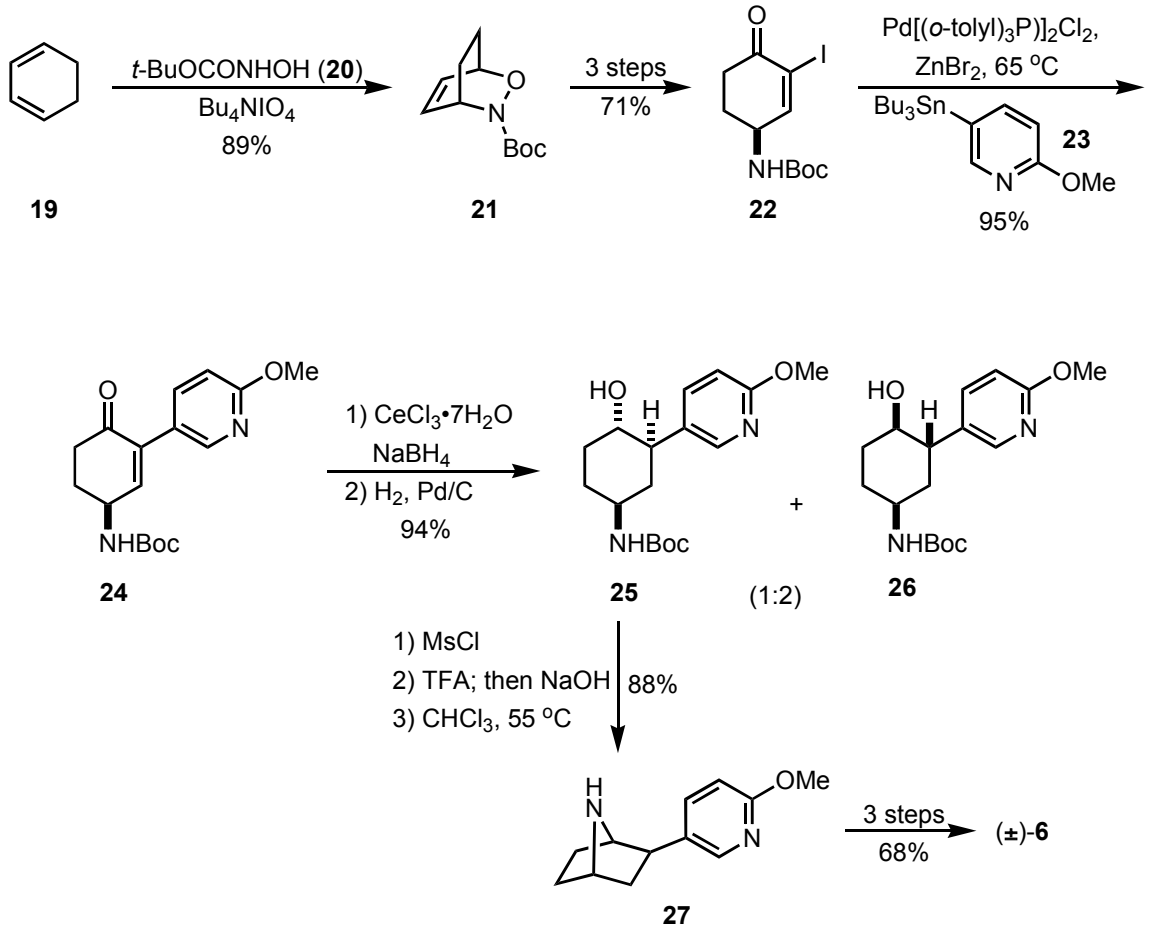


1.4.4 Johnson 1998: Transannular Nucleophilic Displacement

Johnson and Sirisoma adopted the widely employed transannular nucleophilic displacement strategy during their synthesis of (±)-**6**.[15] Their strategy showcased a facile preparation of the α-iodocycloalkenone (**22**) that formally intersected a previous synthesis of (–)-**6** conducted by Trost.[16] The protocol commenced with the Diels-Alder cycloaddition between 1,3-cyclohexadiene (**19**) and the acylnitroso species generated *in situ* from the hydroxamic acid **20** according to Scheme 3. The resulting *N*,*O*-acetal **21**

was transformed to **22** by an additional three operations. Compound **22** underwent a Stille coupling with the aryl stannane **23** to provide **24**. Subsequent Luche reduction and catalytic hydrogenation resulted in the formation of a mixture of diastereomeric alcohols of which the minor diastereomer **25** was the desired product. Chromatographic separation rendered pure **25** that was further transformed into the advanced azabicyclic intermediate **27** by mesylation of the secondary alcohol and deprotection of the carbamate. The resulting amine was heated for four days to effect the desired transannular intramolecular displacement of the mesylate.

Scheme 3

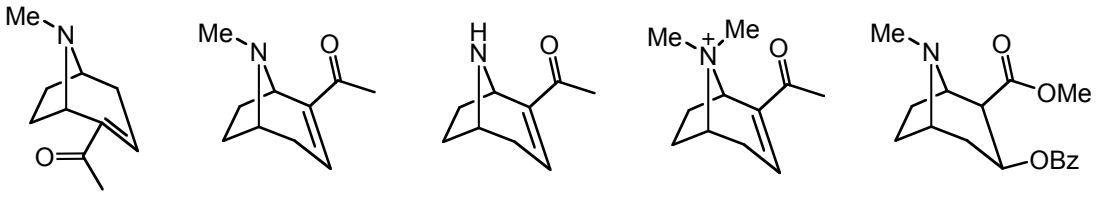


The synthesis was concluded after an additional three steps to form the chloropyridyl ring. This approach provided (±)-**6** in 13 steps and 13% overall yield from **19**. As in the case of the reductive Heck arylation protocols discussed previously, Johnson's synthesis allows for the introduction of structural diversity at the stage of the Stille coupling event, thereby facilitating the pursuit of analog development studies. The major limitations presented by this approach are the overall length of the sequence to prepare **6** and the poor diastereoselection obtained during the conversion of **24** to **25**.

1.5 FERRUGININE

1.5.1 Background

Ferruginine [(+)-**7**] is an azabicyclo[3.2.1]octane (tropane) alkaloid isolated from the arboreal species *Darlingia ferruginea*[17] and *D. darlingiana*.[18] Unlike **6**, the natural dextrarotary isomer (+)-**7** fails to efficiently bind nAChRs, whereas (–)-**7**, its normethyl counterpart (–)-**28**, and (–)-*N*-methylferruginine [(–)-**29**] are all agonists of the nAChRs.[19] This demonstrates the stereospecific binding preferences of the nAChRs for some structurally rigid ligands.



(+)-**7** (–)-**7** (–)-**28** (–)-**29** (–)-**30**

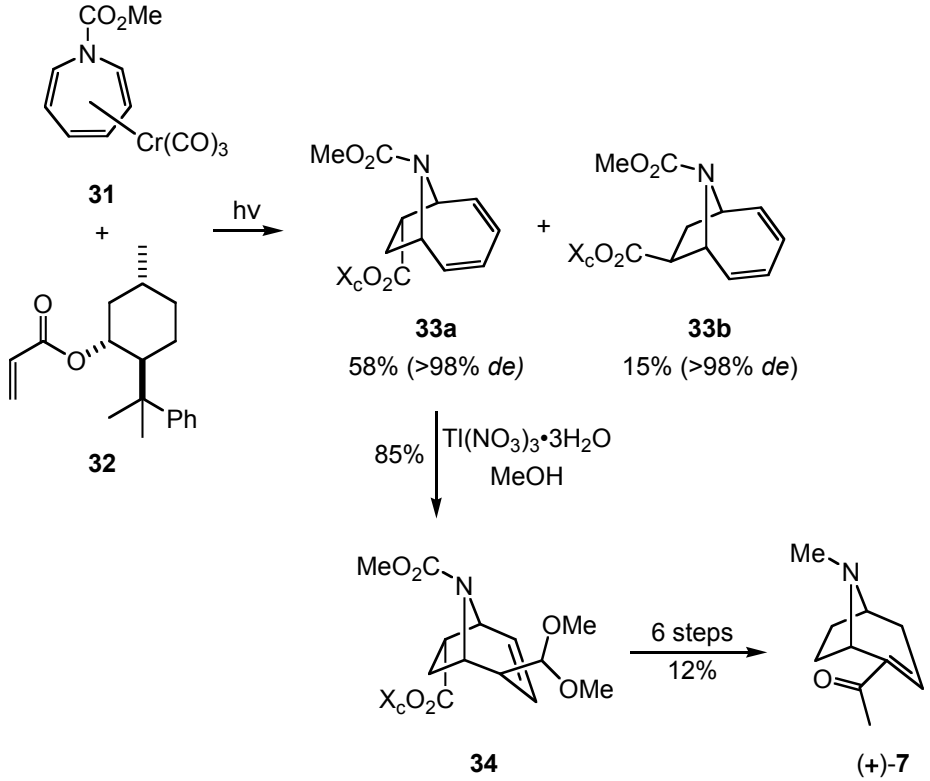
From a therapeutic perspective, (–)-**7** and derivatives thereof have failed to elicit the same attention from medicinal chemists as many of the other known nAChR agonists due to their diminished potency compared to compounds **4**, **5**, and **6**. As such, they have not been thoroughly investigated as potential drug candidates. Therefore, the preparation of **7** has largely become an exercise in the development of new strategies for the assembly of the tropane nucleus. Numerous synthetic approaches to **7** have been completed, a few of which will be highlighted as elegant constructions of the azabicyclo[3.2.1]octane skeleton. In all but two instances, these syntheses have provided **7** either as its racemate or as the natural dextrarotary isomer (+)-**7**. Of the two reported preparation of (–)-**7**, one was accomplished in five chemical operations from (–)-cocaine (**30**).[20] However, **30** is not an ideal raw material for the undertaking of an asymmetric

synthesis, due to its illicit nature and the variations in its optical purity depending upon its origin. Consequently, this synthesis will not be presented.

1.5.2 Rigby 1995: [6+2]-Cycloaddition of Chromium Complexed Azepines

In the first asymmetric synthesis of **7**, Rigby and Pigge demonstrated the utility of metal-promoted [6+2] cycloadditions between chromium complexed azepines and auxiliary modified unsaturated ketones to access the homotropane skeleton.[21] The synthesis of the homotropane core was achieved by the photoinduced, asymmetric [6+2] cycloaddition of the chromium(0)-azepine complex **31** and the phenylmenthylacrylate **32** (Scheme 4). The resulting mixture of *endo*- and *exo*-adducts was separated to provide the desired *endo*-product **33a** with greater than 98% *de*. A Taylor-Mckillop Tl(III)-promoted oxidative rearrangement of the conjugated diene produced the tropane **34** as a single regioisomer without any degradation of optical purity. An additional series of six steps generated (+)-**7** with a modest 6% overall yield from **31**. Although quite elegant, Rigby's synthesis of (+)-**7** suffers from extremely poor atom economy owing to the use of the chromium complex **31** and menthylacrylate auxiliary **32**. In addition, the use of toxic chromium and thallium reagents deters from the overall attractiveness of the method.

Scheme 4

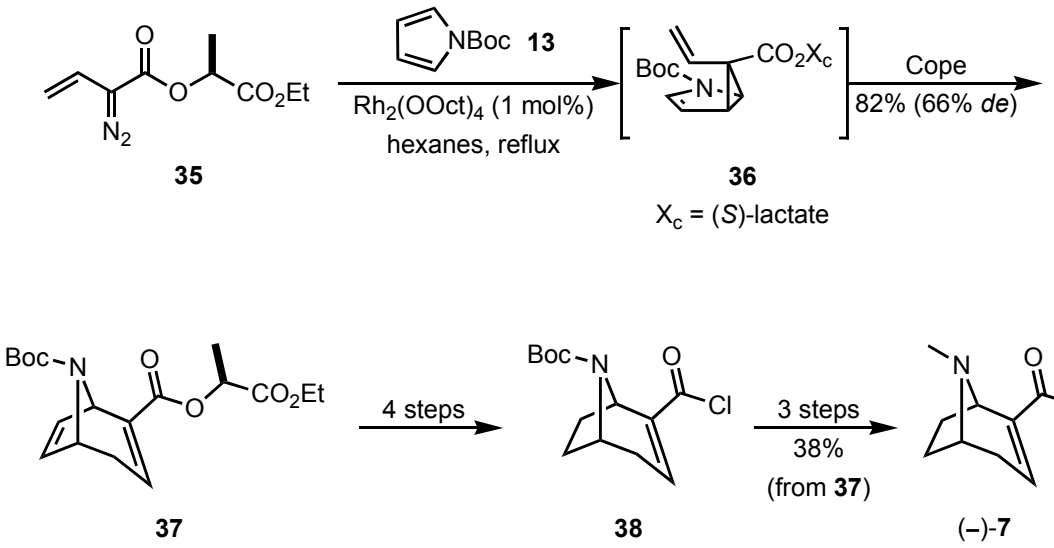


1.5.3 Davies 1997: Rhodium Catalyzed [3+4] Annulation

A rapid synthesis of the azabicyclo[3.2.1]octane skeleton was developed by Davies and coworkers as an extension of their interest in the chemistry of vinylcarbenoids. They found that the reaction of pyrroles with vinyldiazomethanes under rhodium(II) catalysis resulted formally in a [3+4]-annulation to afford tropane derivatives.[22] The reaction, which occurs by a tandem asymmetric cyclopropanation/Cope rearrangement, was utilized for the synthesis of (–)-**7** according to Scheme 5. The functionalized tropane nucleus was prepared by the tandem rhodium-catalyzed asymmetric cyclopropanation of *N*-Boc pyrrole (**13**) with the chiral vinyldiazomethane **35** to afford the intermediate species **36**, which underwent a subsequent Cope rearrangement to afford **37**. Four additional operations provided the

intermediate acid chloride **38** that was further elaborated to (–)-**7** in three steps. Davies synthesis of (–)-**7** proceeded in 31% yield and eight linear steps from **36**. The synthetic protocol was also conducted with various substituted pyrroles and vinyldiazomethanes to afford more structurally diverse tropanes that might serve as a basis for further structural refinement leading to useful analogs of (–)-**7**. Additionally, the acid chloride intermediate **38** may serve as a point of functionalization by its transformation into a variety of different ketones via organometallic coupling reactions with stannanes, zincates, or Grignard reagents.

Scheme 5

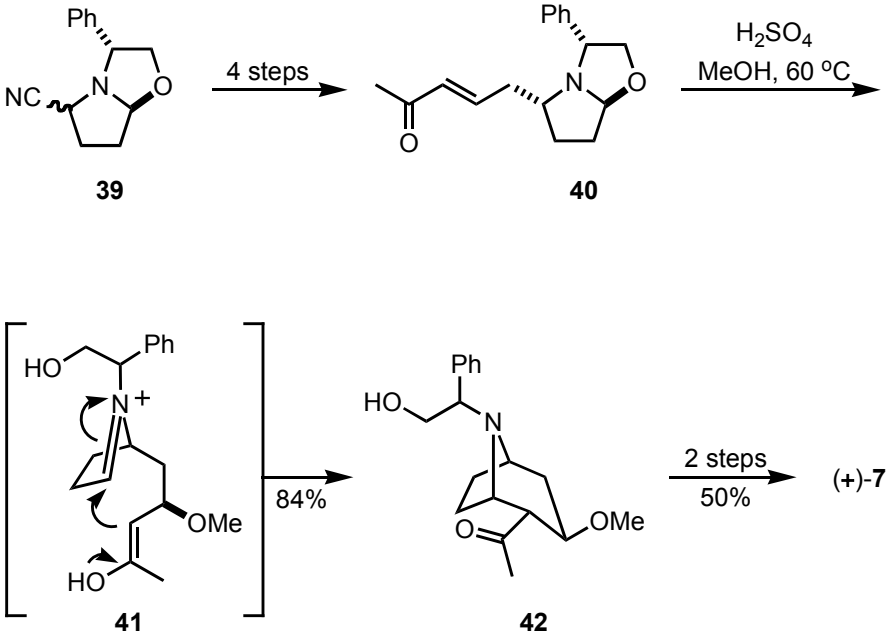


1.5.3 Husson 1997: CN(*R*,*S*) Method

Husson and coworkers utilized the well established CN(*R*,*S*) method for one of the shortest syntheses of (+)-**7** to date.[23] The synthesis commenced with the four-step conversion of the nitrile **39** to the *trans*-enone **40**. Exposure of **40** to a solution of methanolic H_2SO_4 generated the transient iminium ion **41** that was trapped by the pendant enone to afford the β-methoxy ketone **42**. A further two transformations

provided (+)-**7** in seven chemical operations and 20% overall yield from **39**. This method, though concise, does not appear to be easily modified to accommodate the preparation of analogs.

Scheme 6

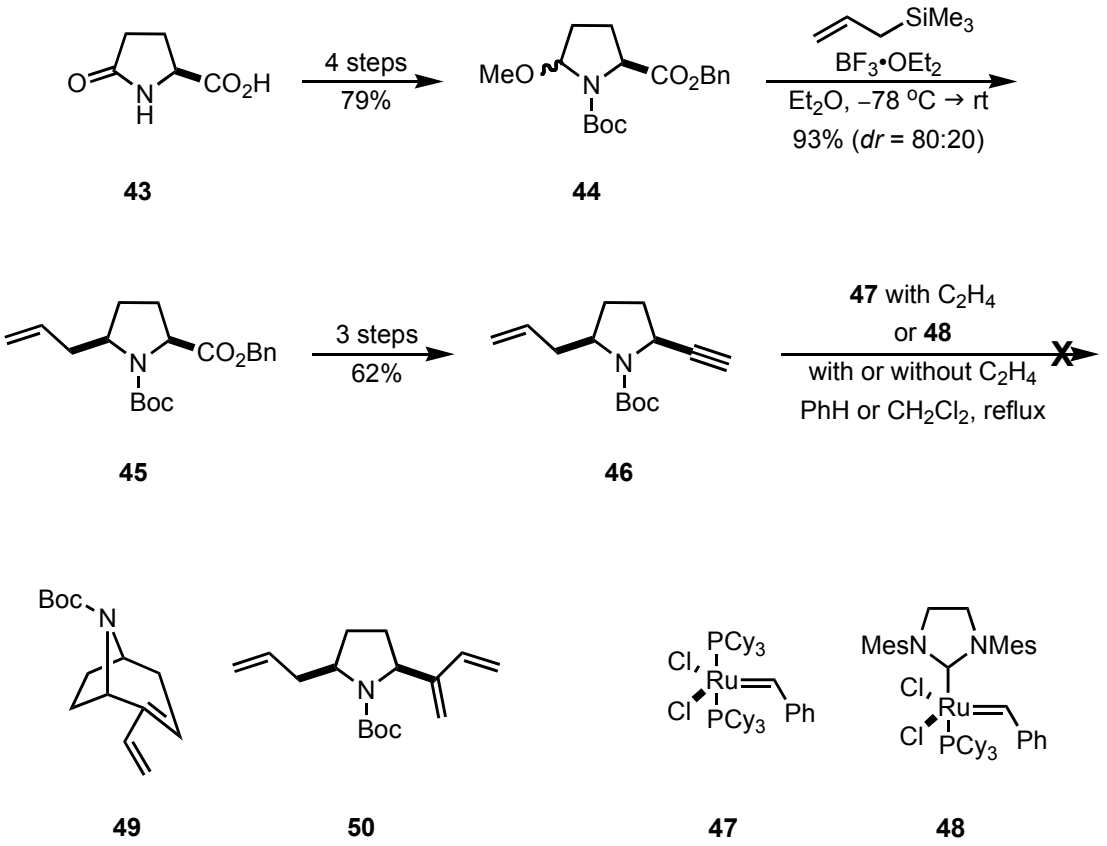


1.5.4 Aggarwal 2004: Aggarwal's Synthesis of (+)-Ferruginine

Subsequent to our own disclosure of a ring-closing enyne metathesis RCEYM approach to anatoxin-a [(+)-**4**] (*vide infra*), two additional reports appeared concerning the application of RCEYM for the preparation of bridged azabicyclic structures. In the first of these reports, Aggarwal detailed the synthesis of (+)-**7** via a strategy that closely resembled a route of our own to (+)-**4**.[151] Beginning from commercially available L-**43**, a series of four operations delivered the aminal **44** (Scheme 7). Installation of an allyl unit was effected using standard *N*-acyliminium chemistry to afford the *cis*-pyrrolidine **45** as a mixture of diastereomers (*dr* = 80:20). Following chromatographic separation, the pure *cis*-compound was elaborated in three steps to the enyne **46**. In accordance with our own

findings, exposure of **46** to either the Grubbs first-generation catalyst **47** or the second-generation catalyst **48** in the presence of ethylene led predominately to the formation of the triene **50**. In the absence of ethylene catalyst **48** provided only traces of the desired RCEYM adduct **49** owing to a competitive dimerization pathway.

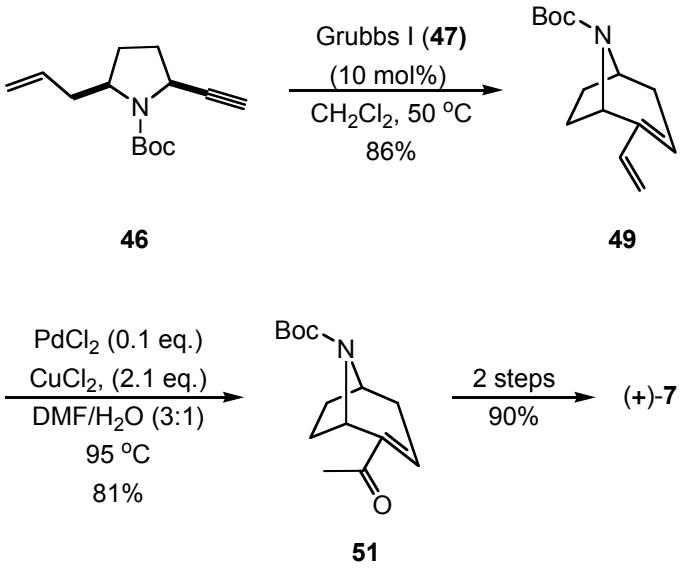
Scheme 7



Also in line with our own results pertaining to the synthesis of anatoxin-a [(+)-**4**] (*vide infra*), Aggarwal found that **47** catalyzed the desired RCEYM of **46** in the absence of ethylene to deliver the azabicycle **49** (Scheme 8). The conversion of the exocyclic vinyl moiety to a methyl ketone was accomplished using Wacker oxidation conditions to provide **51**. Although no details were provided for this transformation, the reaction was reported to transpire in the absence of an oxygen atmosphere. Two subsequent

transformations were employed to convert **51** into (+)-**7**. The synthesis, which proceeded in twelve steps from commercially available L-**43**, afforded (+)-**7** in 29% overall yield.

Scheme 8



1.6 ANATOXIN-a

1.6.1 Background

(+)-Anatoxin-a (**4**), which was isolated from the toxic blooms of the blue-green freshwater algae *Anabaena flos-aquae* (Lyngb.) de Bréb, is one of the most potent nAChR agonists known.[24] Also referred to as "very fast death factor" (VFDF), **1** has been shown to resist enzymatic degradation by acetylcholine esterase, resulting in respiratory paralysis and eventual death.[24a] Despite its toxicity, **4** has emerged as a valuable probe for elucidating the mechanism of acetylcholine-mediated neurotransmission and the disease states associated with abnormalities in this signaling pathway. In addition, **4** possesses the unusual 9-azabicyclo[4.2.1]nonane skeleton. To date, this molecular architecture has been found only in **4** and **5**. Consequent to its potent pharmacological profile and unique azabicyclic skeleton, **4** has remained an attractive synthetic target since its isolation in 1977.[24]

The most common methods for the preparation of the azabicyclic core involve the ring-expansion of (–)-**30**, the cyclization of cyclooctenes, and the intramolecular cyclization of iminium salts. Though a summation of anatoxin syntheses is absent from the current literature, synthetic approaches for the preparation of **4** through 1996 were outlined in a comprehensive review by Mansell.[25] Hence, only the most elegant of the syntheses prior to 1996 will be presented in this treatise for direct comparison with the state-of-the-art methods that have been developed more recently for the assembly of the 9-azabicyclo[4.2.1]nonane skeleton. In addition, the ring-expansion syntheses utilizing (–)-**30** for the assembly (+)-**4** will be omitted, as these routes are impractical from a

general standpoint due to the inaccessibility of this precursor to the majority of the synthetic and medicinal communities.

1.6.2 Highlighted Synthetic Approaches to Anatoxin-a Through 1996

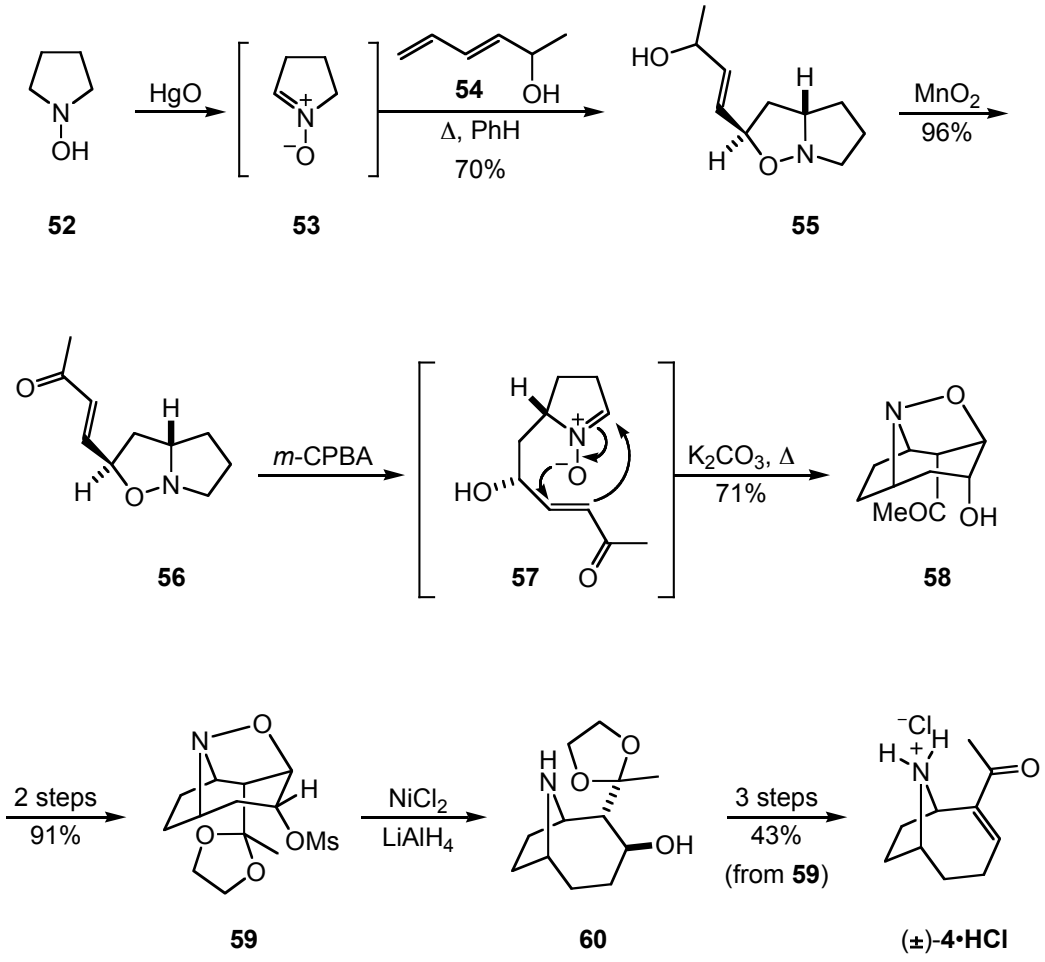
1.6.2.1 Tufariello 1984: Nitrone Cycloadditions

In 1984 Tufariello and coworkers disclosed a synthesis of (±)-**4** from 1-hydroxypyrrolidine (**52**) using a series of nitrone cycloaddition reactions.[26] The synthesis began with the oxidation of **52** to the nitrone **53** that underwent a subsequent dipolar cycloaddition reaction with 3,5-hexadien-2-ol (**54**) (Scheme 9). Allylic oxidation of the resulting bicyclic *N*,*O*-acetal **55** afforded enone **56** as the sole product, suggesting an *exo*-selective cyclization manifold between **53** and **54**. Exposure of **56** to *meta*-chloroperoxybenzoic acid (*m*-CPBA) resulted in the oxidative cleavage of the *N*,*O*-acetal to provide the nitrone **57** that subsequently underwent a thermally promoted regioselective intramolecular nitrone cyclization to deliver the bicyclic adduct **58**. Consistent with previous methodological studies, Tufariello and coworkers did not observe the formation of the cycloadduct resulting from 6-membered ring-closure due to the preference of nitrones to react at the β-position of α,β-unsaturated carbonyl systems.[27] Adduct **58** was transformed into the advanced intermediate **59** after two additional steps. Cleavage of the *N*,*O*-acetal and reduction of the mesylate was accomplished in a single operation using the nickel hydride species generated from ($NiCl_2$) and $LiAlH_4$ to produce **60**. The stable salt (±)-**4·HCl** was obtained after three further manipulations.

Tufariello's synthesis provided (±)-**4·HCl** in nine chemical operations and 19% overall yield from **52**. The major limitation of this synthesis is the inability to obtain

optically pure material via the present route. Furthermore, it would seem that analog preparation would be limited to derivatives from which dienes related to **54** could be prepared.

Scheme 9



1.6.2.2 Danheiser 1985: Electrocyclic Cleavage-Transannular Cyclization

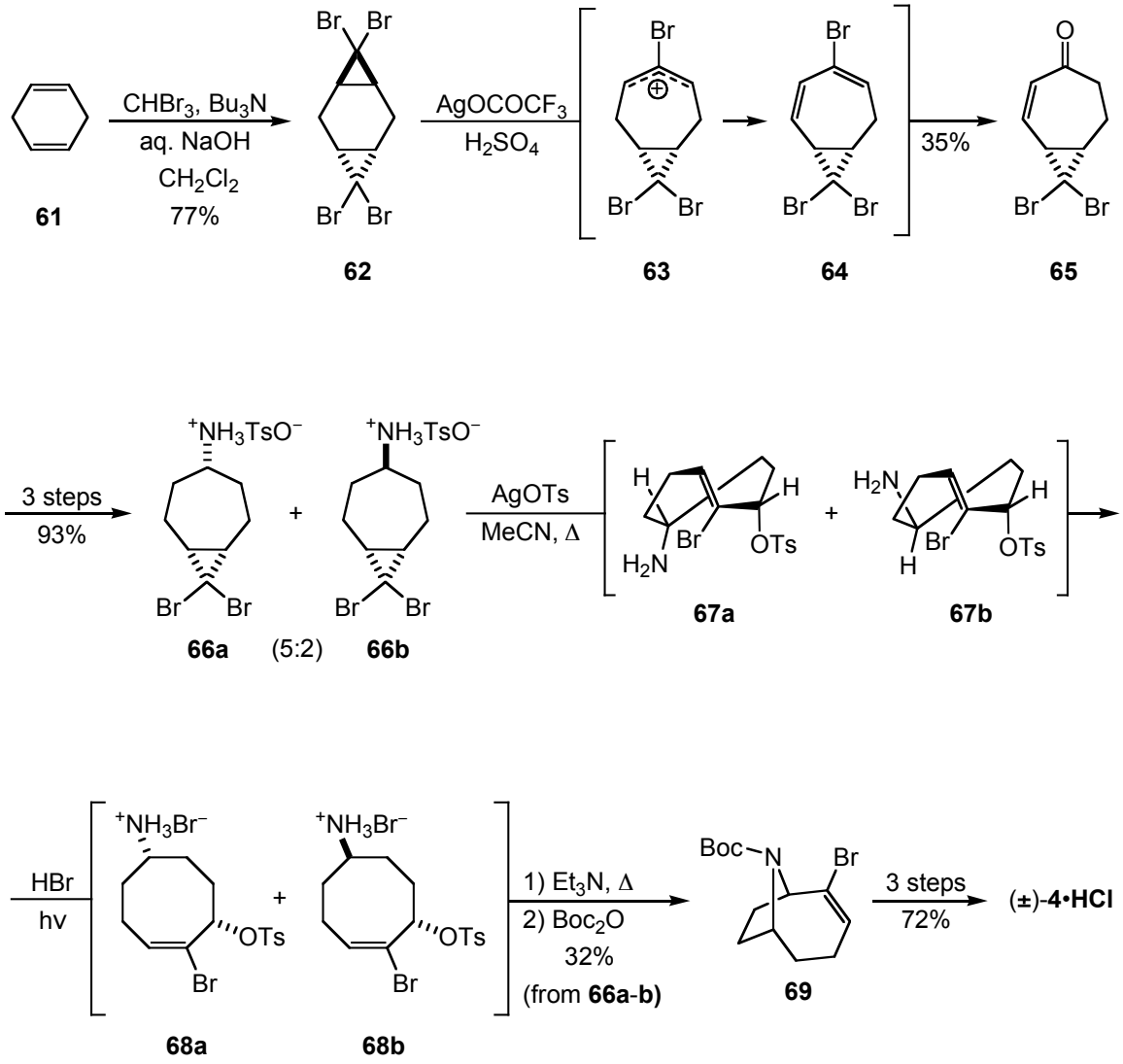
Danheiser and coworkers reported an elegant synthesis of (±)-**4** using a transannular cyclization strategy reminiscent of those discussed previously for the preparation of **6**.[28] The key feature of their strategy was the development of two independent electrophilic cleavage events in which dibromocyclopropane precursors

were ring-expanded to generate the homotropane nucleus of **4**. The synthesis commenced with the dibromocyclopropanation of 1,4-cyclohexadiene (**61**) to provide **62** (Scheme 10). Earlier work by Birch and coworkers had demonstrated that the electrocyclic cleavage of **62** could be restricted to one of the two cyclopropane rings, thereby generating a bicyclo[5.1.0]octane derivative.[29] Toward this end, **62** and $AgOCOCF_3$ were combined in a biphasic mixture of H_2SO_4 and CH_2Cl_2 to afford **65**. The reaction is believed to proceed first by the disrotary electrocyclic cyclopropane opening to generate the cationic intermediate **63**, which was converted to the diene **64** upon abstraction of a proton. Vinyl bromide **64** was then hydrolyzed to **65** by the acidic reaction media. Three subsequent transformations produced a mixture of the *endo*- and *exo*-isomeric ammonium tosylates **66a** and **66b** respectively. The mixture of ammonium tosylates **66a-b** underwent a silver tosylate (AgOTs)-mediated electrocyclic cyclopropane cleavage to produce the diastereomeric cyclooctenes **67a-b**. The resulting *trans*-cyclooctene derivatives **67a-b**, were converted to the requisite *cis*-cyclooctenes **68a-b** by photoisomerization of the corresponding hydrobromide salts. The azabicycle **69** was obtained upon heating the mixture of **68a-b** with Et_3N to induce the intramolecular displacement of the tosylates, followed by protection of the amine as the *t*-butyl carbamate. The synthesis of (±)-**4** was concluded after three further transformations.

This synthesis of (±)-**4** proceeded in eleven chemical operations and 6% overall yield from **61**. However, this synthesis suffers from the need to use stoichiometric quantities of costly silver salts and suffers from a very low yield during the conversion of **62** to **65**. Furthermore, this approach to **4** is limited to the preparation of racemic material

unless suitable conditions to effect the diastereoselective assembly of **66a** or **66b** can be developed.

Scheme 10

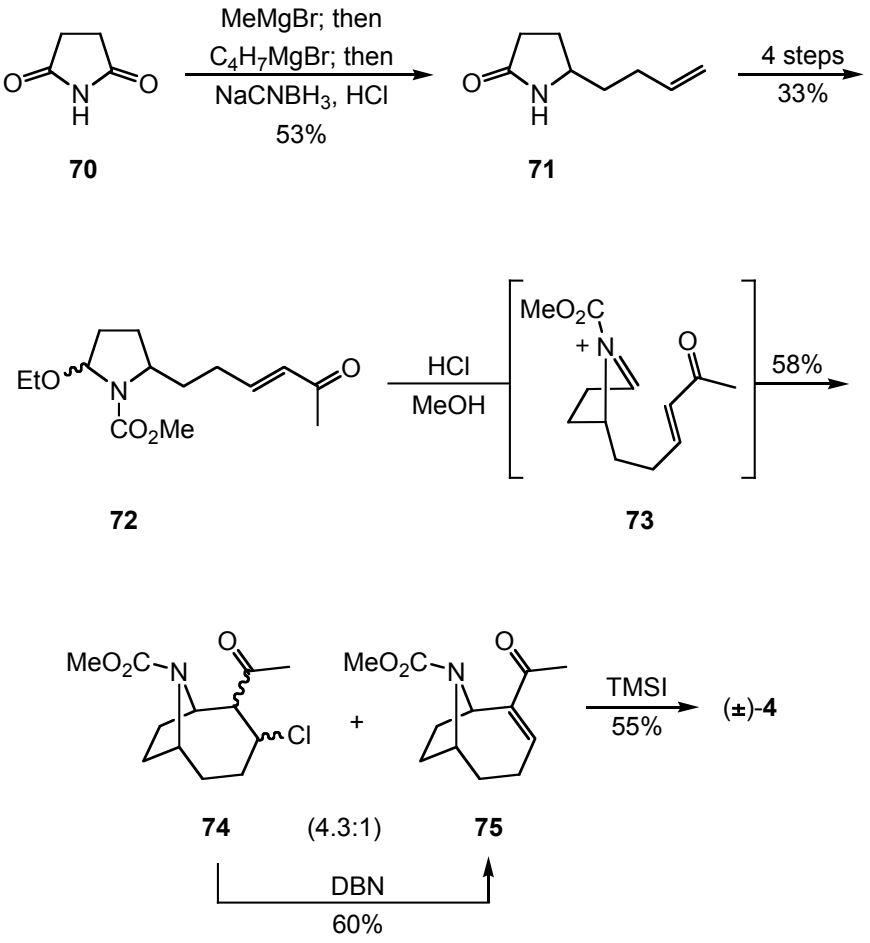


1.6.2.3 Speckamp 1986: N-Acyliminium Cyclization

Rapoport and coworkers were the first to disclose the utility of *N*-acyliminium ion cyclizations for the generation of azabicycloalkanes,[30] both enantiomers of **4**,[31] and for anatoxin-a analogs.[32] A number of synthetic approaches utilizing variations of this strategy have since appeared for the preparation of **4**.[33] Speckamp and coworkers

disclosed one such variation of this general strategy during their synthesis of (±)-**4**.[34] Their approach featured an intramolecular Mannich cyclization between an *N*-acyliminium ion and a tethered enone. This protocol was chosen to facilitate the direct introduction of the unsaturated ketone portion of **4**.

Scheme 11



Accordingly, succinimide (**70**) was converted to the butenylpyrrolidone **71** in a one-pot operation (Scheme 11). A series of four standard protocols were utilized to transform **71** into the *N*-acyliminium precursor **72**. Dissolution of **72** in methanolic HCl effected the desired Mannich cyclization via intermediate **73** to produce a mixture of **74** and **75** in 47% and 11% yield respectively. Dehydrochlorination of the mixture was

achieved under basic conditions to yield pure **75**. The synthesis was completed upon deprotection of the methyl carbamate, thereby affording (±)-**4** in eight steps and 3% overall yield from **70**. This synthesis, though quite rapid, suffers from a very low overall yield of racemic **4**. Also, in its present from, the synthesis is not amenable to the preparation of optically pure **4** or analogs thereof.

1.6.3 Highlighted Synthetic Approaches to Anatoxin-a Since 1996

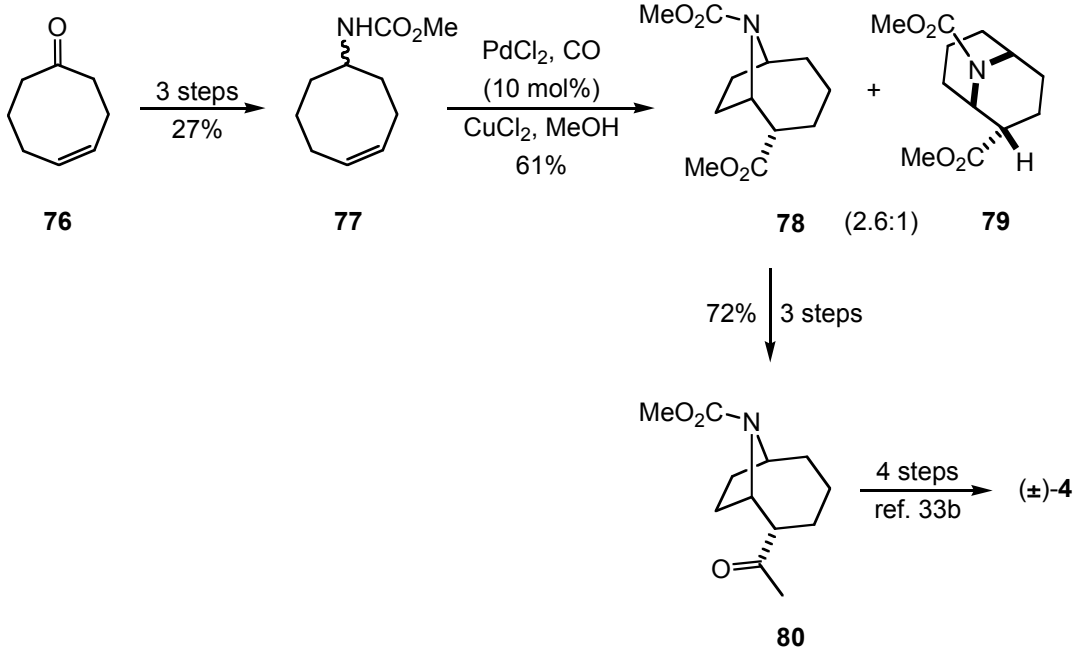
During the period since Mansell's review of anatoxin-a syntheses, considerable progress has been made in the understanding and development of metal-catalyzed bond-forming reactions. The discovery of new catalytic systems has undoubtedly increased the scope of such processes for assembling complex functionalized targets, often presenting an opportunity to induce high levels of asymmetry through the incorporation of chiral ligands. As such, the few so-called "state-of-the-art" strategies disclosed since 1996 have primarily utilized new metal-catalyzed processes for the construction of the azabicyclic skeleton of **4**. Of the five reported syntheses of **4** from the years 1996-2003, two utilize palladium-catalyzed methods to form the azabicycle,[35] whereas the remaining three syntheses reported modifications to existing procedures for the improved synthesis of the natural product.[36]

1.6.3.1 Ham 1998: Intramolecular Aminocarbonylation

Hegedus and coworkers were the first to demonstrate the utility of palladium-catalyzed intramolecular amination reactions for the preparation of alkaloid frameworks.[37] Numerous other research groups have since utilized this strategy and improvements thereupon in the context of preparing nitrogen heterocycles. In 1998 Ham and coworkers reported a formal synthesis of (±)-**4** using an intramolecular palladium-

catalyzed aminocarbonylation reaction that had previously been highlighted during their formal synthesis of (±)-**7**.[38,35a] Although not the first to realize the utility of intramolecular aminocarbonylation sequences for alkaloid syntheses, they were the first group to apply this method to the syntheses of the tropane and homotropane skeletons. Their synthesis of (±)-**4** began with the conversion of the known ketone **76** into the racemic cyclization precursor **77** (Scheme 12). The key intramolecular aminocarbonylation reaction was accomplished upon exposure of **77** to conditions commonly used to effect such transformations. The reaction proceeded stereospecifically to deliver a mixture of the regioisomeric cyclization products **78** and **79**, of which **78** was the desired product. For simplicity compound **78** is represented as only one stereoisomer. Following the isolation of pure **78**, three additional manipulations provided the ketone **80** that was previously elaborated to the natural product.[33b]

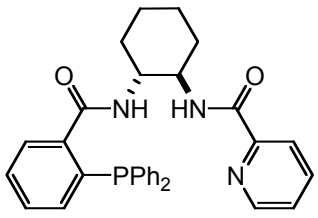
Scheme 12



The formal synthesis target **80** was prepared in seven chemical operations and 12% overall yield from **76**. However, the modest regioselectivity observed during the aminocarbonylation detracts from the overall utility of this method.

1.6.3.2 Trost 1999: Palladium-Catalyzed Asymmetric Allylic Alkylation

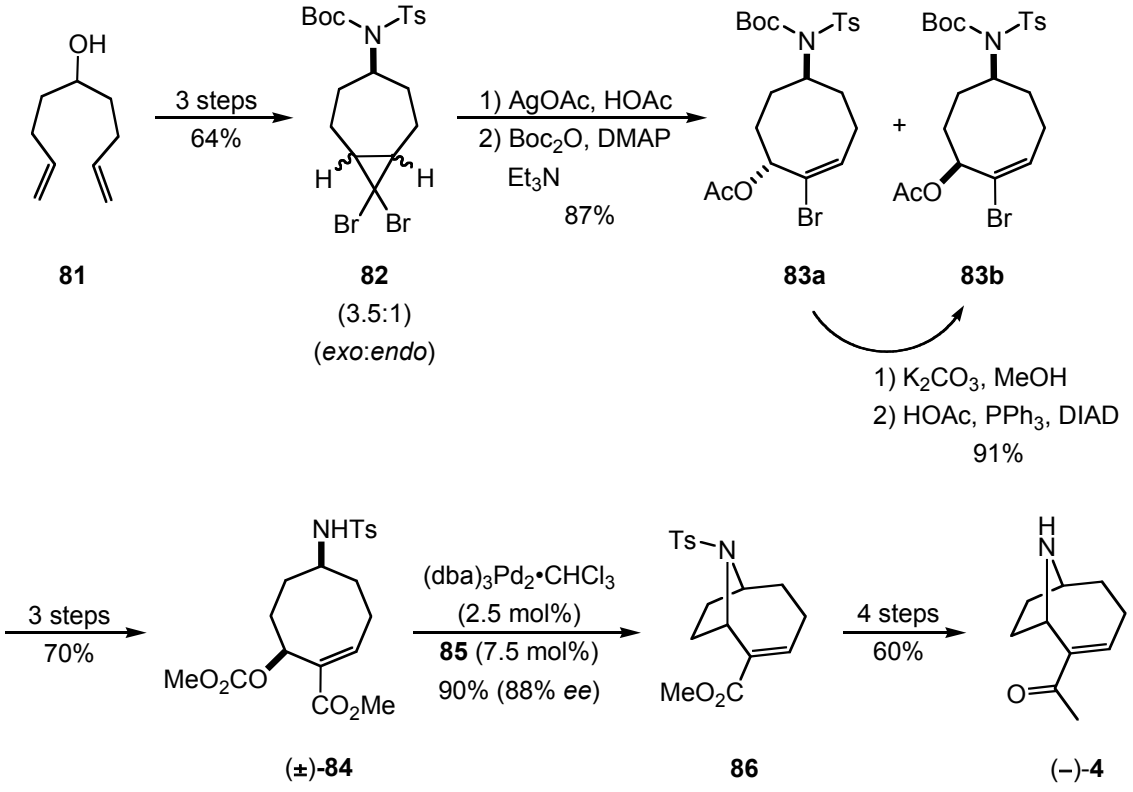
In the context of exploring the scope and utility of asymmetric metal-catalyzed allylic alkylations, Trost and Oslob undertook the synthesis of (–)-**4**.[35b] It was envisioned that the synthesis would provide insight into whether medium-sized rings could be efficiently utilized in asymmetric intramolecular palladium-catalyzed allylic alkylations. As this synthesis was primarily "method driven", a protocol was utilized that closely paralleled the Danheiser route (*vide supra*). The synthesis commenced with the transformation of 5-hydroxy-1,8-nonadiene (**81**) into a mixture of the diastereomeric dibromocyclopropanes **82** (Scheme 13). Solvolytic ring-opening of **82** was achieved with silver acetate (AgOAc), and reinstallation of the carbamate protecting group lost during the process delivered a mixture of the *trans*- and *cis*-amidoacetates **83a**-**b**, respectively. Inversion of the free alcohol of **83a** via a Mitsunobu reaction afforded additional **83b**. Three subsequent transformations provided the racemic cyclization precursor **84**. The key palladium-catalyzed cyclization to produce the desired azabicyclic skeleton was effected using **85** as the ligand to afford **86** in high yield and good enantioselection.



(***S***,***S***)-**85**

Attempted cyclization of **84** in the presence of alternative ligands failed to produce the azabicyclic core with any appreciable asymmetric induction. Compound **86** was then converted to the natural product using known procedures. The asymmetric synthesis of (–)-**4** was accomplished in 15% overall yield and in sixteen steps from **81**. From a methodological standpoint, the synthesis highlighted the development of the new chiral allylic alkylation catalyst **85**. However, from a synthetic standpoint Trost's route to (**–**)-**4** is rather lengthy and fails to address the scope of substrates that are tolerated by the allylic alkylation protocol, leading one to wonder whether the method is general for the preparation of analog structures or additional azabicycles of varying ring size.

Scheme 13



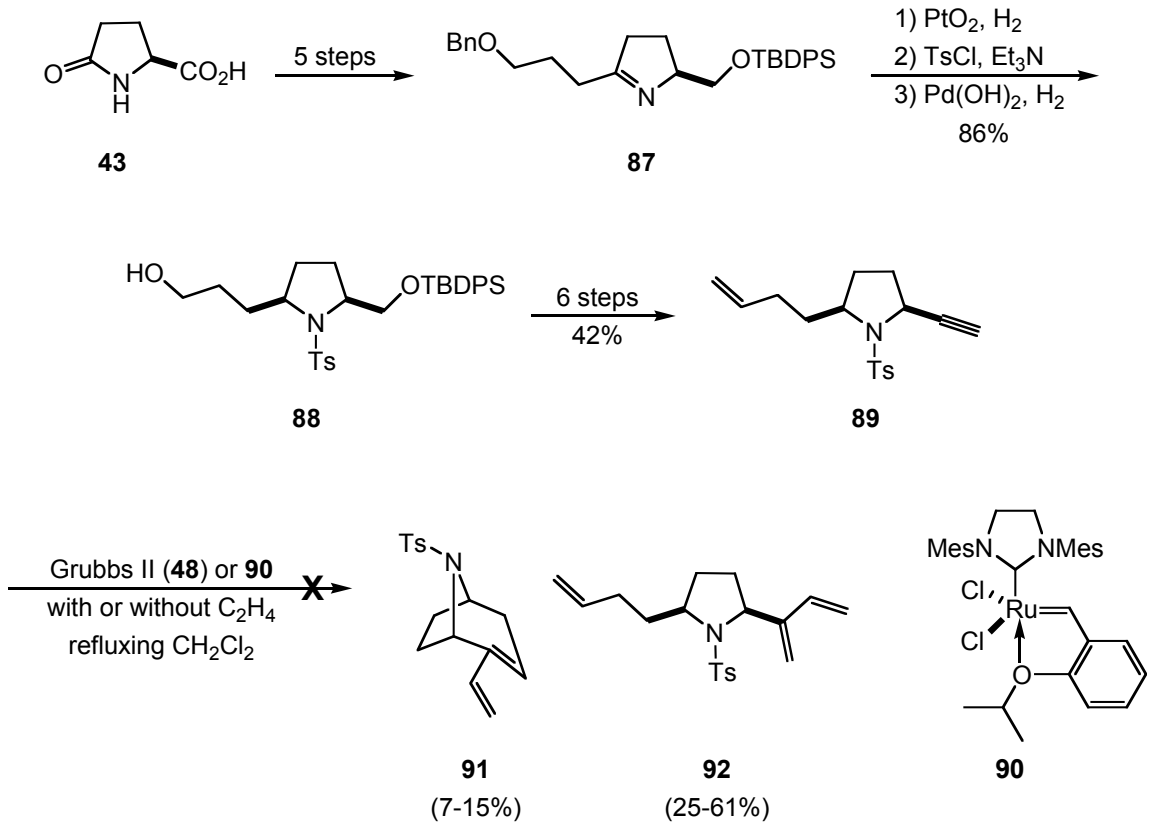
81 **82** (3.5:1) (*exo*:*endo*) **83a** **83b**

(±)-**84** **86** (–)-**4**

1.6.3.3 Mori 2004: Mori's Formal Synthesis of Anatoxin-a

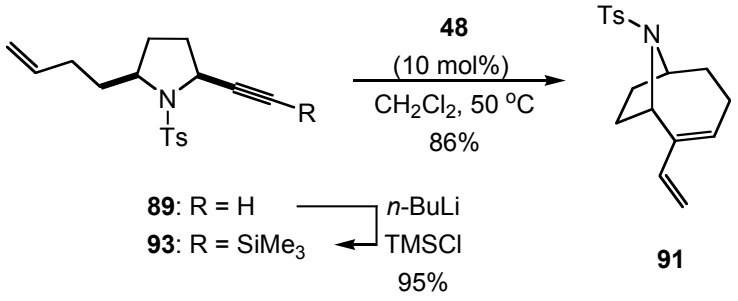
Following Aggarwal's synthesis of (+)-**7** (*vide supra*), Mori disclosed another intramolecular RCEYM approach to **4**, virtually identical with our own (*vide infra*).[39] The synthesis commenced with the conversion of L-**43** to the imine **87** (Scheme 14). Reduction of the imine by catalytic hydrogenation and then two subsequent functional group manipulations afforded the *cis*-pyrrolidine **88**. The EYM substrate **89** was obtained following a series of six further operations. As previously documented, exposure of enyne **89** to the Grubbs second-generation catalyst **48** or the Hoveyda-Grubbs second-generation catalyst **90** in the presence of ethylene resulted in the predominate generation of the triene **92**. Also in accord with previous findings, metatheses conducted with **48** or **90** in the absence of ethylene led to polymerization.

Scheme 14



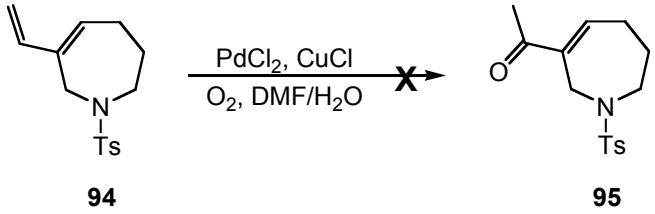
In an effort to circumvent the undesired side-reactions that occurred with the terminal acetylene **89** during the key RCEYM event, Mori prepared the silylalkyne **93** (Scheme 15). Exposure of **93** to catalyst **48** produced the azabicyclic diene **91** lacking the TMS-group. A mechanistic rationale to explain the protodesilylation was not presented.

Scheme 15



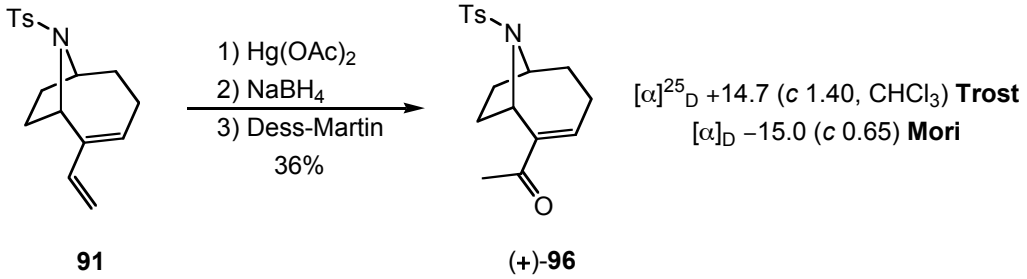
The elaboration of the exocyclic vinyl moiety to the requisite methyl ketone was to be accomplished using Wacker oxidation conditions. However, attempted installation of an enone via this strategy proved wholly unsuccessful on the model azepine system **94** (Scheme 16).

Scheme 16



The exocyclic vinyl group of **91** was alternatively converted to a methyl ketone in three steps via an oxymercuration-demercuration protocol shown in Scheme 17.

Scheme 17



91 (+)-**96**

Using this protocol, Mori reportedly obtained the enone (+)-**96**, which had previously served as an intermediate in Trost's synthesis of (**–**)-**4**.[35b] At this point several discrepancies arise concerning the validity of Mori's reported synthesis. To begin with, the formation of (+)-**96** is expected from L-**43**. However, Mori reported a negative optical rotation for this compound, which appears to have been taken directly from a previous synthesis of (**–**)-**96** by Somfai and coworkers.[33c] Additionally, (+)-**96** would provide (**–**)-**4** as opposed to (+)-**4** upon removal of the *N*-tosyl group, in sharp contrast to Mori's claim to have completed a formal synthesis of (+)-**4**.

1.6.4 Anatoxin-a Analogs

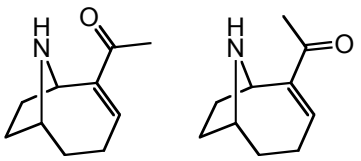
1.6.4.1 Background

Due to the lethal toxicity associated with anatoxin-a itself, the pursuit of receptor-selective nAChR agonists with equipotent but non-toxic pharmacological properties is of great interest to the medicinal chemistry community. It is recognized that analogs incorporating the azabicyclo[4.2.1]nonane skeleton exhibit high-affinity binding profiles for the neuronal nAChRs. Current analog development, which can primarily be attributed to three research groups, has focused on the preparation of side-chain modified derivatives in which the enone moiety of **4** is substituted for an alternate hydrogen bond

acceptor motif. It is believed that subtle modifications of the side-chain will further enhance the selectivity for which the analogs bind the $\alpha4\beta2^*$ receptor, which is the neuronal receptor subclass primarily targeted for the treatment of neurological disorders. Successful development of an exogenous ligand with little or no binding affinity for the additional nAChRs, especially those of the peripheral CNS, should lead to the development of therapeutic agents devoid of any toxic liability. Although numerous analogs of other known nAChR agonists including **6** and **7** have been developed, the typically poor degrees to which these ligands selectively bind individual nAChRs precludes a discussion of these synthetic targets. As such, this treatise will only seek to present the development of nAChR agonists containing the azabicyclo[4.2.1]nonane nucleus.

1.6.4.2 Early Pyridyl-Fused Anatoxin-a Variants

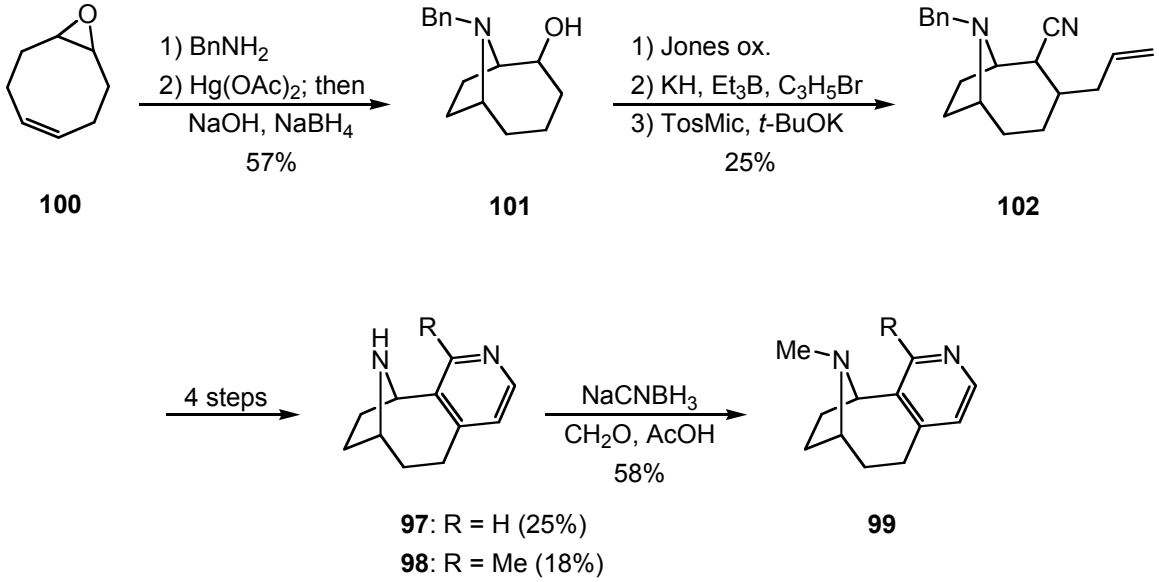
The first reported synthesis of an anatoxin-a analog was set forth by Kanne and coworkers in the mid-1980's.[40] Kanne prepared the first pyridylhomotropanes (PHT) **97-99** (Scheme 18).[41] The preparation of these conformationally constricted analogs of **4** was undertaken in order to determine which of the two possible conformers, (s-*cis*)-**4** or (s-*trans*)-**4**, was required for high-affinity binding to nAChRs. The pyridyl derivatives were specifically chosen to provide fused analogs in which the hydrogen bond acceptor (the pyridyl nitrogen) would reside roughly within the same spatial orientation as the lone-pairs of the enone oxygen of (s-*cis*)-**4**. It was anticipated that the preparation of such derivatives would provide a better understanding of the chemical and spatial requirements of the nAChRs as well as the identity of the conformer of **4** capable of high affinity binding.



(s-*trans*)-**4** (s-*cis*)-**4**

The synthesis of the pyridohomotropanes began with the ring-opening of the known epoxide **100** with benzylamine ($BnNH_2$) (Scheme 18). Aminomercuration, followed by demercuration delivered the azabicyclic alcohol **101**. Three further operations provided the nitrile **102**. Compounds **97** and **98** were each prepared in four steps from **102**, while an additional reductive amination step converted **97** into **99**.

Scheme 18



100 **101** **102**

97: R = H (25%)
98: R = Me (18%)

99

Subsequent binding assays indicated that (±)-**97** was equipotent with (±)-**4**, but that the methylated analogs (±)-**98** and (±)-**99** exhibited markedly decreased potency. The authors did not present any conclusions regarding the identity of the biologically active conformation of **4**. Based on the comparable binding affinities displayed by **4** and **97**, one might conclude that the *s-cis* conformer is responsible for nAChR agonism. However due

to the different skeletal features displayed by each ligand, one cannot rule out the influence of additional subtle factors including hydrophobicity, solubility and pKa differences on the binding data obtained.

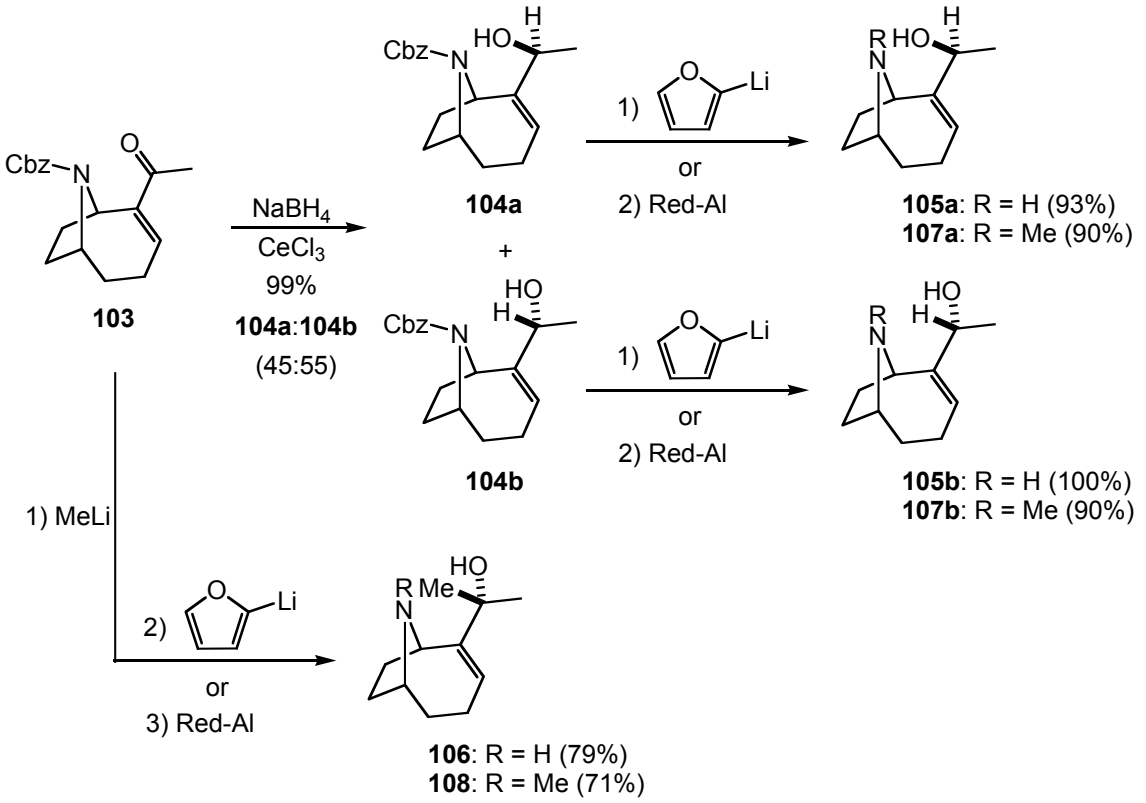
Following the initial reports regarding the synthesis and biological activity of the PHT ligands, the preparation of pyridohomotropanes was essentially abandoned. It wasn't until the isolation and structural elucidation of **6** that interest in ligands of this topology was renewed. Instead, the trend in analog development shifted in favor of preparing acyclic side-chain extended analogs of **4**, though a few conformationally constricted carbocyclic derivatives also emerged during the period.

1.6.4.3 Side-Chain Modified Analogs

In addition to preparing the *N*-methyl and methiodide salts of **4**, Rapoport and coworkers were the first to synthesize analogs incorporating structural modifications at the position of the methyl ketone moiety.[32b] Luche reduction of **103**[32b] provided a nearly equal composition of the separable anatoxinols **104a-b** (Scheme 19). Subsequent deprotection of the benzyl carbamate was most efficiently achieved by nucleophilic displacement with 2-lithiofuran[42] to afford the free bases **105a-b**. The tertiary anatoxinol **106** was prepared via treatment with MeLi prior to deprotection of the carbamate as before. The corresponding *N*-methyl anatoxinols were also prepared by reduction of the carbamate moieties, thus delivering compounds **107a-b** and **108**.

It was thought that analogs **105-108** would be used to probe the receptor requirements for hydrogen bond acceptor motifs within exogenous ligands. Unfortunately, the authors did not disclose any subsequent data concerning the evaluation of the analogs **105-108** in nAChR binding affinity assays.

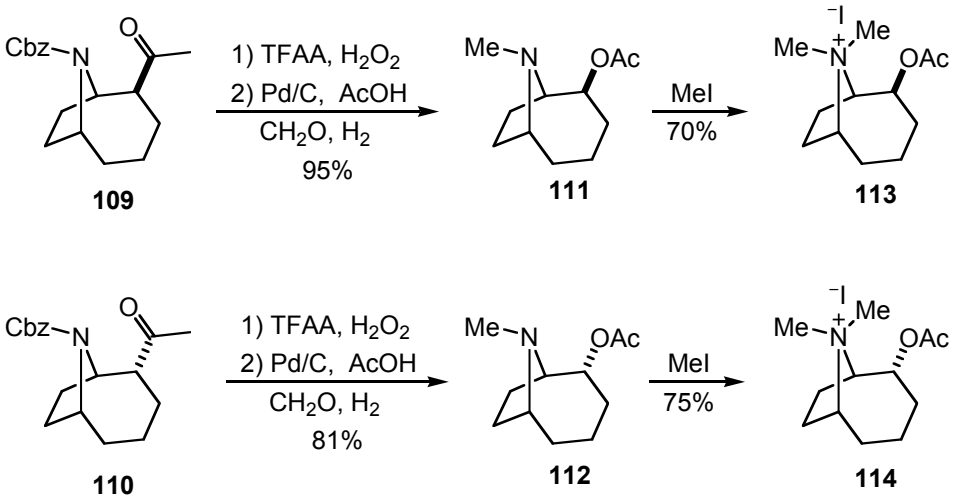
Scheme 19



The acetoxy-analogs **111-114** were also synthesized for biological evaluation. It was believed that these derivatives would resemble constrained analogs of the *syn* and *anti* conformations of **1**.[43] The ligands **111** and **112** were prepared from ketones **109** and **110**,[32b] respectively, by Baeyer-Villiger oxidation, followed by debenzylation and reductive amination (Scheme 20). *N*-Methylation of these compounds provided the salts **113** and **114**.

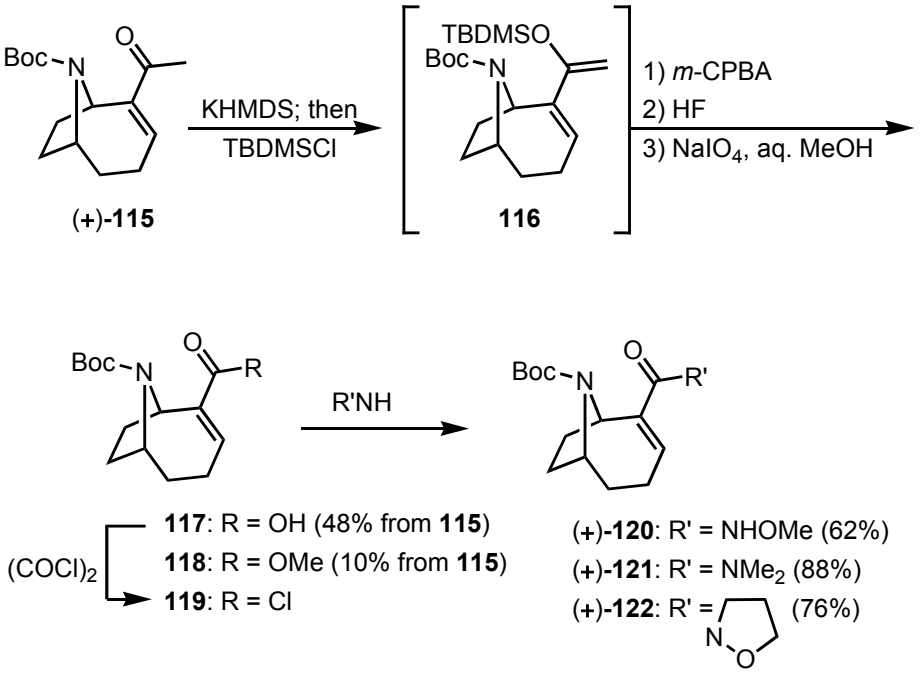
Binding data is also lacking for the acetoxy derivatives **111-114**. However, the corresponding free-bases of the dihydroanatoxinoids **109** and **110** were found to be reasonably potent binders of the neuronal and peripheral nAChRs, but theses ligands failed to exceed the potency exhibited by **4** itself.[44]

Scheme 20



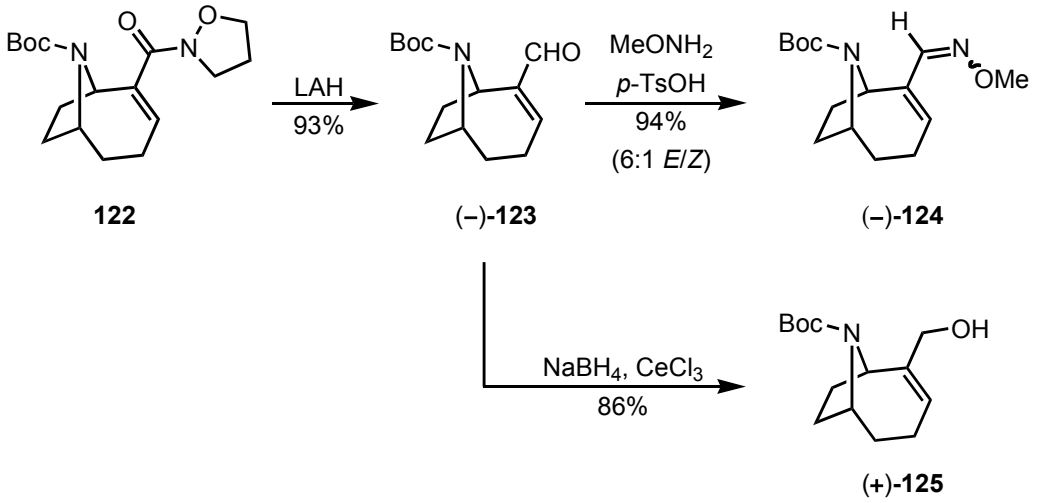
In a later report, Rapoport and coworkers detailed the preparation of several analogs originating from intermediate **115**.[45,46]

Scheme 21



The synthetic protocol commenced with the four-step conversion of **115** to the carboxylic acid **117** during which a small quantity of the ester **118** was also formed (Scheme 21). Compound **117** was further elaborated to the acid chloride **119** which was immediately used to prepare the amides **120**-**122**. Additionally, compound **122** was reduced to the aldehyde **123** and condensed with *O*-methylhydroxylamine (H_2NOMe) to produce the oxime **124** (Scheme 22). Alternatively **123** was reduced under Luche conditions to deliver the allylic alcohol **125**.

Scheme 22



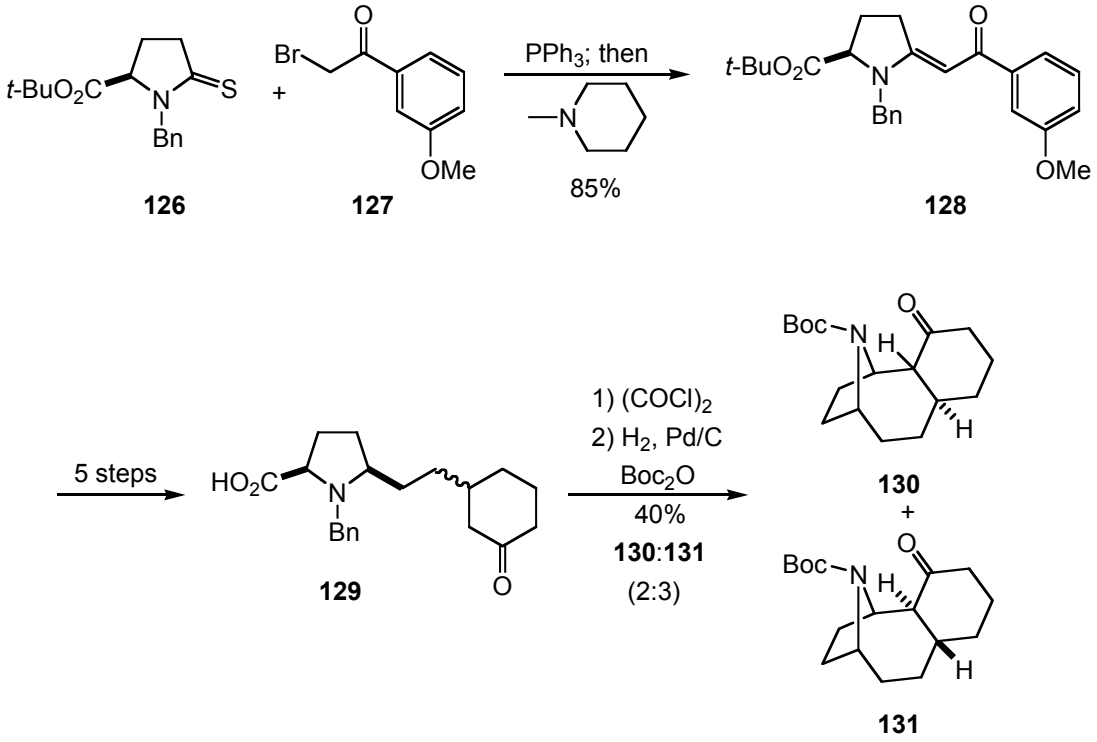
122 (–)-**123** (–)-**124** (+)-**125**

It was found during the course of binding assays that ligands **120**-**125** exhibited markedly decreased binding affinities for any of the neuronal receptor types compared to **4**.[44] Only the methyl ester **118** maintained potency on par with the parent compound **4**.

A final series of analogs prepared by Rapoport and coworkers were the ring-fused carbocycles **130** and **131** that are structurally similar to **5**.[32a] These compounds served to lock the enone in the s-*trans* configuration in order to assess the identity of the conformer responsible for potent bioactivity. Compounds **130** and **131** were prepared by the

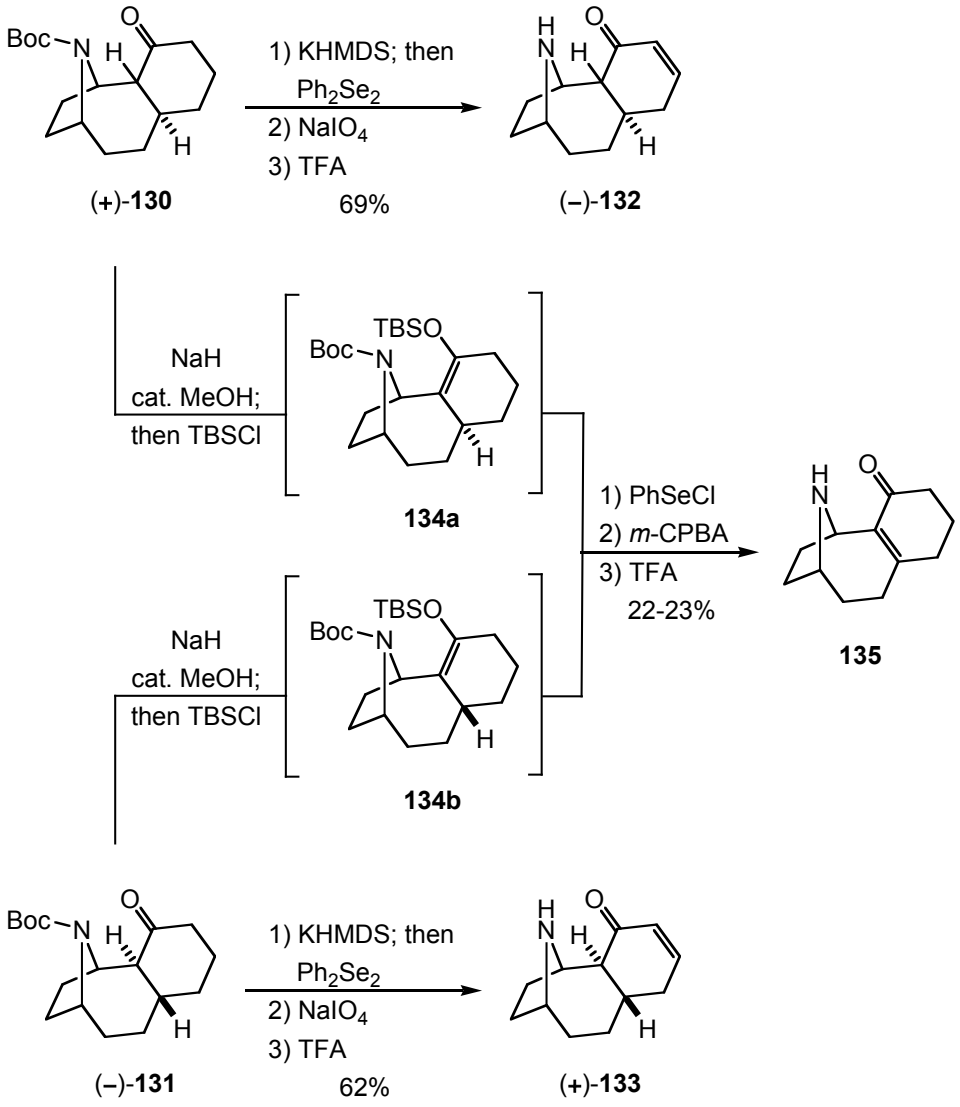
alkylation of the thiolactam **126** with **127** (Scheme 23). The ensuing Eschenmoser sulfide contraction afforded the vinylogous amide **128** that was further transformed into the mixture of diastereomeric ketoacids **129**. Decarbonylation of the mixture delivered the fused azabicycles. Debenzylation and reprotection of the free amines as the corresponding Boc-carbamates provided **130** and **131**.

Scheme 23



The unsaturated tricycles **132** and **133** were prepared from **130** and **131** respectively using a kinetically controlled α-selenation and elimination protocol (Scheme 24). Alternatively, thermodynamically controlled enolization of **132** and **133** provided the silyl enol ethers **134a**-**b** that were immediately subjected to a similar dehydroselenation sequence to afford **135**. Currently, there are no data regarding the potency and selectivity of the corresponding free bases of the fused ligands **130**-**133** and **135**.

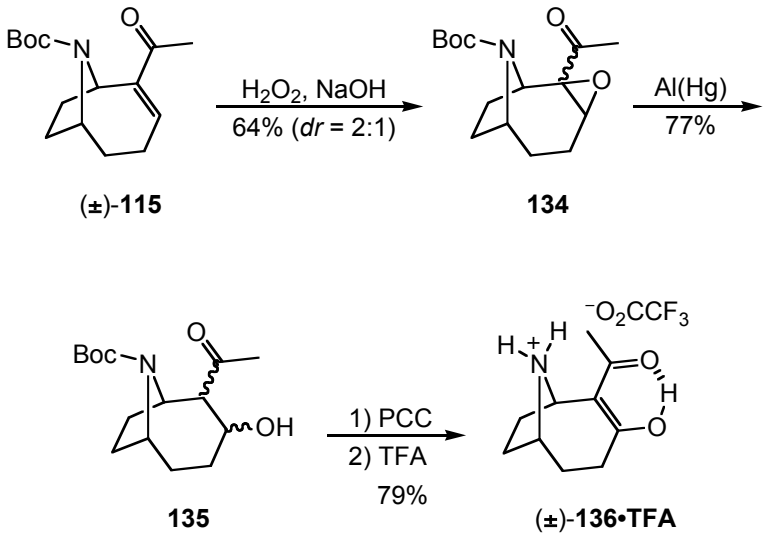
Scheme 24



Gallagher and coworkers set out to prepare a conformationally restricted s-*cis* analog of **4**. This was accomplished via the synthesis of racemic **136** (hydroxyanatoxin-a).[47] Compound **136** exists predominately as the enol tautomer, stabilized by an intramolecular hydrogen bond. For simplicity, the *endo*-enol tautomer is shown, though it is unclear whether this species or the corresponding *exo*-enol tautomer is preferred based on solid-state analyses. The synthesis of **136** began with the epoxidation of (**±**)-**115** to

give the diastereomeric epoxyketones **134** (Scheme 25). Reductive cleavage of the epoxide was effected after considerable experimentation to provide **135**. Subsequent oxidation and deprotection afforded **136** as the corresponding trifluoroacetate salt.

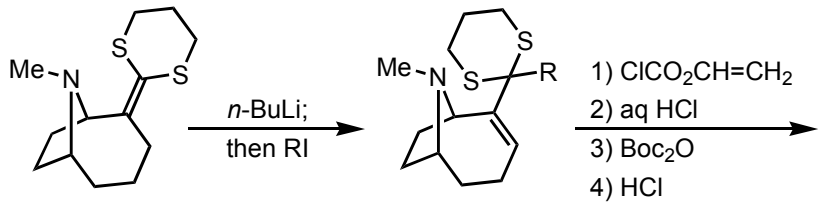
Scheme 25



Binding assays conducted by Gallagher and coworkers showed that **136** exhibited extremely poor binding affinity for nAChRs, which contrary to the results obtained by Kanne, suggested that the bioactive conformer of anatoxin-a is (s-*trans*)-**4**. However, the significant structural differences between **4** and **136** make this claim difficult to verify on the basis of these results. In support of this claim, subsequent computational studies demonstrated that the s-*trans* enone is 9.4 kJ mol^{-1} more stable than the s-*cis* conformer at physiological pH. Additionally, when the s-*trans* and s-*cis*-enones were used to model the receptor-excluded volumes according to the "active analog approach" developed by Hacksell and Mellin,[48] it was shown that the s-*trans*-enone displays a smaller receptor excluded volume than the s-*cis*-enone, thereby suggesting that the s-*trans* enone would bind more efficiently to the receptor active site.

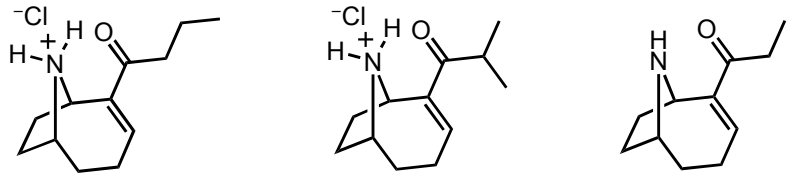
Gallagher and coworkers also prepared several analogs of **4** via side-chain modifications at the site of the methyl ketone. Earlier binding assays had suggested that the side-chain elongation of the enone moiety was not detrimental to potency. As such, the racemic ketones **140** and **141** were prepared according to Scheme 26.[49] The syntheses began with an adaptation of a protocol developed by Stjernlöf for the synthesis of **4** from (–)-**30**.[50] Thus, the known dithioketeneacetal **137** underwent allylic deprotonation and α-alkylation with ethyl iodide (EtI) and isopropyl iodide (*i*-PrI) to afford **138** and **139**, respectively. Subsequent thioacetal cleavage, *N*-demethylation, and acidic hydrolysis of the intermediate carbamates delivered the ketones **140** and **141**. The newly prepared ketones were screened for binding affinity and receptor selectivity alongside racemic **4**. In addition, the naturally occurring toxin **142** (homoanatoxin-a) was evaluated.[51] In the assays, compounds **141** and **142** exhibited increased binding affinity for the α4*β*2* nAChRs compared to **4**, but their ability to bind the α7 receptors increased as well. Ligand **140** was slightly less potent than **4** at the α4*β*2* nAChRs, but exhibited an enhanced binding capacity for the α7 receptors compared to the other ligands. The data revealed that chain-elongation at the position of the ketone moiety provided more potent but less receptor-selective agonists than **4**. In addition, the assays demonstrated the ability of the nAChRs to accommodate additional chain-extended ligands of increased hydrophobicity. A rationale for the dramatic increase in α7 selectivity observed with **140** was not provided, but the authors did suggest that this result could potentially signal the emergence of a strategy for the development of α7 receptor-selective ligands

Scheme 26



(±)-**137**

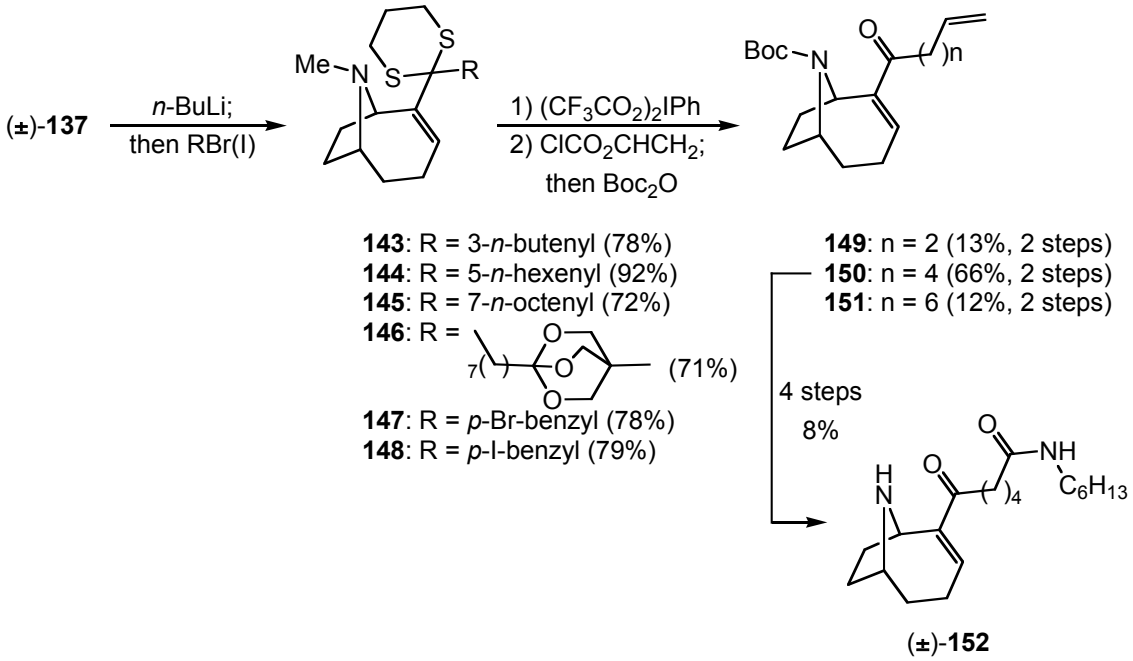
138: R = Pr (68%)
139: R = *i*-Pr (84%)



(±)-**140•HCl** (48%) (±)-**141•HCl** (59%) **142**

Gallagher and coworkers also developed solid-phase techniques to prepare analogs of anatoxin-a for affinity chromatography experiments.[52] The syntheses of these compounds paralleled the route used to prepare compounds **140** and **141** (Scheme 27). Thus, **137** underwent allylic deprotonation and α-alkylation with a variety of alkyl halides to provide **143**-**148**. Thioacetal cleavage and *N*-demethylation of **143**-**145** generated **149**-**151**. Ketone **150** was transformed into the amide **152** after four additional operations. The *n*-hexylamide moiety was chosen to simulate the amino-terminus of the AH-Sepharose 4B solid support to be used in future affinity chromatography experiments. As the authors did not provide the results of subsequent binding assays for the series of compounds presented in Scheme 27, it remains to be seen whether the derivatives **143**-**152** are suitable ligands for nAChR affinity chromatography experiments.

Scheme 27

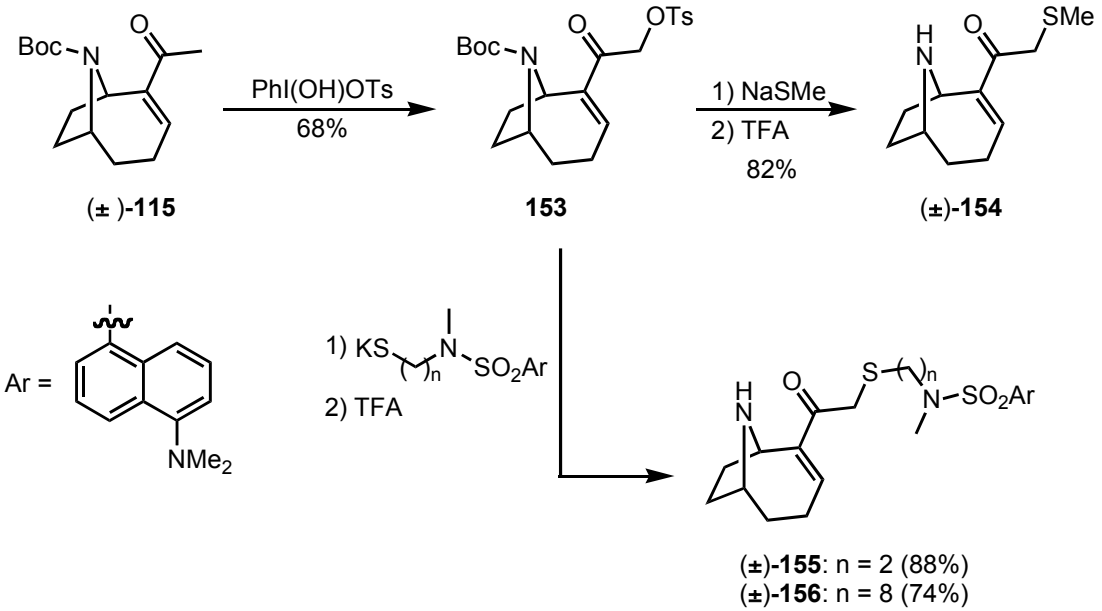


A series of thioether analogs were also prepared by Gallagher and coworkers in an effort to obtain fluorescent ligands that could serve as structural probes in nAChR binding assays.[53] The preparation of a fluorescently tagged analog of **4** proceeded most efficiently via the introduction of a dansylated thioether spacer according to Scheme 28. Treatment of (±)-**115** with Koser's reagent [PhI(OH)OTs] afforded intermediate **153**. Displacement of the tosylate group with methanethiolate and removal of the carbamate moiety afforded **154**. Additionally, displacement of the tosylate by two fluorescently tagged thiolates and subsequent removal of the carbamates moieties provided the ketones **155** and **156**.

Binding assays revealed ketone **154** to be equipotent with racemic **4**, but the ketones **155** and **156** exhibited a negligible potency. The authors speculated that the binding inhibition observed for **155** and **156** was likely due in part to the dansyl moiety,

since the thioether **154** exhibited useful potency. Further details to support the authors' hypothesis regarding the diminished binding capacity of ligands **155** and **156** were not provided.

Scheme 28

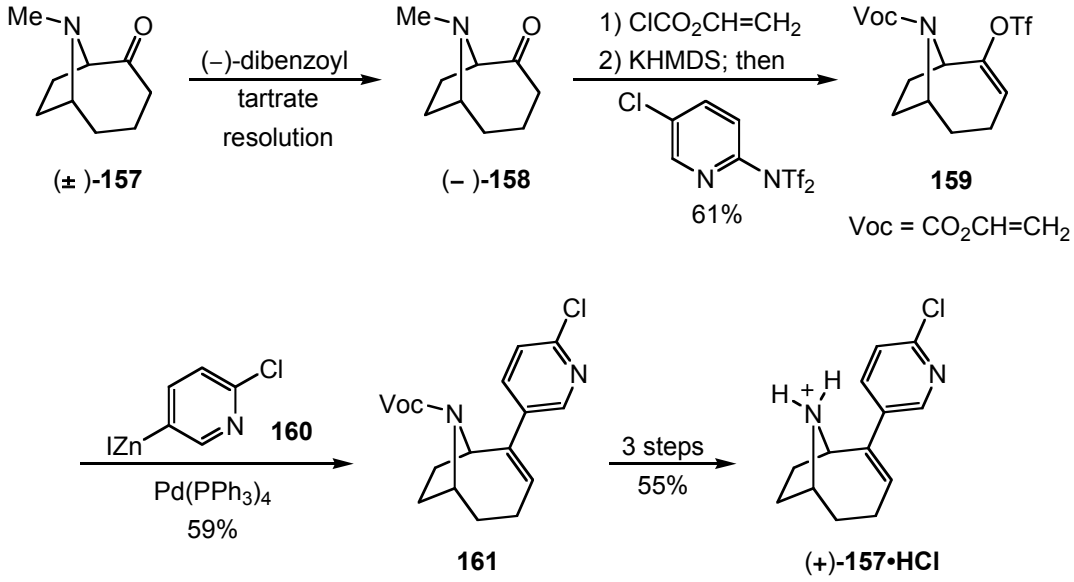


1.6.4.4 UB-165 and Related Isosteres

The epibatidine/anatoxin-a hybrid UB-165 (**157**), was designed by Gallagher and coworkers in the context of elucidating the structural requirements for high-affinity binding of neuronal nAChRs.[54] Ligand **157** was prepared both in racemic and optically pure forms from the known ketone (±)-**158**, according to Scheme 29. Resolution of (±)-**158** provided (+)-**158** and (–)-**158**. Compounds (±)-**158**, (+)-**158**, and (–)-**158** were all carried through the same reaction sequence, but only the transformation of (–)-**158** will be shown for simplicity. Demethylation with vinyl chloroformate and subsequent elaboration of the resulting vinyl carbamate to the enol triflate **159** proceeded using standard protocols. Negishi coupling of the triflate with the pyridyl zincate **160** generated

the advanced intermediate **161**. Ligand (**–**)-**157** was obtained as the corresponding hydrochloride salt after three additional operations.

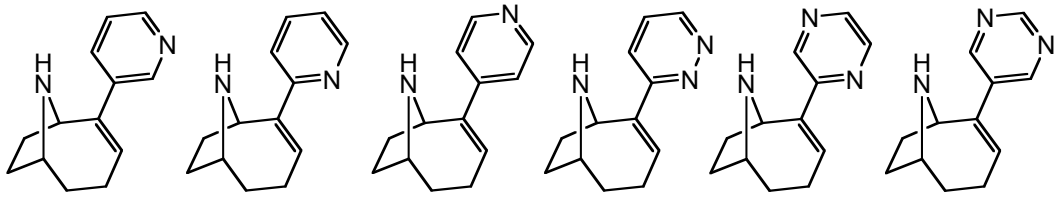
Scheme 29



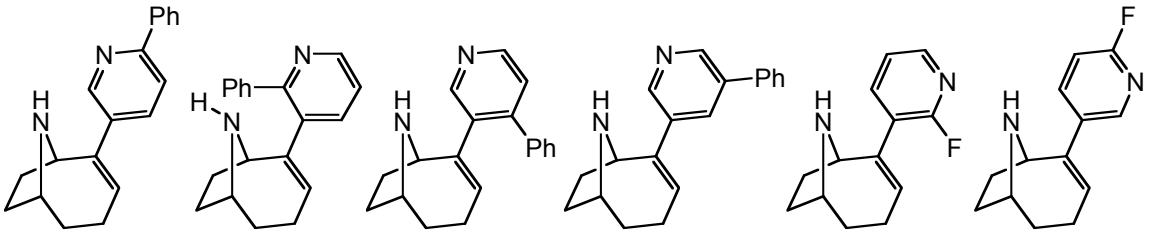
Compounds **(±)-157**, (+)-**157**, and (–)-**157**, were compared with (±)-**4** and (±)-**6** in binding assays. It was determined that both **(±)-157** and (+)-**157** exhibited binding affinities intermediate between those observed for (±)-**4** and (±)-**6**. Only (+)-**157** demonstrated high-affinity binding to the nAChRs, though the racemate was sufficiently potent to warrant its use in biological assays. The discovery of the promising agonist **157** prompted the development of additional pyridyl isosteres. Thus, Gallagher and coworkers utilized the intermediate triflate (±)-**159** to prepare the additional ligands **162**-**173** by Negishi coupling.[4,55]

Evaluation of the binding profiles of **162**-**173** revealed that the replacement of the original chloropyridyl ring of **157** with other heterocycles failed to produce any ligands exhibiting enhanced binding potency for the α4*β*2* receptor compared to **157**. However,

the deschloro-compound **162** (DUB-165) and the 4'-substituted pyridines **170** and **172** showed a marked increase in their capacity to bind the α7 nAChRs.

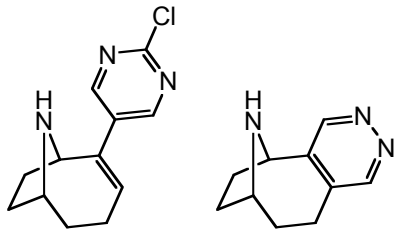


162 **163** **164** **165** **166** **167**



168 **169** **170** **171** **172** **173**

Seitz and coworkers contemporaneously made many of the same derivatives that were disclosed by Gallagher.[56] In addition, Seitz prepared the chloropyrimidine **174** and the fused diazine **175**.[57]

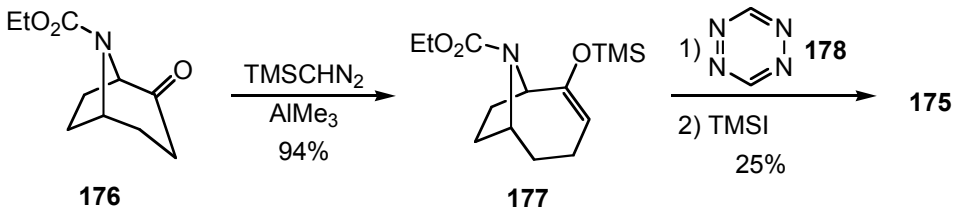


174 **175**

Compound **174** was assembled in a nearly identical fashion to the route utilized by Gallagher with the exception that a Stille reaction was employed to cross-couple the bicyclic enol triflate to the pyridylstannane. The diazine **175** was prepared by ring-expansion of compound **176** according to Scheme 30. An inverse electron demand Diels-

Alder cycloaddition between the silyl enol ether **177** and the tetrazine **178,** followed by the extrusion of nitrogen (N_2) and trimethysilanol (TMSOH) afforded **175** after deprotection of the carbamate. Unfortunately compounds **174** and **175** did not exceed the degree of receptor selectivity and binding affinity exhibited by the parent compound **157**.

Scheme 30



1.7 PINNAMINE

1.7.1 Background

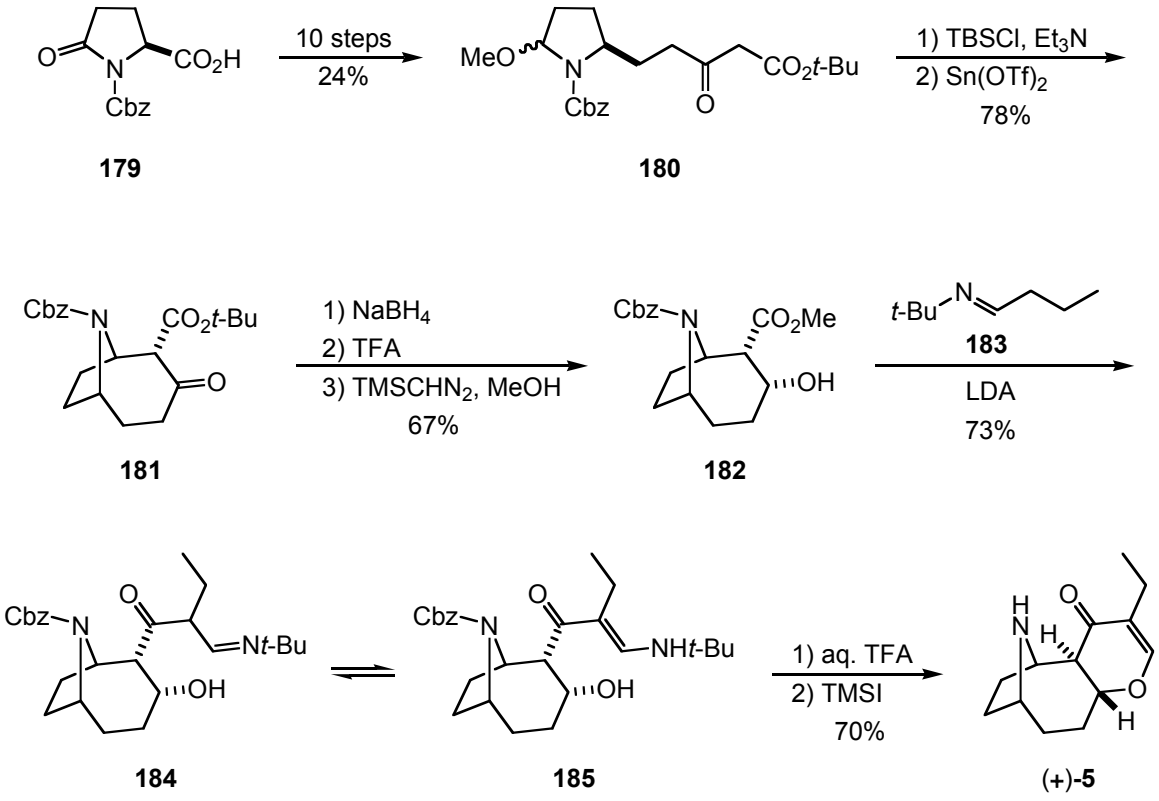
Pinnamine (**5**) is a marine toxin isolated from the Okinawan bivalve *Pinna muricata*.[58] This alkaloid has been shown to exhibit high-affinity binding to nAChRs with roughly the same potency as **4**. Pinnamine was isolated solely as the dextrarotary isomer. Striking is the close resemblance of **5** with the conformationally constrained fused compound (**–**)-**133** prepared by Rapoport (*vide supra*). As a result of its recent isolation in minute quantities, it has not been possible to evaluate the biological profile of **5** and determine the scope of its therapeutic potential. Pinnamine has only been synthesized twice to date, and the development of analogs is still in its infancy.

1.7.2 Kigoshi 2001: *N*-Acyliminium Cyclization

Kigoshi and coworkers disclosed the first total synthesis of (+)-**5**.[59] The synthesis, which closely resembles Rapoport's strategy for the preparation of (+)-**4**, began with the ten-step conversion of **179** to the cyclization precursor **180** (Scheme 31).

Tin-mediated addition of the corresponding silyl enol ether formed the azabicycle **181**, which was transformed into **182**. Condensation of **182** with the lithioenamine derived from *t*-butylbutyrylaldimine (**183**) provided a mixture of the ketoimine **184** and the vinylogous amide **185**. Cyclization of the mixture containing **184** and **185** led to the formation of the desired dihydropyranone ring with a concomitant epimerization of the stereocenter adjacent to the ketone. The synthesis was completed upon removal of the carbamate to afford (+)-**5** in eighteen chemical operations and 7% overall yield from **179**.

Scheme 31

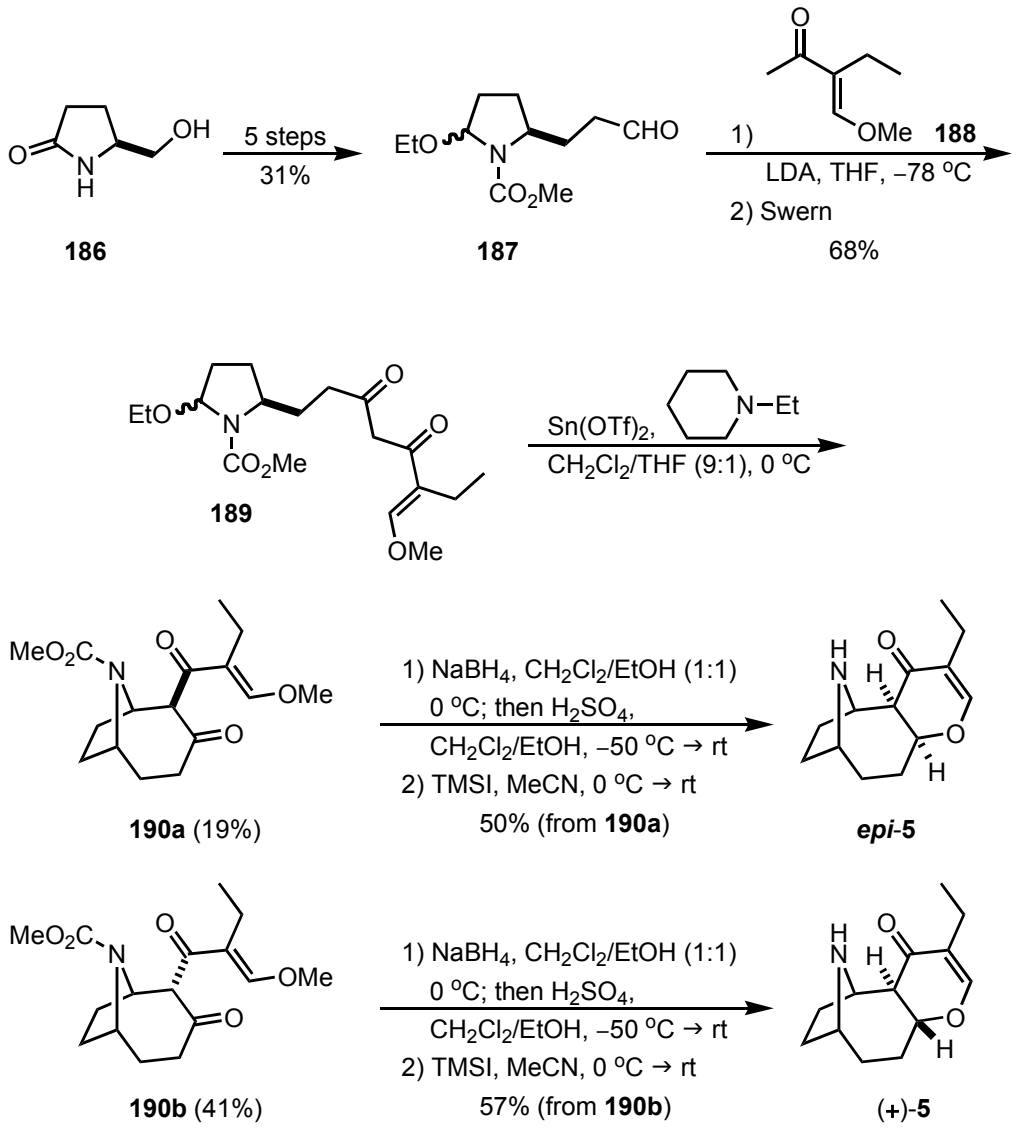


1.7.3 Tanner 2005: *N*-Acyliminium Cyclization

The most recent synthesis of (+)-**5** has been disclosed by Tanner and coworkers.[60] Their synthesis of pinnamine, which closely resembles Kigoshi's route to (+)-**5**, utilized an *N*-acyliminium cyclization protocol to assemble the azabicyclo[4.2.1]nonane nucleus.

The key iminium ion precursor **189** was prepared by the addition of the lithium enolate of the vinylogous ester **188** to the aldehyde **187**, followed by oxidation of the resulting secondary alcohol to the corresponding ketone (Scheme 32).

Scheme 32



The aldehyde **187** was prepared in five chemical operations from the commercially available pyroglutaminol **186**. As in Kigoshi's synthesis of (+)-**5**, the key *N*-acyliminium cyclization was effected under Lewis acidic conditions using $Sn(OTf)_2$.

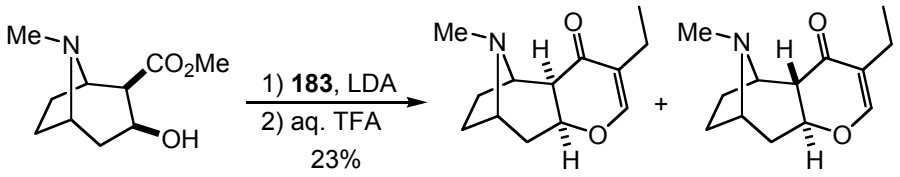
However, only a modest yield of the diastereomeric azabicycles **190a-b** was obtained. Following chromatographic separation, the cyclic ketones of compounds **190a-b** were reduced to provide the corresponding alcohols, which cyclized to form the dihydropyranone rings after acidification of the crude reaction mixtures. Subsequent deprotection of the methyl carbamate with TMSI generated *epi*-**5** and (+)-**5** respectively. Interestingly, the authors reported that the complete epimerization of the dihydropyranone ring obtained from **190b** occurred during the carbamate deprotection leading to (+)-**5**.

Tanner's synthesis of (+)-**5** proceeded in 5% overall yield and in ten chemical operations from commercially available **186**. However, the synthesis, which is essentially a slight variation of Kigoshi's route to pinnamine, suffers from the low yielding and poorly diastereoselective *N*-acyliminium cyclization reaction employed to form the azabicyclic skeleton of (+)-**5**.

1.7.4 Pinnamine Analogs

Shortly after Kigoshi's reported synthesis of (+)-**5**, Seitz utilized the same general protocol to prepare the tropane analogs **192** and **193**.[61] Utilizing ecgonine methyl ester **191**, which was obtained from (−)-**30**, as a starting point, these tropane analogs were prepared according to Scheme 33. As in the Kigoshi synthesis, the dihydropyranone ring was assembled by the addition of **183** to the ester of **191** to provide an intermediate that was subsequently treated with aqueous acid to effect cyclization and epimerization events.

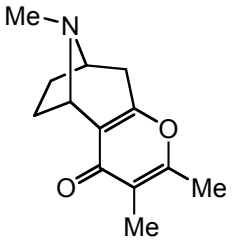
Scheme 33



191 (–)-**192** (–)-**193**

The resulting diastereomeric analogs **192** and **193** were evaluated as potential high affinity ligands for the neuronal nAChRs, and both were found to be much less potent and selective than (+)-**5**. Surprisingly, no effort was made to demethylate the analogs and evaluate the potency of these compounds, as it has been established that *N*-methylation of **4** greatly reduces binding capacity.[51,62]

It should be noted that compounds **192** and **193** are closely related to the pyranotropane darlingine (**194**).[18] This compound has been prepared previously in racemic[63] and optically pure form[64] but no biological data has been provided.



(–)-**194**

1.8 SUMMARY

The preparation of several potent synthetic and naturally occurring bridged azabicyclic nAChR agonists has been reviewed. While the highlighted syntheses enable the preparation of different azabicyclo[m.n.1]alkanes of varying ring size, few of these protocols offer a unified strategy for synthesizing the entire set of azabicyclic structures that have been shown to elicit potent biological activity. Furthermore, the limited scope and lack of divergency demonstrated by many of these methods prohibits the generation of analogs en route to receptor selective and non-lethal therapeutic agents. Many of the presented syntheses offer little advantage for the preparation of gram-scale quantities of advanced intermediates and their corresponding derivatives due to low yielding transformations, lengthy reaction sequences, or the use of costly reagents.[65] In addition, the majority of the strategies generated the racemic azabicycles. Because the racemates are often poor indicators of biological potency due to the potential for allosteric antagonism by a stereoisomer unable to efficiently ligate the rigidly stereodefined binding sites of the neuronal nAChRs, these synthetic protocols would need to be modified to permit the generation of optically pure compounds for adequate biological testing.

Thus, the development of a concise chirospecific method for the divergent preparation of azabicyclic nAChR analogs would advance the search for a non-lethal drug candidate potentially capable of managing a variety of neurological disorders. In particular, a new method for the rapid construction of the highly potent azabicyclo[4.2.1]nonane skeleton, found in compounds **4**, **5**, and the hybrid structures related to **157** would be advantageous. The protocol should be scalable and utilize

readily available precursors. It should also be flexible enough to permit the generation of rationally designed analogs from a common synthetic precursor in order to probe critical SAR relationships between the nAChRs and the agonists. A method capable of addressing these requirements would be a useful contribution to the protocols presented in this chapter.

CHAPTER 2: (+)-ANATOXIN-a SYNTHETIC METHODOLOGY

2.1 INTRODUCTION

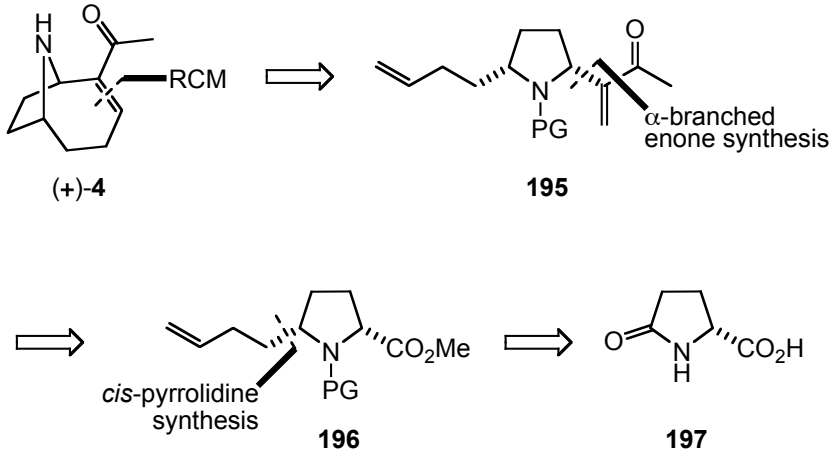
A number of methods for the synthesis of anatoxin-a (**4**) have been reported, but few are general in their capacity to prepare the natural product and analogs thereof in a divergent fashion. Many of the most efficient syntheses afford the desired compounds as racemates, or utilize precursors such as cocaine [(**–**)-**30**]. An efficient asymmetric synthesis of **4** utilizing readily accessible starting materials would have obvious advantages. A synthetic protocol of this nature should also permit the preparation of various analogs from a common intermediate.

In the context of ongoing efforts to expand the scope and utility of ring-closing metathesis (RCM) reactions for the preparation of biologically relevant nitrogenous frameworks, we were prompted to consider the possibility of preparing the azabicyclo[4.2.1]nonane skeleton through the implementation of a ruthenium-catalyzed RCM protocol. Inspired by our previous successful application of RCM reactions to prepare bridged azabicycles (*vide infra*), we set out to develop a new RCM method for the synthesis of the azabicyclo[4.2.1]nonane skeleton.

2.2 INITIAL SYNTHETIC STRATEGY

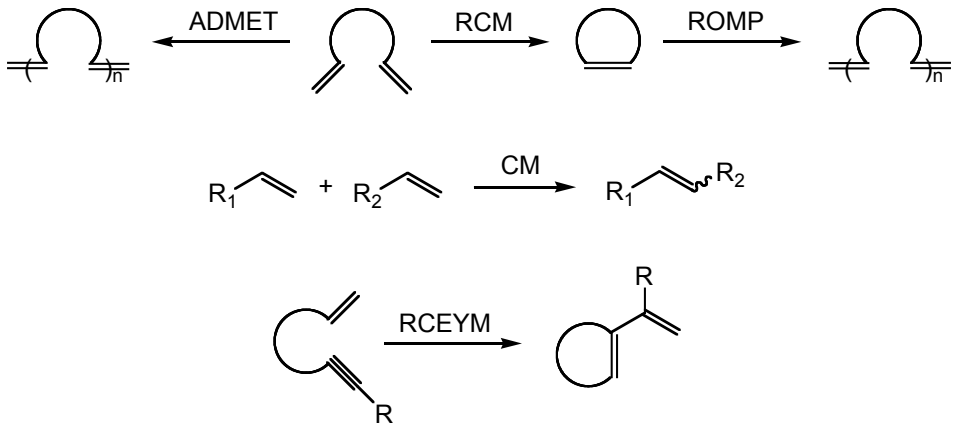
Our goal was to develop a RCM strategy for the synthesis of the fully functionalized azabicyclo[4.2.1]nonane skeleton of (+)-**4**. A retrosynthetic analysis of (+)-**4** led to the key bond disconnections shown below. The azabicycle would be created by a RCM of the 2,5-*cis*-disubstituted pyrrolidine **195**. The requisite α-branched enone would be prepared via manipulation of the C-2 pendant ester of an intermediate corresponding to **196**. Compound **196** would in turn be prepared from commercially

available D-pyroglutamic acid (**197**) using a method for the construction of *cis*-pyrrolidines.



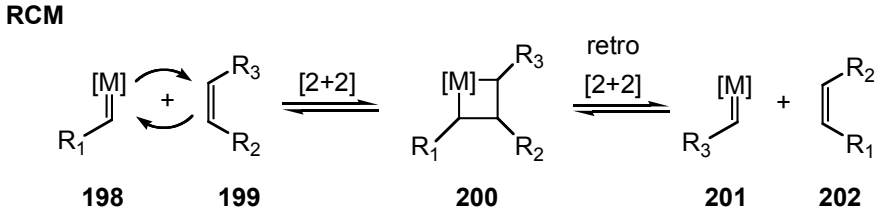
2.3 RING-CLOSING METATHESIS (RCM)

Experiments conducted during the early 1960's to expand the scope of the Ziegler and related polymerization reactions resulted in the discovery that certain transition metal carbenes were capable of catalyzing the metathesis reactions of unsaturated hydrocarbons. Pioneering work by Chauvin[66] and Katz[67] concerning the mechanism of olefin metathesis and their concurrent syntheses of various Fisher carbene catalyst systems set the stage for the development of the well-defined titanium, tantalum, tungsten and molybdenum catalysts. Continued advances in catalyst design, in particular the development of relatively stable ruthenium precatalysts, and an increased understanding of the mechanistic aspects of metathesis reactions have resulted in the emergence of RCM as a powerful tool for the construction of carbon-carbon bonds. As such, RCM has seen numerous applications in acyclic diene metathesis polymerization (ADMET), ring-opening metathesis polymerization (ROMP), cross-metathesis (CM), and ring-closing enyne metathesis (RCEYM), general examples of which are provided below.



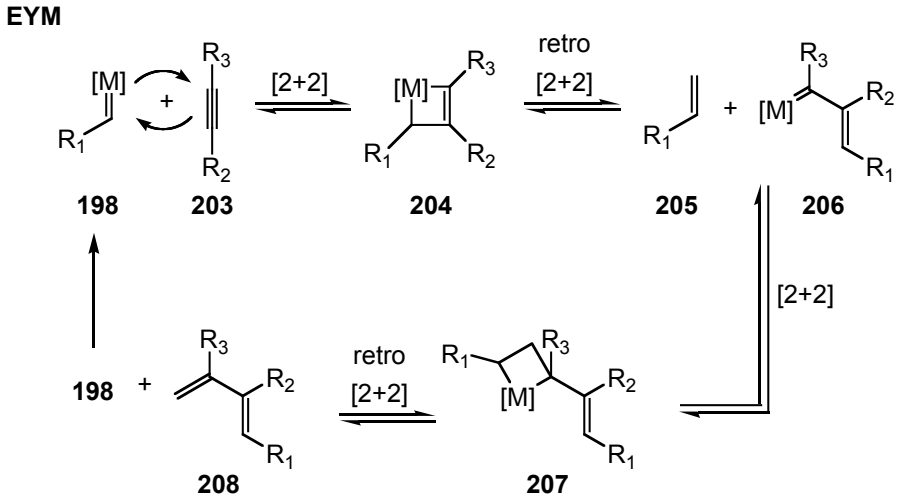
Mechanistically, olefin metatheses occur via a [2+2] cycloaddition between a metal alkylidene **198** and an alkene **199** to produce a metallocyclobutane **200** that undergoes a subsequent cycloreversion to liberate a new metal carbene **201** and a new alkene **202** (Scheme 34).

Scheme 34

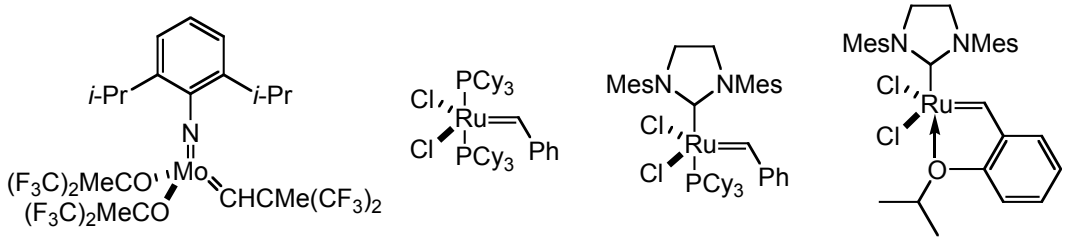


Enyne metatheses (EYM) are believed to proceed in a similar fashion with the exception that a metallocyclobutene **204** is formed following the initial [2+2] cycloaddition event (Scheme 35). Cycloreversion of this species produces a stabilized vinyl carbene **206** that reacts with an olefinic partner **205** rather than another molecule of alkyne via a second [2+2] cycloaddition to generate a metallocyclobutane **207**. Electrocyclic ring opening regenerates the catalyst and provides a butadiene **208**.

Scheme 35



Numerous metal alkylidene species have been shown to effect carbon-carbon bond metatheses. The most commonly employed such organometallic reagents are the molybdenum and ruthenium catalysts **47-48**, **90** and **209**. The development of these reagents, which are technically precatalysts as the active metathesis catalysts are the corresponding metal methylidenes, was prompted by a desire to find reagents that could affect the metatheses of substituted and electron poor olefins, as well as to increase the functional group tolerances of the organometallic reagents, thereby facilitating their use on substrates other than simple hydrocarbons.



The Schrock molybdenum catalyst **209** was the first catalyst developed to address these needs.[68] Catalyst **209** successfully promoted the metatheses of olefins possessing

various levels of substitution, and it remains one of the most powerful catalysts for the metatheses of densely substituted olefinic substrates, even after the development of highly reactive ruthenium-based catalysts.[69] However, catalyst **209** is not useful for EYM reactions due to the tendency of the highly reactive molybdenum carbene to polymerize alkynes.[70] Two additional limitations of catalyst **209** are its incompatibility with a variety of functional groups including alcohols, aldehydes, and carboxylic acids and its sensitivity to air and moisture.[71] Following the advent of the more stable and functional group tolerant ruthenium catalysts **47**-**48** and **90**, the use of **209** has all but ceased for most synthetic applications with the exception of the optically pure molybdenum catalysts prepared by Hoveyda to effect asymmetric olefin RCM reactions.[72]

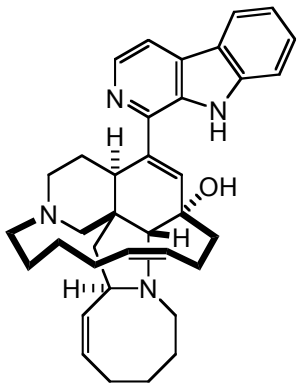
Grubbs introduced the ruthenium catalysts **47**[73] and **48**[74] to circumvent the problems associated with the molybdenum-based catalyst systems. Both catalysts exhibit high-reactivity and functional group compatibility, and both can be utilized to effect EYM reactions. Catalysts **47** and **48** are commercially available and can be handled without special precautions. Due to the stabilizing affect of the imidazolinylidene carbene ligand, catalyst **48** exhibits enhanced reactivity and stability compared to **47**. The strongly electron donating carbene ligand contributes greater electron density to the ruthenium center than the corresponding phosphine ligand, thereby facilitating the required disassociation of one phosphine ligand to produce the sixteen electron methylidene species responsible for metathesis. Furthermore, the electron rich carbene ligand decreases the rate of phosphine reassociation, which has been shown to be rate limiting in kinetic studies concerning the catalytic cycles of various metathesis catalysts.[75] As a result of its enhanced reactivity and increased half-life, catalyst **48** is

typically preferred over catalyst **47** for applications requiring the metatheses of substituted olefins, electron deficient coupling partners, and in systems in which highly strained rings are created.

The phosphine-free alkylidene **90** was discovered serendipitously and then developed by Hoveyda and coworkers to permit the recovery of the catalyst and to simplify purification during instances in which adventitious coelution of catalyst byproducts and the RCM product were problematic.[76] Catalyst **90** maintains the high level of reactivity exhibited by **48**, but reisolation of the catalyst is made possible by the return of the bidentate styrenyl alkoxide ligand during the propagation of the ruthenium carbene species. Catalyst **90** has become particularly effective for the preparation of tri- and tetrasubstituted olefins and is often the catalyst of choice during CM involving electron deficient coupling partners.

2.4 APPLICATION OF RCM TO THE SYNTHESIS OF BRIDGED AZABICYCLES

Following a series of seminal papers by Grubbs and Fu describing the successful synthesis of oxygen and nitrogen heterocycles by RCM,[77] our group quickly realized the potential of this powerful technique for the construction of the azabicyclic structures found in a variety of alkaloid natural products. In the context of methodological studies directed toward the synthesis of the anti-cancer alkaloid manzamine A (**210**), our group developed the first successful application of RCM reactions for the preparation of fused azabicycles.[78] Prompted by the success of these studies and their subsequent application to the total syntheses of **210** and related alkaloids,[79] our group undertook the development of the first RCM approach to prepare the bridged azabicyclo[m.n.1]alkene skeletons found in a number of biologically significant alkaloids.



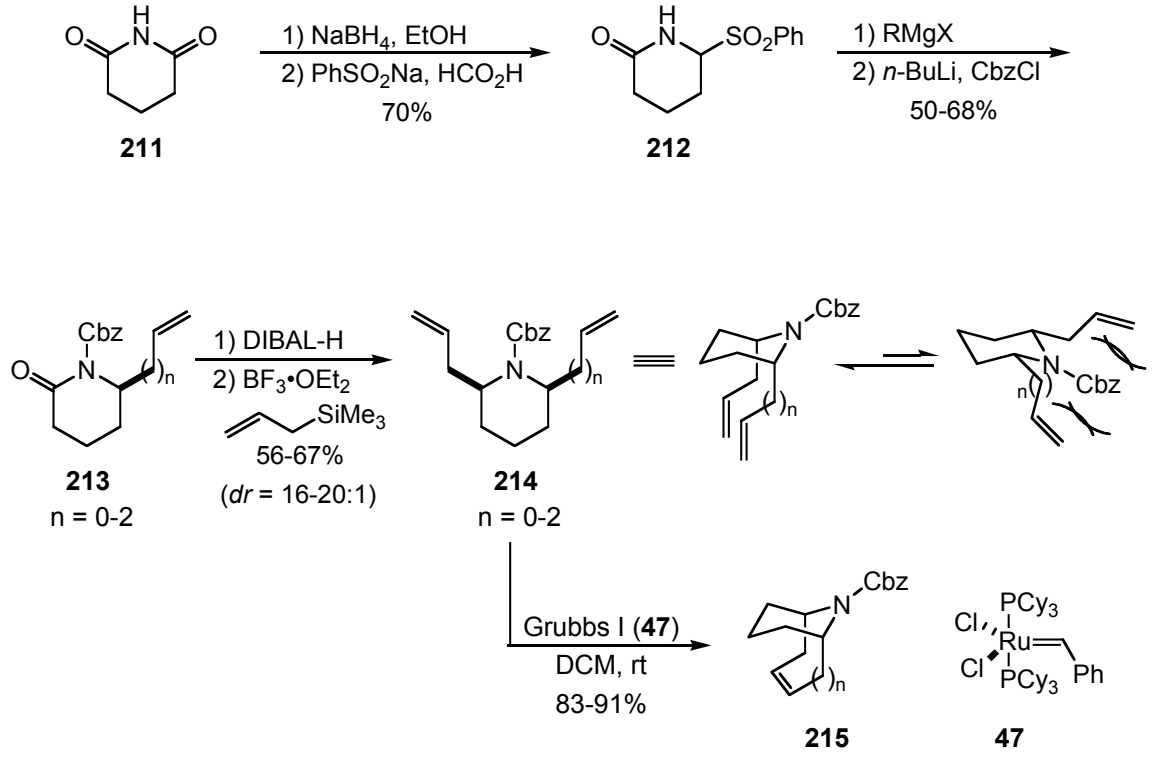
210

2.4.1 Neipp and Martin 2002: Preparation of Azabicyclo[m.n.1]alkenes

The preparation of fused azabicyclic heterocycles by RCM was quickly established, but it was only recently proven to be useful for the construction of functionalized bridged azabicyclic compounds.[80] We have previously disclosed a RCM strategy for the facile preparation of azabicyclo[m.n.1]alkenes from glutarimide or 4-methoxypyridine.[81] The synthetic protocol began with the conversion of glutarimide (**211**) to the sulfone **212**. Treatment of **212** with vinyl-, allyl-, or 3-butenylmagnesium bromide followed by protection of the lactams as the corresponding benzyl carbamates afforded **213** (n = 0-2). Reduction of the lactam carbonyls to the *N*-acyl hemiaminals, followed by the stereoselective addition of an allyl group in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) delivered the *cis*-2,6-dialkenyl-*N*-acyl piperidines **214**. Subsequent exposure of these intermediates to **47** provided the azabicyclo[n.3.1]alkenes **215** (Scheme 36). The successful RCM of the *cis*-2,6-dialkenyl-*N*-acyl piperidines is ostensibly dependent on the preorganization of the unsaturated side-chains in axial orientations, thereby positioning the olefinic units within proximity of one another for ring-closure. The requisite conformational bias in compounds like **214** is achieved due to the $A^{1,3}$-strain created between the substituents at the 2- and 6-positions

of the ring with the carbonyl of an *N*-acyl or *N*-alkoxycarbonyl group.[82] The necessity of an *N*-acyl substituent for the successful RCM of such dienes is evident from the work of Kibayashi (*vide infra*).

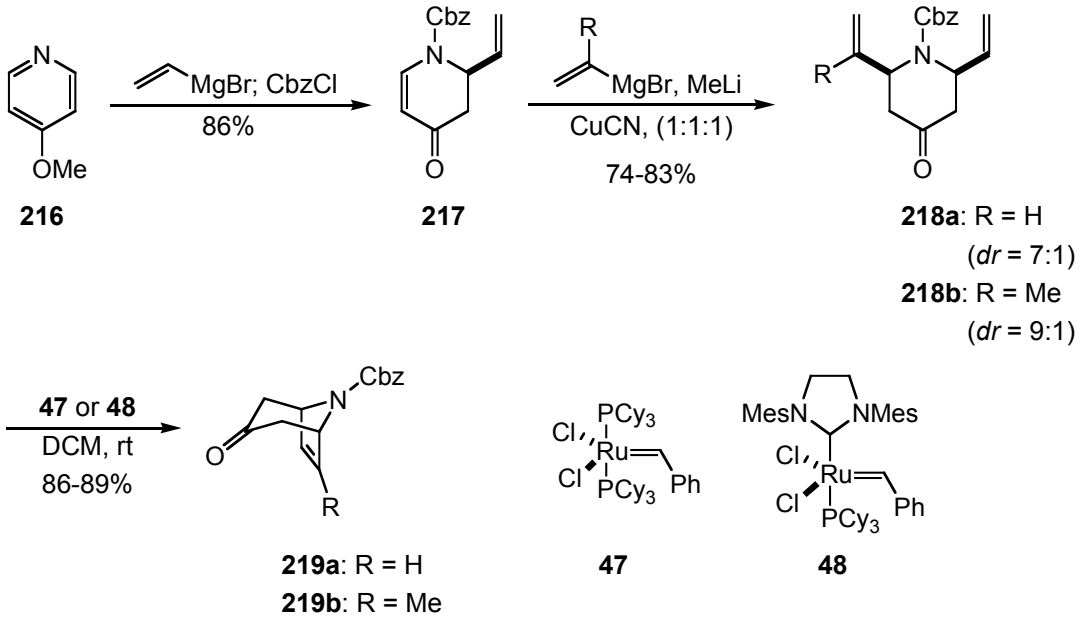
Scheme 36



The preceding studies demonstrated that RCM could be used to prepare bridged azabicycloalkenes, but the synthesis of the requisite *cis*-2,6-dialkenyl piperidine derivatives **214** was too lengthy. In order to address this problem, an improved route to such compounds was developed and applied specifically to the preparation of the tropane skeleton. In the event, the requisite metathesis precursors of general structure **218** were prepared from 4-methoxypyridine (**216**) using chemistry inspired by the work of Comins (Scheme 37).[83] The *cis*-2,6-divinyl-*N*-acyl piperidone **218a** underwent facile conversion

to the tropane derivative **219a** upon exposure to catalyst **47**. The more reactive catalyst **48** was required to cyclize the corresponding isopropenyl derivative **218b** to **219b**.

Scheme 37

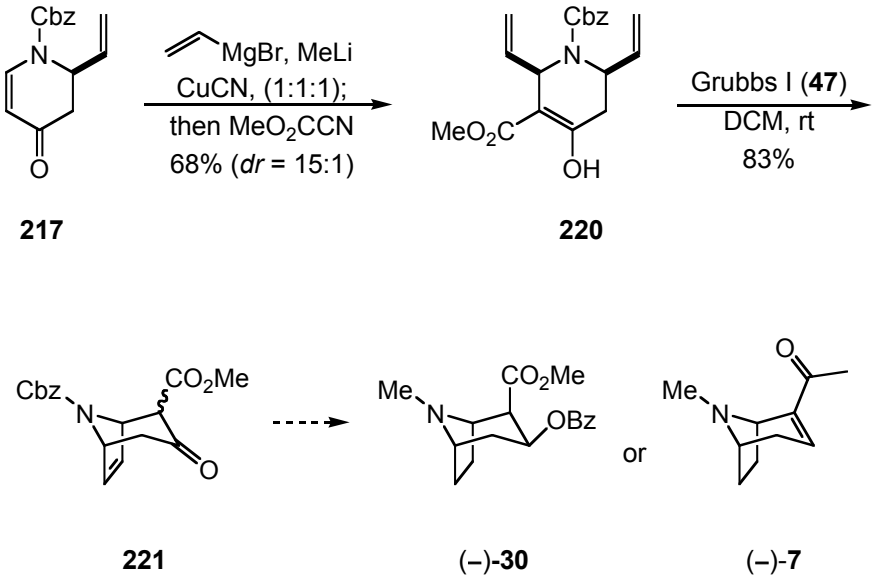


216 **217** **218a**: R = H (*dr* = 7:1) **218b**: R = Me (*dr* = 9:1)

219a: R = H **219b**: R = Me **47** **48**

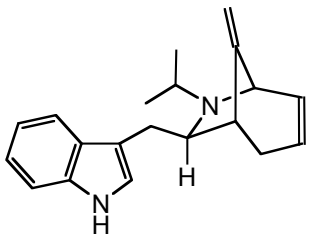
Inspired by the successful development of a RCM approach to the tropane nucleus, our group highlighted the utility of the method by the rapid assembly of **221**, a functionalized precursor of cocaine (–)-**30**, (–)-ferruginine ((–)-**7**), and other related tropane alkaloids. The desired metathesis precursor **220** was obtained by the conjugate addition of vinyl cuprate to **217**, thereby providing an intermediate enolate that was trapped with methyl cyanoformate (MeO_2CCN) (Scheme 38). Subsequent cyclization of **220** in the presence of catalyst **47** afforded **221**, whose conversion to (–)-**30** or (–)-**7** can be easily envisioned.

Scheme 38



2.4.2 Washburn and Martin 2003: Synthesis of (−)-Peduncularine

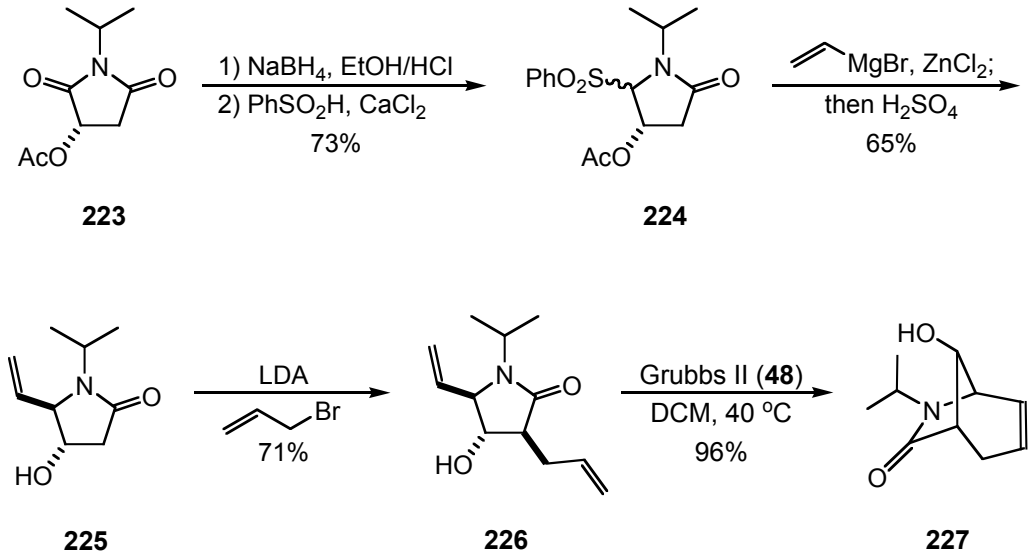
In the context of ongoing endeavors to exploit RCM for the efficient construction of biologically active natural products, an adaptation of our original RCM protocol for the preparation of tropane skeletons was employed to synthesize the 6-azabicyclo[3.2.1]octene nucleus of the anticancer alkaloid (–)-peduncularine [**(–)-222**].[84] The target for a formal synthesis of **(–)-222** was the 6-azabicyclo[3.2.1]octene **227**, which had served as a key intermediate in Speckamp's total synthesis of (–)-peduncularine.[85]



(–)-222

The synthesis commenced with the transformation of the imide **223**[85] to the sulfone **224** (Scheme 39). Stereoselective addition of a vinyl zincate to **224** and subsequent acidic hydrolysis of the acetate afforded the lactam **225**. Allylation of **225** proceeded to afford the metathesis precursor **226** as a single diastereomer. The Grubbs first-generation catalyst **47** failed to induce the RCM of **226** presumably due to chelation by the free hydroxyl, although it did promote the cyclization of the corresponding TMS ether. Exposure of **226** to the Grubbs second-generation catalyst **48** gratifyingly provided **227** in near quantitative yield. This approach to the azabicyclic lactam **227** required a mere five chemical operations and proceeded in 32% overall yield from **223**.

Scheme 39

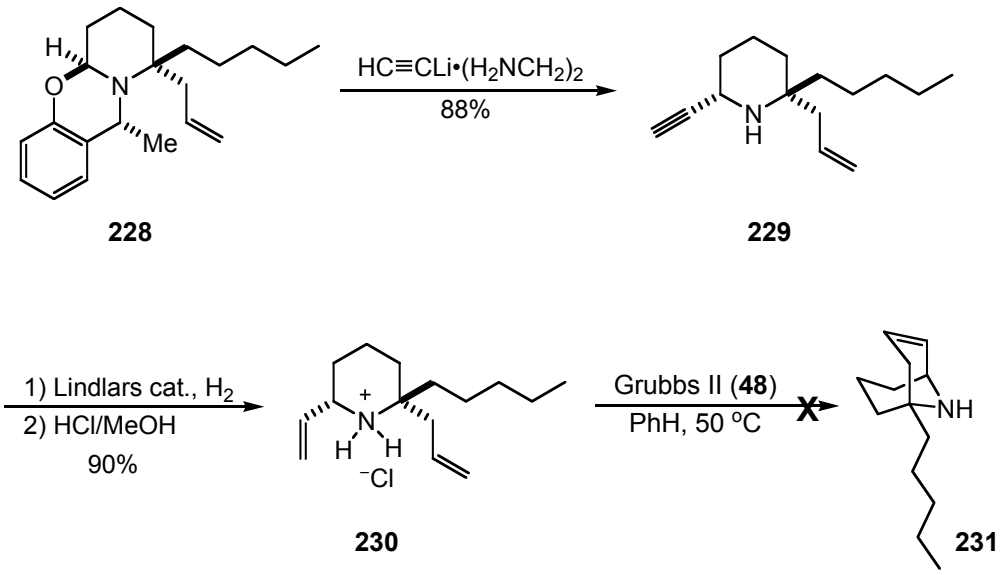


2.4.3 Kibayashi 2002: Synthesis of (−)-Adaline

Although the first examples of RCM reactions to prepare azabicyclo-[3.3.1]alkenes were reported by Neipp and Martin,[81] the first application of this construction for a total synthesis was disclosed by Kibayashi during the preparation of the ladybug defensive alkaloid (–)-adaline [(**−**)-**234**].[86] The synthesis of (**−**)-**234** began

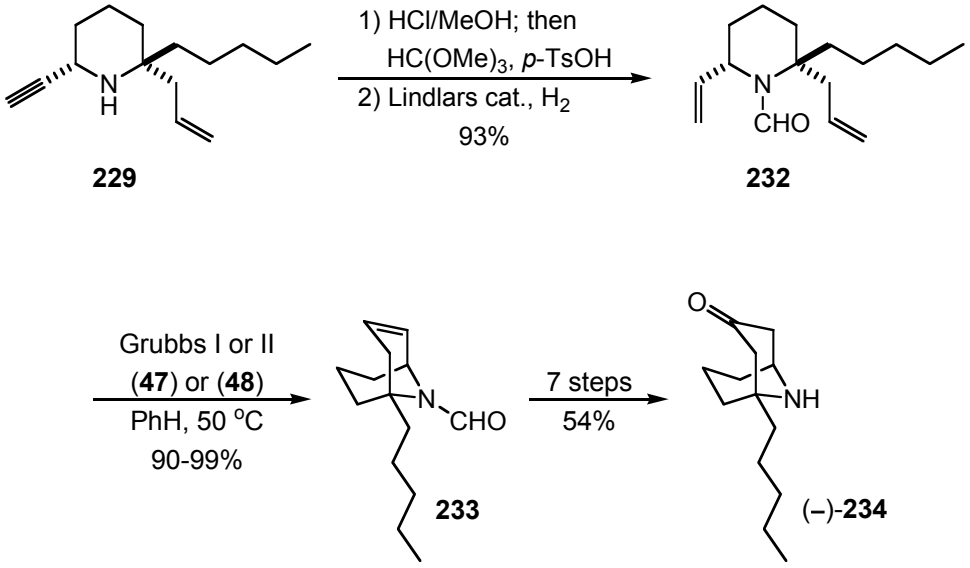
with the three-step transformation of **228** to the *cis*-2,6-disubstituted piperidine **229** via the stereoselective addition of lithium acetylide to the *N*,*O*-acetal (Scheme 40). The alkyne was reduced to the olefin, and the secondary amine was protected as the corresponding hydrochloride salt to afford **230**. Kibayashi observed that **230** failed to undergo RCM to afford the 9-azabicyclo[3.3.1]nonene **231**, presumably owing to a diequatorial arrangement of the alkenyl substituents in the absence of the $A^{1,3}$-strain created by an *N*-acyl protecting group.

Scheme 40



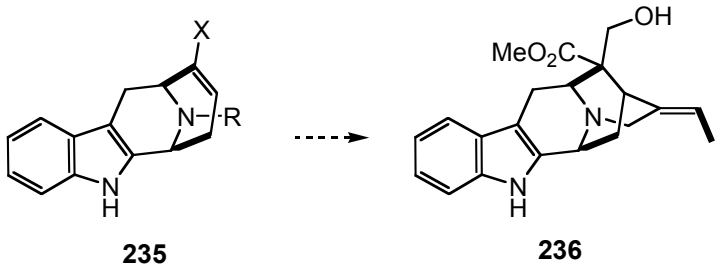
This problem was circumvented by the conversion of **229** to the *N*-formyl derivative **232** (Scheme 41). Intermediate **232** underwent facile ring-closure in the presence of either the Grubbs first- or second-generation catalysts **47** or **48** to afford **233**. This result supported our original hypothesis that the $A^{1,3}$-strain created by an *N*-acyl protecting group was crucial for a successful RCM (*vide supra*). Compound **233** was subsequently converted to (**–**)-**234** via a series of straightforward functional group manipulations.

Scheme 41



2.4.4 Neipp and Martin 2003: Indole-Substituted Azabicyclo[3.3.1]alkenes

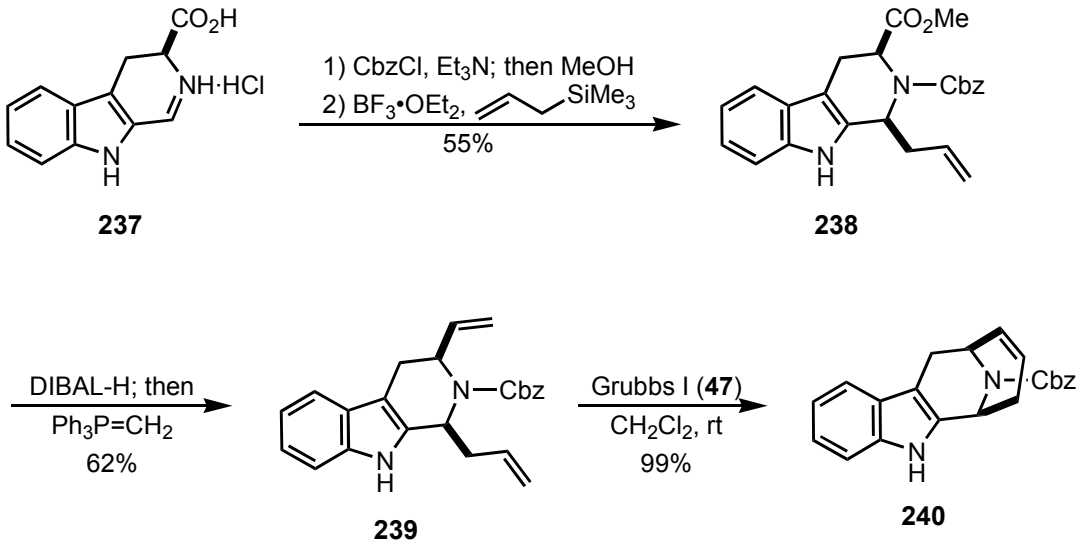
Shortly after Kibayashi's synthesis of (**–**)-**234**, our group revealed a new approach to the indole-substituted azabicyclo[3.3.1]nonane **235**, which is a key structural subunit in the alkaloids of the *Sarpagine* family, represented by the μ-selective opioid receptor agonist akuammidine (**236**).



The synthesis of a model compound related to **235** commenced with the two-step conversion of the carboline **237**[87] into the diene **238** (Scheme 42). A one-pot reduction and Wittig olefination sequence provided the metathesis precursor **239**. Exposure of **239**

to the Grubbs first-generation catalyst (**47**) afforded essentially a quantitative yield of the model compound **240**.

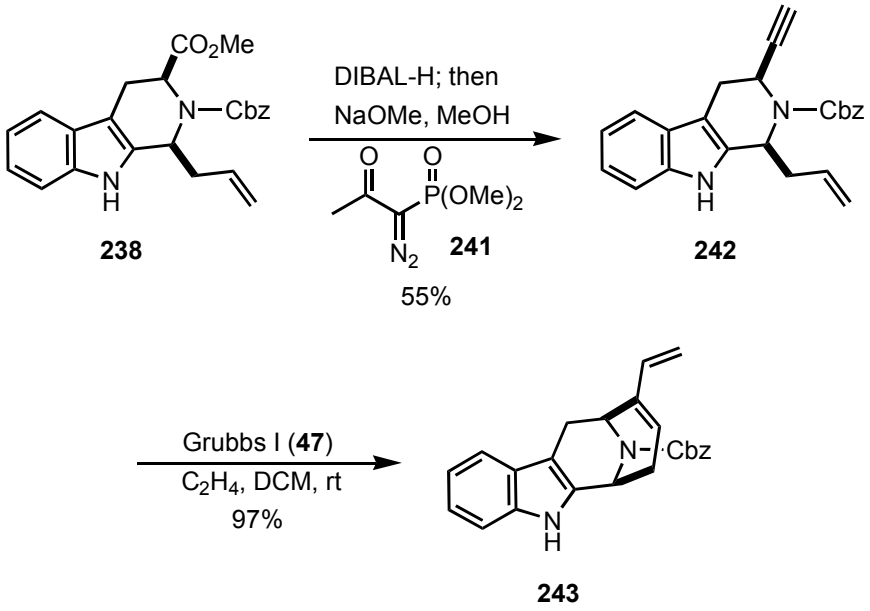
Scheme 42



237 **238** **239** **240**

The success of this transformation prompted us to explore a route to a more densely functionalized compound related to **235**. An enyne metathesis was selected to provide a vinyl substituent in the product that could be utilized in further transformations to access the more complex target alkaloids. As such, enyne **242** was constructed from **238** according to Scheme 43. This sequence of transformations highlighted a one-pot homologation protocol developed within our group for the conversion of esters into terminal acetylenes.[88] The RCEYM was initiated upon exposure of **242** to catalyst **47** under an atmosphere of ethylene to deliver the azabicyclic diene **243** in excellent yield. The conversion of **243** into **236** and other indole alkaloids of the *Sarpagine* and *Ajmaline* families is the subject of ongoing research within our laboratories.

Scheme 43



Based upon the successful application of metathesis reactions by our own group and others for the construction of bridged azabicycles, we were confident that a similar metathesis-based approach to anatoxin-a would be feasible. However, prior to the initiation of the proposed reaction sequence presented at the start of this chapter, we were surprised to find an absence of suitable protocols for the preparation of compounds of the general structures **195** and **196** in the literature. As such, we would first need to develop an efficient method to prepare a *cis*-pyrrolidine incorporating an unsaturated side-chain, and then discover a route to transform esters or other carboxylic acid derivatives into α-branched enones without epimerization.

2.5 PREVIOUS SYNTHESES OF UNSATURATED 2,5-*CIS*-DISUBSTITUTED PYRROLIDINES

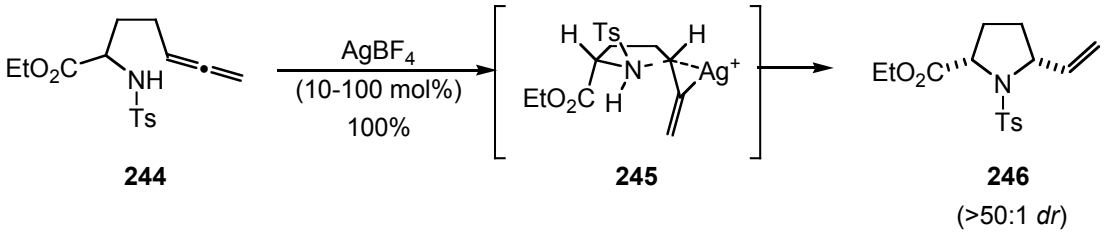
A number of protocols for the preparation of *cis*-pyrrolidines can be found in the literature.[89] However, methods for the efficient and highly diastereoselective synthesis of

cis-2,5-disubstituted pyrrolidines incorporating unsaturated moieties is very limited.[90] This is because the majority of tactics utilized to form *cis*-pyrrolidines are either incompatible with unsaturated moieties[91] or provide only modest diastereoselection depending on the nature of the substrate. As such, a brief overview of approaches for the preparation of *cis*-2,5-disubstituted pyrrolidines incorporating unsaturated moieties will be presented.

2.5.1 Gallagher 1991: Ag(I)-Catalyzed Cyclization of Allenic Sulfonamides

During the course of a synthesis of racemic **4**, Gallagher and coworkers developed a silver-catalyzed intramolecular cyclization protocol for the preparation of *cis*-2,5-disubstituted pyrrolidines.[92] In the event, the allenic sulfonamide **244** was treated with $AgBF_4$ at ambient temperature to afford **246** according to Scheme 44.

Scheme 44



244 **245** **246** (>50:1 *dr*)

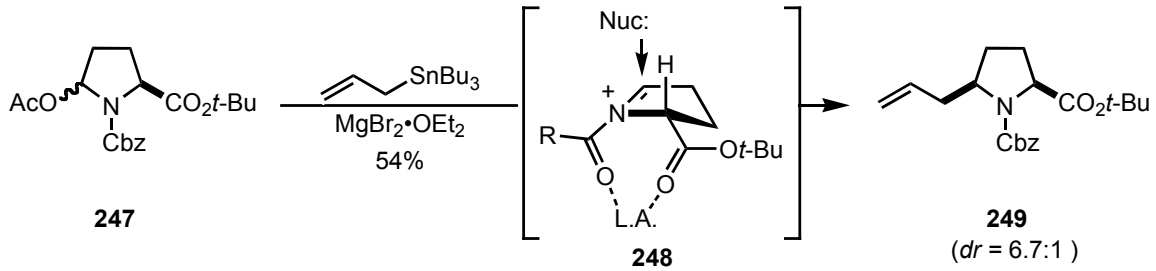
The reaction was reported to proceed in quantitative yield with >50:1 *cis*-diastereoselection via the transition state structure **245**. The bulky tosyl group is thought to adopt a conformation that minimizes unfavorable 1,2-interactions with the adjacent ester and the activated allene. Similar high levels of *cis*-selectivity were observed with additional *N*-protecting groups (Boc, Bn, and CO_2Me), although the yields were uniformly lower than those obtained with the sulfonamide. In accord with the postulated

rationale for diastereoselection, the cyclization provided a nearly equal mixture of *cis*- and *trans*-pyrrolidines in the absence of a nitrogen-protecting group.

2.5.2 Scolastico 1996: N-Acyliminium Additions

Scolastico and coworkers reported the formation of *cis*-pyrrolidines bearing an allyl side-chain.[90c] Allylation of the acetoxy aminal **247** with allytributyltin (H_2C=$CHCH_2SnBu_3$) in the presence of magnesium bromide diethyl etherate ($MgBr_2 \cdot OEt_2$) produced the *cis*-pyrrolidine **249** in 54% yield and with modest diastereoselection (Scheme 45). The attack of the nucleophile is thought to proceed via the rigid transition state structure **248**. This hypothesis is in accord with previous studies conducted by Woerpel regarding the additions of nucleophiles to five-membered-ring oxocarbenium ions[93] and our own *ab initio* calculations to account for the additions of nucleophiles to five-membered ring iminium ions.[94] Approach of the nucleophile from inside the envelope of the lower energy conformer possessing a pseudo-axially disposed ester would afford the observed *cis*-2,5-disubstituted pyrrolidine **249**. Additional Lewis acids were screened during an unsuccessful effort to improve the *cis*-selectivity of the process. Numerous variations of this procedure have been reported elsewhere with similar efficiency and diastereoselectivity.[95]

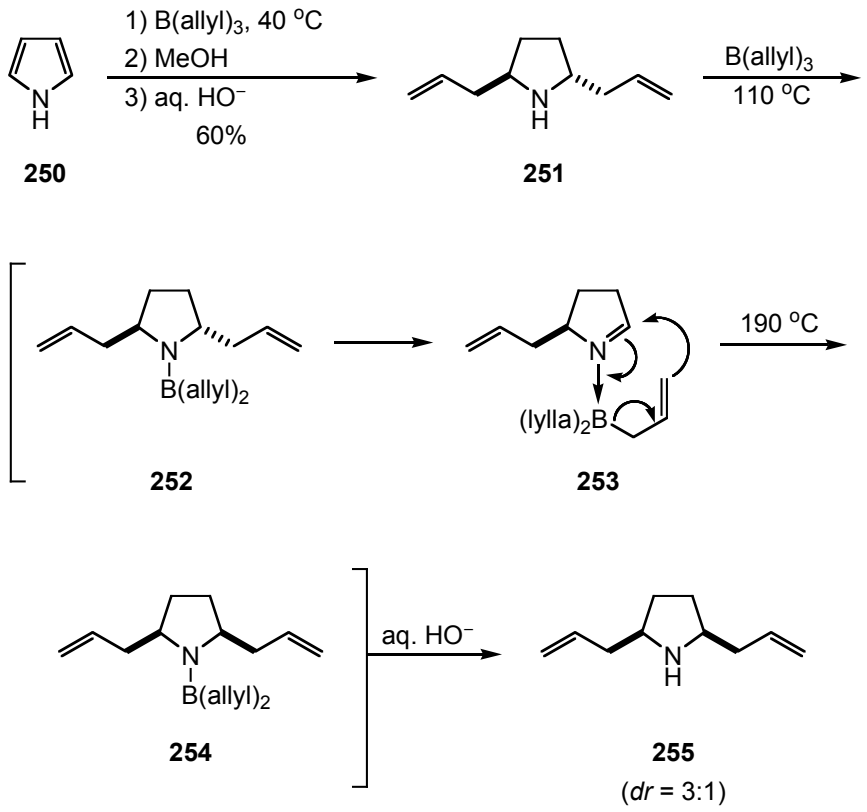
Scheme 45



2.5.3 Bubnov 1999: Reductive Allylation of Pyrroles

Bubnov and coworkers disclosed a synthesis of *cis*-2,5-diallyl pyrrolidines from pyrrole.[90d] The sequence commenced with the reductive diallylation of pyrrole (**250**) by triallylborane [$B(allyl)_3$] to afford the *trans*-2,5-diallylpyrrolidine **251** according to Scheme 46.

Scheme 46



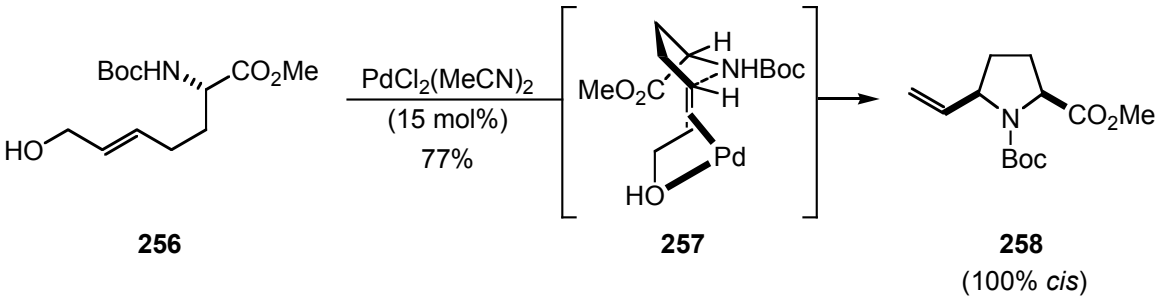
Isomerization of **251** to a mixture, comprised predominately of the corresponding *cis*-diastereomer **255**, was effected upon heating in the presence of additional $B(allyl)_3$. The isomerization is believed to proceed via the deallylboration-allylboration sequence involving intermediates **252**-**254**. Alkyl boranes failed to promote the reductive alkylation of **250** regardless of the conditions employed. Using this to their advantage,

the authors effected the successful monoallylation or monoprenylation using B(allyl)Pr_2 or B(prenyl)Pr_2 respectively, while bisprenylation was accomplished with B(prenyl)$_3$.

2.5.4 Yamamoto 2005: Palladium-Catalyzed Intramolecular N-Alkylation

Yamamoto and Eustache disclosed an adaptation of a palladium-catalyzed intramolecular *N*-alkylation procedure originally developed by Hirai[96] for the synthesis of the *cis*-2,5-disubstituted pyrrolidine **258**.[97] Compound **258** was prepared from the allylic alcohol **256** by a palladium(II)-catalyzed cyclization reaction (Scheme 47). The desired pyrrolidine was obtained in good yield as a single diastereomer via the proposed half-chair like transition state structure **257**.

Scheme 47



256 **257** **258** (100% *cis*)

Though methods exist for the preparation of *cis*-2,5-disubstituted pyrrolidines containing unsaturated moieties, these routes are typically confined to the preparation of pyrrolidines containing vinylic or allylic moieties. As such, the limited scope of the substrates obtainable by these methods would preclude their use for the preparation of a compound such as **196** (Chap 2.2).

2.6 α-BRANCHED ENONES

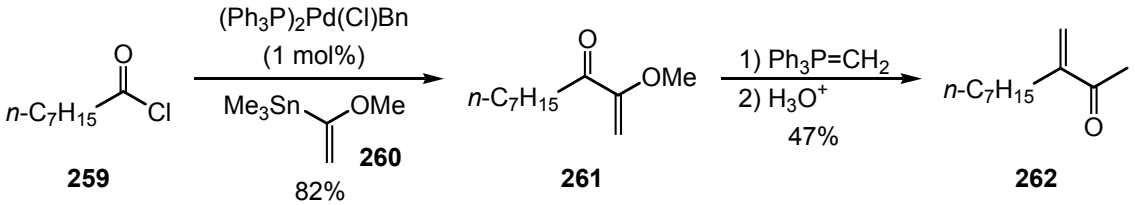
A number of procedures are available for the preparation of α-branched enones from ketone precursors. The majority of these syntheses employ Mannich condensations

with iminium salts[98] or the palladium-catalyzed decarboxylation-deacetoxylation[99] of allyl α-acetoxymethyl-β-ketocarboxylates. A survey of the literature however, provided only two general approaches for the transformation of carboxylic acid derivatives into α-branched enones. The two general strategies for this synthetic transformation are presented in order to highlight the state-of-the art protocols available during the initial phases of our methodological development.

2.6.1 Soderquist 1983: Palladium-Catalyzed Coupling Reactions

Metal-catalyzed coupling reactions between acyl chlorides and vinyl organometallics are a well-documented method for the preparation of α,β-unsaturated ketones.[100] However, the application of these tactics for the coupling of acyl anion equivalents such as α-alkoxyalkenyl metal reagents for the purpose of generating unsymmetrical ketones is limited.[100c,j,k,101] Of the few available methods to effect this type of transformation, only the strategy disclosed by Soderquist is readily adapted for the purpose of converting carboxylic acid derivatives into α-branched enones.[100i] The method proceeded by the palladium-catalyzed coupling of the acid chloride **259** with (α-methoxyvinyl)trimethyltin (**260**) according to Scheme 48. Following the cross-coupling, the resulting enone **261** was subjected to a Wittig olefination to provide an intermediate butadienyl species that was then hydrolyzed to deliver the α-branched enone **262**.

Scheme 48



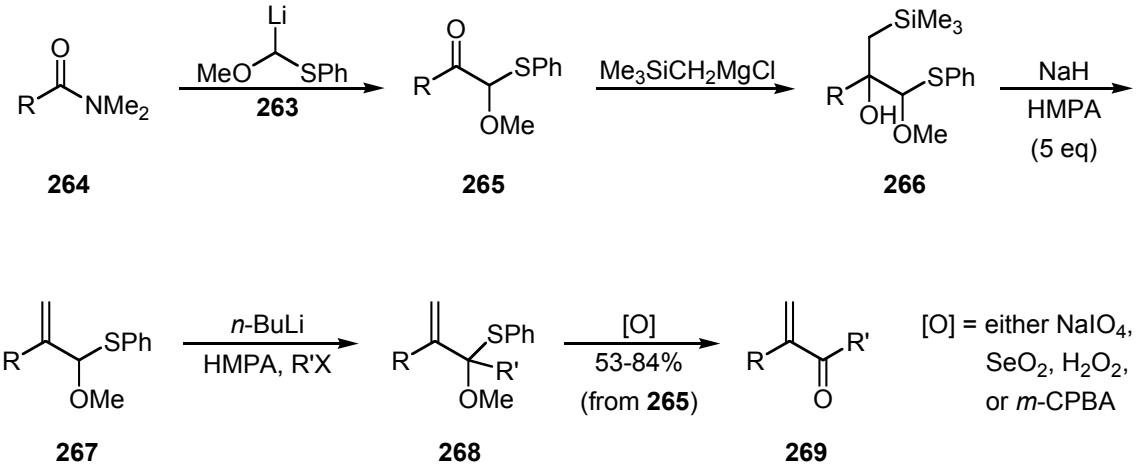
259 **260** **261** **262**

Although this method would be amenable to the conversion of the methyl ester moiety of **196** into an α-branched enone, the use of highly toxic stannanes and the minimum four-step sequence that would be required to effect the desired transformation led us to explore alternative routes toward this end.

2.6.2 Otera 1984: α-Methoxyallyl Sulfides

Otera and coworkers disclosed a method for the synthesis of α-branched enones from amides. The strategy featured the addition of the lithium salt of α-methoxyphenylsulfide (**263**) to an amide **264** to generate ketones of general structure **265** according to Scheme 49. Treatment of **265** with trimethylsilylmethylmagnesium bromide (Me_3SiCH_2MgBr) provided the tertiary carbinols **266**. A base-promoted Peterson olefination delivered the α-methoxyallyl sulfides **267**. Regiospecific alkylation of the anion generated from **267** afforded **268**. Subsequent oxidation of the thiophenyl ether to the corresponding sulfoxides and concomitant elimination of phenylsulfinic acid (PhSOH) produced the desired α-branched enones **269**.

Scheme 49



Although this method could be utilized to prepare a suitable RCM precursor from **195**, a lengthy six-step sequence would be required to convert the ester moiety into an α-branched enone. Furthermore, Otera reported that the alkylation of **267** only proceeded in acceptable yields when allyl- or benzyl bromides were employed as electrophiles, thereby greatly limiting the scope of this transformation. Hence, it became clear to us that a new and concise method for converting carboxylic acid derivatives into α-branched enones would need to be developed to enable the efficient synthesis of a compound corresponding to **195**.

CHAPTER 3: THE TOTAL SYNTHESIS OF ANATOXIN-a AND PROGRESS TOWARD THE TOTAL SYNTHESIS OF PINNAMINE

Prior to undertaking our own exercise toward preparing anatoxin-a, we recognized an opportunity to develop new synthetic methodologies for the synthesis of α-branched enones from carboxylic acid derivatives and for the formation of *cis*-pyrrolidines incorporating unsaturated moieties. The shortcomings of the preexisting methods outlined in the preceding chapter for effecting these transformations prompted us to investigate more efficient and general routes toward their preparation, which would in turn be applied to the syntheses of anatoxin-a [(+)-**4**] and pinnamine [(+)-**5**]. We envisioned that the development of these new methodologies would facilitate the exploration of a new RCM strategy for the preparation of the azabicyclo[4.2.1]nonane skeleton according to the retrosynthesis presented in Chapter 2.2.

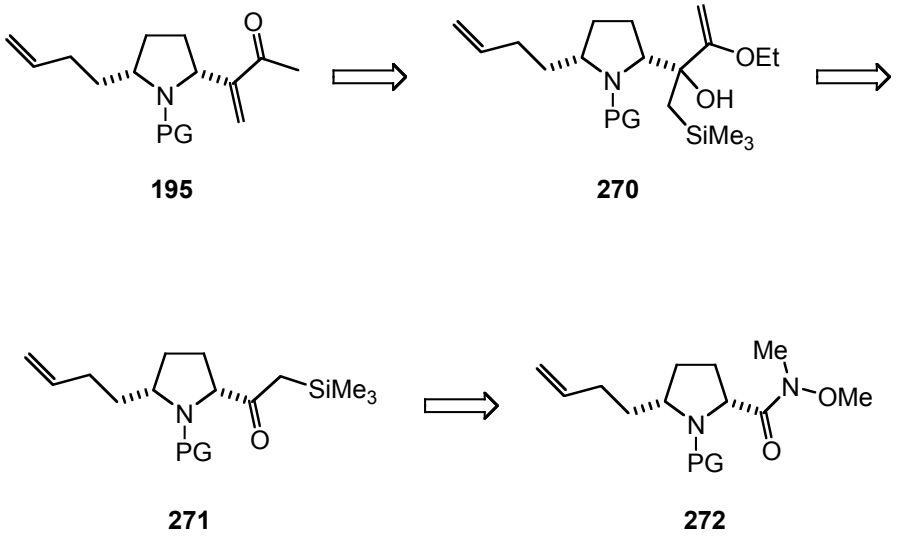
3.1 DEVELOPMENT OF A NEW α-BRANCHED ENONE SYNTHESIS

From the onset, we realized that if we were to develop a method for the synthesis of α-branched enones that it would need to be concise. In addition, our synthetic protocol would need to preserve the integrity of the epimerizable C-2 stereocenter of a *cis*-pyrrolidine intermediate such as **196** (Chap. 2.2) and permit the formation of not only the methyl ketone required for the synthesis of (+)-**4**, but potentially for the formation of a propyl ketone en route to a synthesis of (+)-**5**. A retrosynthesis for the preparation of a suitable α-branched enone metathesis precursor such as **195** is shown in Scheme 50. Our proposed strategy for the assembly of **195** is an adaptation of Otera's original protocol. We sought to shorten the length of Otera's method via the installation of an acyl anion

equivalent that would not require further functionalization in order to liberate a ketone moiety.

As such, we planned to treat an α-silyl ketone such as **271** with an anion derived from an enol ether.[102] A subsequent Peterson elimination was expected to provide an α-branched enone of general structure **195** after hydrolysis of the intermediate enol ether **270**. The α-silyl ketone **271** was to be prepared by the addition of Me_3SiCH_2M (M = Li or MgCl) to the *N*,*O*-dimethyl amide **272**, which in turn would be formed by the addition of the corresponding aluminum amide to an ester corresponding to **196**.

Scheme 50

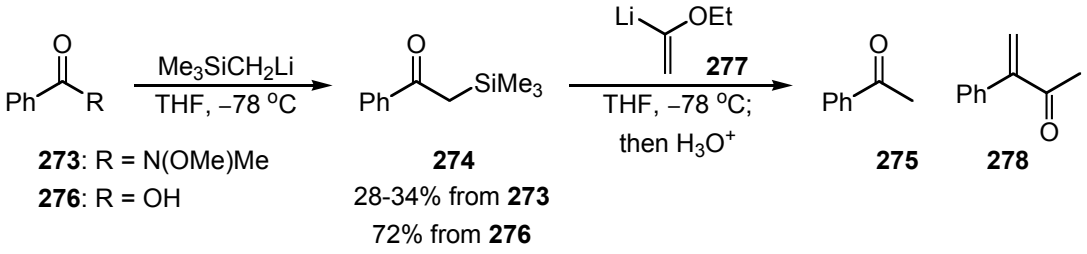


195 **270** **271** **272**

To explore the feasibility of the proposed method, we chose the benzamide **273** as model system in place of the *cis*-pyrrolidine **196**. In accord with our plan, **273** was treated with a solution of commercially available Me_3SiCH_2Li in THF (Scheme 51). Indeed, the desired ketone **274** was isolated, albeit in poor yield owing to competitive protodesilylation to produce acetophenone (**275**) (possibly via a retro-Brook type rearrangement) during the workup and purification steps.

As a result of our inability to prepare cleanly the α-silylketone using neutral isolation conditions that avoided the formation of **275**, we sought to prepare **274** from benzoic acid according to the procedure of Gaffney.[103] In the event, freshly sublimed benzoic acid (**276**) was treated with 2.2 eq of Me_3SiCH_2Li to provide **274** in 72% yield after filtration of the crude reaction mixture through neutral alumina (Al_2O_3). To our dismay however, treatment of **274** with α-ethoxyvinyllithium (**277**) failed to provide the desired enone **278**. Rather **275** was consistently isolated as the major product of the reactions after acidic workup. Our inability to successfully add the vinyl anion to the carbonyl group of **274** may have resulted from the steric congestion created by the adjacent trimethylsilyl group. An alternative protocol in which the trimethylsilylmethyl nucleophile would be added following the addition of the acyl anion equivalent was adopted in order to circumvent this scenario.

Scheme 51



273: R = N(OMe)Me
276: R = OH

274
28-34% from **273**
72% from **276**

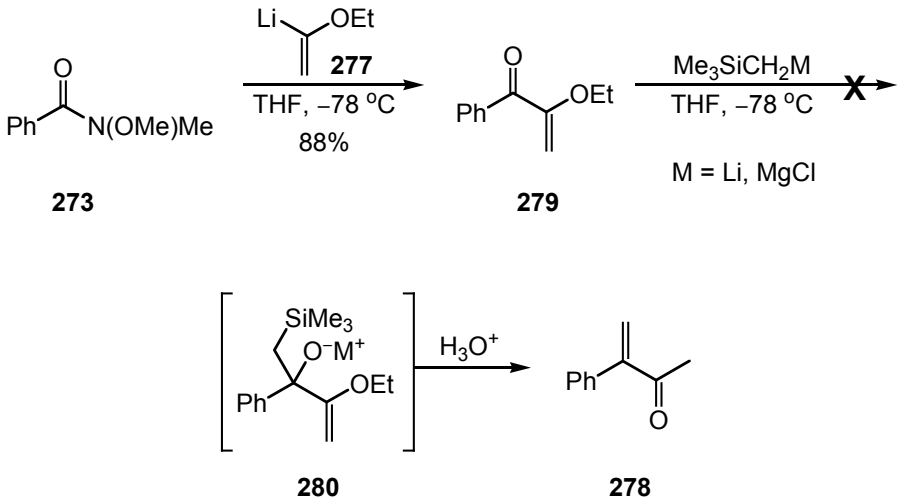
275

278

In our new approach, **273** was treated with **277** to afford the unstable enone **279** in good yield (Scheme 52). A one-pot conversion of **279** into the intermediate tertiary alkoxide **280**, which under ideal conditions would have spontaneously underwent a Peterson elimination to afford the α-branched enone **278,** was envisioned. Treatment of **279** with Me_3SiCH_2Li or Me_3SiCH_2MgCl failed to afford any of the desired enone **278** after acidic workup. In light of these results, we began to wonder now whether steric

congestion around the carbonyl of **279** might prevent the addition of the bulky silyl nucleophile. As such, an alternative protocol for the introduction of the trimethylsilylmethyl group was sought.

Scheme 52

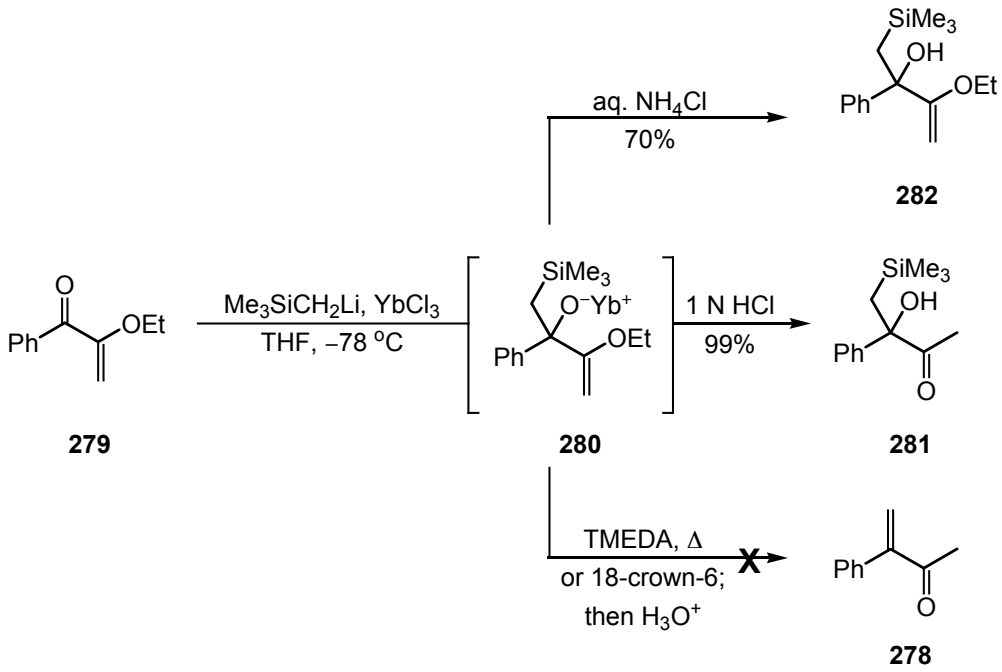


Molander and Fujiwara independently reported the use of organoytterbium species for the selective 1,2-addition of nucleophiles to hindered ketones and enones.[104] Hence, we set out to prepare the organoytterbium derivative of our trimethylsilylmethyl nucleophile. It also seemed prudent to investigate the use of the corresponding organocerium reagent due to its ease of preparation and wider acceptance in the synthetic community.[105]

We began our investigation with the addition of the nucleophile obtained from the reaction of anhydrous $YbCl_3$ with Me_3SiCH_2Li to compound **279** (Scheme 53).[106] As a result of our expectation that a spontaneous Peterson elimination would occur following the addition of the nucleophile, the reaction mixture was acidified to effect the hydrolysis of the enol ether. A near quantitative yield of the ketone **281** was obtained, suggesting

that the intermediate ytterbium alkoxide **280** would not undergo the desired elimination to produce the enone under these conditions.

Scheme 53



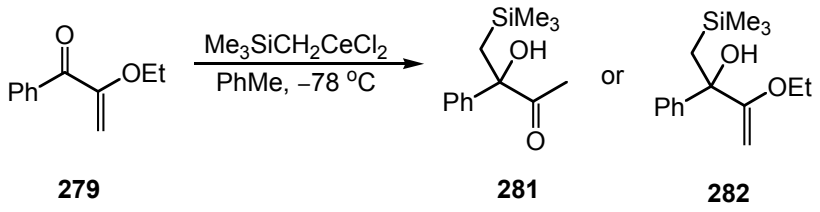
Suspecting that the stability of **280** was to blame for the lack of reactivity, we sought to intercept and complex the cation in order to liberate the naked alkoxide. The addition of chelating additives such as *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA)[107] or 18-crown-6 to the alkoxide species failed to induce the desired olefination resulting in the isolation of **281** or **282** depending upon the nature of the workup. Heating the alkoxide species to 100 °C also failed to produce the α-branched enone **278**. Accordingly, in subsequent trials we isolated the carbinol **281**, with the hope of carrying out the desired Peterson olefination in a separate operation.

It should be noted, that the yields for the transformation of **279** to **281** were often variable depending on the process utilized for the drying of the $YbCl_3 \cdot 6H_2O$.[108] Also, the

rate of addition of Me_3SiCH_2Li to the anhydrous $YbCl_3$ appeared to have a dramatic affect on the outcome this transformation, leading us to believe that the identities of the organoytterbium species formed are dependent on the conditions employed to prepare them.[109] The resulting variability in the yields of **281** obtained from reactions employing $YbCl_3$ led us to explore the corresponding organocerate nucleophile.

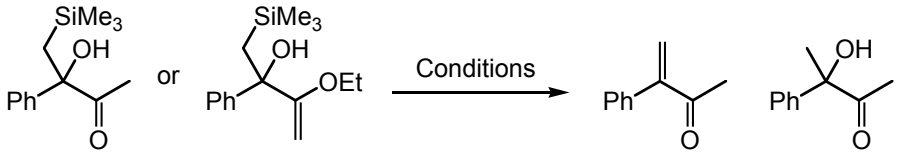
In a similar fashion, enone **279** was treated with the nucleophile obtained from the reaction of anhydrous $CeCl_3$ and Me_3SiCH_2Li. Initial reactions produced **281** in modest yields (22-54%) owing to the incomplete consumption of **279**, although the yield of recovered **279** was not determined. Switching the reaction solvent from tetrahydrofuran (THF) to toluene (PhMe), resulted in complete consumption of the enone to afford **281** or **282** in reproducibly good yield (>90%) depending on the workup protocol employed (Scheme 54).

Scheme 54



279 **281** **282**

With a reliable protocol for generating **281** and **282** in hand, conditions to effect a Peterson olefination of **281** or **282** were explored. A survey of standard basic- and fluoride-mediated conditions used to effect the olefination was undertaken.[110,111] Acidic conditions were not attempted due to the potential destruction of the resulting enone **278** in this media. The results of the elimination experiments are presented in Table 1.



281 **282** **278** **283**

Table 1

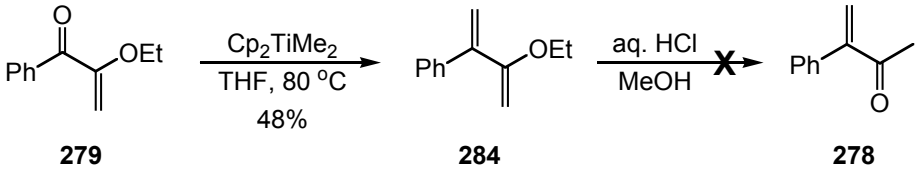
Entry	Substrate	Reagent	T (^{o}C)	Yield (%)
1	**281**	TBAF	25	30 (**283**)
2	**281**	HF-Pyr	25	IM[a]
3	**281**	$BF_3{\cdot}OEt_2$	0 → 50	47 (**283**)
4	**281**	KH	0 → 25	IM[a]
6	**281**	LDA	–78 → 25	78 (**281**)
7	**282**	KH	0 → 25	67 (**281**)
8	**282**	KH, 18-cr-6	22 → 55	IM[a]

[a] IM = Intractable Mixture.

The attempted fluoride-promoted olefination[111] of **281** resulted primarily in protodesilylation to afford **283**, whereas no detectable consumption of starting material was observed in basic media unless forcing conditions were applied, which in turn resulted in the production of dark-colored tars comprised of unidentifiable side-products. Due to the protodesilylation observed with substrate **281**, compound **282** was not subjected to the fluoride-mediated olefination conditions. Of interest though, was the isolation of **281** after acidification of the potassium hydride (KH) experiment employing substrate **282** (entry 7). This result in contrast to the intractable mixture obtained with the ketone **281** (entry 4) would seem to indicate that either **281** or **278** formed during the olefination reaction undergoes a competitive decomposition pathway under this set of basic conditions.

Having failed to effect the desired Peterson olefination under standard conditions, we turned our attention to the alternative non-basic olefination method of Petasis.[112] Treatment of **279** with freshly prepared dimethyltitanocene (Cp_2TiMe_2)[113] produced the butadiene **284** in modest yield (Scheme 55). Attempted hydrolysis of **284** produced a greenish-black tar devoid of any **278**.

Scheme 55



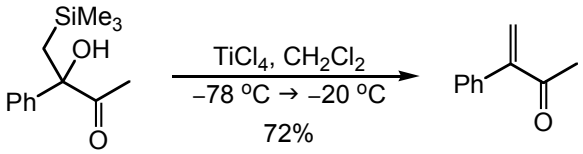
279 **284** **278**

It became evident that a new set of conditions would be required to effect the desired olefination event. We believed the addition of a strongly oxophilic Lewis acid such as $TiCl_4$ would coordinate in a bidentate fashion between the tertiary alcohol and carbonyl or enol functionalities of our substrates, thereby removing electron density from the benzylic carbon. If this position could be made sufficiently electron deficient, we hypothesized that a stepwise reaction beginning with the loss of a titanium alkoxide might occur to generate a benzylic carbocation. The additional stabilization provided to the carbocationic intermediate by the β-silyl group might further facilitate this pathway for the elimination of the elements of $HOSiMe_3$.[114] Another mechanistic possibility would be the bidentate coordination of the $TiCl_4$ with expulsion of a chloride ion that could cleave the C-Si bond and result in the loss of an oxotitanium species in a concerted fashion. However, the potential exists for the chloride ion to form a tight ion-pair with the electron deficient benzylic carbon, thereby stabilizing the benzylic position and decreasing the likelihood that a titanium oxide species would be expelled. Regardless of

the operative mechanistic pathway, it seemed prudent to conduct the experiment to determine whether the proposed transformation could be effected with $TiCl_4$.

Ketone **281** was thus treated with $TiCl_4$ at –78 °C and the resulting mixture was allowed to warm to –20 °C. Following workup and purification, we were delighted to obtain **278** in 72% yield (Scheme 56). Subsequent trials confirmed the reproducibility of this transformation. It should be noted, that the substitution of Ti(O*i*-Pr)$_4$ for $TiCl_4$ resulted in no reaction, whereas reactions utilizing TiF_4 did produce **281** albeit in lower yield than when $TiCl_4$ was employed owing to the formation of some **283**.

Scheme 56

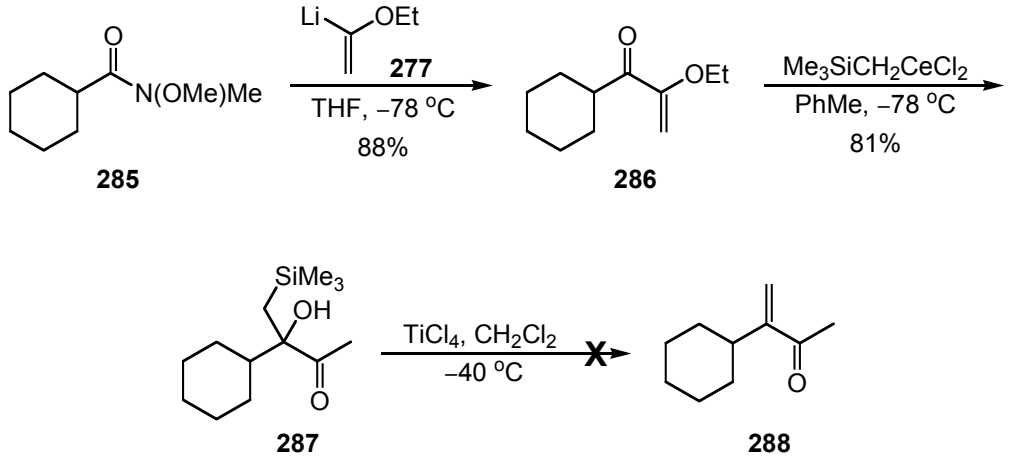


281 **278**

Having successfully established a new titanium-mediated Peterson olefination protocol to prepare **278**, we set out to determine whether the method would find general applicability with additional substrates and whether either of our proposed mechanistic hypotheses could be experimentally validated. Toward this end, the amide **285** was prepared from the corresponding acid using standard conditions.

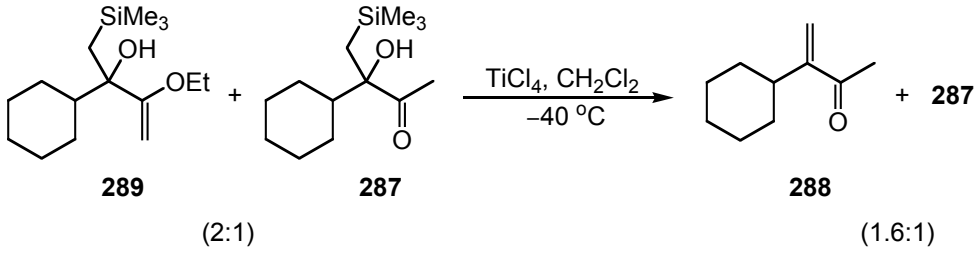
The previously established sequence of operations was utilized to prepare the carbinol **287** (Scheme 57). However, treatment of **287** with $TiCl_4$ failed to provide any of the desired enone **288**, instead extensive decomposition of the substrate was observed.

Scheme 57



Unsure as to why this transformation failed to proceed with substrate **287**, we reattempted the reaction this time with a 1:2 mixture of **287** and the enol ether **289** that was on hand (Scheme 58).

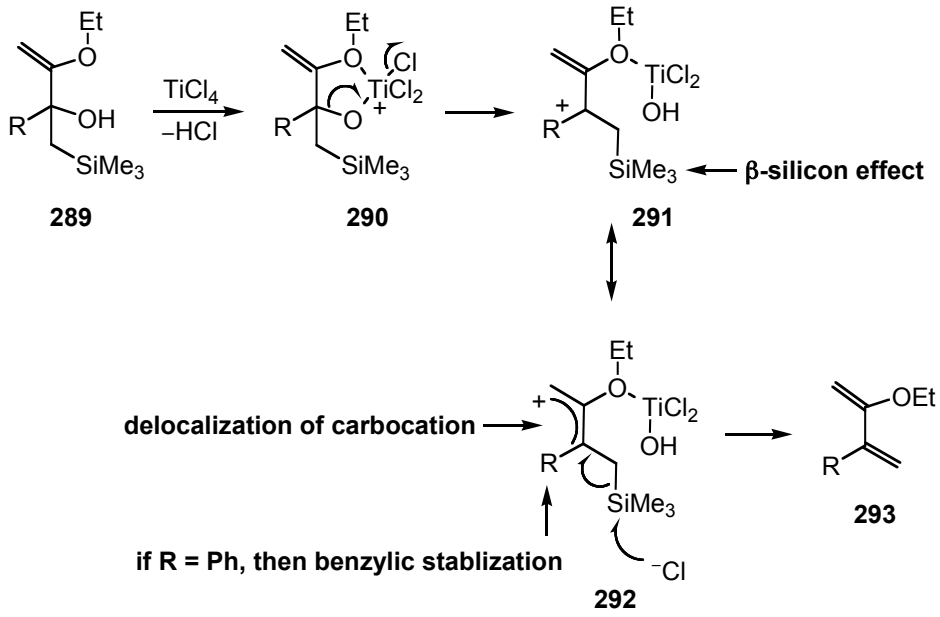
Scheme 58



We were surprised to find that indeed the reaction now proceeded to afford the desired enone **288**. Furthermore, we recovered nearly the same amount of **287** from the reaction that we had initially used as starting material. Although not conclusive, this result seemed to indicate that only the enol ether **289** participated in the olefination. We rationalized this finding by the ability of the enol ether moiety to stabilize a developing positive charge on the adjacent tertiary carbon via delocalization into the allylic π-system (Scheme 59). A mechanistic proposal to account for this result, as well as the ability of

ketone **281** to undergo the desired olefination reaction is provided in Scheme 59. Our experimental findings support a mechanism by which HCl is lost during the formation of an intermediate oxotitanium species corresponding to **291**. As mentioned, formation of a carbocation adjacent to the enol ether would benefit from stabilization via delocalization as in structure **292**, where additional β-silyl stabilization may also contribute to the stability of this intermediate. Attack of a liberated chloride ion upon silicon would then facilitate the desired cleavage leading to the enone precursor **293**.

Scheme 59

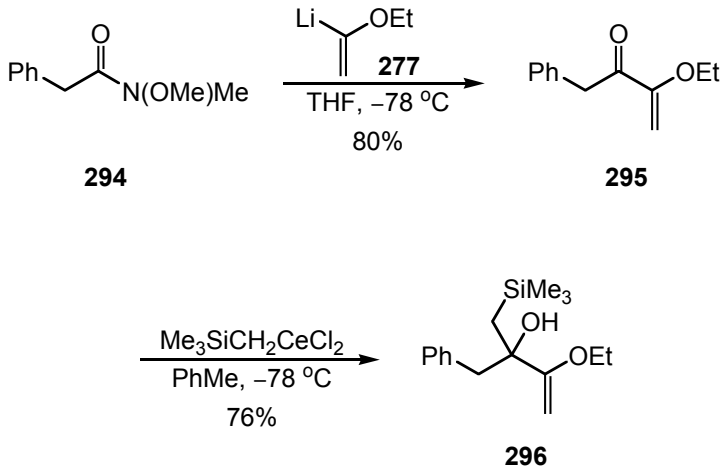


The ability of ketone **281** to undergo olefination may arise via the added benzylic stabilization of the carbocation intermediate, which may serve to overcome the destabilizing affects created by the generation of a positive charge adjacent to the ketone.

Taking this mechanistic hypothesis into account, experiments were then conducted with pure **289**. When **289** was subjected to the same reaction conditions, we obtained **288** in 43% yield along with an undetermined amount of **287**. The appearance

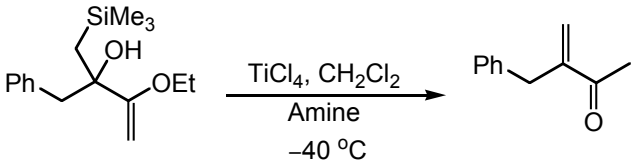
of **287** in the absence of an acidic workup suggested a competitive hydrolysis of the enol ether by acid generated during the course of the olefination in accord with our proposed mechanism. Distillation of the $TiCl_4$ under reduced pressure immediately prior to use and subsequent manipulations using Schlenk techniques were employed to eliminate the possibility of introducing HCl with the reagent. We reasoned that the addition of an amine base would serve to scavenge the HCl liberated during the olefination and prevent the hydrolysis of the enol ether, thereby increasing the yield of **288**. At this point, several additional substrates were prepared to further explore the substrate scope tolerated by our protocol. Due to the ease of handling, lower volatility, and simplified spectral characteristics, the phenethyl substrate **294** was prepared in order to optimize the titanium-mediated olefination conditions. Carbinol **296** was prepared from the amide **294** according to Scheme 60.

Scheme 60



A survey of amine bases was undertaken during the olefination event to transform **296** into the enone **297**. The use of a non- or at least weakly coordinating amine base was crucial to obtaining suitable yields of **297**, presumably due the ability of unhindered

amines to ligate the titanium species, thereby decreasing its Lewis acidity via the donation of electron density by nitrogen. As a result, 2,6-lutidine proved to be an especially effective base for the olefination reaction (Table 2).



296 **297**

Table 2

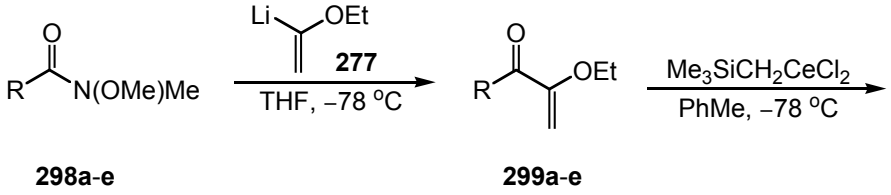
Entry	Amine	Yield (%)
1	None	54[a]
2	TMEDA	21
3	Pyridine	50
4	2,6-Lutidine	82

[a] 12% of the corresponding ketone resulting from hydrolysis of the enol ether was also obtained.

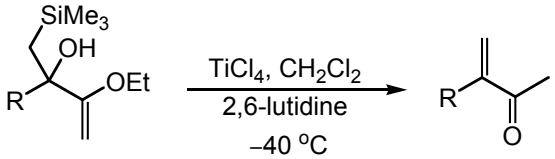
With an optimized protocol for the olefination reaction in hand, the additional amides **298a-e** were prepared and converted to the corresponding enones **301a-e** according to Table 3.[115,116,117]

Our new method was successfully applied to substrates possessing various degrees of substitution at the α-position. In addition, heteroatoms capable of chelating titanium during the olefination event were well tolerated (substrates **300c-e**). As evident by the results in Table 3, the method may be successfully applied to substrates with varying degrees of branching in the α-position, as well as those having protected amine and alcohol functions. In the case of entry e, the proline-derived sulfonamide was obtained in good yield with less than 3% epimerization during the conversion of **298e-301e** as determined by chiral phase HPLC, rendering this method applicable to the

preparation of stereochemically pure enones.[118] Additionally, the scale of the reaction sequence can be increased with ease and with nearly identical yields as was demonstrated by the conversion of **298b** to **301b** on 0.4 mmol and 4 mmol scale in 85% and 84% yields respectively over the three-step sequence.

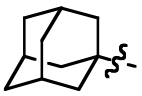
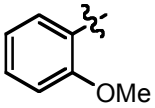
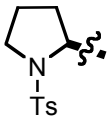


298a-e **299a-e**



300a-e **301a-e**

Table 3

Entry	R	Yield **299** (%)	Yield **300** (%)	Yield **301** (%)
a	*n*-hexyl–	95	94	86
b[a,b]		93(91)	98(99)	93(93)
c[b]		81	89	88
d[b]	$BnO(CH_2)_4$–	87	94	82
e[b]		69	93	63

[a] Reaction conducted on 0.4 mmol and 4.0 mmol scales with identical yields (4.0 mmol scale yields given in parentheses).
[b] Reaction sequences conducted by David Kummer.

We also found that the efficiency of the three-step process can be improved with only a slight (<10%) decrease in the overall yield by directly treating the cerium alkoxide

intermediates obtained by addition of $Me_3SiCH_2CeCl_2$ to **299a**–**e**, with a pre-mixed solution of $TiCl_4$ and 2,6-lutidine at –45 °C to generate the enones directly without the need to isolate the intermediate carbinols (Table 4).

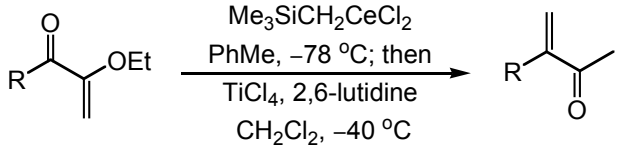
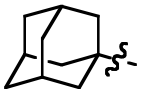
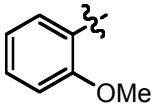


Table 4

Entry[a]	R	Yield Enone (%)
a	Ph	67 (**278**)
b	$PhCH_2$	55 (**297**)
c		84 (**301b**)
d		60 (**301c**)

[a] All reactions conducted by David Kummer.

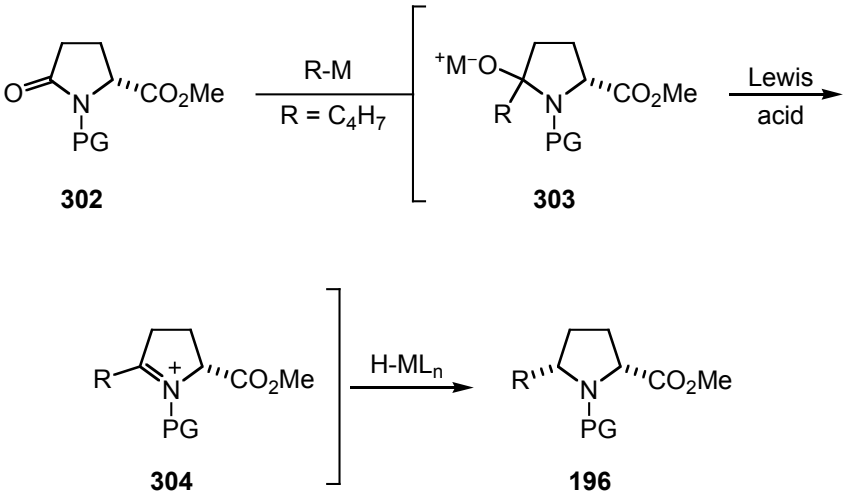
3.2 Development of a New *Cis*-2,5-Disubstituted Pyrrolidine Synthesis

3.2.1 Methodological Strategy

The task of developing a suitable method for the purpose of synthesizing unsaturated *cis*-pyrrolidines in a highly diastereoselective fashion was originally undertaken by Dr. Rainer Machauer from our group. After a careful survey of the literature pertaining to the synthesis of *cis*-2,5-disubstituted pyrrolidines, he opted for an *N*-acyliminium ion based approach for the synthesis of a compound of general structure **196**. This strategy was chosen to facilitate the introduction of the widest range of unsaturated side-chains via the corresponding organometallic nucleophiles. As such, he required a method for the selective reduction of the transient iminium ion **304** generated

upon addition of a 3-butenyl organometallic nucleophile to the imide precursor **302** (Scheme 61). The conditions of the reduction would need to be compatible with the different unsaturated moieties as well as the C-2 pendant ester needed for our proposed synthesis of anatoxin-a. In addition, he wished to utilize reaction conditions that would not result in the loss of the nitrogen-protecting group.

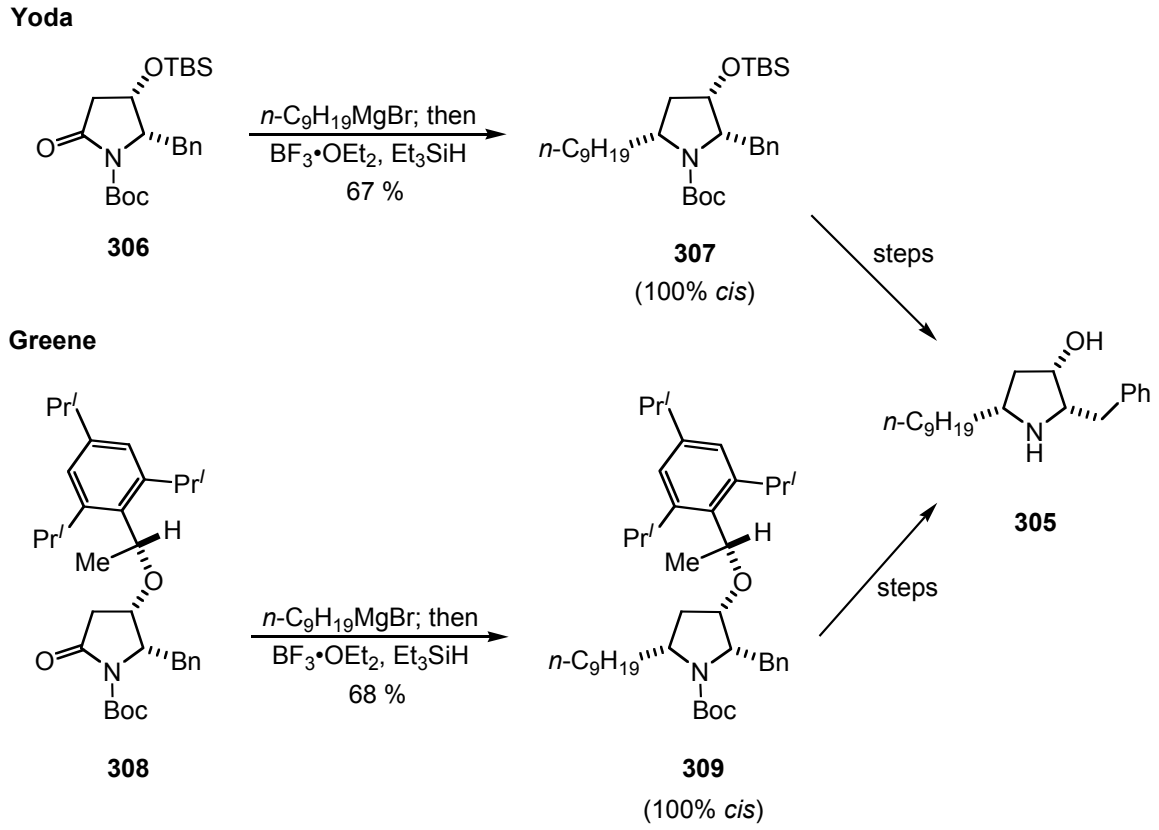
Scheme 61



The groups of Yoda[119] and Greene[120] independently disclosed protocols that would satisfy these requirements during the preparation of the antifungal alkaloid (+)-preussin (**305**). Both groups found that the imides **306** and **308** could be converted to the *cis*-pyrrolidines **307** and **309**, respectively via sequential treatment with nonylmagnesium bromide and then $BF_3{\cdot}OEt_2$ and triethylsilane (Et_3SiH) (Scheme 62). The authors proposed that the complete *cis*-diastereoselection resulted from the preferential delivery of a hydride to the face of the iminium ion opposite the bulky C-3 directing groups. We reasoned that a similar protocol for preparing *cis*-pyrrolidines resembling **196** could be achieved by the reaction of the appropriate *N*-acyl pyroglutamate with an unsaturated organometallic reagent followed by the stereoselective hydride reduction of the transient

iminium ion that would be generated by ionization of the intermediate *N*, *O*-acetal. In the absence of a large C-3 substituent, the use of a bulky hydride reducing agent would be expected to deliver preferentially a hydride to the iminium ion from the face opposite the C-2 substituent (Scheme 61). A method of this nature would also allow isolated double bonds to be maintained without competitive reduction as silanes are generally poor reductants of alkenes.

Scheme 62

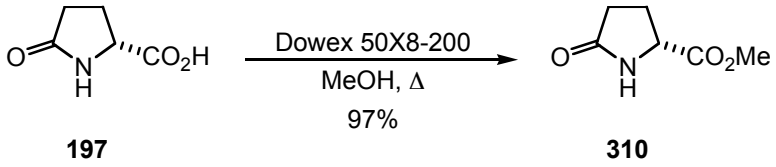


3.2.2 Development of the Method

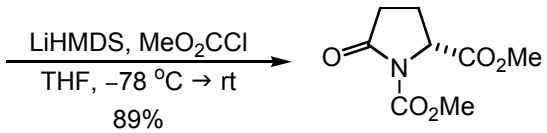
As shown previously in Scheme 61, our synthetic plan was to assemble a *cis*-pyrrolidine of general structure **196** in a one-step process in which the product of an organometallic addition to a pyroglutamate derived imide would be reduced *in situ* by a

metal hydride reagent to afford the *cis*-pyrrolidines. The next task would be to determine whether the transient iminium ion generated during the process could be reduced with the same degree of diastereoselection observed by Yoda and Greene (*vide supra*) in the absence of a large directing group. Toward this end, Machauer chose the imide **311** for initial exploratory studies. Imide **311** was prepared from D-pyroglutamic acid (**197**) in two steps according to Scheme 63.

Scheme 63



197 **310**

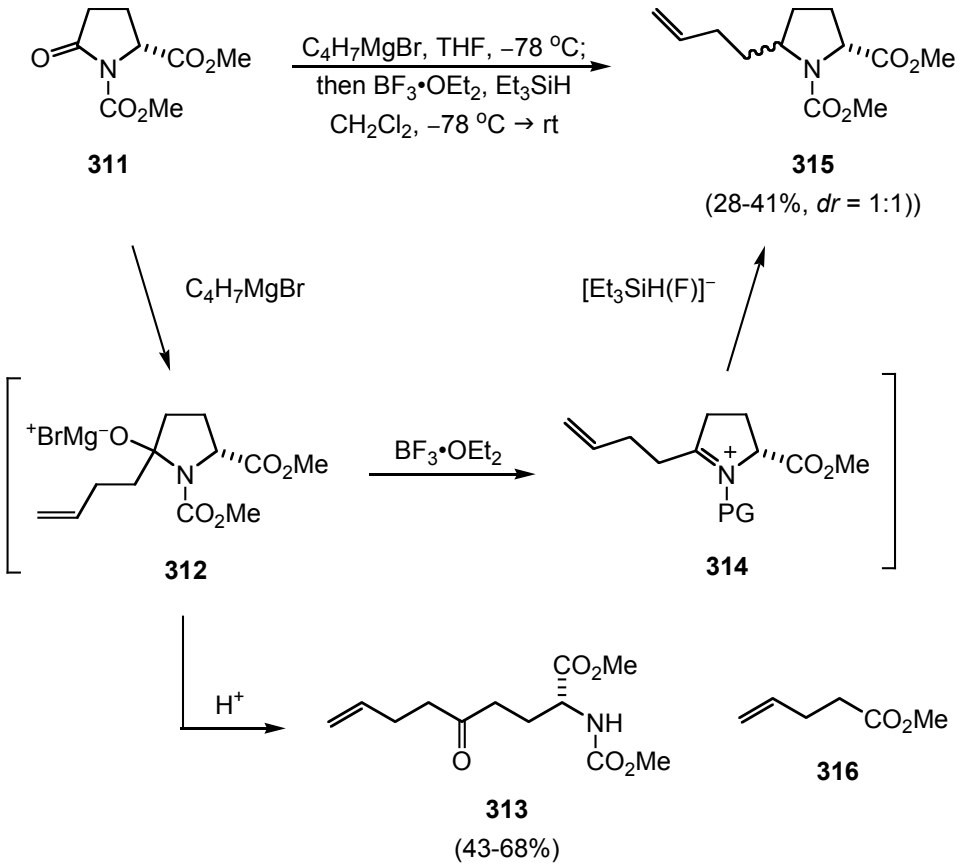


311

Unfortunately, the initial one-pot experiments conducted by Machauer on the imide **311** proved far less efficient for the isolation of the *cis*-pyrrolidines than had been reported by Yoda and Greene. Rather, the ketone **313** was consistently isolated as the major reaction product along with an equal mixture of the diastereomeric pyrrolidines **315**, and an undetermined quantity of the volatile ester **316** that arose via competitive addition of the organometallic reagent into the carbamate carbonyl (Scheme 64). The isolation of the ketone **313** was surprising as no mention was made of any ring-opened side-products in the reports provided by Yoda and Greene, though in the absence of $BF_3 \cdot OEt_2$ and a silane, the isolation of the ketone as opposed to a cyclic aminal is in

accord with previous reports in the literature.[121] It seems likely that the ketone **313** arose via the collapse of the intermediate magnesium alkoxide **312** upon addition of a proton source (Scheme 64). The incomplete formation of the iminium ion **314** from **312** may have resulted from the coordination of the THF used as solvent to the $BF_3 \cdot OEt_2$, thereby decreasing the likelihood that the Lewis acid would coordinate to the magnesium alkoxide and produce intermediate **314**.

Scheme 64

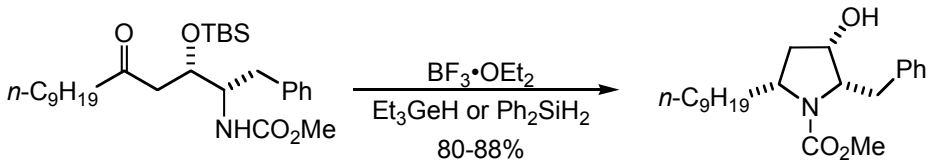


The yield of **315** could be improved to 54-58% by removal of nearly all of the THF utilized during the Grignard addition under reduced pressure using Schlenk techniques, followed by treatment of the crude residue with $BF_3 \cdot OEt_2$ and silane in CH_2Cl_2. However, these yields were much lower that we had hoped to achieve, and the

lack of any diastereoselection during the one-pot process forced us to explore an alternative protocol for the preparation of **315**.

The question remained as to whether the modest yields of **315** obtained from the one-pot sequences, were the result of the inactivation of $BF_3 \cdot OEt_2$ by the ethereal solvent utilized during the Grignard additions. As such, we wondered whether a two-step sequence in which the ketone **313** was isolated and purified following the Grignard addition might improve the yields of **315**. Based on the precedented reductive cyclization of **317** to **318** performed by Kitahara and coworkers,[122] we were confident that the cyclization event conducted with **313** as part of a two-step sequence would provide the desired *cis*-pyrrolidine **315** with comparable efficiency (Scheme 65).

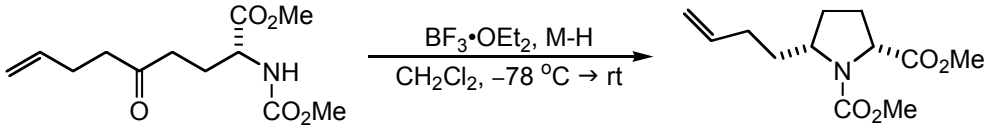
Scheme 65



317 **318** (100% *cis*)

Along these lines, Machauer isolated the ketone **313** from the addition of 3-butenylmagnesium bromide to the imide **311** (Table 5). The yield of **313** was low owing to substantial deprotection of the carbamate by the Grignard reagent as evident by the isolation of **316**. At this stage, no effort was made to suppress the undesired reaction manifold leading to loss of the carbamate protecting-group. Instead, ketone **313** was to be converted to **315** according to the method of Kitahara (Scheme 65). Machauer had previously determined during the one-pot trials that Et_3SiH was not suitable for the diastereoselective reduction the transient iminium ion **314** to the *cis*-pyrrolidine **315**. To

overcome the apparent lack of facial bias during the reduction of the transient iminium ion, the steric bulk of the reductant was increased. Machauer performed a survey of reductants for the conversion of **313** to **315**. As evident from the results provided in Table 5, triphenylsilane (Ph_3SiH) proved to be most effective for the preparation of **315**.



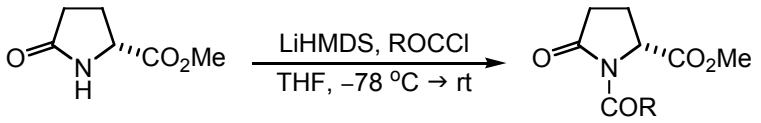
313 **315**

Table 5

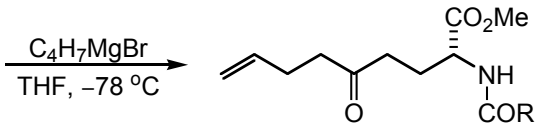
Entry	M-H	Yield[a] (%)	*cis*:*trans*[b]
1	Et_3SiH	83	1.1:1
2	*n*-Bu_3SiH	54	1.3:1
3	$NaCNBH_3$	62	4.7:1
4	$NaBH_4$	50	4.5:1
5	Ph_3SiH	94	15.9:1

[a] Yields are based upon products isolated by column chromatography.
[b] Ratios determined by GC.

Having successfully effected the cyclization/reduction of **313** to **315**, we wished to improve the yield of the initial organometallic addition step by examining carbamate-protecting groups that would be less susceptible to nucleophilic attack by the Grignard reagent. The series of imides **319a-g** were thus prepared and treated with 3-butenylmagnesium bromide to afford the keto carbamates **320a-g**. As evident by examination of Table 6, relatively unhindered or strongly electron withdrawing carbamates were efficiently cleaved in the presence of 3-butenylmagnesium bromide. Only the *i*-propyl and *t*-butyl (Boc) carbamate protected imides **319f-g** gave the keto carbamates **320f-g** in acceptable yields.



310 **319a-g**



320a-g

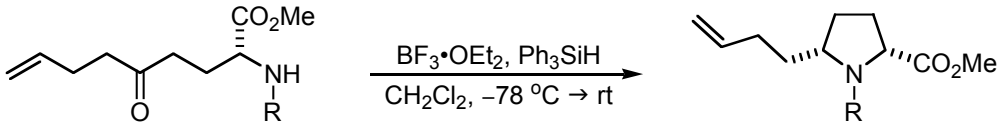
Table 6[a]

Entry	R	Yield **319**[b] (%)	Yield **320**[b] (%)
a[c]	*t*-Bu	94	78
b	Cl_3CCH_2O	91	16
c[c]	$(Cl_3C)CMe_2O$	95	34
d	BnO	100	44
e	CyclopentylO	59	59
f	*i*-PrO	84	79
g	*t*-BuO	89	92

[a] Unless otherwise noted, results obtained by J. Brenneman.
[b] Yields are based upon products isolated by column chromatography.
[c] Reaction sequence performed by R. Machauer.

When Machauer treated the ketocarbamate **320f** with $BF_3{\cdot}OEt_2$ and Ph_3SiH, the *cis*-pyrrolidine **321** was isolated in near quantitative yield and >30:1 diastereoselectivity as judged by GC analysis (Scheme 66). Attempts to induce the cyclization/reduction of **319g** under the same conditions resulted in extensive loss of the *t*-butyl carbamate moiety to provide **322**. Furthermore, the pivaloyl protected substrate **319a** failed to undergo the cyclization event altogether. Undeterred, Machauer opted to utilize compound **321** for all further transformations.

Scheme 66



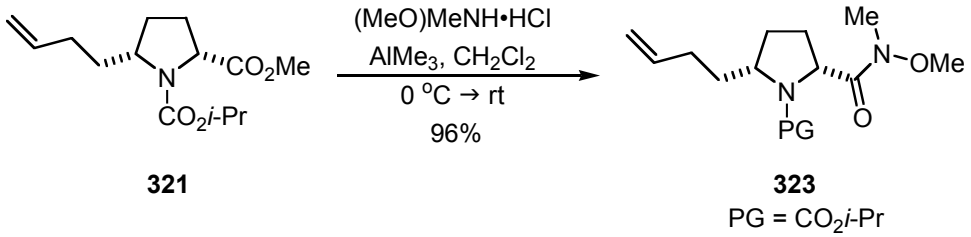
320f: R = CO_2*i*-Pr
320g: R = Boc

321: R = CO_2*i*-Pr (99%)
(*dr* = >30:1)
322: R = H (44%)

3.3 APPLICATION OF THE α-BRANCHED ENONE METHOD

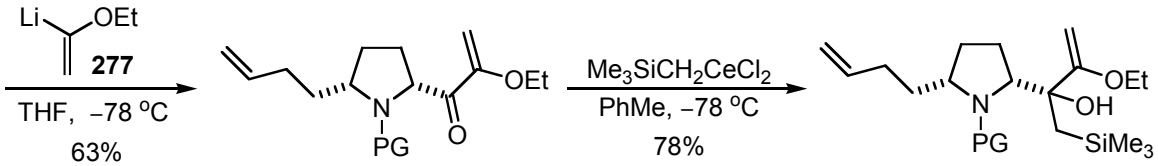
With a successful new method in hand for the conversion of amides into α-branched enones, Machauer undertook the construction of the RCM precursor **326** according to Scheme 67.

Scheme 67



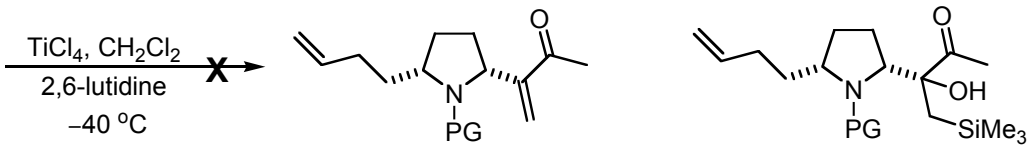
321

323
PG = CO_2*i*-Pr



324

325



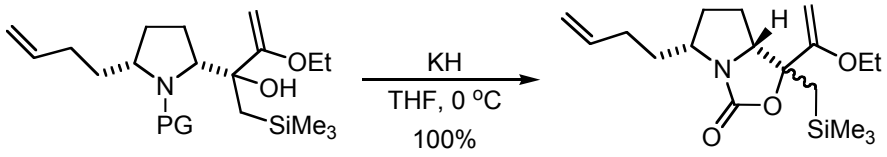
326

327

The *cis*-pyrrolidine **321** was converted to the amide **323** using standard conditions. Treatment of **323** with **277** afforded **324** in 63% yield. Addition of $Me_3SiCH_2CeCl_2$ to **324** produced the carbinol **325**. Unfortunately, exposure of **325** to the titanium-mediated olefination conditions used to prepare the enones **301a-e** (Table 3) failed to provide any of the enone **326**. Rather an unidentifiable mixture of compounds was isolated along with an unspecified amount of the hydrolysis product **327**.

After several failed attempts to effect the desired Peterson olefination leading to enone **326** by the exposure of **325** to $SOCl_2$ in pyridine or mesyl chloride (MsCl) and Et_3N, Machauer treated the carbinol **325** with KH in and effort to promote a base-induced elimination. Under these conditions, the cyclic carbamate **328** was obtained in essentially quantitative yield (Scheme 68).

Scheme 68

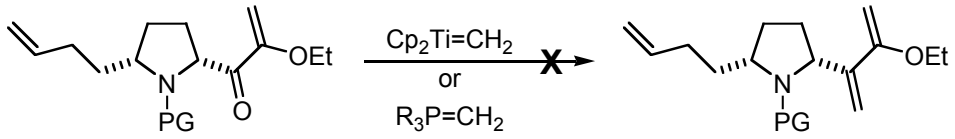


325
PG = CO_2*i*-Pr

328

No attempts were made to exploit **328** in a subsequent elimination protocol. Rather a direct olefination strategy was pursued in an attempt to convert **324** to **326** as was previously applied to the preparation of **284** (Scheme 55). Unfortunately, exposure of **324** to Cp_2TiMe_2 or the phosphoranes $Me_3P{=}CH_2$ and $Bu_3P{=}CH_2$ failed to produce any of the butadiene **329**. Instead only **324** was recovered in an unspecified yield (Scheme 69).

Scheme 69

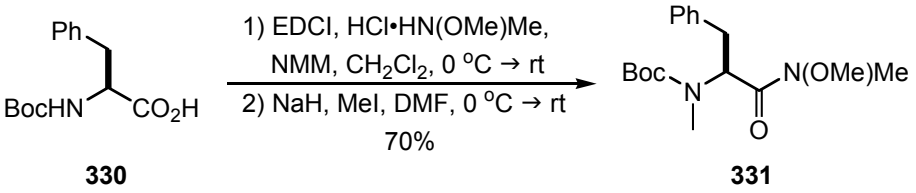


324
PG = CO_2*i*-Pr

329

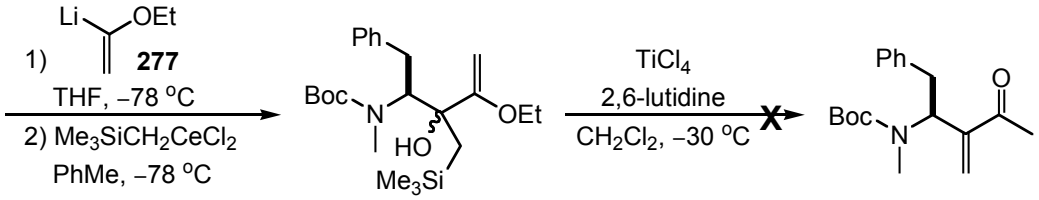
Machauer's unsuccessful attempts to convert **324** or **325** to **326** prompted David Kummer and I to return to the titanium-mediated olefination reactions conducted on **325**. We were curious whether the carbamate moiety of **325** was responsible for the failed olefination attempts using the titanium-mediated conditions. To test this hypothesis, we prepared the phenylalanine-derived substrate **332** according to Scheme 70.

Scheme 70



330

331



332

333

Exposure of **332** to the titanium-mediated olefination conditions resulted in the generation of an intractable mixture of compounds. Likewise, treatment of **332** with KH or fluoride sources also failed to produce any of the enone **333**. These findings paralleled those observed by Machauer, but remained in contrast to Kummer's successful

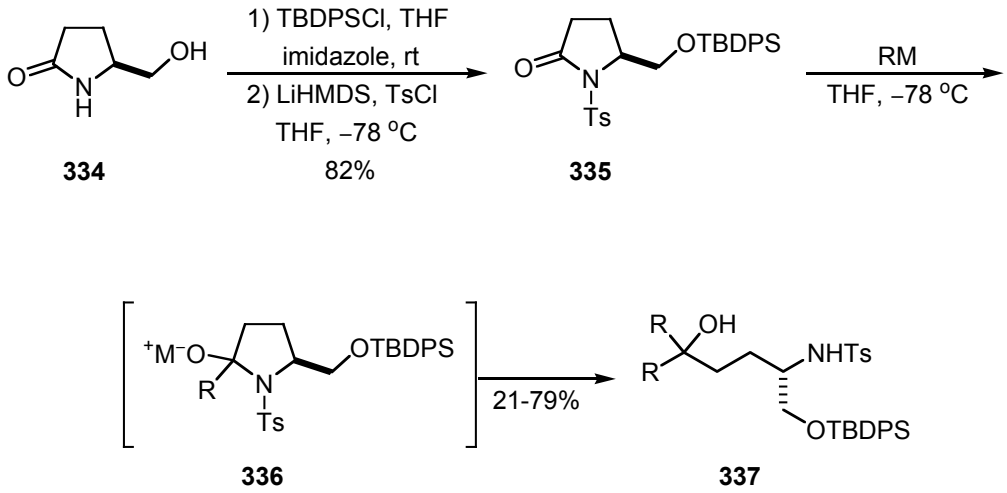
elaboration of the proline-derived sulfonamide **300e** to the corresponding enone **301e** (Table 3).

At this stage of the project Machauer completed his tenure within our group and I was charged with the transformation our route into a viable protocol for the preparation of anatoxin-a. However, it seemed unlikely at this point that the desired enone **326** could be formed from **325** using our titanium-mediated protocol. In order to unequivocally determine whether the carbamate moiety was contributing to the factors preventing the conversion of **325** to **326**, we set out to prepare the corresponding sulfonamide.

The sulfonamide **335** was prepared from L-pyroglutaminol (**334**) according to Scheme 71. The less expensive L-isomer of **334** was utilized to prepare a model olefination substrate. The protected alcohol of **335** was employed to prevent the preferential addition of organometallic nucleophiles to the C-2 pendant methyl ester, as this had been observed during initial experiments using pyroglutamate-derived sulfonamides. The preferential addition of nucleophiles to the ester rather than the lactam carbonyl presumably was the result of steric crowding about the lactam by the large sulfonamide protecting-group. Exposure of **335** to a variety of organometallic nucleophiles resulted in the isolation of the carbinols of general structure **337**. The strongly electron withdrawing sulfonamide promoted the collapse of the initial addition adduct **336** to produce a ketone that underwent a second nucleophilic addition to provide **337**. Attempts to prevent the collapse of the cyclic tautomer **336** via the implementation of strongly oxophilic metals such as titanium and lanthanum failed to circumvent the undesired reaction pathway leading to **337**. Conducting the addition reactions at lower temperatures (–98 ^{o}C) or the addition of sub-stoichiometric quantities of the

organometallic reagents to **335** also failed to prevent the formation of compounds corresponding to **337**.

Scheme 71



RM = *n*-BuLi, allylMgBr, C_4H_7MgBr,allylMgBr/$TiCl_4$, EtMgCl/$ZnCl_2$, *n*-BuLi/$La(OTf)_3$

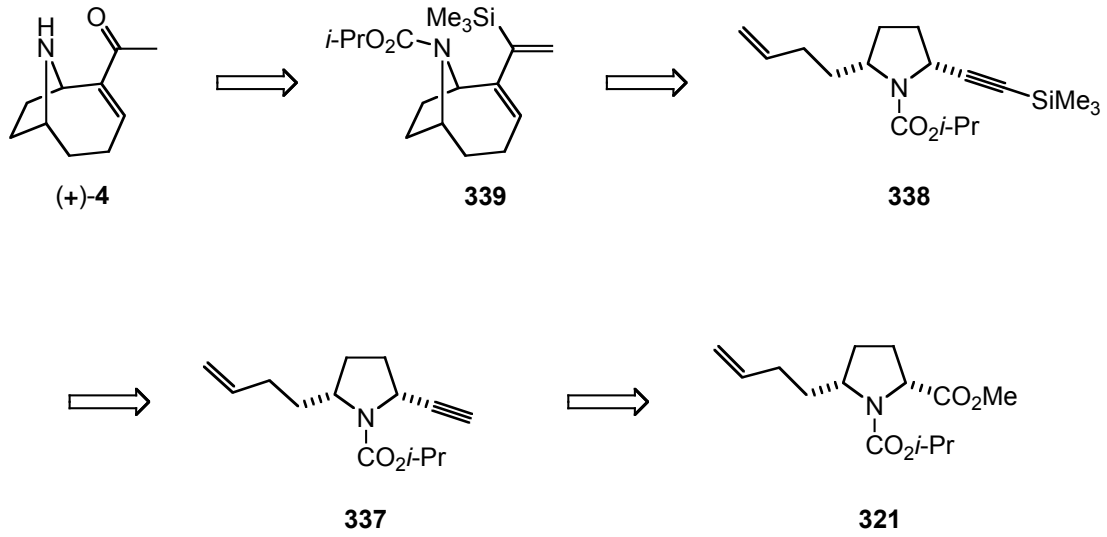
Our inability to prepare the α-branched enone RCM precursor **326** or a sulfonamide-protected counterpart led us to investigate an alternative metathesis protocol for the preparation of the azabicyclo[4.2.1]nonane skeleton. It was at this point that we began to explore the possibility of preparing anatoxin-a via an enyne metathesis reaction.

3.4 SILYLALKYNE-ALKENE METATHESIS

A number of problems were encountered during the course of our efforts to prepare anatoxin-a [(+)-**4]** via the intramolecular RCM of an α-branched enone precursor such as **327** (*vide supra*). As such, we sought to utilize an alternative protocol for the assembly of the azabicyclic skeleton of (+)-**4**. We were intrigued by the possibility of employing an intramolecular enyne metathesis to generate the azabicyclic skeleton of (+)-**4** bearing a functionality that could be readily unmasked to form a methyl ketone. We thus envisaged that a RCEYM involving a TMS-substituted alkyne would generate a

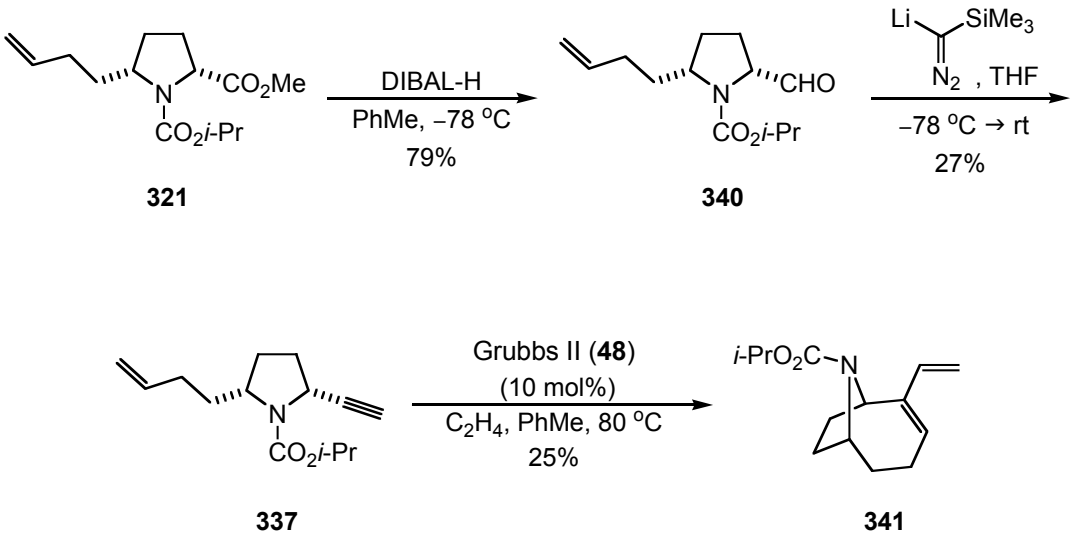
vinylsilane that could be further elaborated to a methyl ketone using known protocols.[123] The proposed silylalkyne **338** was to be prepared from **321** according to the retrosynthesis provided in Scheme 72.

Scheme 72



Toward this end, **321** was reduced to the corresponding aldehyde **340** (Scheme 73). Treatment of the aldehyde **340** with lithiotrimethylsilyldiazomethane[124] afforded the terminal acetylene **337** in poor yield. Owing to the low yield of **337** obtained from the homologation reaction, subsequent generation and trapping of the corresponding acetylide anion with chlorotrimethylsilane (Me_3SiCl) to yield **338** was not attempted. Instead, the RCEYM reaction of **337** was effected with the Grubbs second-generation catalyst **48** to produce a small quantity of **341**. This constituted the first example of the construction of the azabicyclo[4.2.1]nonane skeleton by RCM. However, due to the lack of sufficient quantities of **337**, this transformation was not optimized.

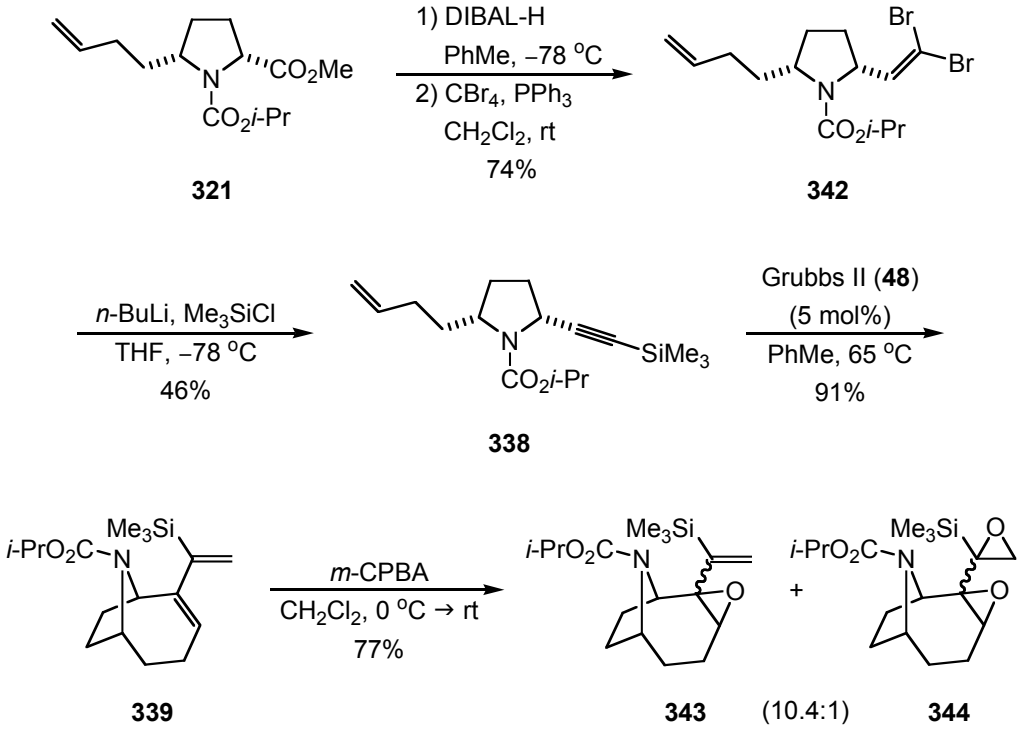
Scheme 73



321 **340** **337** **341**

The low yields obtained during this sequence suggested an alternative route to the silyl alkyne **338** might warrant exploration. As such, **321** was reduced to the aldehyde **340**, which was then converted to the vinyldibromide **342** using the Corey-Fuchs protocol (Scheme 74).[125] Treatment of **342** with *n*-BuLi followed by quenching of the intermediate acetylide anion with Me_3SiCl provided the metathesis precursor **338**. The modest yield obtained during the conversion of **342** to **338** was attributed to the displacement of the carbamate by *n*-BuLi based upon the formation of highly polar compounds. Regardless, the stage was set for the key RCEYM reaction. Exposure of **338** to the Grubbs second-generation catalyst **48** produced the azabicycle **339** in excellent yield. Unfortunately, our plan to convert the vinylsilane moiety of **339** to a methyl ketone by selective epoxidation, followed by an acid-catalyzed hydrolysis and an ensuing Peterson elimination was doomed at the outset.[123] Namely, epoxidation of the pendant olefin of **339** with *m*-CPBA furnished the undesired epoxide **343** as the major product contaminated with smaller quantities of the bis-epoxide **344** in a combined 77% yield (10.4:1 ratio respectively).

Scheme 74

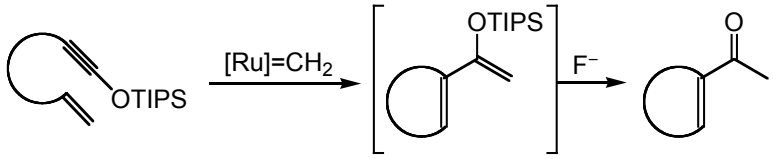


Although an alternative procedure that was developed by Mukaiyama was considered for the hydrolysis of the vinylsilane moiety of **339** to the requisite ketone,[126] the operational complexity of the procedure made this option less attractive than a more direct route that we had begun to explore.

3.5 SILOXYALKYNE-ALKENE METATHESIS

Our revised strategy led us explore a method that was later reported by Kozmin and coworkers for the preparation of cyclic enones via the RCEYM of siloxyalkynes according to the general Scheme 75.[127] For example, the siloxyalkynes of general structure **345** underwent a RCEYM to produce the siloxydienes **346**. Protodesilylation liberated the enones **347**.

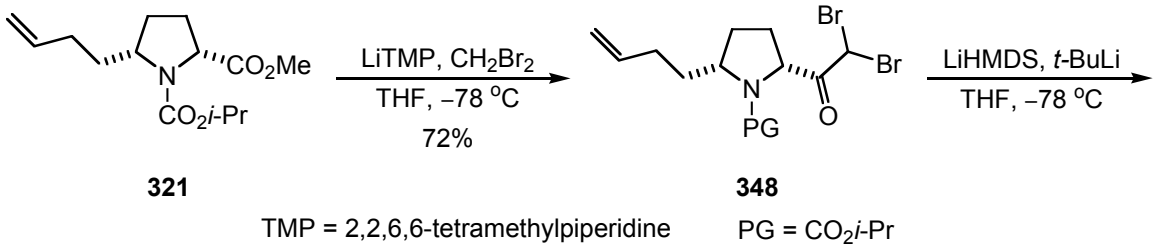
Scheme 75



345 **346** **347**

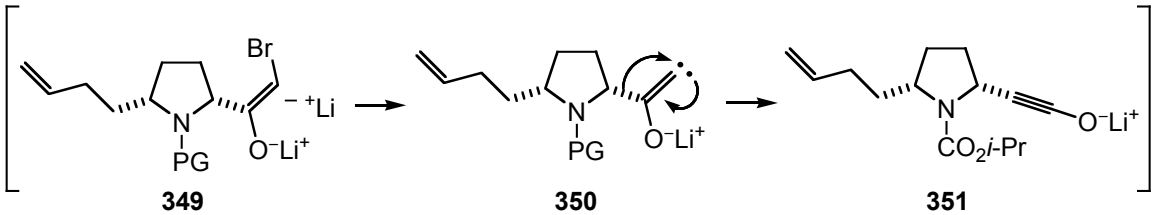
Inspired by these results, we set out to effect an analogous RCEYM reaction to prepare anatoxin-a. Our new strategy commenced with the conversion of the *cis*-pyrrolidine **321** into the unstable dibromoketone **348** (Scheme 76).

Scheme 76

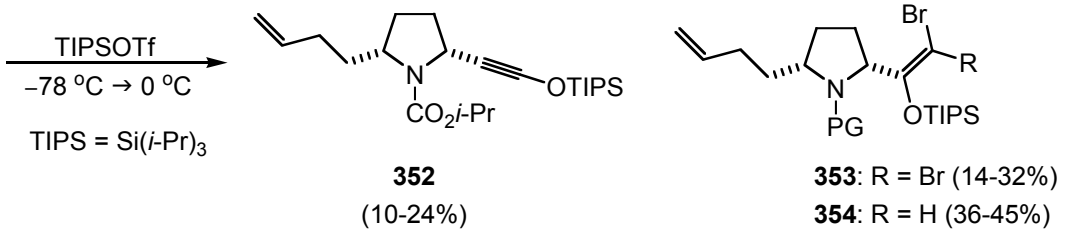


321 **348**

TMP = 2,2,6,6-tetramethylpiperidine PG = CO_2*i*-Pr



349 **350** **351**



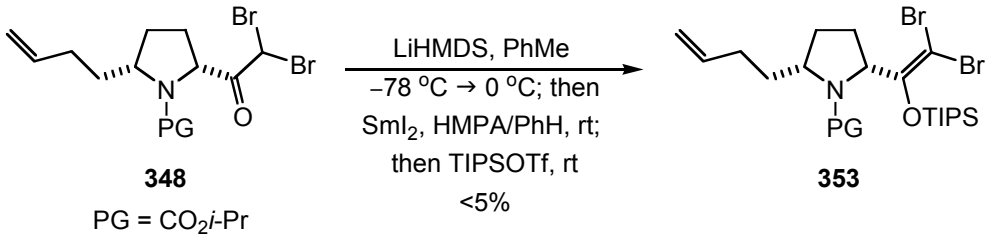
352 (10-24%)

353: R = Br (14-32%)
354: R = H (36-45%)

The subsequent transformation of **348** into the metathesis precursor **352** was effected using the procedure of Kowalski.[128,129] Numerous unsuccessful attempts were made to optimize the reaction conditions and increase the yields of **352** by the alteration of the reaction temperatures, times, and bases employed. However, the conditions shown in Scheme 76 provided the highest yields of **352**. Unfortunately, compounds **353** and **354** were consistently isolated as the major products of the reactions owing to incomplete metal-halogen exchange during the formation of **349** and failed generation of the carbene species **350**. Assuming **350** was produced, one cannot rule out the possibility that this species was being quenched via radical abstraction of the α-proton of THF.

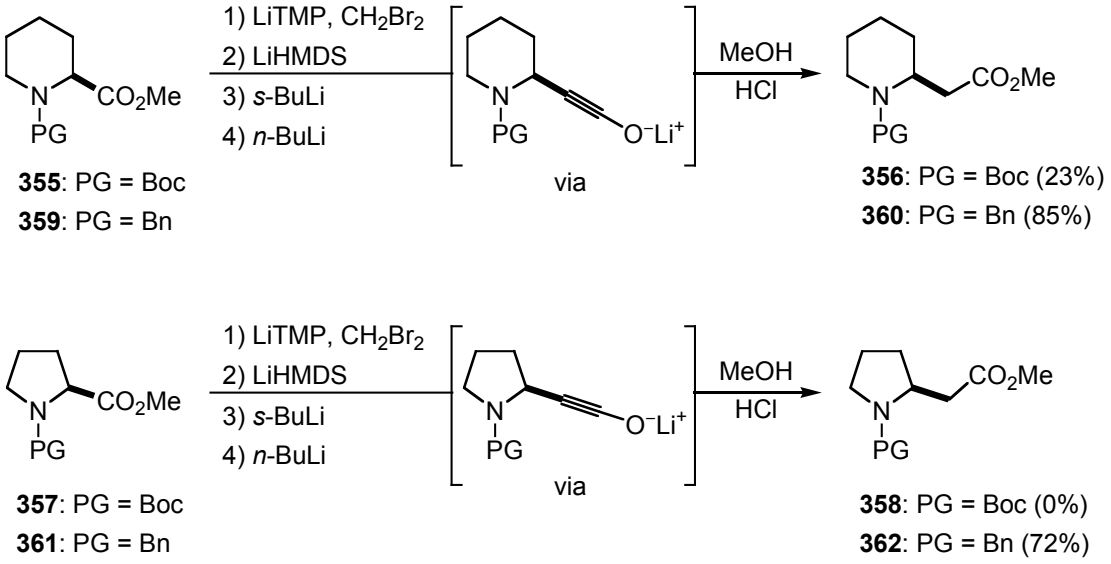
The poor yields of **352** obtained by the Kowalski protocol led us to investigate alternative routes to this compound. Believing the slow metal-halogen exchange and subsequent carbene forming steps to be the sources of these poor yields, we turned our attention to a report detailing the SmI_2-mediated transformation of vinyl dibromides into alkynes.[130] The reactions are believed to proceed via the formation of an intermediate vinyl carbene as in the case of the Kowalski protocol. As such, we wondered whether samarium carbene species corresponding to **350** could be prepared using this method, and if so, whether the desired rearrangement to the ynolate **351** would transpire. In order to determine the feasibility of the approach, the lithium enolate derived from **348** was added to a solution of SmI_2 in benzene containing HMPA, followed by the addition of triisopropylsilyl triflate (TIPSOTf) (Scheme 77). The reaction failed to produce any **352**. Rather a small quantity of **353** was obtained as the only identifiable product.

Scheme 77

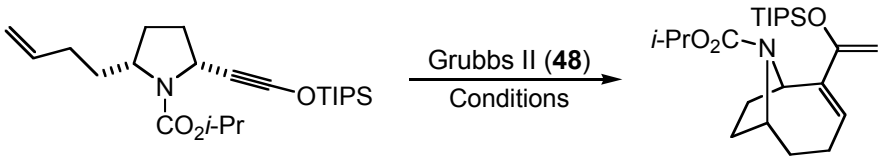


The poor results obtained during our efforts to prepare **352** forced us to evaluate whether the conversion of a pyrrolidine such as **321** to an ynolate anion would ever be possible in good yield. The fact that the Kowalski and samarium-mediated homologation protocols had never been utilized in conjunction with α-amino esters, led us to wonder whether the migratory aptitude of the heterocyclic portions of these derivatives was low enough to prevent the desired carbene-rearrangement leading to product.[131] Subsequent to our own studies, Gallagher and coworkers found that the successful application of the Kowalski ester homologation protocol to cyclic α-amino esters was highly dependent on the nature of the nitrogen protecting-group.[132] They discovered that the use of carbamate-protected substrates **355** and **357** resulted primarily in the formation of unidentifiable side-products from both pipecolic acid and proline derived substrates (Scheme 78). However, the corresponding *N*-benzyl derivatives **359** and **361** were smoothly converted to the optically pure homologated esters **360** and **362** respectively. The authors did not attempt to rationalize the very different reactivity observed between the carbamate and *N*-benzyl series. Hence, one can only wonder as to the role played by either protecting group during the reaction sequence.

Scheme 78



As Gallagher's results were unavailable during our attempts to apply the Kowalski homologation protocol to the preparation of **352**, we remained optimistic that the transformation of **348** to **352** could be improved through additional experimentation. Prior to the investment of additional time and material for this purpose, we set out to establish whether the key RCEYM of **352** would afford the fully functionalized azabicyclic skeleton of anatoxin-a. The limited quantities of **352** on hand were subjected to the RCEYM conditions reported by Kozmin. The desired azabicycle **363** was obtained albeit in modest yield (Table 7, entry 1). Conducting the metathesis event under an atmosphere of ethylene, which has been shown to be beneficial during RCEYM reactions of substituted alkynes, [133] provided an identical yield of **363**. However, the time required for complete consumption of **352** was decreased from 22 h to 2.5 h in the presence of this additive (entry 2). Increasing the catalyst loading also had a beneficial effect on the yield of **363** (entry 3).



352 **363**

Table 7

Entry	**48** (mol %)	Additive[b]	Solvent	T (^{o}C)	Time (h)	Yield[a] (%)
1	5	None	C_6D_6	65	22	46
2	5	C_2H_4	PhMe	80	2.5	46
3	20	C_2H_4	PhMe	70	5	55

[a] Isolated yields following purification by column chromatography.
[b] Entries 2 and 3 were conducted under 1atm of ethylene.

We were delighted to find that the RCEYM reaction of **352** successfully delivered **363**, but the limited quantities of **352** available precluded the optimization of this process until further refinements could be made to the Kowalski homologation protocol (*vida supra*). In the meantime, we sought to utilize the small quantity of **363** obtained from the metatheses to prepare anatoxin-a [(+)-**4**]. We envisioned the completion of the synthesis via a global deprotection of the silyl enol ether and carbamate moieties of **363**. A survey of the literature revealed but a few examples for removing isopropyl carbamates. The known conditions included exposure to $AlCl_3$,[134] gaseous HF,[135] or to mixtures of H_2SO_4 in TFA.[136] It seemed reasonable that application of these conditions to **363** might simultaneously cleave both the carbamate and silyl-protecting group. Although the silyl enol ether was readily transformed into a methyl ketone under a variety of conditions, the isopropyl carbamate was stable. The use of HF-pyridine in place of gaseous HF also unmasked the enone but failed to remove the carbamate. Attempts to force the reaction under acidic conditions led to decomposition. We explored several other methods used to deprotect carbamates, including *n*-BuLi,[137] Super-Hydride,[138] and basic hydrolysis with

LiOOH. We were again unable to remove the carbamate. Finally, attempts to remove the carbamate by hydrolysis of the corresponding silyl-, trifluoromethanesulfonyl-,[139] or alkyl imidates[140] were unsuccessful. Owing to the known stability of tertiary isopropyl carbamates, we had anticipated difficulties, but we had optimistically predicted an eventual success that was not to be. It was thus evident that a more labile carbamate would be required for the synthesis of (+)-**4**.[141] Furthermore, the poor yield obtained for the conversion of **348** to **352** signaled that an alternative strategy for the synthesis of a functionalized bicyclic intermediate suitable for conversion to anatoxin-a was essential.

3.6 AN *N*-BOC PYRROLIDINE ROUTE TO ANATOXIN-a

Following the unsuccessful attempts to remove the *i*-propyl carbamate-protecting group from **363**, we revisited the Boc-protected imide **319g**. We sought to utilize this substrate in a revised synthesis of anatoxin-a as a result of the high yields of the ketone **320g** obtained during the addition of C_4H_7MgBr to **319g**. Unfortunately, we had previously observed the cleavage of the carbamate moiety during the subsequent $BF_3{\cdot}OEt_2$-promoted cyclization-reduction protocol. We initially believed that the generation of acid during the course of the reaction might be facilitating the deprotection of the acid labile Boc-group. To test this hypothesis, **320g** was treated with a mixture of BF_3OEt_2, Ph_3SiH, and Cs_2CO_3 in CH_2Cl_2. It was hoped that the added base would scavenge any acid liberated as $B(OH)_3$ or HF, thereby preventing deprotection. Unfortunately, the carbamate was efficiently removed under these conditions, even in the presence of excess Cs_2CO_3, implicating yet another mechanism for deprotection.

Concurrent experiments aimed at determining whether alternative reducing agents could be employed in conjunction with $BF_3{\cdot}OEt_2$ to effect the desired cyclization-

reduction event proved moderately successful. In this approach, the direct conversion of the imide **319g** into **365** was achieved via the trapping of the intermediate cyclic magnesium aminal **364a** generated during the addition of C_4H_7MgBr to **319g**, followed by iminium ion formation and subsequent reduction (Table 8).

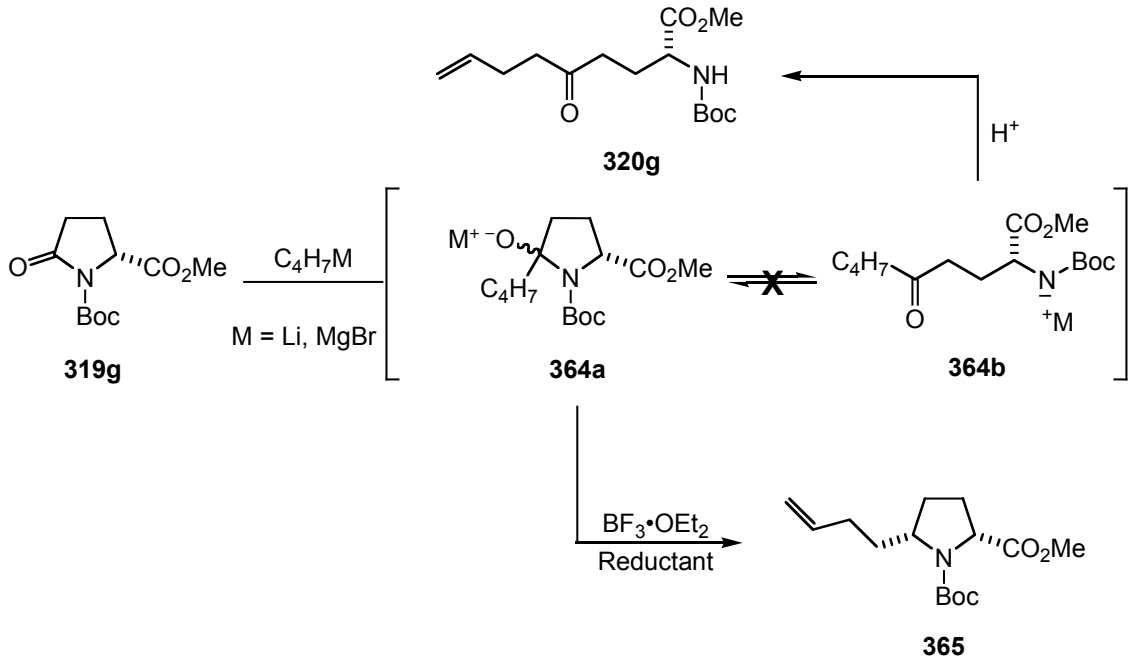


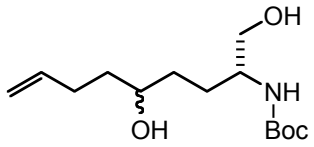
Table 8

Entry	Reductant	Equiv.	M =	Solvent[a]	T (°C)	Yield **365** (%)
1	Ph_3SnH	2.0	Li	PhMe/ Et_2O	−78 → 25	10
2	$PhNEt_2 \cdot BH_3$	2.0	Li	PhMe/ Et_2O	−78 → 25	6
3	PMHS[b]	2.0	Li	THF/ Et_2O	−78 → 25	IM[f]
4	$NaBH(OAc)_3$	1.1	Li	PhMe/CH_2Cl_2/Et_2O[c]	−78 → 25	21
5	DIBAL-H	3.1	Li	PhMe/ Et_2O	−78	33
6	DIBAL-H	4.0	Li	PhMe[d]	−78	26
7	Red-Al	3.1	Li	PhMe/ Et_2O	−78 → 25	53 (**366**)
8	L-Selectride	3.3	Li	PhMe/ Et_2O/THF [e]	−78	25
9	L-Selectride	3.0	Li	PhMe/THF[d,e]	−78	35
10	L-Selectride	4.0	MgBr	THF	−78	27

[a] Et_2O present from Li-I exchange reaction used to prepare 3-butenyllithium.
[b] PMHS = polymethylhydrosiloxane.
[c] $NaBH(OAc)_3$ insoluble in PhMe/Et_2O, so added as a concentrated solution in CH_2Cl_2.
[d] Et_2O removed at –78 °C using Schlenk techniques.
[e] THF introduced as part of the solution of L-Selectride.
[f] Intractable Mixture.

Since the formation of the ketone **320g** was never observed even if an excess of the organometallic nucleophile was used, we believed that **364a** was maintained in solution until the addition of a proton source. The absence of any carbinol resulting from diaddition of the nucleophile to the ketone suggested that there was no equilibrium between **364a** and **364b** under the conditions of the initial organometallic addition.[142]

The one-pot transformations were mediated by a combination of $BF_3 \cdot OEt_2$ and various reducing agents, using both the 3-butenyllithium[143] and 3-butenylmagnesium bromide nucleophiles. Indeed **365** was formed albeit in modest yields owing to various side-reactions including the addition of C_4H_7Li and hydride to the ester moiety. Additionally, the diol **366** was formed during the process conducted with Red-Al.

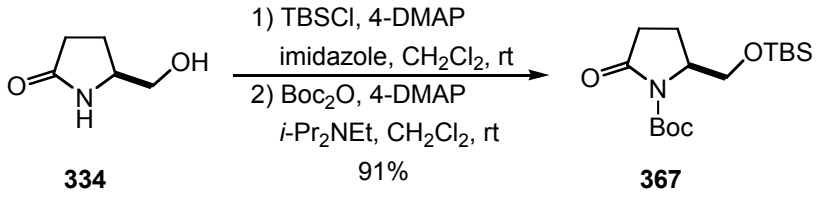


366

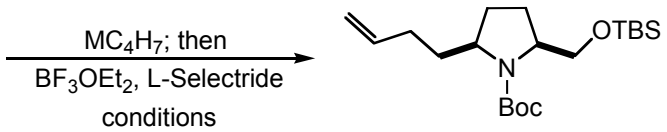
Of the reductants screened, only diisobutylaluminum hydride (DIBAL-H) and L-Selectride [$LiHB(s\text{-}Bu)_3$] provided useful quantities of **365**. Furthermore, we found that higher levels of *cis*-diastereoselection (>95:5) were obtained when L-Selectride was used as the reductant. As such, all subsequent one-pot cyclization/reduction sequences utilized this reagent.

The yields of the one-pot process could be improved significantly by the substitution of the methyl ester moiety of **319g** for a protected hydroxymethyl group. Hence, the imide **367** was prepared in two steps from **334** according to the conditions summarized in Table 9. Treatment of **367** with either C_4H_7Li or C_4H_7MgBr, followed by the addition of $BF_3 \cdot OEt_2$ and L-Selectride afforded the *cis*-pyrrolidine **368** in moderate

yield. However, the reactions employing C_4H_7MgBr were preferred in order to avoid the more labor-intensive lithium-halogen exchange reaction required to prepare the corresponding organolithium nucleophile.



334 **367**



368

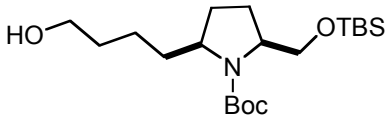
Table 9

Entry	Scale (mg **367**)	M =	Solvent	T (^oC)	Yield **368** (%)
1	103	Li	PhMe	−78	64
2	101	Li	PhMe/ Et_2O	−78	67
3	101	Li	Et_2O	−78	49
4	104	MgBr	THF	−78	63
5	94	MgBr	THF	−78 → −20	77
6	89	MgBr	THF	−78 → 25	79
7	100	MgBr	THF	−78 → 25	71
8	645	MgBr	THF	−78 → 25	53
9[a]	511	MgBr	THF	−78 → 25	44
10[b]	221	MgBr	THF	−78 → 25	23 32 (**369**)

[a] $BF_3{\cdot}OEt_2$ and L-Selectride premixed at 0 ^oC.
[b] $BF_3{\cdot}OEt_2$ and L-Selectride premixed at −13 ^oC.

As evident by the results in Table 9, the yields of the one-pot processes were good on small scale using either organometallic nucleophile. Unfortunately, attempts to increase the scale of the reaction resulted in diminished yields of **348** (entries 8-10). Although the origin of this problem remains unknown, we speculated that the premixing of the $BF_3{\cdot}OEt_2$ and L-Selectride on larger scales might have resulted in the generation of

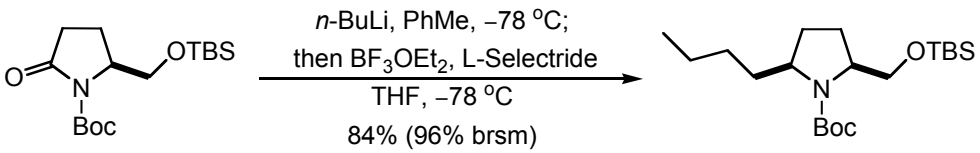
borane as $BH_3 \cdot THF$,[144] or HBF_2.[145] In support of this hypothesis, we isolated the alcohol **369**.



369

The isolation of the alcohol **369** instead of the corresponding boronic acid following an aqueous workup was surprising.[146] As of yet, we can only speculate as to why the alcohol was formed in the absence of an oxidative workup. Of interest however, was the reaction of **367** with *n*-BuLi under similar conditions. In the absence of an olefinic moiety, the adduct **370** was obtained in excellent yield (Scheme 79).

Scheme 79

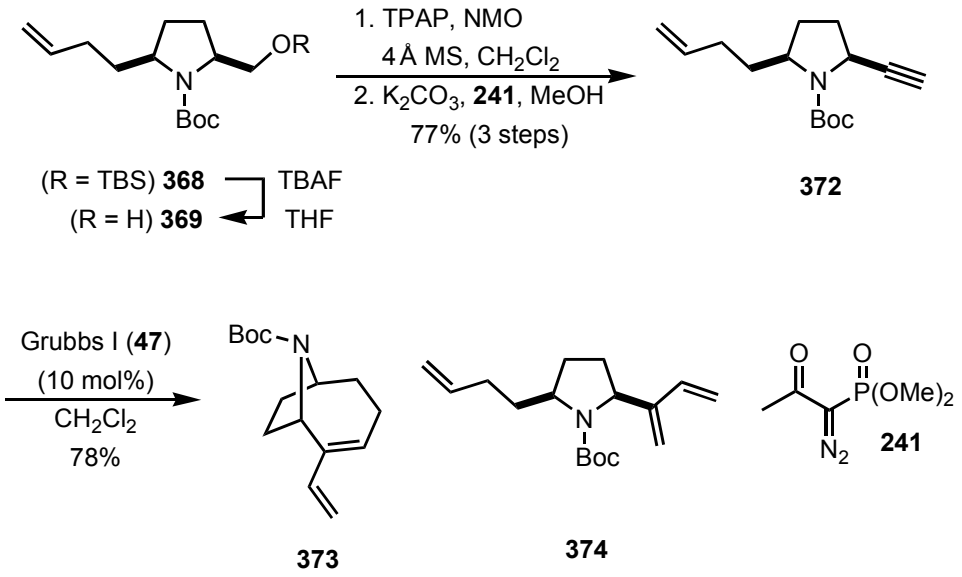


367 **370**

Despite our difficulties in preparing **368** in large quantities, we did obtain enough of this substrate to prepare a suitable EYM precursor. We believed at this stage that it would be prudent to test the key RCM event before investing the effort to optimize the conditions of the cyclization/reduction protocol. Hence, compound **368** was converted to the enyne **372** according to Scheme 80. As a result of the modest yield of **337** obtained during the RCEYM event involving **341** (Scheme 73), we explored several conditions to effect the desired ring-closure. We found that the conversion of **372** to the azabicycle **373** was best achieved with the Grubbs first-generation catalyst **47**. Exposure of **372** to

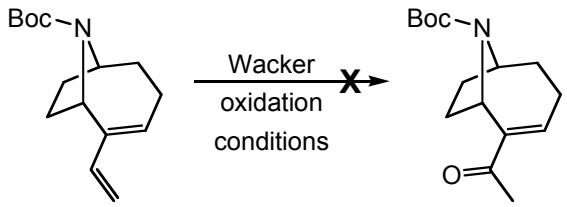
the more reactive second-generation catalyst **48** resulted in diminished yields of **373** owing to the formation of increased amounts of dimeric product. Aggarwal later reported an analogous dimerization process during the synthesis of (+)-ferruginine [(+)-**7**] (Chapter 1.5.4). The reaction of **372** with the Grubbs first-generation catalyst **47** under an atmosphere of ethylene resulted in a cross-metathesis reaction between ethylene and the alkyne to deliver the butadiene **374** as the major product.[147]

Scheme 80



We had envisioned that the dienic moiety of **373** might be elaborated into an enone via a Wacker oxidation to deliver (**–**)-**115**. However, we recognized that the literature precedent did not support this plan, as there were no examples of the conversion of conjugated alkenes to enones under Wacker conditions. Rather, in one instance a stable palladium-diene species was isolated and characterized,[148] and in another an oxidative cleavage of a vinylic carbon-carbon bond to afford what appeared to be an aldehyde were reported.[149] Likewise, we were unable to oxidize the exocyclic olefin of

373 to a methyl ketone under any of the conditions provided in Table 10.[150] Instead, **373** (41-63%) was recovered in all instances.



373 (–)-**115**

Table 10

Entry	[Pd]	[Cu]	Solvent	T (^{o}C)
1	$PdCl_2$ (10 mol%)	$Cu(OAc)_2$ (20 mol%)	Me_2NAc/H_2O (7:1)	85
2	$PdCl_2$ (20 mol%)	$Cu(OAc)_2$ (200 mol%)	Me_2NAc/H_2O (7:1)	85
3	$PdCl_2$ (10 mol%)	CuCl (100 mol%)	DMF/H_2O (7:1)	65

Following these experiments, we concluded that the desired conversion of **353** to (**–**)-**115** via a Wacker oxidation would likely not be possible.[151] However, subsequent to these trials, Aggarwal reported the successful conversion of the azabicyclic diene **49** to the enone **51** under Wacker oxidations during a synthesis of (+)-ferruginine (Chapter 1.5.4). It is still unclear to us whether the absence of an oxygen atmosphere or an inherent conformational preference for the oxidation of the tropane-derived bicyclic diene contributed to Aggarwal's successful conversion of **49** to the enone **51** in light of our own failed attempts to effect this same transformation.

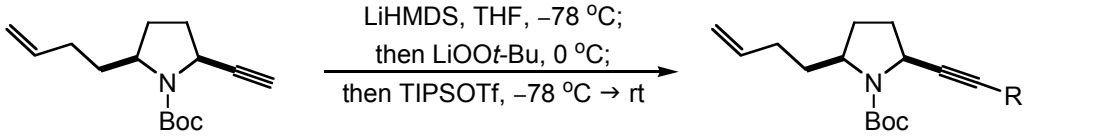
Additionally, we had contemplated arriving at the corresponding enal derivative via a selective ozonolysis of the exocyclic olefin. However, a literature search regarding regioselective ozonolysis reactions provided discouraging results in favor of the cleavage of the trisubstituted olefin of **373**.[152] In support of this finding, an attempt within our

group to selectively ozonolyze the exocyclic olefin of the indole derived diene **243** failed to produce any of the desired enal (*vide supra*).[153] This realization led us to reinvestigate a previously explored tactic to obtain anatoxin-a.

We renewed our efforts to prepare a siloxydiene metathesis precursor. In particular, we sought to assemble the enyne **375** possessing a Boc-carbamate, as we were confident that the Boc-group could be removed from the azabicycle following the RCEYM, using conditions that would also effect the deprotection of the silyl enol ether as was expected with substrate **363** (Table 7). Owing to the low yields obtained during previous attempts to perform the Kowalski siloxyalkyne homologation sequence on the corresponding isopropyl carbamate series, we turned our attention to an alternative method for the preparation of the requisite enyne **375**.

We attempted to trap the lithium acetylide of **372** with lithium *t*-butyl hydroperoxide (Scheme 81).[154,155] The resulting alkynoate was to be quenched with TIPSOTf to deliver the siloxyalkyne **375**. Unfortunately, after several attempts to effect the desired transformation, only the silylalkyne **376** was produced.

Scheme 81



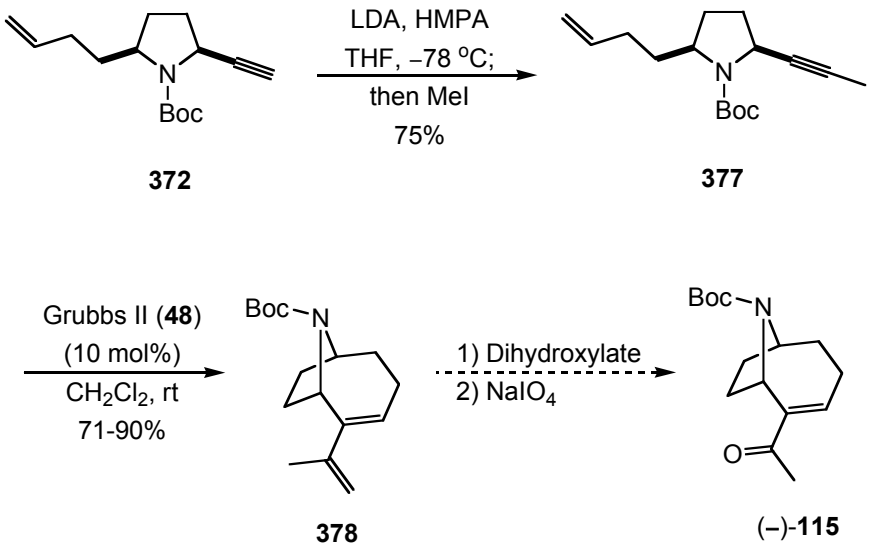
372

375: R = OTIPS (0%)
376: R = TIPS (68%)

A final strategy was envisioned for the preparation of a suitable metathesis precursor containing the necessary functionality for the installment of requisite methyl ketone found in anatoxin-a. The small quantity of **372** that remained following our

attempted preparation of **375** was converted to the propyne **377** using standard conditions (Scheme 82). The RCEYM of **377** to the bicyclic diene **378** was achieved upon exposure to the Grubbs second-generation catalyst **48**. With a small quantity of **378** in hand, we then sought to effect the regioselective dihydroxylation of the pendant isopropenyl group. We then envisioned that the resulting diol would be cleaved *in situ* to provide (**–**)-**115**. Ultimately, the minute quantity of **378** obtained from the metathesis reactions precluded its use in any subsequent transformations.

Scheme 82

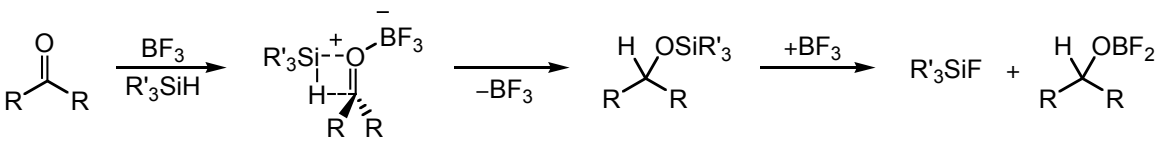


3.7 A NEW BORON LEWIS ACID CATALYZED PYRROLIDINE ROUTE

Clearly one of the major drawbacks of the *N*-Boc pyrrolidine route to anatoxin-a was our inability to prepare the key intermediate **368** in a suitable yield owing to the irreproducibility of the L-Selectride reduction step on scale (Table 9). At this point, we wondered whether our original silane-mediated reduction protocol could be modified to allow for the generation of **365** or **368** without effecting the deprotection of the carbamate. A possible explanation for the lability of the Boc-group led us to investigate

the nature of the reducing species in solution. Mechanistic studies have shown that BF_3/silane reductions of ketones initially proceed via coordination of the BF_3 to the Lewis basic carbonyl oxygen to generate the oxonium ion **380** that is subsequently reduced by the silane via the four-membered transition state structure **381** (Scheme 83).[156] It is believed that the resulting silyl ether then reacts with BF_3 to produce the fluorosilane **382** and difluoroborate ester **383**. The intermediate **383** may then be hydrolyzed to afford the alcohol or further reduced to an alkane.

Scheme 83

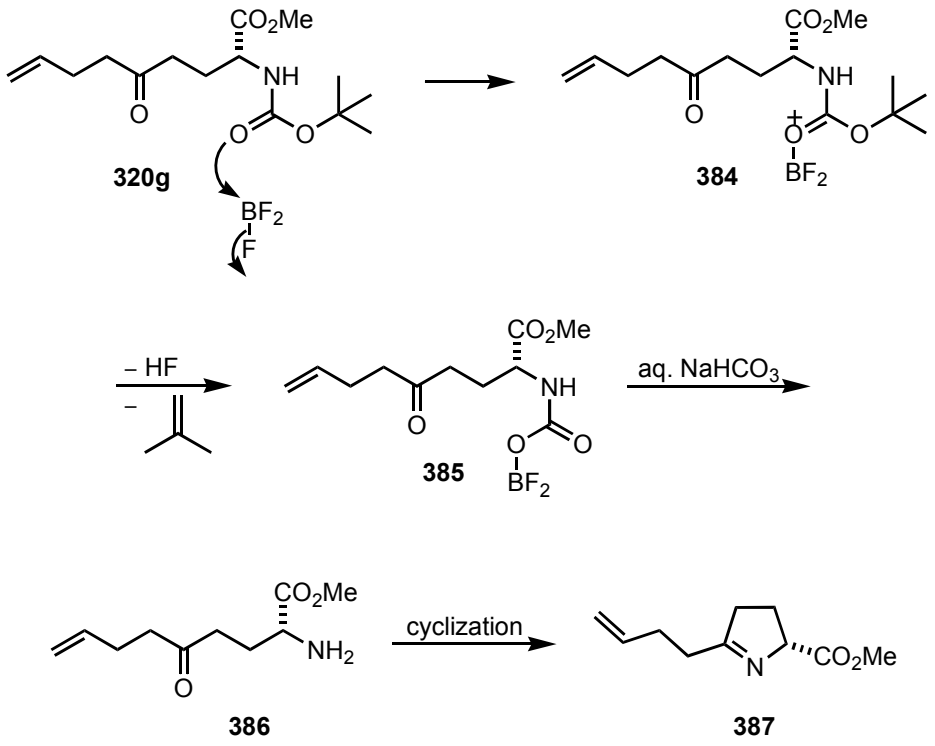


379 **380** **381** **382** **383**

As it is known that esters and amides are inert to reduction by the combination of $BF_3{\cdot}OEt_2$ and Et_3SiH,[156a] we were inclined to rule out the possibility that a mechanism similar to the one presented in Scheme 83 was operative in the reduction of the Boc-carbamate. Our notion was further supported by the stability of the methyl and isopropyl carbamates to this set of reducing conditions. Having ruled out the possibility that the carbamate was removed by acid liberated during the cyclization and reduction event (*vida supra*), we sought an alternative rationale for the loss of the Boc-group.

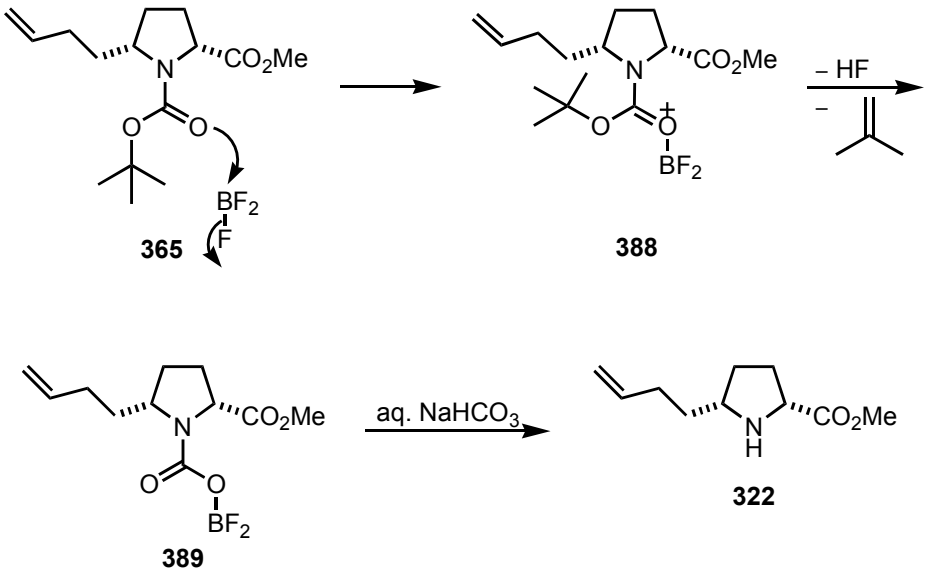
In our substrates, the most Lewis basic oxygen atom is present in our carbamate. If free BF_3 coordinates with this carbonyl prior to the cyclization event, the fluoride ion initiated loss of isobutylene from intermediate **384** and subsequent hydrolysis of the difluoroborate ester **385** would liberate the imine **387** upon hydrolysis according to Scheme 84.

Scheme 84

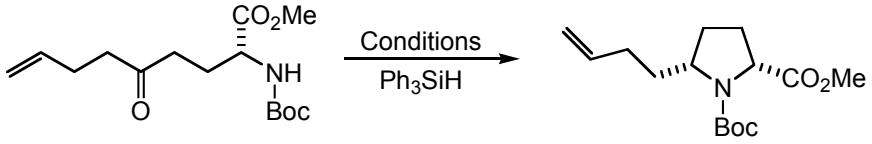


However, the amine **322** was isolated instead, suggesting that the loss of the carbamate occurs after the cyclization-reduction event according to Scheme 85.

Scheme 85



One possible solution to prevent the liberation of reactive fluoride ion believed to be responsible for the carbamate cleavage was to change the Lewis acidic species present in solution. The results of the cyclization-reduction experiments employing alternative Lewis acids are presented in Table 11.



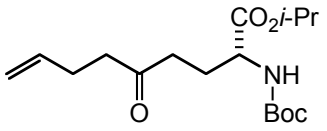
320g **365**

Table 11

Entry	Lewis Acid	Equiv.	Solvent	T (°C)	Time (h)	% Yield
1	$BF_3 \cdot OEt_2$	6.0	CH_2Cl_2	−78 → 25	5	44 (**322**) 3 (**365**)
2	$BF_3 \cdot OEt_2$	6.0	CH_2Cl_2	−78	3	68 (**320g**)
3	$BF_3 \cdot OEt_2$	6.0	THF	−78 → 25	5	22 (**365**) 48 (**303g**)
4	$B(O\textit{i}\text{-}Pr)_3$	2.2	CH_2Cl_2	−78 → 25	5	NR[b]
5	Bu_2BOTf	6.0	CH_2Cl_2	−78 → 25	19	IM[c]
6	Et_3B	6.0	CH_2Cl_2/hexanes	−78 → 25	20	NR[c]
7	Et_2AlCl	2.2	PhMe	−78 → 25	8	IM[c]
8	$TiCl_4$	1.0	CH_2Cl_2	−78 → 25	8	IM[c]
9	$Ti(O\textit{i}\text{-}Pr)_4$	2.2	CH_2Cl_2	−78 → 25	7	**390**[a]
10	LiBr	2.2	THF	−78 → 25	8	NR[b]
11	$MgBr_2$	6.0	CH_2Cl_2/Et_2O	−78 → 25	14	47 (**387**)
12	5M $LiClO_4$	20.0	Et_2O	−78 → 25	15	IM[b]
13	$Sm(OTf)_3$	3.0	Et_2O	−78 → 25	19	IM[b]
14	TMSOTf	2.5	CH_2Cl_2	−78 → 25	8	**322**[a]

[a] Yield not determined due to the presence of inseparable impurities.
[b] NR = No reaction as evident by TLC comparison to authentic materials.
[c] IM = Intractable Mixture.

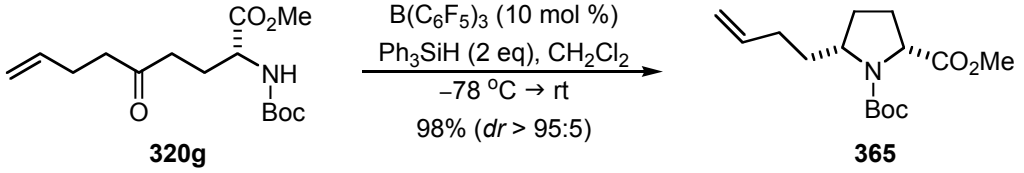
Unfortunately, the majority of trials failed to produce any of the desired *cis*-pyrrolidine **365**. Instead, the experiments typically resulted in either no consumption of the ketone **320g**, or in the isolation of baseline mixtures that could not be identified. The absence of any **365** formed from the reactions employing Lewis acids other than $BF_3 \cdot OEt_2$ led us to believe that these reagents were either incapable of promoting the cyclization of ketone **320g** to generate an iminium ion or were too harsh to permit the survival of the carbamate. Of interest are the entries 1-6, where the subtle attenuation of the Lewis acidity of the boron species had a profound effect on the product distributions. Furthermore, we found that very little reaction occurs at –78 ^{o}C (entry 2). Later experiments confirmed that the consumption of starting material leading to the appearance of baseline mixtures began to occur in the temperature range between –30 → –20 ^{o}C. Additionally, the transesterification product **390** was obtained when Ti(O*i*-Pr)$_4$ was employed as the Lewis acid (entry 9).



390

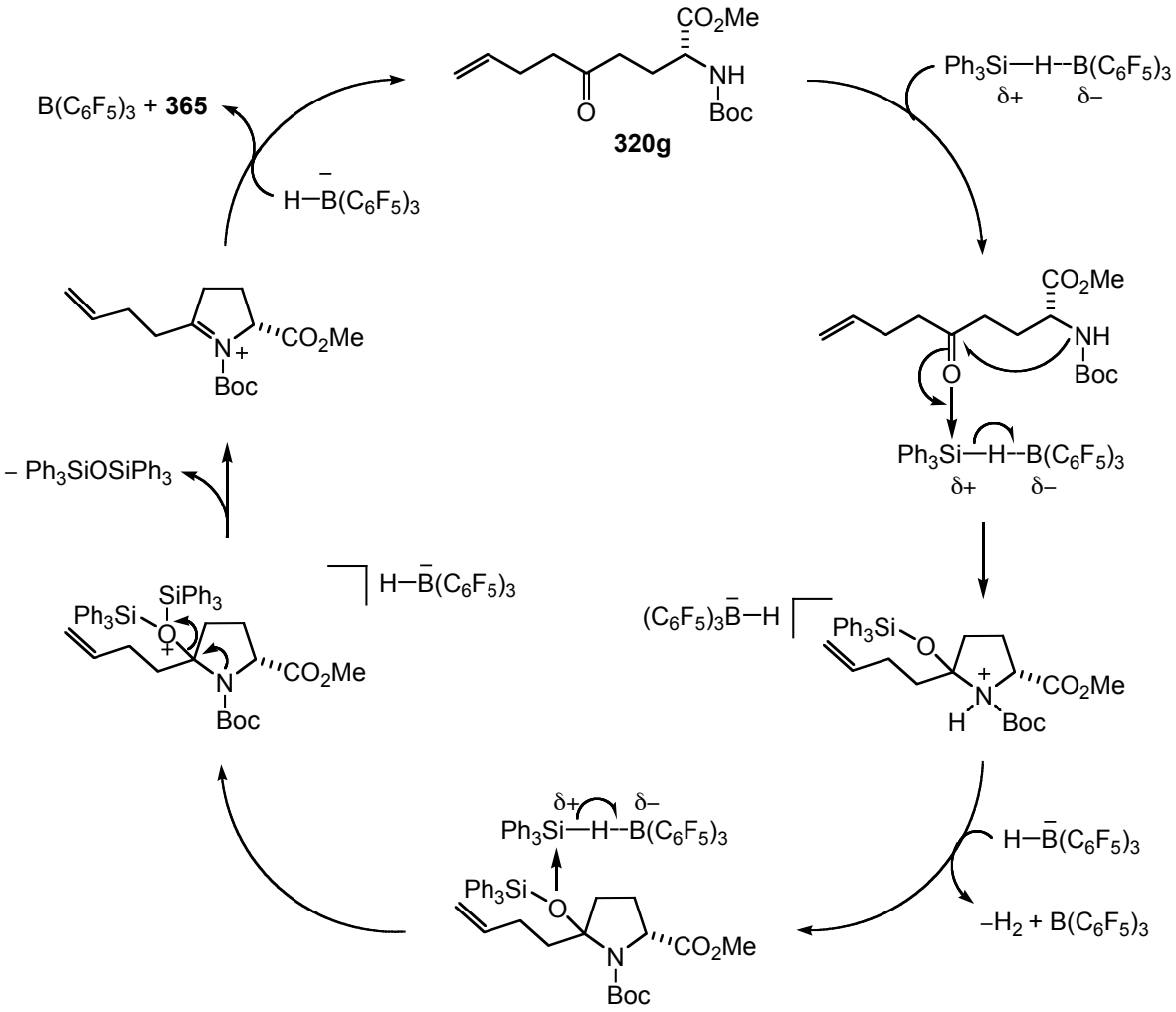
We later found that the Lewis acid $B(C_6F_5)_3$ [tris(pentafluorophenyl)borane], which exhibits Lewis acidity comparable to BF_3,[157] without the problems associated with reactive B-F bonds, could be used to prepare **365**.[158] The combination of Ph_3SiH and a catalytic amount of $B(C_6F_5)_3$ promoted the smooth conversion of the Boc-protected ketoamide **320g** to **365** in high yield and >95:5 *cis*-diastereoselectivity (Scheme 86).

Scheme 86



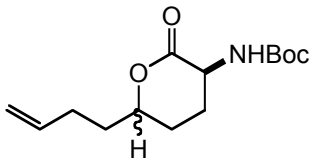
A mechanistic proposal to account for the successful transformation of **320g** to **365** in the presence of a catalytic portion of $B(C_6F_5)_3$ is proposed in Scheme 87.

Scheme 87



Other groups have determined that the active reducing agent generated during the reaction of $B(C_6F_5)_3$ and various silanes is the hydridoborate species $[HB(C_6F_5)_3]^-$.[159] This reductant is formed via the bridging ate-complex $[R_3Si\text{-}H\text{-}B(C_6F_5)_3]$, which has been observed spectroscopically. It the context of carbonyl and alcohol reductions, it has been shown that the silicon atom (as the silylium ion) of this complex serves to activate the oxygen atoms of the species to be reduced, resulting in the formation of bis(silyl)ethers. In accord with this proposal, we have isolated $Ph_3SiOSiPh_3$ from the reactions employing Ph_3SiH as the hydride source. Also in accord with the proposed mechanism, the conversion of **320g** to **365** requires at least two equivalents of Ph_3SiH to reach completion.

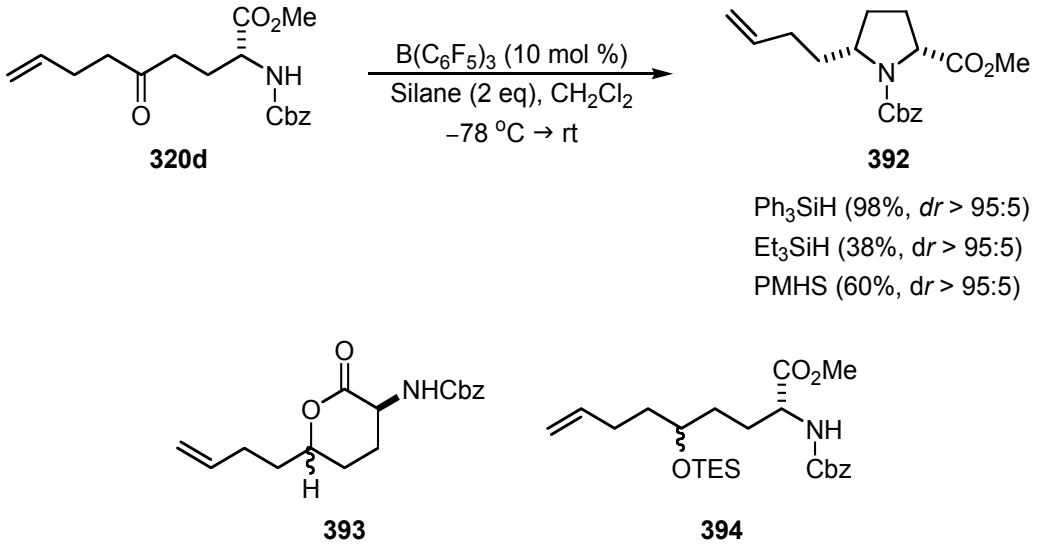
The excellent diastereoselectivity obtained during the reduction of the transient iminium ion by $[HB(C_6F_5)_3]^-$ correlated well with the results obtained from the cyclization and reduction reactions of the methyl and isopropyl-protected ketocarbamates in the presence of $BF_3{\cdot}OEt_2$ and Ph_3SiH. Furthermore, as the active reductant is the hydridoborate $[HB(C_6F_5)_3]^-$, we reasoned that a less expensive and more atom economical silane than Ph_3SiH might be employed as a hydride source. The cyclization and reduction protocol employing 10 mol% of $B(C_6F_5)_3$ and excess Et_3SiH (2-4 equivalents) also provided **365** in 90% yield (*dr* >95:5) along with 6% of the lactone **391** (*dr* = 2:1).



391

With a new catalytic method for the preparation of **365** in hand, we sought to expand the scope of this process to accommodate additional ketocarbamates. As such, the Cbz-protected ketone **320d**, which had been made available in quantity earlier, was used to evaluate the generality of the method. Application of the same procedure to the Cbz-protected compound **320d** provided the *cis*-pyrrolidine **392** in 98% yield (*dr* > 95:5) when Ph_3SiH was employed as the hydride source (Scheme 88). The, reactions carried out with Et_3SiH provided significant quantities of the diastereomeric lactones **393** (43%, *dr* = 3.8:1) and the hydrosilylation adduct **394** (6%). Experiments employing the even less expensive polymeric hydride source polymethylhydrosiloxane (PMHS) provided **392** in 60% yield along with 9% of the lactone **393**. The hydrosilylation adduct **394** was not observed.

Scheme 88



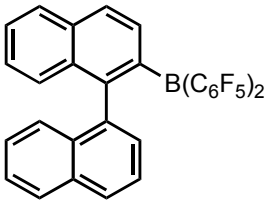
We rationalized the decreased yields of **392**, which are accompanied by substantial byproduct formation, to be the result of the increased reactivity of the Et_3SiH and PMHS derived boron ate complexes with respect to sterically more demanding

Ph_3SiH complex. Mayr has shown that the front strain (or steric interaction incurred during coordination) associated with hydride abstraction from Ph_3SiH by carbenium ions is greater than that for Et_3SiH, and thus the reactivity of the more sterically hindered silanes is decreased in such transfer processes.[160] By analogy, the slower rate of hydride transfer between Ph_3SiH and $B(C_6F_5)_3$ should result in the slower generation of $[HB(C_6F_5)_3]^-$.

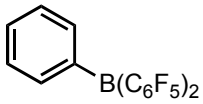
However, a more important factor contributing to the reactivity differences may be the transition state stabilization of the silicenium ion character on silicon during the rate-limiting hydride transfer step to boron. Mayr has also shown that trialkyl-substituted silicenium ions are inductively stabilized to a greater extent than the triaryl analogs since π-conjugation plays only a minor role in stabilizing these intermediates. Although the experiment has not been performed, greater insight into the reactivity differences may be obtained if the cyclization-reduction protocol is conducted with *n*-Bu_3SiH or *n*-Hex_3SiH, as these alkyl groups should provide even greater inductive stabilization to a transient silicenium ion thereby increasing the rate of hydride transfer to $B(C_6F_5)_3$. Should a decreased yield of **392** be obtained using these silanes relative to Et_3SiH, the inductive argument proposed to account for the reactivity differences observed between the triaryl- and trialkylsilanes would be corroborated to some extent, although a combination of electronic and steric factors are most likely operative in these transformations.

Pleased with out initial success in effecting the desired cyclization-reduction protocol with the ketoamides **320d** and **320g** to give **392** and **365** respectively, we wished to explore the role played by the size and Lewis acidity of the boron catalysts in controlling the diastereoselection of the overall process. Toward this end, the boron

Lewis acids **395** and **396** were obtained as a generous gift from Professor Warren Piers of the University of Calgary.



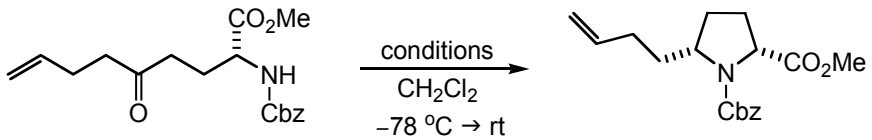
(±)-**395**



396

We envisioned that the large binaphthyl ligand present in catalyst **395** would increase the preference of the corresponding hydridoborate species to reduce the transient iminium ion from the less sterically encumbered face opposite the C-2 pendant ester moiety. Catalyst **396** was tested in order to ascertain whether a less Lewis acidic analog of $B(C_6F_5)_3$ might moderate the reactivity of the catalyst system so as to prevent the formation of the undesired side-products **393** and **394**. The results of the experiments utilizing **320d**, and the various silanes and Lewis acid catalysts are presented for comparison in Table 12.

As expected, the diastereoselectivity of all the reactions was uniformly high. Indeed, the use of the less Lewis acidic (and hence less electrophilic) catalysts **395** and **396** minimized the extent to which the side-products **393** and **394** were formed when utilized in conjunction with Ph_3SiH, but these reactions failed to proceed to completion, resulting in the recovery of **320d** and the formation of intractable baseline materials. Based on these results, and the ease of handling and commercial availability of $B(C_6F_5)_3$, this boron Lewis acid was used for all subsequent reductions.



320d **392** (*dr* > 95:5)

Table 12

Entry	Lewis Acid	Silane	**392** (%)	Rsm (%)	Side Product (%)
1	$BF_3 \cdot OEt_2$	Ph_3SiH	99	0	0
2	$B(C_6F_5)_3$	Ph_3SiH	94	0	0
3	$B(C_6F_5)_3$	Et_3SiH	38	0	43 (**393**) 16 (**394**)
4	$B(C_6F_5)_3$	PMHS	60	0	9 (**393**)
5	**395**	Ph_3SiH	42	44	7 (**394**)
6	**395**	Et_3SiH	trace	0	IM[a]
7	**396**	Ph_3SiH	77	21	0

[a] IM = Intractable Mixture.

In an effort to expand the scope of this new catalytic cyclization-reduction protocol, we wished to determine whether $B(C_6F_5)_3$ could efficiently transfer other nucleophiles to iminium ions. We reasoned that silanes of general structure R_3SiX, in which "X" is a group capable of forming a bridging ate complex with the catalyst might also be transferred in the same fashion as hydride. To test this hypothesis, substrate **320d** was treated with the combinations of $B(C_6F_5)_3$ and silanes possessing bridging azide and nitrile ligands (Table 13). As of yet, only the nitrile and azide ions were screened due to convenience and their utility in subsequent synthetic transformations.

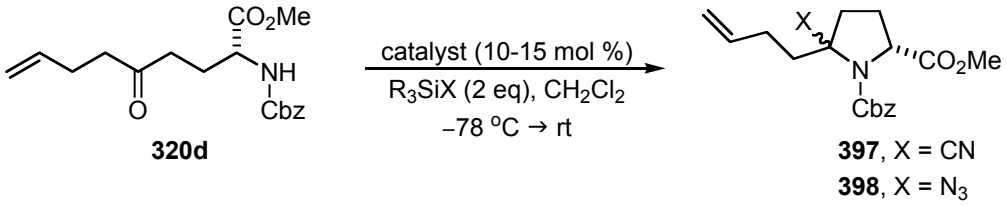


Table 13

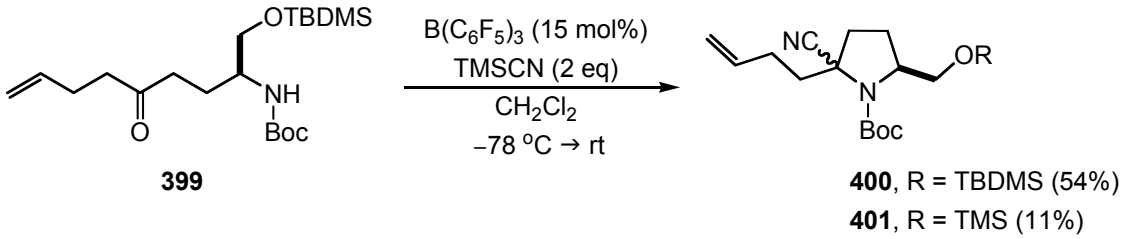
Entry	Lewis Acid	R_3SiX	**397** or **398** (%)	*dr*[a]	Rsm (%)
1	$BF_3{\cdot}OEt_2$	Ph_3SiCN	97	1.8:1	0
2	$B(C_6F_5)_3$	Me_3SiCN	66	1.1:1	27
3	**395**	Me_3SiCN	94	1.2:1	0
4	**396**	Me_3SiCN	90	1.3:1	0
5	$B(C_6F_5)_3$	*t*-$BuMe_2SiCN$	96	1:1	0
6	$B(C_6F_5)_3$	Me_3SiN_3	84	2:1	8

[a] Diastereomeric ratios obtained from the isolation of both pure diastereomers. However, assignment of the *cis*- or *trans*-relationships between the ester and unsaturated side-chain cannot be made as of yet.

Indeed we were able to add efficiently both nitrile and azide groups to the cyclic iminium ion generated from **320d**, albeit with poor diastereoselection. In all instances, the diastereoselectivity was low enough to be limit the utility of the current method from a synthetic standpoint regardless of catalyst system or silane employed. In entry 2, a low yield of **397** was obtained because the catalyst loading was lowered from 15 mol% to 10 mol%. Surprisingly, with catalysts **395** and **396**, the diastereoselectivity appears to be reversed in preference for the formation of the minor pyrrolidine product obtained from the sequences employing $B(C_6F_5)_3$ (entries 3 and 4). The reasons for this reversal in selectivity are still unclear. A more thorough study of the identity of the active catalyst in the reactions involving nitriles and azides might potentially provide insight into the nature of this phenomenon. We have however shown that $B(C_6F_5)_3$ efficiently provides the desired aminonitriles and aminoazides.

In an effort to circumvent this problem, we wished to determine whether a simple substrate modification could enhance the diastereoselectivity of these processes. To test this hypothesis, we replaced the methyl ester function for a much larger silyl protected hydroxymethyl group, with the idea that the larger C-2 substituent would improve the *cis*-selectivity (Scheme 89).

Scheme 89

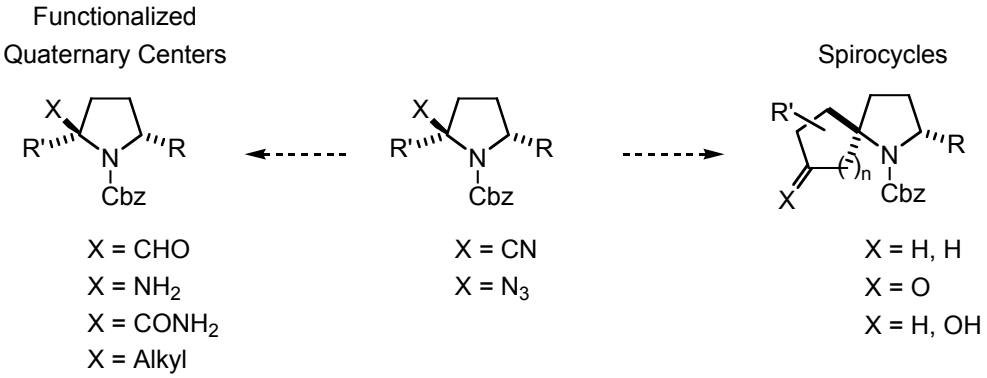


399

400, R = TBDMS (54%)
401, R = TMS (11%)

The results of an unoptimized process using the ketone **399**, which was prepared from **367**, are still inconclusive in part due to the silyl exchange reaction that led to the formation of **401**. Additionally, the diastereoselection could not be determined by simple ^{1}H-NMR analysis because attempts to separate **400** from **401** have yet to prove successful, while the deprotection of the mixture of silyl ethers was not attempted due to the small quantity of material isolated. This reaction should be repeated with TBDMSCN to determine whether **400** can be cleanly isolated. If high levels of diastereoselection can be achieved by substrate control, it should be possible to effect the diastereoselective construction of a variety of α-aminonitriles and azides that could be further elaborated to α-heteroatom quaternary centers, all carbon quaternary centers, or spirocyclic derivatives via reductive processes or by the generation of the stabilized α-aminoorganolithiums as demonstrated by Rychnovsky (Scheme 90).[161]

Scheme 90



3.8 MODIFICATION OF THE ORIGINAL *CIS*-PYRROLIDINE ROUTE

3.8.1 The Methyl Carbamate Series

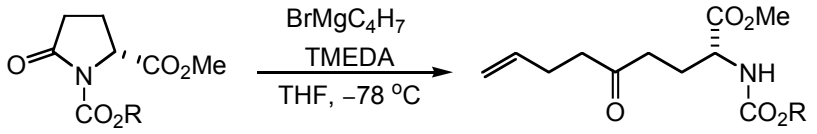
Prior to the development of the $B(C_6F_5)_3$ catalyzed method to prepare *cis*-pyrrolidines, our group conducted experiments with the purpose of optimizing the original synthetic protocol that Machauer had developed to prepare *cis*-pyrrolidines. During these studies, Rudolph found that the undesirable side-reaction leading to the deprotection of the carbamate protecting-group of **311** could be suppressed by the addition of *N*,*N*,*N'*,*N*'-tetramethylethylenediamine (TMEDA) to the solution of the Grignard reagent, thereby dramatically improving the yield of ketone **313**.[162] We believed the deprotection of the carbamate arose via the Lewis acidic activation of the carbamate carbonyl by free $MgBr_2$, resulting in attack at this position as opposed to the less Lewis basic lactam carbonyl. In tetrahydrofuran, Grignard solutions are known to exist predominately as a mixture of the monomeric species R_2Mg and MgX_2 according to the Schlenk equilibrium.[163]

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$

The complexation of RMgBr by TMEDA results in the formation of the complex RMgBr·TMEDA,[164] which does not disproportionate even under forcing conditions to R_2Mg and MgX_2.[163] As such, our reactions employing TMEDA should follow the same trend, resulting in the formation of C_4H_7MgBr·TMEDA free of $MgBr_2$ that would otherwise activate the carbamate carbonyl toward nucleophilic attack. Furthermore, the increased steric constraints of the diamine-Grignard complex may further contribute to the coordination of the organometallic reagent to the less hindered lactam carbonyl.

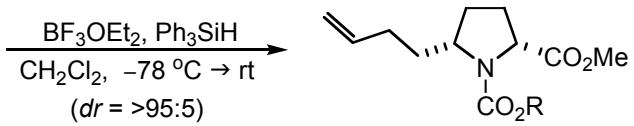
This amended Grignard addition protocol provided an opportunity to prepare additional *cis*-pyrrolidines in synthetically useful yields without the loss of the carbamate protecting groups. Hence, the methyl, ethyl and benzyl carbamate protected *cis*-pyrrolidines **315**, **404** and **392** were all explored for the preparation of a suitable metathesis precursor en route to anatoxin-a. The synthesis of these *cis*-pyrrolidines was accomplished according to the conditions summarized in Scheme 91.

Scheme 91



311: R = Me
402: R = Et
319d: R = Bn

313: R = Me (65%)
403: R = Et (88%)
320d: R = Bn (73%)

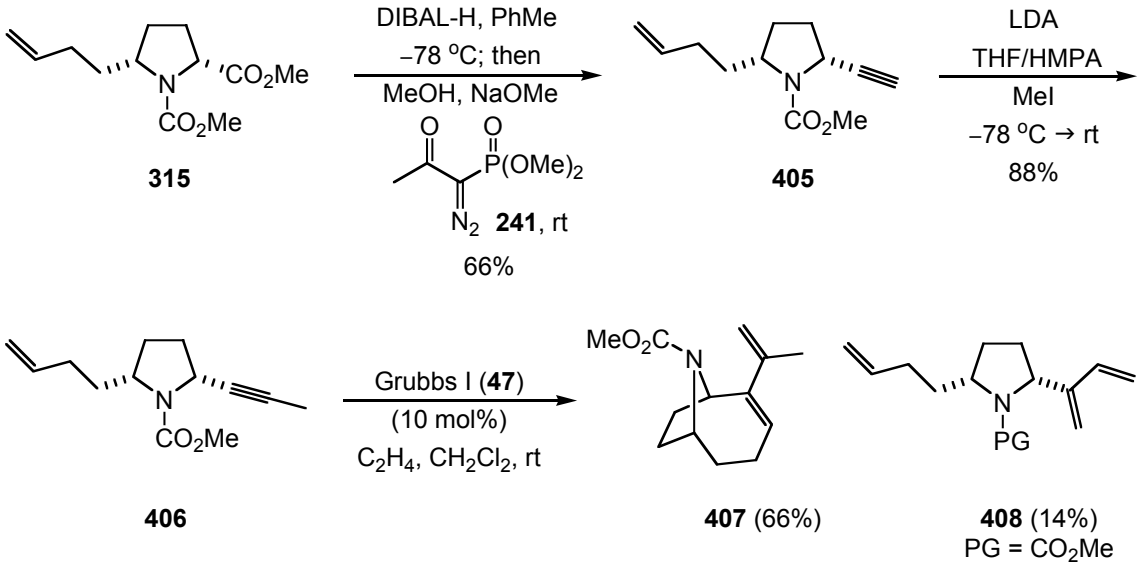


315: R = Me (94%)
404: R = Et (98%)
392: R = Bn (98%)

Treatment of the imides **311**, **402** and **319d** with 3-butenylmagnesium bromide in the presence of excess TMEDA (50 equivalents) afforded the corresponding ketones. Exposure of these ketones to Machauer's cyclization/reduction conditions produced the pyrrolidines in high yield and with excellent *cis*-diastereoselection (>95:5).

With the various *cis*-pyrrolidines in hand, we began our exploratory studies with the methyl carbamate protected substrate **315**. We chose the methyl carbamate-protected pyrrolidine as the removal of this carbamate from anatoxin-a had been documented.[33b,34] Compound **315** was elaborated to the enyne **405** using the one-pot homologation protocol discussed previously (Scheme 92). Alkylation of the corresponding lithium acetylide afforded the EYM precursor **406**. Exposure of **406** to the Grubbs first-generation catalyst **47** under an atmosphere of ethylene provided the azabicycle **407** along with some of the butadiene containing side-product **408**. We found it convenient to conduct the metathesis of the substituted alkyne **406** under an atmosphere of ethylene when the less reactive catalyst **47** was used. In the absence of ethylene, the RCEYM proceeded very slowly.

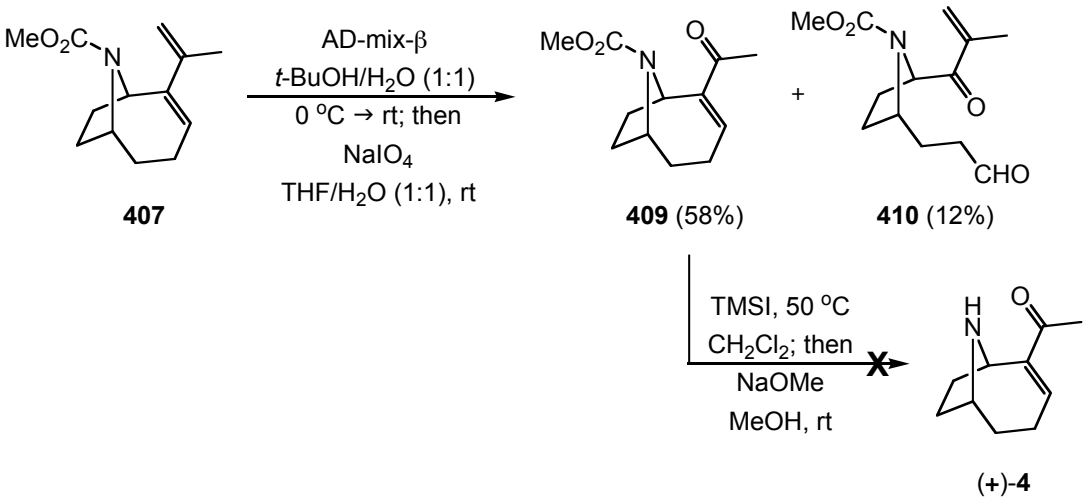
Scheme 92



In accord with our proposed strategy for the installation of the requisite methyl ketone moiety to substrate **378** (Scheme 82), the diene **407** was to be converted to the enone **409** using the Sharpless dihydroxylation protocol.[165] These conditions in particular were chosen in an effort to selectively dihydroxylate the less substituted olefin of the isopropenyl moiety. In support of this reasoning, Andrus has shown that the regioselective dihydroxylation of dienes can be effected using the Sharpless AD-mixes.[166] He has proposed that the selective osmylation of the least substituted olefin of a diene containing substrate occurs as a result of the sterically more demanding environment around the ligand-bound OsO_4 relative to unbound OsO_4. These findings were also corroborated by Sharpless in a related study.[167,168] Evaluation of the relevant literature suggested we utilize the AD-mix-β system to effect the desired one-pot dihydroxylation and cleavage sequence, as this system is particularly useful for the oxidation of 1,1-disubstituted olefins.[168] Furthermore, the β-mix, as opposed to the α-mix, was expected to preferentially access the more accessible *exo*-face of the isopropenyl moiety based on work by Sharpless and coworkers regarding the facial selectivities obtained with the various chinchona-based ligands utilized in the Ad-mixes.[168] As such, the dihydroxylation of **407** was conducted with AD-mix-β to provide the enone **409** along with some of the ketoaldehyde **410** following the periodate ion mediated cleavage of the resulting diols (Scheme 93). The ketoaldehyde **410** that resulted from the dihydroxylation of the cyclic olefin was removed by column chromatography to afford pure **409**, thereby completing a formal synthesis of anatoxin-a.[169] Unfortunately, the deprotection of the methyl carbamate using conditions reported in the literature[169] failed to produce any of the natural product. Rather an intractable tar was obtained

following an attempt to prepare the corresponding hydrochloride salt. It is likely that the decomposition of (+)-**4** occurred upon exposure of the free base to a strongly acid solution of methanolic HCl. However, we were unable to repeat the deprotection reaction to verify this hypothesis owing to the lack of any more **409**.

Scheme 93

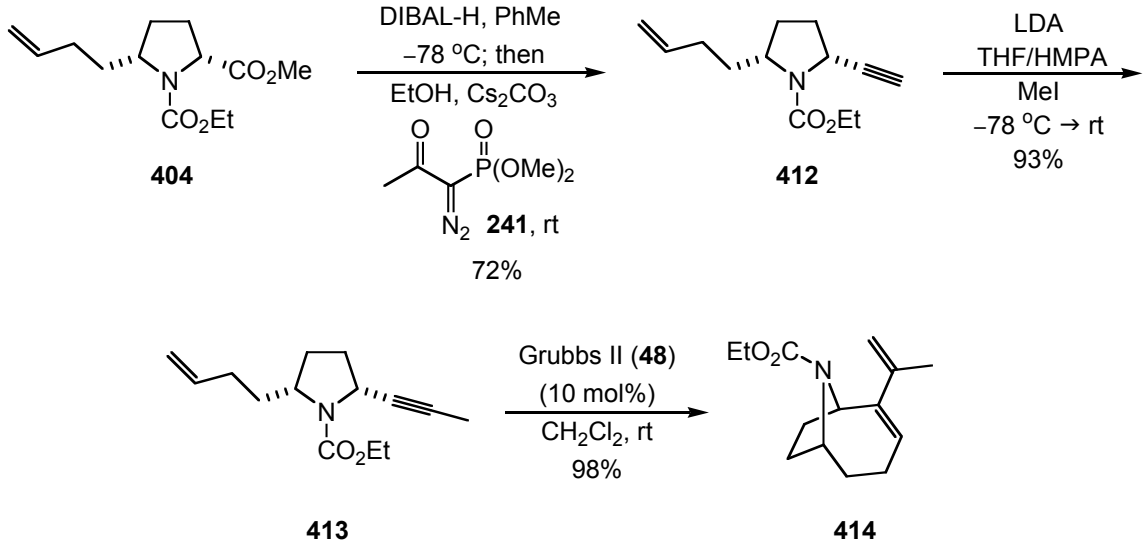


3.8.2 The Ethyl Carbamate Series

Though a successful formal synthesis of anatoxin-a [(+)-**4**] had been achieved using the methyl carbamate series of compounds, the dihydroxylation event to provide **409** proved less selective for the oxidation of the isopropenyl moiety than we had envisioned. Additionally, the yields obtained during the initial phases of the synthetic protocol leading to (+)-**4** were lower than those obtained with either the ethyl or benzyl carbamate protected substrates. As such, we chose to utilize the *cis*-pyrrolidine **404** in an attempt to improve the overall yield of the series of transformations leading to (+)-**4**, and to provide suitable quantities of material to determine the optimal conditions for the removal of the carbamate protecting-group.

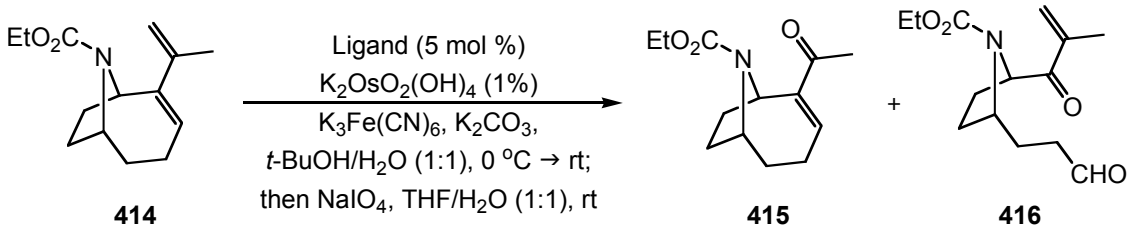
Compound **404** was converted to the enyne **412** using a modified version of our original one-pot alkyne homologation procedure (Scheme 94). The new protocol was adopted in order to minimize the extent of epimerization (6-14%) that had been observed at the C-2 stereocenter when the homologation procedure was conducted in the presence of preformed sodium ethoxide (NaOEt). The deprotonation of ethanol by Cs_2CO_3 generated small quantities of ethoxide *in situ*, thereby decreasing the extent of epimerization to less than 5%. Transformation of **412** to the propyne **413** proceeded as before without incident. Exposure of **413** to the Grubbs second-generation catalyst **48** delivered the azabicyclic diene **414** in excellent yield. As catalyst **48** is more reactive than the Grubbs first-generation catalyst **47**, the reaction was carried out efficiently in the absence of ethylene.

Scheme 94



The improved yields of the route to **413** beginning with **404** allowed for the synthesis of ample quantities of **414** for the purpose of determining the optimal protocol for the regioselective dihydroxylation of the isopropenyl moiety. As such, the conversion

of **414** to the enone **415** was performed using a variety of readily available Sharpless ligands (Table 14). As was the case with diene **407** (Scheme 93), the ketoaldehyde **416** was also isolated in varying quantities depending on the ligand employed. Once again, AD-mix-β (entry 1) proved to be the most selective reagent combination for the cleavage of the exocyclic olefin, affording the enone **415** in nearly identical yield to **409**.



414 **415** **416**

Table 14

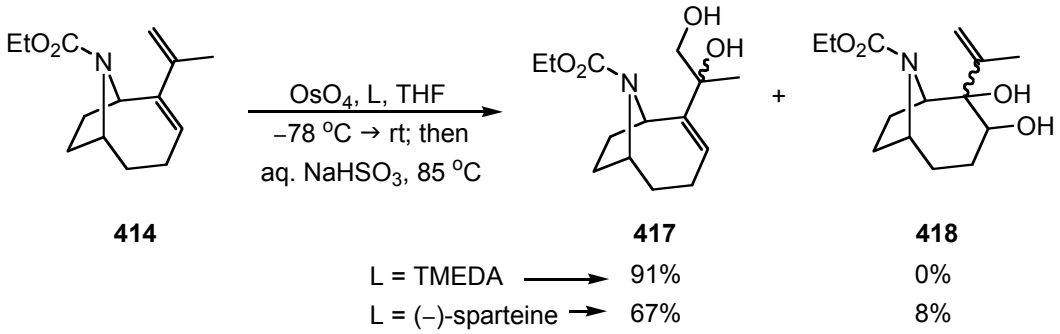
Entry	Ligand	Yield **415** (%)	Yield **416** (%)
1	$(DHQD)_2PHAL$	57	15
2	$(DHQ)_2PHAL$	13	38
3	$(DHQD)_2PYR$	3	75
4	$(DHQ)_2PYR$	36	54

Our inability to improve the regioselectivity of the osmylation processes governed by the Sharpless ligands forced us to investigate an alternative protocol to install the requisite enone. Namely, we wished to determine whether other amines could be used to improve the regioselectivity of the dihydroxylation. We were therefore intrigued by the work of Corey regarding the asymmetric dihydroxylation of olefins by chiral diamine complexes of OsO_4.[170] The complexes, which are stoichiometric in both OsO_4 and ligand form stable osmate esters following the proposed [3+2] cycloaddition with olefins. As such, the presence of free unligated OsO_4 is excluded. We reasoned that the chelation of OsO_4 with an appropriately sized amine ligand should provide an osmylation reagent

with sufficient steric bulk so as to render it incapable of accessing the more substituted and presumably more hindered cyclic olefin of our azabicyclic dienes.

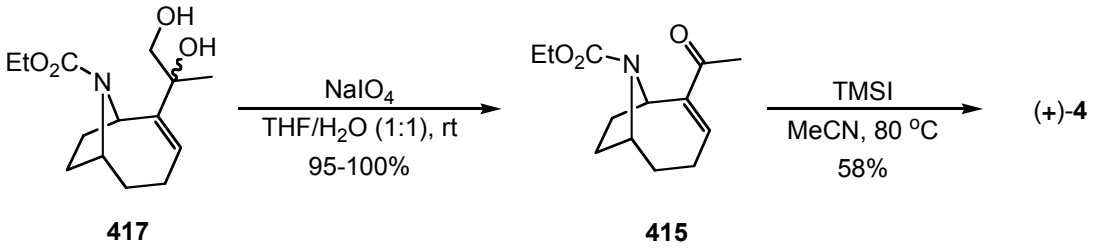
We began our investigations with the readily available diamines TMEDA[171] and (−)-sparteine. The osmium-complexes generated form both diamines were utilized to convert **414** to diol **417** (Scheme 95). The diol **417** was obtained exclusively in high yield using the TMEDA-derived osmylation system, whereas the (−)-sparteine complex afforded a small amount of the chromatographically separable undesired diol **418** and 12% of recovered **414**.

Scheme 95



With a reliable dihydroxylation process utilizing stoichiometric OsO_4 in hand, diol **417** was cleaved with sodium periodate ($NaIO_4$) to afford near quantitative yields of the enone **415** (Scheme 96). Subsequent *N*-deprotection of **415** was conducted according to a previously published procedure.[36c] Unfortunately, the yields of anatoxin-a [(+)-**4**] were substantially lower than those reported.[36c] Using freshly distilled iodotrimethylsilane (TMSI) from commercial sources in acetonitrile (MeCN) at 80 °C, a 58% yield of (+)-**4** was obtained after acid-base workup and column chromatography on silica (SiO_2). Generation of TMSI *in situ* according to the method of Olah[172] also provided (+)-**4** in yields ranging from 35-47%.

Scheme 96

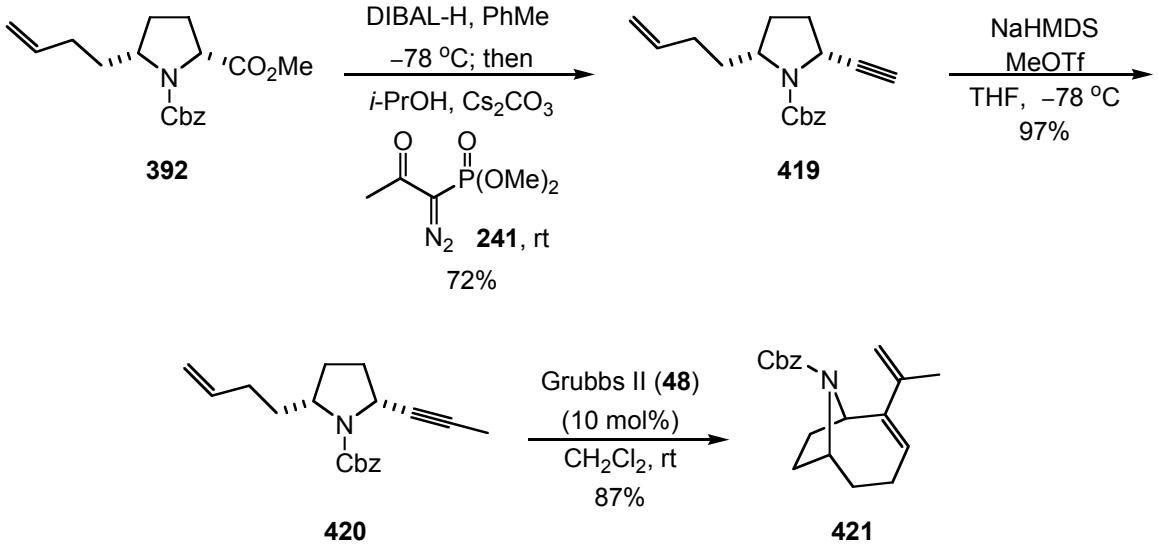


In all instances, the reaction mixtures were highly complex after prolonged heating, and extensive purification was required. Exhaustive purification strategies were impractical owing to the incredible instability of (+)-**4** to light.[173] In accordance with the literature, proton-NMR spectra taken at varying time increments confirmed that the light-induced decomposition of (+)-**4** was occurring. To complicate matters further, attempts to directly convert the crude free-base to the corresponding hydrochloride or fumarate salts were unsuccessful, resulting in the formation of brown tars. Ferguson and coworkers observed a similar phenomenon during the deprotection of Boc-anatoxin with ethereal HCl at temperatures above 50 ^{o}C.[174] We believed that the elevated temperatures required to remove the ethyl carbamate produced a number of decomposition products as evident by TLC analysis. Also, the light-induced decomposition of (+)-**4** during the purification of the complex reaction mixtures further contributed to the diminished yields of the free base. Our solution to this problem was to utilize the Cbz-protected *cis*-pyrrolidine **392** in an analogous sequence of events leading to (+)-**4**, as this protecting group is readily cleaved at low-temperature.

3.8.3 The Benzyl Carbamate Route to Anatoxin-a

The final optimized route for the preparation of (+)-**4** commenced with the one-pot conversion of *cis*-pyrrolidine **392** to the enyne **419** (Scheme 97).

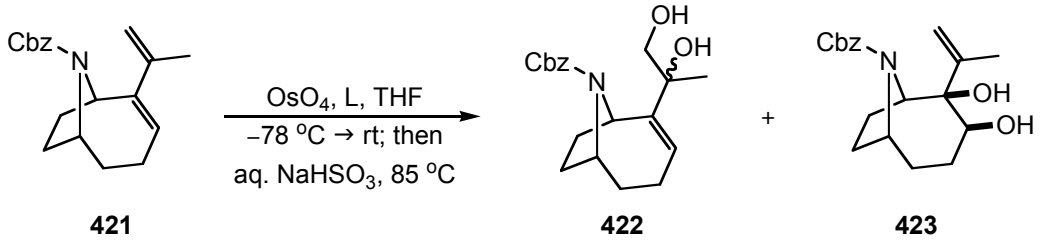
Scheme 97



In these experiments, we found that the use of isopropanol in place of ethanol during the homologation reaction led to the formation of the enyne **419** without any detectable epimerization of the C-2 stereocenter. Attempted methylation of the corresponding lithium acetylide following the protocol used for the methyl and ethyl carbamate series failed to produced the propyne **420** in greater than 22% yield. The production of highly polar compounds during the course of the reaction suggested a competitive deprotection process leading to the loss of the Cbz-group. We speculated that the loss of the Cbz-group occurred due to a faster attack of the lithium acetylide on the carbamate group than its alkylation with methyl iodide (MeI). Alkylation with methyl triflate (MeOTf) resulted in a marginal increase (41%) in the yield of **420**. The use of the corresponding sodium acetylide of **419**, which was generated with sodium hexamethyldisilazide (NaHMDS), provided a reliable and high yielding route to **420**. The RCEYM event was conducted using the Grubbs second-generation catalyst **48** to provide the azabicycle **421** in good yield. As with the ethyl carbamate series, we discovered that

the RCEYM to afford **421** proceeded most efficiently using the more reactive catalyst **48** in the absence of ethylene.

With **421** in hand, we attempted the same regioselective dihydroxylation protocol that had been used to prepare the diol **417**. To our surprise, only **421** was recovered from the reaction. However, the use of quinuclidine or Et_3N to ligate the OsO_4 afforded **422** in good yield along with a small amount of the undesired diol **423** (Table 15). As the results obtained with quinuclidine and Et_3N were essentially identical, all further dihydroxylations were conducted with the readily available and less expensive Et_3N.



421 **422** **423**

Table 15

Entry	Ligand	Yield **422** (%)	Yield **423** (%)
1	TMEDA	0	0
2	Quinuclidine	74	11
3	Et_3N	76	13

The stereochemistry of the diol **423** was established by X-ray crystallography (Figure 1). As expected, the osmylation event occurred via the more accessible *exo*-face of the cyclic olefin.

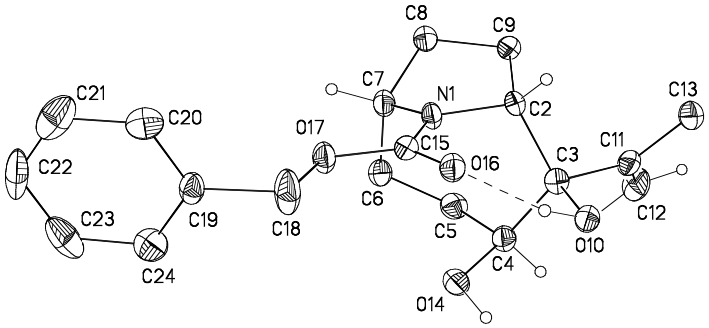
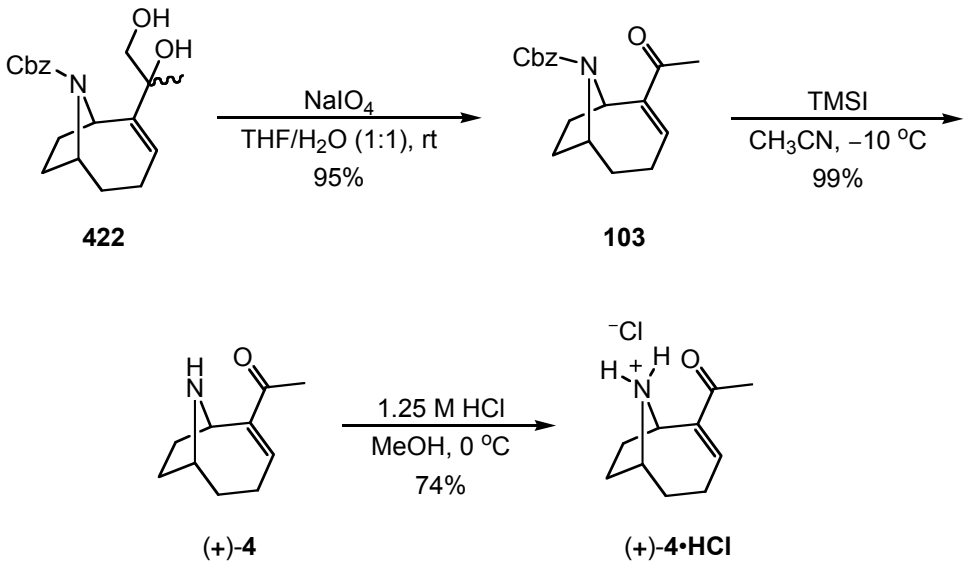


Figure 1. Crystal structure of diol **423**.

Following the chromatographic separation of the diols, pure **422** was transformed into the enone **103** (Scheme 98).

Scheme 98



The optical purity of **103** was established by comparison of its optical rotation [α_D^{26}] –36.1 (*c* 1.42, MeOH) to the literature value [α_D^{22}] –37.5 (*c* 1.12, MeOH) reported by Rapoport.[32b] The benzyl carbamate was quantitatively removed from **103** in less than

0.5 h at low temperature using TMSI and without any noticeable decomposition by TLC following an alkaline workup to remove silyl by-products.

The hydrochloride salt of (+)-**4** was prepared to prevent the light-induced decomposition of the free base. Slow recrystallization of the crude salt from 3% MeOH in Et_2O resulted in the formation of colorless prisms of pure (+)-**4·HCl** ($[\alpha]_D^{26}$ = +33.3 (*c* 2.08, abs. EtOH) (lit.[20] $[\alpha]_D^{24}$ = +36.0 (*c* 0.85, abs. EtOH)). All of the characterization data for (+)-**4** and (+)-**4·HCl** were consistent with those reported, and the structure of (+)-**4·HCl** was further confirmed by X-ray crystallographic analysis.[31,45]

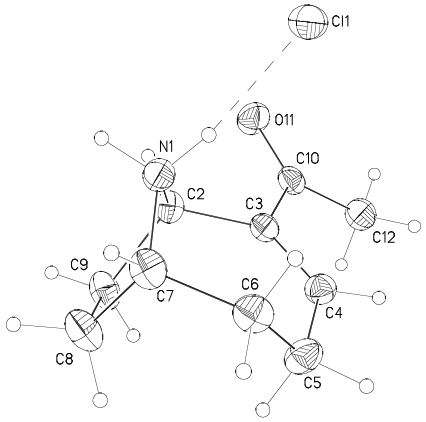


Figure 2. Crystal structure of (+)-anatoxin-a hydrochloride.

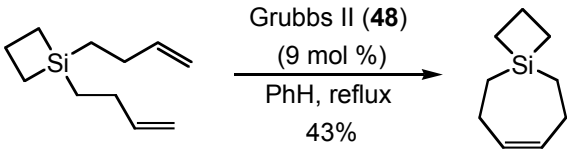
Our application of an intramolecular RCEYM strategy to prepare the azabicyclo[4.2.1]nonane skeleton allowed us to complete a practical and concise synthesis of anatoxin-a.[175] The sequence, which featured the first application of a RCM event to form the azabicyclo[4.2.1]nonane skeleton, proceeded in only nine chemical operations and in 27% overall yield from commercially available **310**.

Although we were pleased with our successful application of an intramolecular RCEYM approach to the azabicyclo[4.2.1]nonane skeleton, we felt that our route to

anatoxin-a could be further shortened if a more concise method for the introduction of the requisite enone moiety could be developed. Our goal was to utilize the readily oxidized methyl silacyclobutyl moiety as a masked methyl ketone group. Recent examples by Dudley and coworkers had shown that methyl silacyclobutanes undergo facile Tamao oxidation under mild conditions (KF, 30% H_2O_2).[176] It was our goal to install this silyl group prior to the key metathesis step and then to oxidatively cleave the group to the desired methyl ketone of (+)-**4**, thereby reducing the length of our previous synthesis by one step.

Prior to undertaking of this approach, we found a single example of a ruthenium-catalyzed metathesis occurring in the presence of a silacyclobutane.[177] The reaction proceeded in low yield according to Scheme 99 to afford **425** without remark.

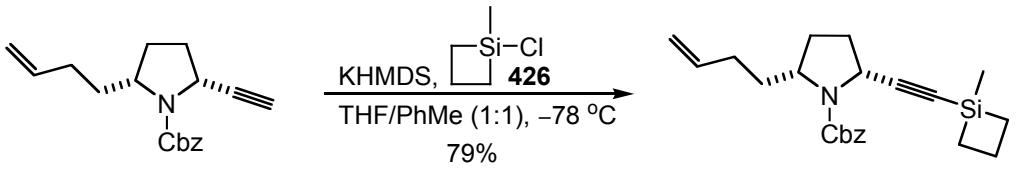
Scheme 99



424 **425**

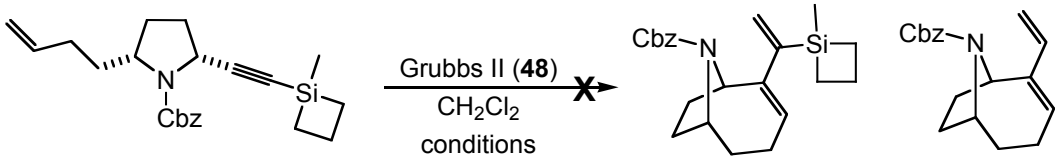
Encouraged by these results, we began our approach to a suitable metathesis substrate with the terminal acetylene **419**, which had been previously employed in our original synthesis of anatoxin-a. Alkylation of the potassium acetylide of **419** with chloromethylsilacyclobutane (**426**) proceeded in 79% yield to afford **427** (Scheme 100).

Scheme 100



419 **427**

Unfortunately, attempts to convert **427** to the azabicycle **3428** were unsuccessful (Table 16). Compound **427** was recovered as the major reaction component from metathesis trials conducted at room temperature. Elevation of the reaction temperature (50-80 °C) resulted in the predominate formation of the protodesilylated azabicycle **429** along with 9% of **419**. The isolation of **419** from the reactions carried out at elevated temperatures suggests a loss of the methylsilacyclobutyl group prior to metathesis.



427 **428** **429**

Table 16

Entry	**48** (mol %)	T (°C)	Rsm (%)	Yield **428** (%)	Yield **429** (%)
1	10	25	73	0	4
2[a]	21	50 → 80	8	0	76

[a] Reaction conducted at 50 °C for 26 h using 10 mol% of **48**, then an additional 11 mol% of **48** was added and the reaction temperature was increased to 80 °C for 22 h.

We were curious as to the pathway by which the protodesilylated compound **429** was formed. It is well-documented that metals such as Pt, Fe, Mn, Rh, and Ru oxidatively add to the Si-C bonds of strained silacycles, resulting in ring-opening polymerization reactions.[178] In particular, silacyclobutanes (estimated ring-strain = 24.5 kcal/mol)[179] have

been shown to readily undergo oxidative insertion reactions with transition metals at temperatures between 60-90 ^{o}C to form 1-metalla-2-silacyclopentanes; a decrease in ring-strain is postulated as the driving force for such a reaction.[178b] It is not unlikely that a similar oxidative insertion process is occurring in our substrate that results in loss of the silacyclobutyl moiety. Regardless of the mechanism, the use of the silacyclobutyl moiety as a masked ketone equivalent was not to be.

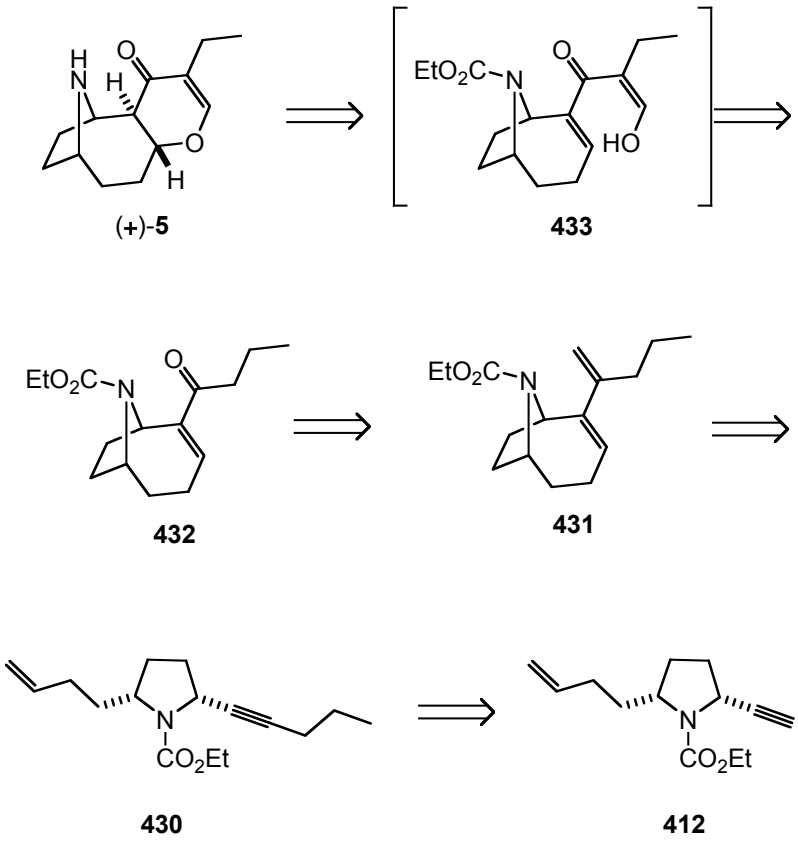
3.9 PROGRESS TOWARD THE SYNTHESIS OF (+)-PINNAMINE

3.9.1 Initial Synthetic Strategy

Commensurate with our efforts to prepare (+)-**4**, we undertook the synthesis of pinnamine [(+)-**5**]. In order to highlight the flexibility of our RCEYM approach to aza[4.2.1]bicyclics, we sought to utilize the advanced enyne intermediate **412** from our previous synthesis of anatoxin-a as a precursor for the construction of (+)-**5** according to the retrosynthesis provided in Scheme 101.[180] The ethyl carbamate protected series was employed during the initial synthetic strategy since our streamlined approach utilizing the Cbz-series had not yet been developed.

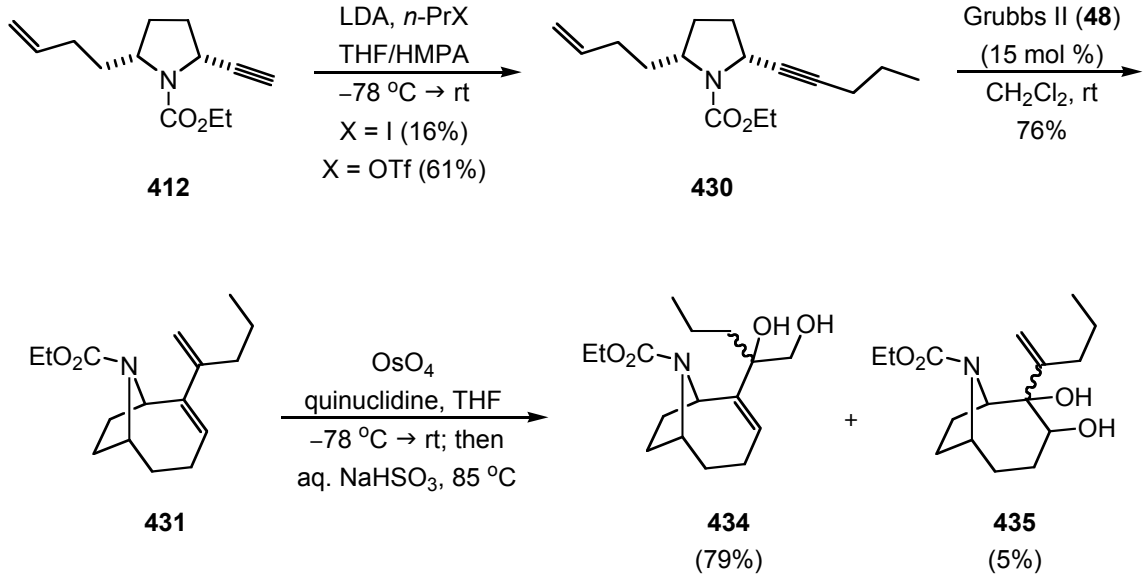
Alkylation of the terminal acetylenic moiety of **412** would afford the propyne **430**. The series of events required to convert **430** to the enone **432** would be analogous to those employed during the synthesis of anatoxin-a. Formylation of **432** was expected to furnish the vinylogous aldehyde **433**, which under ideal circumstances was envisioned to undergo an intramolecular oxo-Michael addition to produce the γ-dihydropyranone ring of pinnamine with the correct stereochemical arrangement following epimerization to the more stable *trans*-fused bicycle in the presence of acid.

Scheme 101



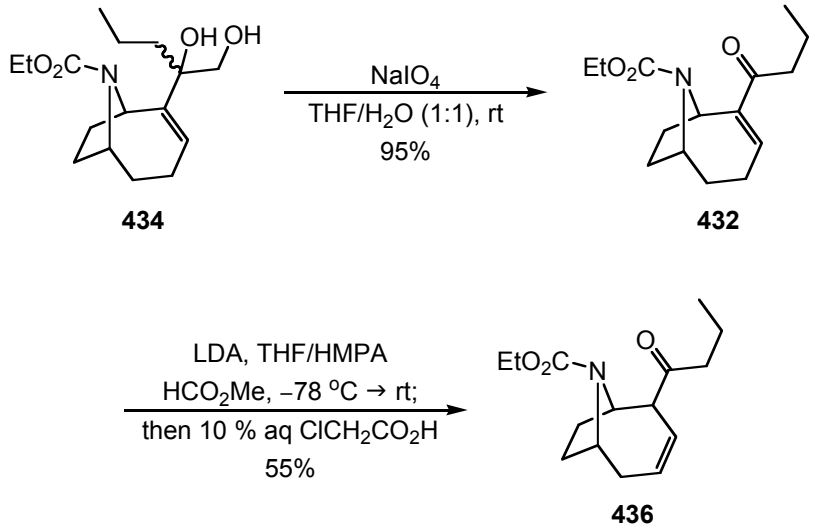
In a preliminary series of experiments, the alkylation of the lithium acetylide of **412** with *n*-propyl iodide (*n*-PrI) proceeded in low yield (14-16%) to produce **430**. The yield of **430** was increased to 61% when the acetylide was treated with *n*-propyl trifluoromethanesulfonate (*n*-PrOTf) (Scheme 102). The metathesis of **430** to the bridged-bicycle **431** was accomplished in 76% yield with the Grubbs second-generation catalyst **48**. Regioselective dihydroxylation with the complex generated between OsO_4 and quinuclidine provided the desired diol **434** along with a small quantity of the diol **435**.

Scheme 102



Following the separation of the isomeric diols, **434** was transformed into **432** upon exposure to the periodate ion (Scheme 103).

Scheme 103

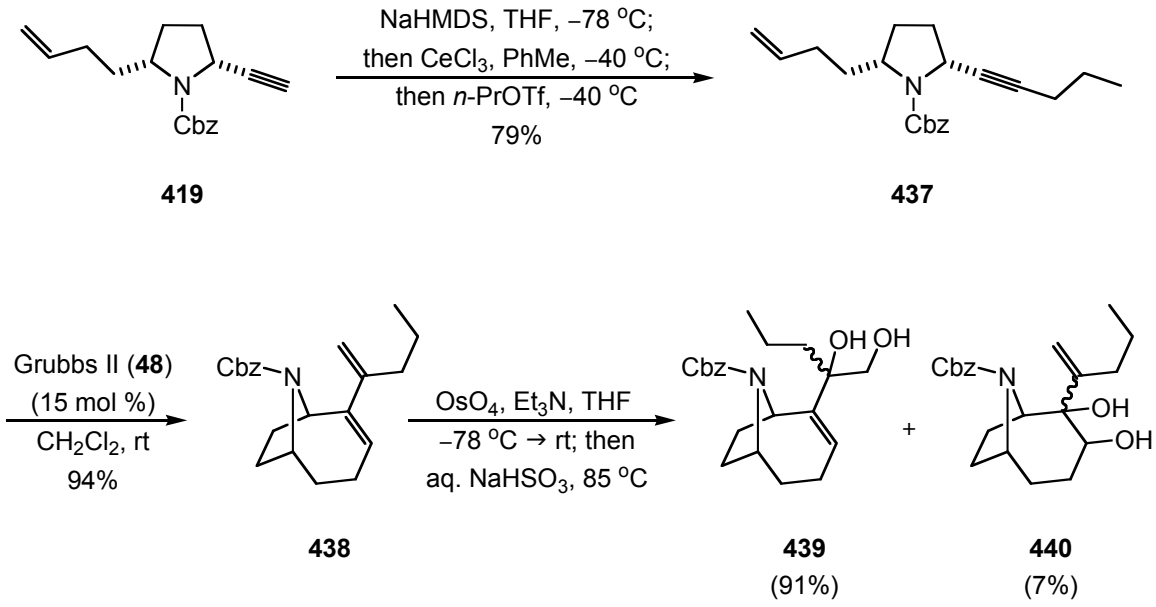


An attempt to prepare the γ-dihydropyranone ring via a cross-Claisen condensation with methyl formate (HCO_2Me)[181] led to mainly the formation of the

deconjugated ketone **436**. Although one could envision the isomerization of **436** to **432** in the presence of $RuCl_3$, an alternative strategy to obtain the tricyclic core of pinnamine was investigated.

At this stage, the newly developed route to the Cbz-protected series of substrates made the enyne **388** available for use. Hence, the alkylation of **419** was performed using the corresponding cerium acetylide and *n*-PrOTf (Scheme 104).

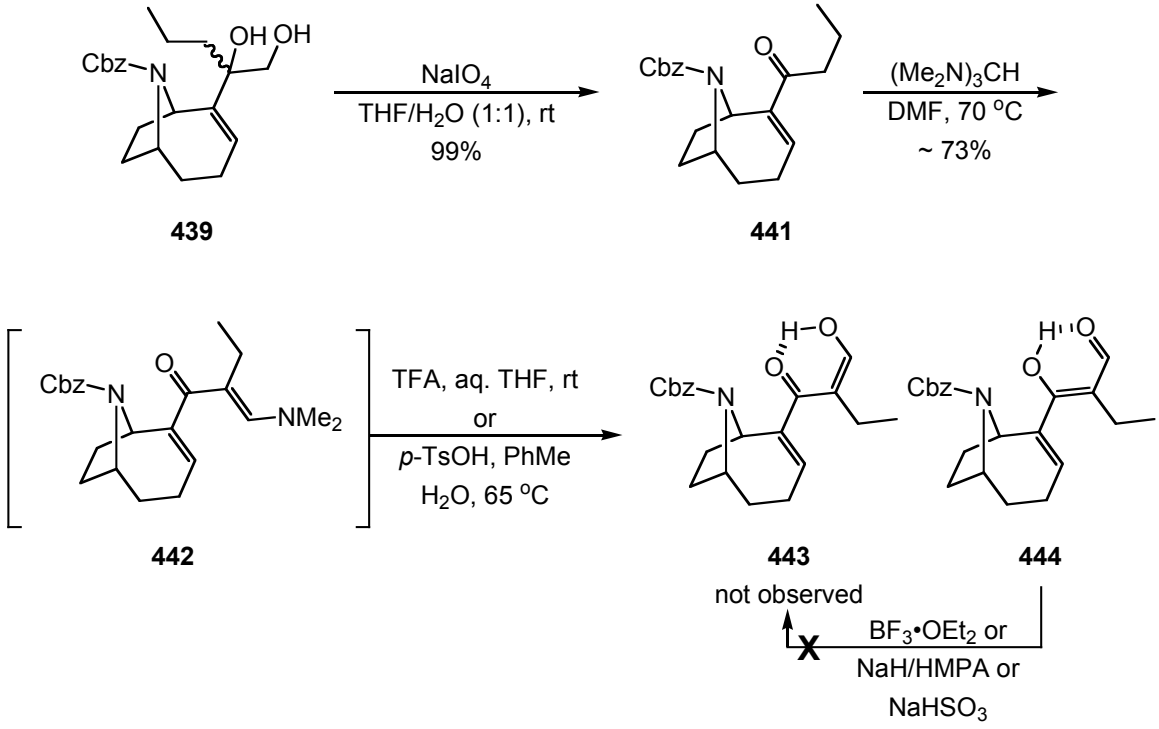
Scheme 104



The use of the sodium acetylide of **419** had been successfully implemented in our recent synthesis of anatoxin-a, but failed to provide satisfactory yields of the desired alkylation product **437**. The recovery of **419** from the alkylations employing large excesses of base and electrophile led us to speculate that the acetylide anion was quenched by the electrophile via a deprotonation-elimination pathway that generated propene. Transmetallation of the sodium acetylide to the less basic organocerate followed by alkylation with *n*-PrOTf resulted in reliably good yields of **437**. The RCEYM of **437**

was conducted without incident in the presence of the Grubbs second-generation catalyst **48**. Transformation of the isopentenyl side chain to a propyl ketone was performed using the complex obtained from the reaction of OsO_4 with Et_3N to provide the desired diol **439** in 91% yield along with the readily separable diol **440** in 7% yield. The use of quinuclidine in the dihydroxylation afforded **439** in 71% yield along with 20% of **440**, whereas *i*-Pr_2NEt produced **439** in 80% yield along with 13% of **440**. Following the separation of **440**, the pure diol **439** was cleaved to the enone **441** with the periodate ion (Scheme 105).

Scheme 105



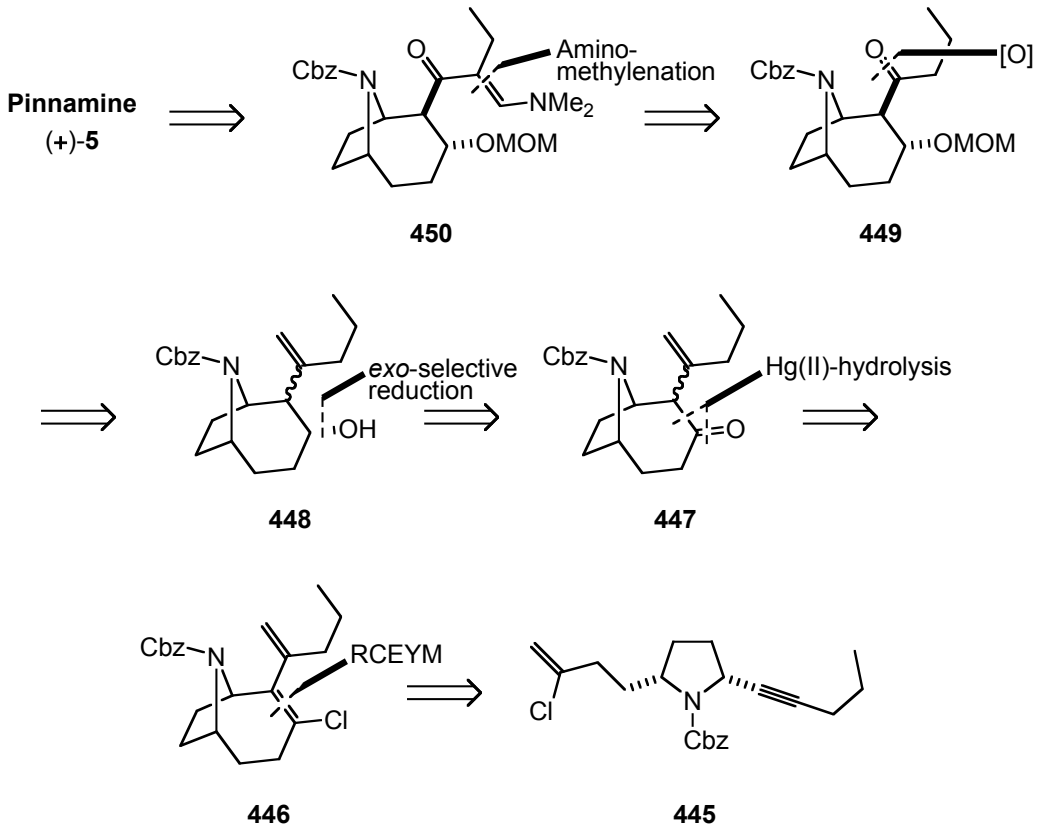
As part of an alternative approach to the formation of the γ-dihydropyranone ring, we treated enone **441** with tris(dimethylamino)methane [$(Me_2N)_3CH$] to afford the vinylogous amide **442**. Hydrolysis of the crude reaction mixture containing **442** with aqueous solutions of TFA or *p*-TsOH was expected to provide the intermediate enol **443**,

which under ideal circumstances would cyclize to form the dihydropyranone ring. Unfortunately, the fully conjugated enol tautomer **444** was obtained exclusively, and we were unable to shift the equilibrium in favor of the enol **443** under a variety of conditions.

3.9.2 The Vinyl Chloride RCEYM Route

Failing all attempts to produce an intramolecular cyclization of the ketoaldehyde **443**, we opted to pursue an alternative method for preparing the γ-dihydropyranone ring. We were intrigued by a report from Weinreb and coworkers detailing the successful RCM between olefins and vinyl chlorides.[182] Earlier work from within our own group had demonstrated a protocol for the hydrolysis of vinyl chlorides to ketones.[183] Taken in conjunction, these two findings led us to propose the RCEYM presented in Scheme 106.

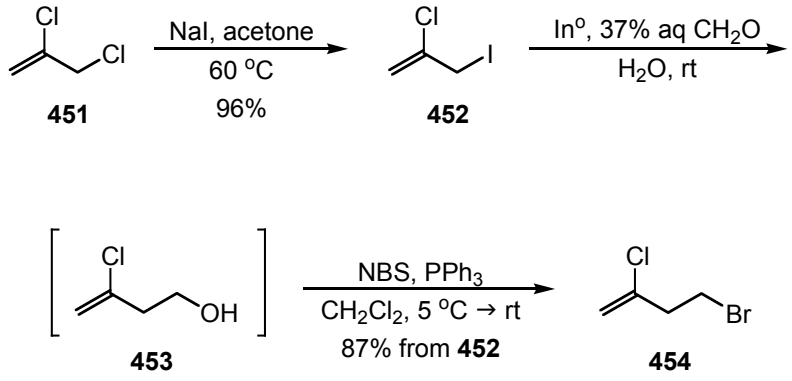
Scheme 106



The RCEYM of **445** would generate the azabicyclic diene **446**. Hydrolysis of the vinyl chloride would afford ketone **447**, which should undergo selective reduction from the more accessible *exo*-face of the azabicycle to deliver **448**. A series of functional group manipulations paralleling our previous experiments would permit the assembly of **450**. Exposure of this material to acid followed by deprotection of the carbamate should produce pinnamine.

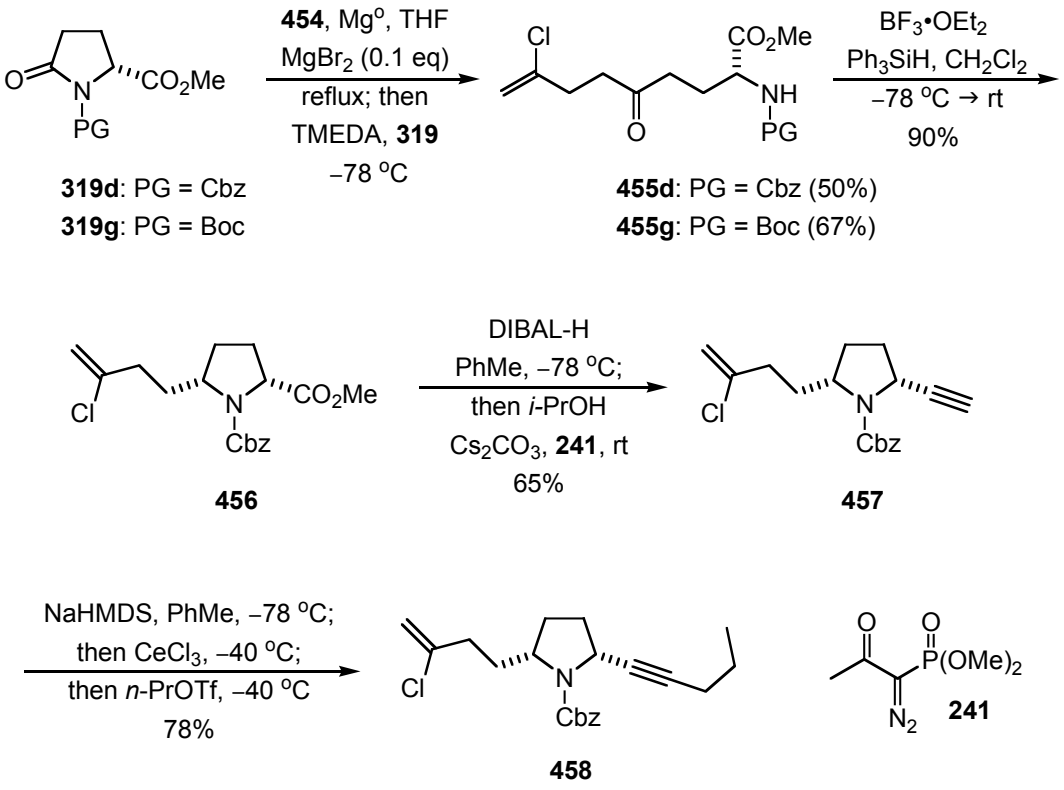
Our synthesis of enyne **445** began with the preparation of the bromide **454** according to Scheme 107. Commercially available 2,3-dichloropropene (**451**) was converted to the corresponding iodide **452** according to the literature.[184] An indium-mediated Barbier reaction between **452** and formaldehyde was achieved under aqueous conditions to produce the intermediate alcohol **453**. The volatile alcohol was sufficiently pure after workup to permit its direct conversion to **454**.

Scheme 107



The imides **319d**,**g** were treated with the Grignard reagent derived from **454** to afford the ketones **455d**,**g** respectively (Scheme 108). Having more of the imide **319d** on hand, we opted to prepare the ketone **438d** on scale and utilize this substrate in all further transformations.

Scheme 108



Exposure of the ketone **455d** to our standard cyclization-reduction protocol provided the *cis*-pyrrolidine **456** (*dr* >95:5). The one-pot homologation of the C-2 ester moiety to a terminal acetylene also proceeded without incident to afford **457**. Subsequent alkylation of the corresponding cerium acetylide delivered the metathesis precursor **458**.

Unfortunately, all attempts to perform a RCEYM with substrate **458** were unsuccessful (Table 17). Rather no reaction occurred regardless of catalyst, temperature, or reaction times used, permitting the recovery of **458**. Alternatively, conducting the metatheses under at atmosphere of ethylene led to the formation of the triene **460**.

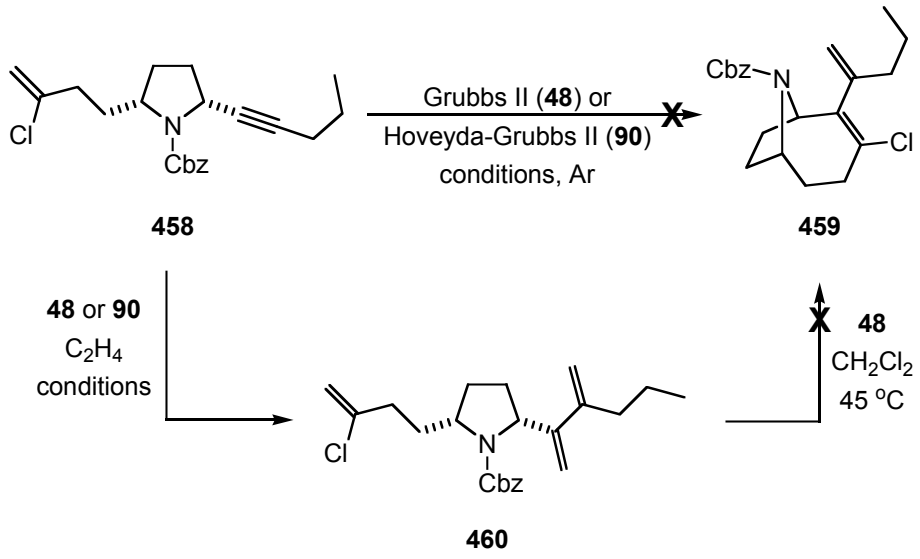


Table 17

Entry	Cmpd.	Catalyst	Mol %	Solvent	Atmosphere	T (°C)	Product[b, c] (%)
1[a]	**458**	**48**	30	PhMe	Ar	65 → 100	NR
2	**458**	**48**	20	PhMe	C_2H_4	70	80 (**460**)
3	**458**	**90**	15	CH_2Cl_2	Ar	25	NR
4	**458**	**90**	15	CH_2Cl_2	C_2H_4	25	>5 (**460**)
5	**460**	**48**	10	CH_2Cl_2	Ar	45	NR

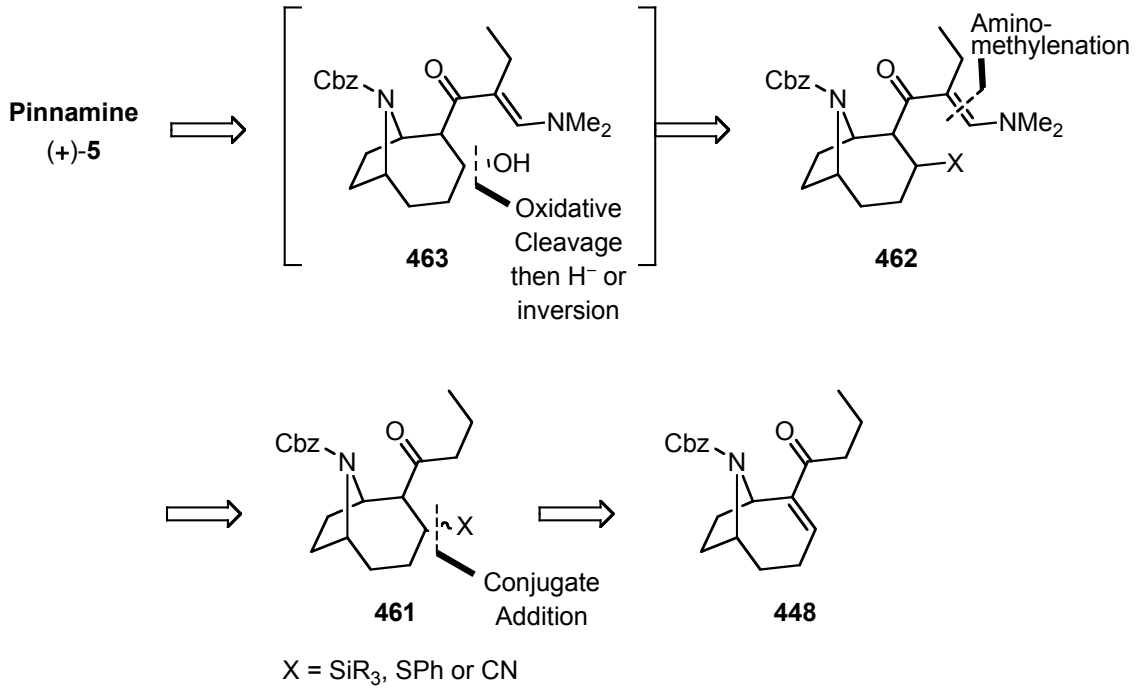
[a] Reaction conducted at 65 °C for 3 h using 15 mol% of **48**, then an additional 15 mol% of **48** was added and the reaction temperature was increased to 85 °C for 2 h, and finally 100 °C for 1 h.
[b] Isolated yields following chromatography.
[c] NR = No reaction occurred.

Of interest was the observed lack of reactivity when the Hoveyda-Grubbs second-generation catalyst **90** was utilized in conjunction with ethylene. Furthermore, attempts to promote the olefin metathesis of **460** failed to produce **459**. Following our own unsuccessful attempts to produce **459** from the vinyl chloride **458**, Weinreb reported on the inability to form tetrasubstituted olefins from vinyl chlorides by RCM.[185] As a result, we abandoned the vinyl chloride route to pinnamine in favor of a new strategy to install the dihydropyranone ring.

3.9.3 Conjugate Addition Strategies

The new synthetic plan would entail the installation of a masked-oxygen equivalent via the conjugate addition of a silicon, sulfur, or nitrile unit to the enone moiety of **448** according to the Scheme 109. Conversion of the aforementioned oxygen equivalents to either an alcohol or a ketone would provide a functional handle for forming the γ-dihydropyranone ring.

Scheme 109

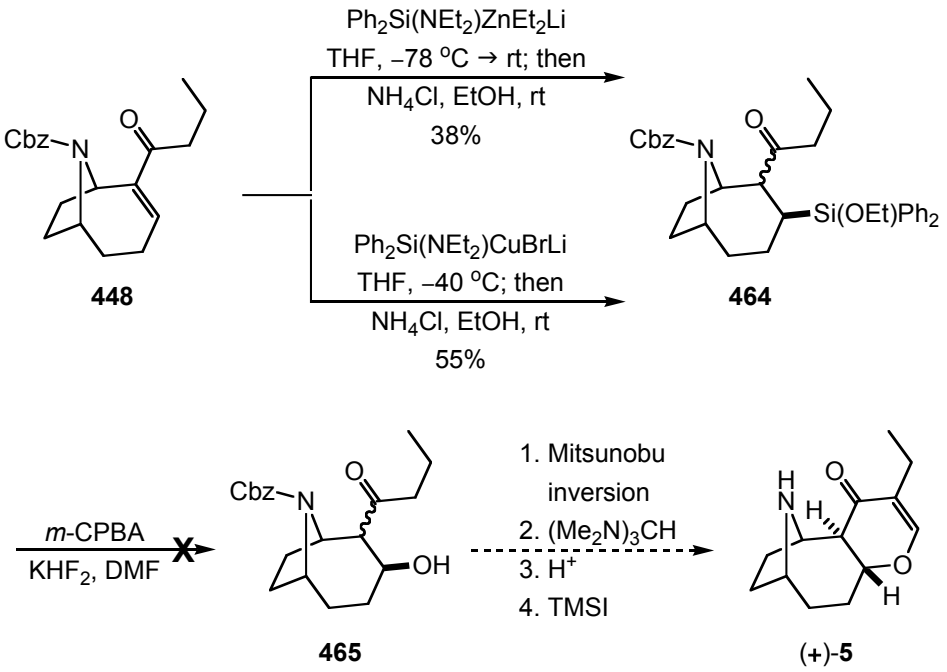


3.9.4 The β-Silylketone Route

We first sought to prepare the β-keto alcohol **465** via the conjugate addition of a silylzincate or silylcuprate to **448** according to Scheme 110. The oxidation of the newly formed carbon silicon bond of **464** was expected to deliver **465**. However, due an anticipated preference for the addition of nucleophiles to the sterically more accessible *exo*-face of the bicyclic enone, we believed that a subsequent Mitsunobu inversion of the

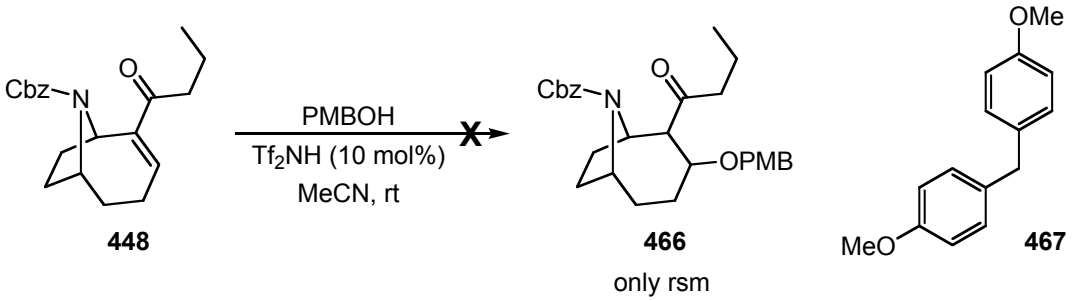
β-hydroxyl would be required in order to obtain the correct stereochemical relationship present in the dihydropyranone ring of pinnamine.

Scheme 110



Unfortunately our attempts to add a masked hydroxyl group to enone **448** in a 1,4-sense were lower yielding that anticipated. The small quantity of the diastereomeric β-silylketones **444** obtained from these initial trials was subjected to Tamao oxidation conditions,[186] but only a mixture of unidentifiable products and recovered starting material was isolated. Parallel attempts to add a hydroxyl to **448** via a 1,4-conjugate mode using potassium trimethylsilanoate (TMSOK) or lithium hydroperoxide (LiOOH) resulted in deprotection of the carbamate and the recovery of starting material respectively. Attempted addition of *p*-methoxybenzyl alcohol (PMBOH) according to the reported method of Spencer[187] failed to produce any of the desired conjugate addition product **466** (Scheme 111). Rather, **448** was recovered along with the biaryl **467**.

Scheme 111

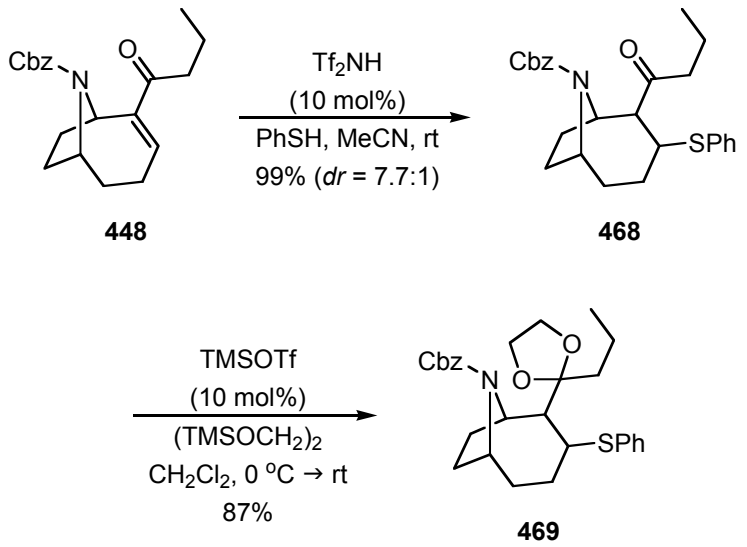


448 **466** only rsm **467**

3.9.5 The β-Sulfoxide and Sulfone Routes

An alternative method for the preparation of a β-oxygenated ketone such as **463** was to install a functional handle that could be directly converted to a ketone. We wished to introduce a masked ketone equivalent via the conjugate addition of thiol to the enone **448**. Based on the precedent provided by Kigoshi during the first synthesis of pinnamine,[59] the hydride-reduction of a β-ketone will occur from the *exo*-face of the azabicycle to provide the desired *endo*-alcohol required for the synthesis of the dihydropyranone ring.

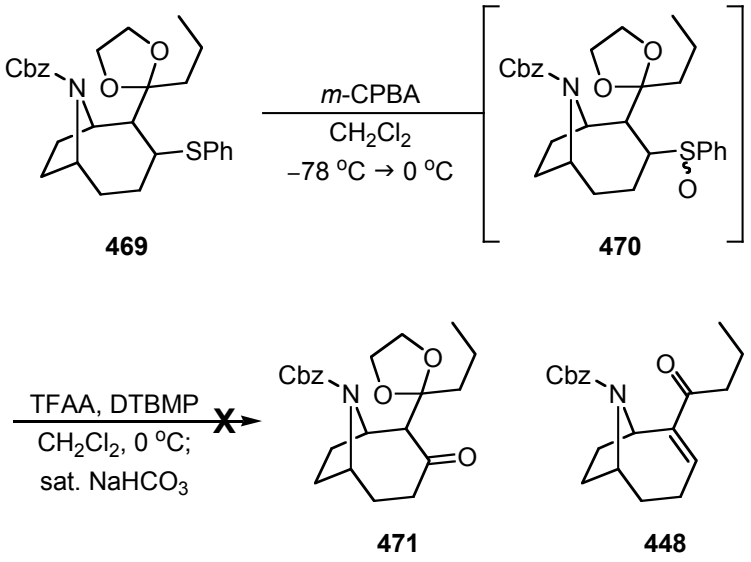
Scheme 112



448 **468** **469**

Toward this end, **448** was elaborated to the β-thiophenyl ketone **468** according to Scheme 112. The ketone group of **468** was protected as the corresponding dioxolane **469**. We envisioned two possible routes for the conversion of the thiophenyl moiety of **469** to a ketone function. We first examined a Pummerer rearrangement approach that mimicked a strategy utilized by Fukuyama and coworkers during their synthesis of phomoidride B.[188]

Scheme 113

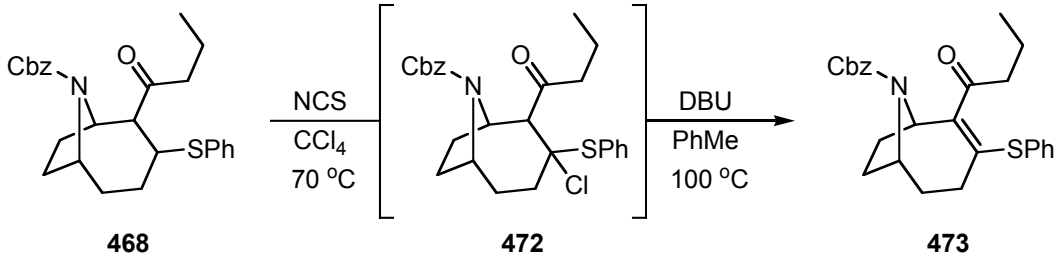


Oxidation of the thiophenyl ether of **469** to the corresponding sulfoxide **470** was accomplished with *m*-CPBA (Scheme 113). The crude mixture of diastereomeric sulfoxides was treated with trifluoroacetic anhydride (TFAA) in the presence of excess 2,6-di-*t*-butyl-4-methyl pyridine (DTBMP), and subsequently quenched with saturated aqueous $NaHCO_3$. Instead of obtaining the desired ketone **471**, the enone **448** was isolated as the major component of the reaction mixture along with a small quantity of recovered **470**, indicating that hydrolysis of the ketal and elimination of the thiophenyl group had occurred during the course of the reaction. The same Pummerer

transformation was attempted using the ketone **468**, but no identifiable products could be isolated from the intractable mixture that was formed.

Alternatively we attempted to effect the desired Pummerer rearrangement using the conditions reported by Magnus and Kriesberg (Scheme 114).[189] As such, **468** was converted to the α-chloro-thiophenyl ether **472**. The crude chlorination products were separated from residual succinimide by filtration and resuspended in PhMe. Addition of DBU and heating of the solution to 100 ^{o}C for 20 min provided an inseparable mixture of compounds in which the enone **473** appeared to be present based on the ^{1}H-NMR

Scheme 114



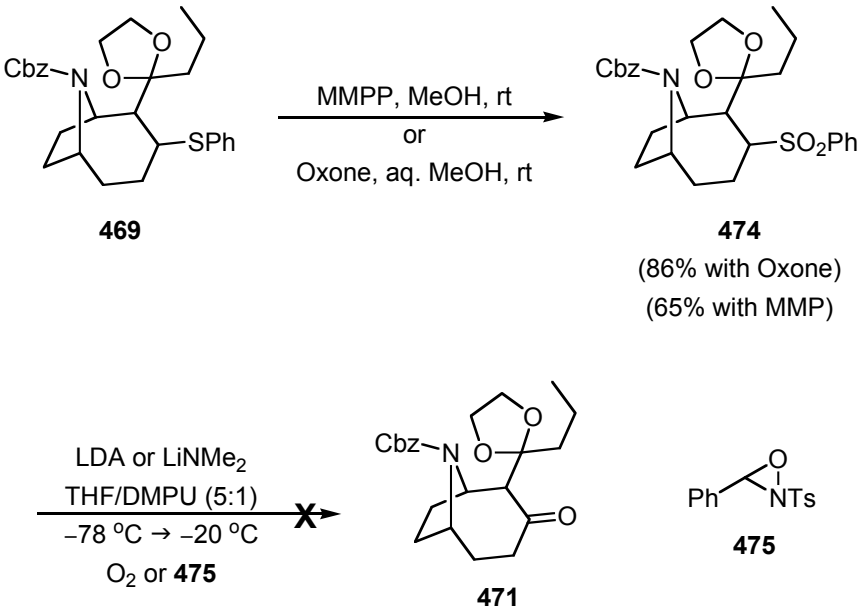
468 **472** **473**

Though **473** might have served as a useful precursor for the installation of the dihydropyranone ring, our inability to cleanly obtain this material from the complex reaction mixture led us to abandon the Pummerer rearrangement approach to pinnamine.

Instead, we chose to explore an oxidative desulfonylation protocol to install the desire ketone moiety. It is well established that ketones may be prepared from sulfones by the oxidation of carbanions generated adjacent to sulfur.[190] The resulting α-hydroperoxy sulfones subsequently collapse to afford ketones upon expulsion of the elements of the sulfone moiety. Toward the exploitation of this method for the synthesis of pinnamine, the thiophenyl ether **469** was oxidized to the corresponding sulfone **474** with either magnesium monoperoxypthalate (MMPP) or Oxone® (Scheme 115).

Attempts to oxidize the α-sulfonyl carbanion obtained from **474** with LDA or $LiNMe_2$ were wholly unsuccessful, resulting in the recovery of **474** in all instances.

Scheme 115



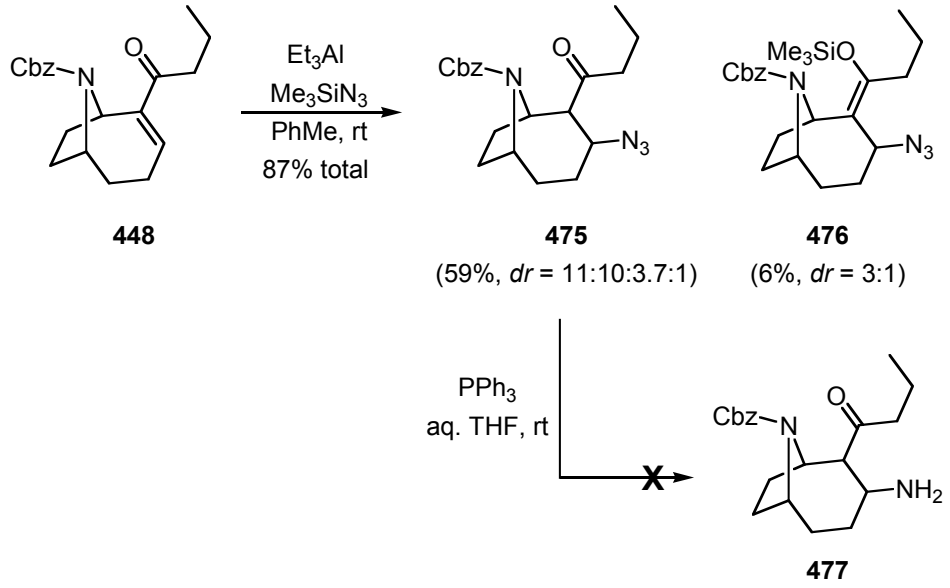
We speculated that the recovery of **474** from the oxidative desulfonylation trials resulted from our inability to generate a carbanion adjacent to the sulfonyl group. It occurred to us that this might be the result of the steric congestion afforded to this position by the sulfone and dioxolane moieties. As such, we turned our attention to the conjugate addition of a less sterically encumbered azide group.

3.9.6 The β-Azidoketone Route

It was envisioned that a β-azide could be reduced to an amine under Staudinger conditions. The resulting amine could be converted to a ketone utilizing a procedure reported by Woodward during the synthesis of erthyromycin[191] or by a variety of other protocols.[192] Namely, the amine would be converted to a chloramine and subsequently dehydrochlorinated to an imine, which would undergo hydrolysis to provide a ketone.

Toward this end, conjugate azidation was accomplished without incident to provide a mixture of the ketone **475** and the silyl enol ether **476** (Scheme 116).[193] An attempted Staudinger reduction of the azide to **477** resulted in the recovery of **475** following workup and purification. Though no further attempts were made to effect this transformation, **477** might potentially be produced if tributylphosphine (PBu_3) is used in place of triphenylphosphine (PPh_3), or if the reaction is conducted at elevated temperatures.

Scheme 116

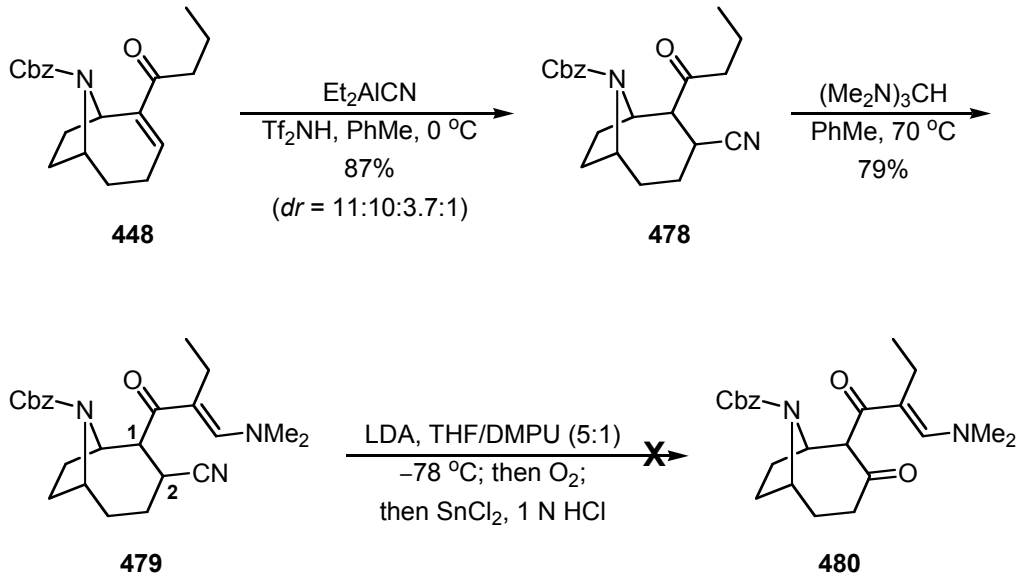


3.9.7 The β-Cyanoketone Route

Concurrent with our attempts to prepare the amine **477**, we embarked upon a strategy to generate the corresponding β-cyanoketone. Once in hand, we anticipated that a derivative of this nature could be transformed to a species resembling **465** via oxidative decyanation. The strategy commenced with the hydrocyanation of enone **448** by the complex generated by the reaction of trifluoromethanesulfonimide (Tf_2NH) and Et_2AlCN (potentially $Tf_2NAl(CN)Et$)[194] to provide all possible diastereomers of the desired β-

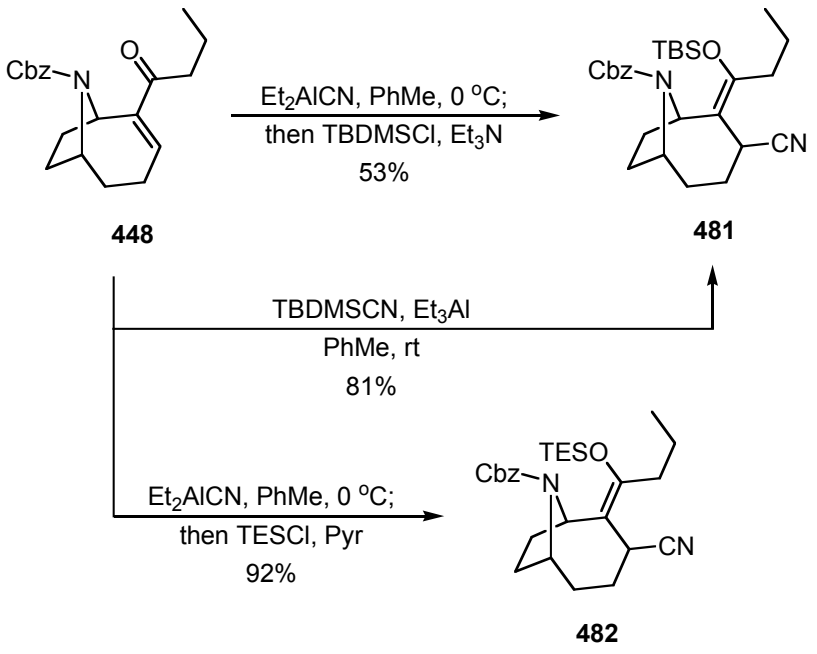
cyanoketone **478** (Scheme 117). This new alternative to the Nagata procedure provided high yields of the hydrocyanation adduct **478** without the requirement for HCN.[195] Subsequent conversion of **478** to the vinylogous amide **479** transpired under standard conditions. Unfortunately, our attempts to effect the oxidative decyanation of the nitrile according to the method of Watt[196] by exposure of **479** to lithium diisopropylamide (LDA) and oxygen, failed to afford any **480**, following exposure of the reaction mixture to conditions that would reduce the intermediate α-hydroperoxy nitrile.[197] As in the case of compound **474**, starting material was recovered in all instances. In order to determine whether any deprotonation had occurred, vinylogous amide **479** was treated with LDA, and then quenched with CD_3OD to afford deuterated **479** (59%) as evident by mass spectral data (2.06:1 MD/MH). Although this experiment revealed that deprotonation had transpired, we were unable to determine whether deuteration had occurred at C-1 or C-2 on the basis of ^{1}H-NMR experiments due to the overlap of the diagnostic methine signals by other aliphatic resonances.

Scheme 117



In order to eliminate the potential for competitive deprotonation at C-1, we sought to protect the ketone of **478** as a silyl enol ether, which could be obtained directly during the conjugate addition of cyanide.[198] Toward this end, **448** was treated with Et_2AlCN and the intermediate aluminum amide was quenched with a mixture of Et_3N and TBDMSCl to deliver **481** in 53% yield as two diastereomers (ratio not determined) (Scheme 118). Alternatively, **481** was prepared in 81% yield using Et_3Al and TBDMSCN.[199] Unfortunately, TBDMS-enol ether **481** proved highly unstable and underwent hydrolysis to the ketone even upon storage at –20 °C in benzene. We did however find that the slightly more stable TES-enol ether **482** could be prepared in high yield also as a mixture of two diastereomers (ratio not determined).

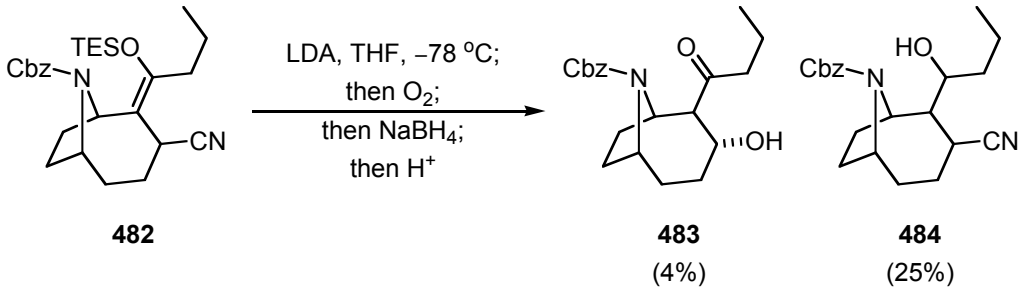
Scheme 118



Deprotonation of **482** with LDA and quenching of the resulting anion with oxygen should have generated an intermediate α-hydroperoxy nitrile, which was to be reduced *in situ* with $NaBH_4$. Acidification of this reaction mixture was expected to

generate the β-hydroxy ketone **483** (Scheme 119). However, we were dismayed to find that only a trace of **483** was obtained (determined by LRMS) along with several diastereomers of **484** as the only other major isolable products.

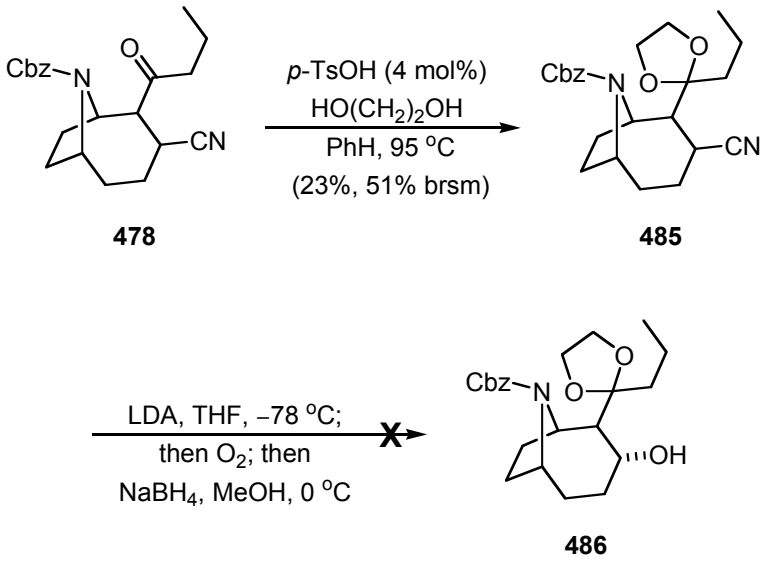
Scheme 119



482 **483** (4%) **484** (25%)

Based on the isolation of the alcohol **484** resulting from loss of the silyl enol during the course of the oxidative decyanation event, it appeared we would need to protect the ketone of **478** as a more robust functional group. Thus, **478** was converted to the dioxolane intermediate **485**, albeit in poor yield, using conditions outlined by Venkateswaran for the similar protection of a β-cyanoketone (Scheme 120).[200]

Scheme 120



478 **485** **486**

As before, attempted oxidative decyanation failed to provide the desired alcohol **486**. The oxidative decyanation of **485** should have afforded **486** if deprotonation of the methine adjacent to the nitrile had occurred. As with the previously discussed sulfone route, the absence of any such product seems to suggest that the environment around this position is to sterically encumbered to accommodate the amide bases that were employed.

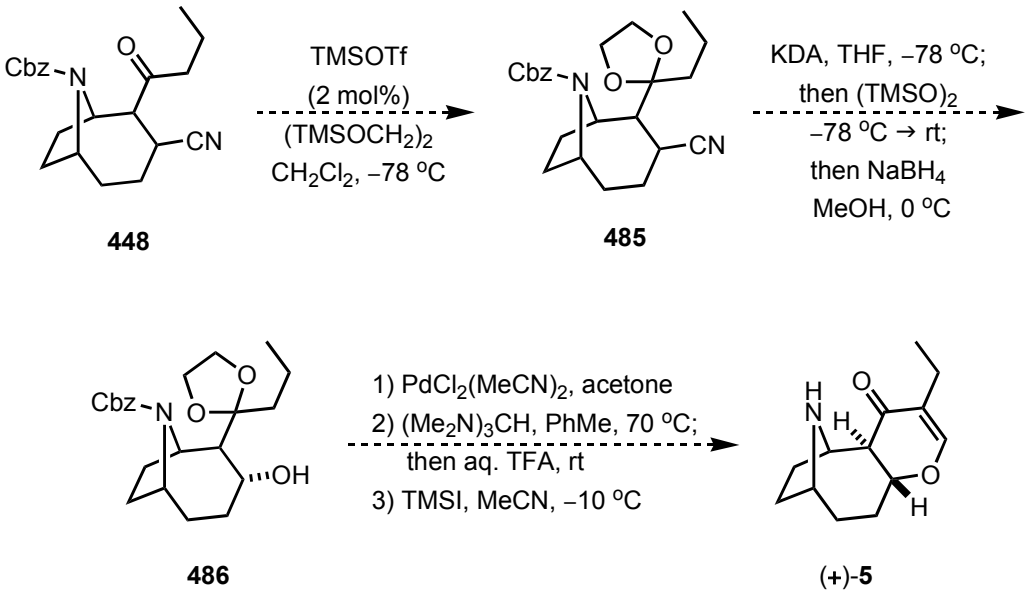
3.9.8 Future Outlook

As mentioned, we have begun to wonder whether the failed attempt to effect the oxidative decyanation of **485** was the result of steric crowding around the nitrile. Several examples in the literature have shown that the deprotonation of sterically hindered secondary nitriles proceeded only when potassium amide bases were employed.[201] As such, we feel that the oxidative decyanation of **485** should be accomplished using potassium diisopropylamide (KDA) or potassium diethylamide ($KNEt_2$).[202] Additionally, the use of bis(trimethylsilyl)peroxide [$(TMSO)_2$][203] has been shown to be a useful alternative to oxygen in oxidative desulfonylation reactions.[204] The use of this reagent will also be explored in order to permit the conduction of the oxidative decyanation reactions at elevated temperatures if needed.

An improved synthesis of **485** is also needed. As such, our new plan to access this key intermediate is provided in Scheme 121. Ketalization of **478** is to be accomplished using the conditions developed by Noyori.[205] The key oxidative decyanation reaction will be performed with KDA and $(TMSO)_2$ as mentioned earlier. The *in situ* reduction of the intermediate ketone that is produced should afford **486**. Deprotection of the ketal moiety under neutral conditions[206] will be performed to prevent the β-elimination of the hydroxyl

group. Aminomethylenation and subsequent acidic hydrolysis of the crude reaction mixture is expected to deliver the tricycle. A final carbamate deprotection step will furnish the natural product.

Scheme 121

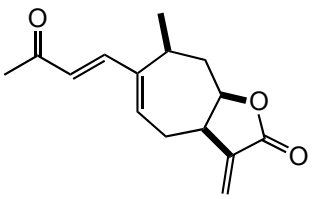


Currently, we have prepared 5.6 grams of the enone **448** using the route shown previously. In addition to providing an ample quantity of material to complete the synthesis of pinnamine, the preparation of this quantity of **448** serves to highlight the scalability of our RCEYM route to prepare bridged azabicycles.

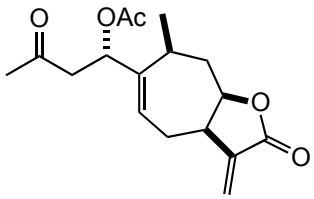
CHAPTER 4: THE TOTAL SYNTHESIS OF 8-*EPI*-XANTHATIN

4.1 BACKGROUND

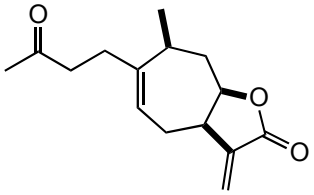
The sesquiterpene lactone 8-*epi*-xanthatin (**487**) was first isolated by Minato and Horibe following the deacetoxylation of the related compound xanthumin (**488**).[207] Compounds **488-491** are representative members of a larger family of structurally diverse xanthanolides isolated from various species of *Xanthium* (cocklebur).[208]



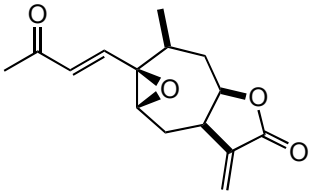
8-*epi*-xanthatin
487



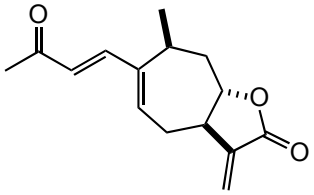
xanthumin
488



tomentosin
489



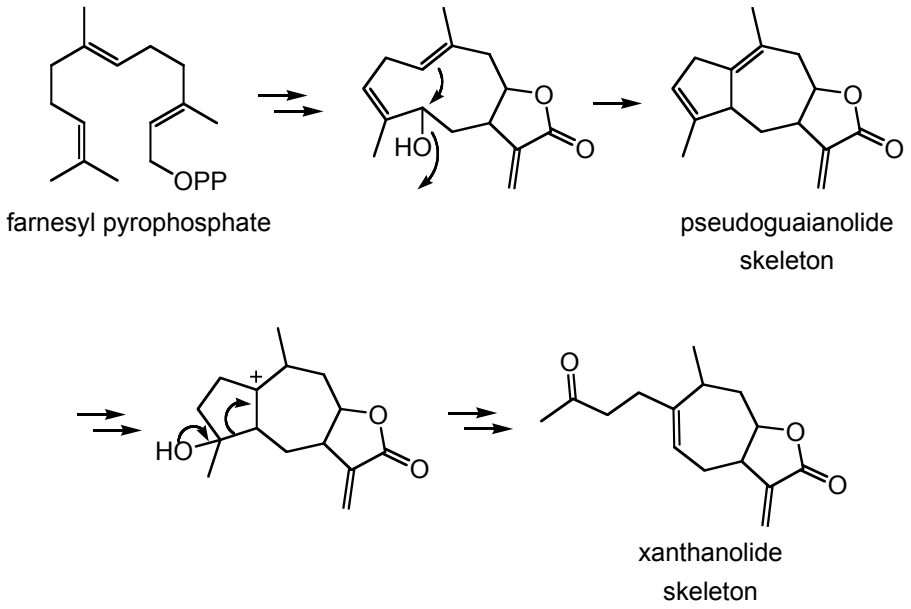
8-*epi*-xanthatin-1β,5β-epoxide
490



xanthatin
491

It has been proposed that the xanthanolides are biogenetically related to the pseudoguaianolides and arise from the probable cleavage of the five-membered ring portion of these precursors (Scheme 122).[209]

Scheme 122



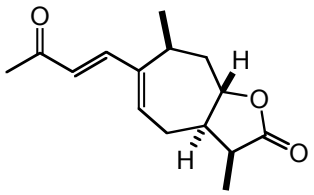
Traditional medicines have commonly comprised the plant materials of the *Xanthium* species, which contain varying quantities of the xanthanolides **487**-**491**, to treat a variety of ailments including malaria, strumous disease, and cancer. Recent studies toward identifying potent anti-cancer therapeutics have been made to determine which of these active principles is responsible for the beneficial medicinal properties that have been observed. This effort has been further stimulated by the low toxicity associated with the active constituents contained within the formulations used in traditional medicine.[210c]

Biological assays have shown that **487**-**491** elicit therapeutically viable cytotoxicity profiles against a wide range of human tumors including the murine lymphocytic leukemias P-388 and L-1210, the A549 and NSCLC-N6 (non-small cell lung/bronchial epidermoid carcinomas), the KB-3 and KB-V1 (nasopharyngeal carcinomas), SK-OV-3 (ovarian adenocarcinoma) SK-MEL-2 (malignant melanoma),

XF-498 (CNS carcinoma), and HCT-15 (colon adenocarcinoma) cell lines.[210] It is has been shown that the conjugated enone and α-methylene lactone moieties are the key structural features responsible for this cytotoxic activity, but little is known about the mode of action.[211] Similar to the antitumor sesquiterpene lactones costunolide, arteminolide, and arglabin, the cytotoxic activities of compounds **487** and **490** result from the inhibition of human lamin-B farnesylation in a dose-dependent manner.[210b,212] As a result of their cytotoxicity, the xanthanolides have attracted the interest of those interested in cancer chemotherapeutic agents.

4.2 PREVIOUS SYNTHETIC APPROACHES TO THE XANTHANOLIDES

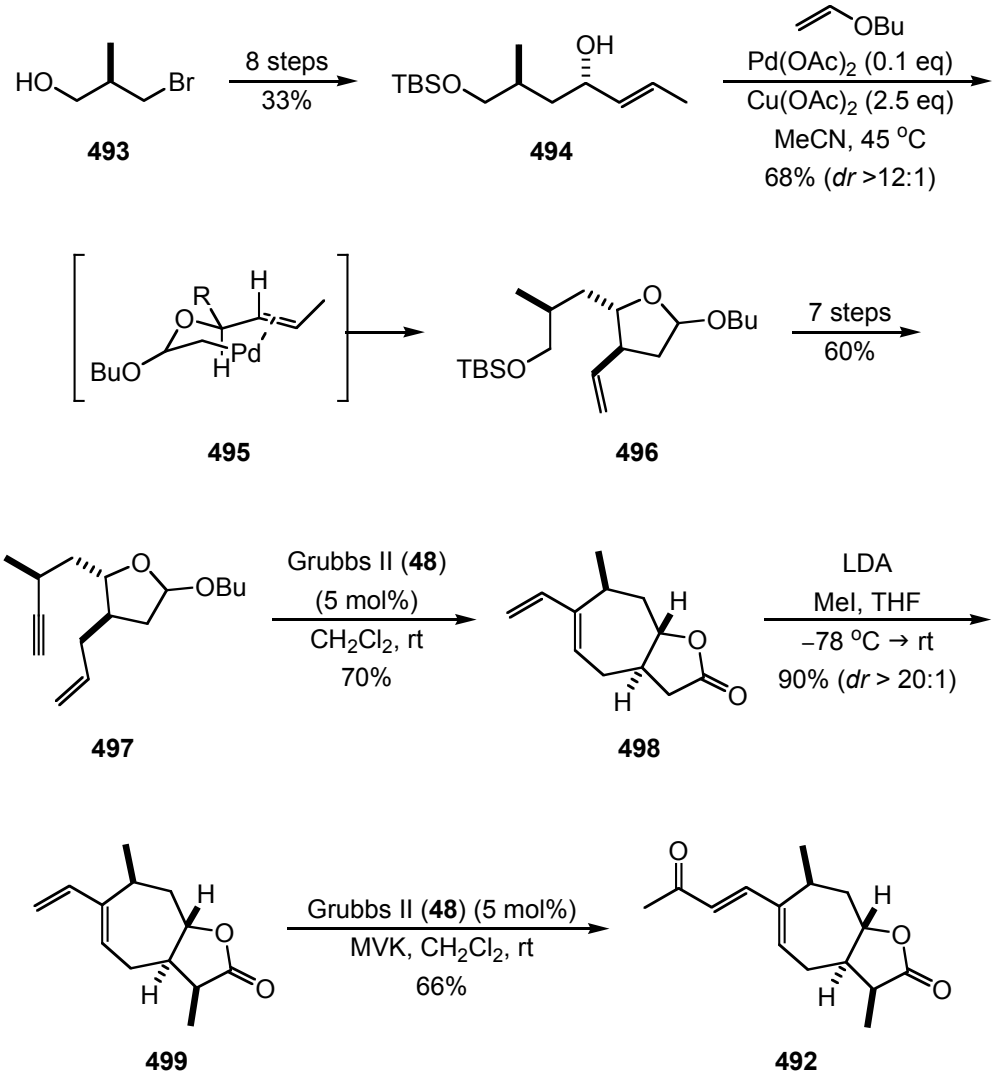
Unfortunately, compounds **487**, **489**, and **490** are isolated as minor components of the total xanthanolide extracts that are obtained from the aerial parts of *Xanthium strumarium*, the primary source of xanthumin sesquiterpene lactones.[213] Consequently, the extent to which their biological activities have been evaluated has remained somewhat limited. Furthermore, until just recently there has been no report of the successful synthesis of any of the xanthanolides.[214] In the first reported total synthesis of a xanthanolide, Morken and Evans utilized a stereoselective Oshima-Utimoto reaction to prepare (−)-dihydroxanthatin (**492**).[215]



492

Their synthetic approach commenced with the preparation of the allylic alcohol **494** from the commercially available bromide **493** (Scheme 123).

Scheme 123



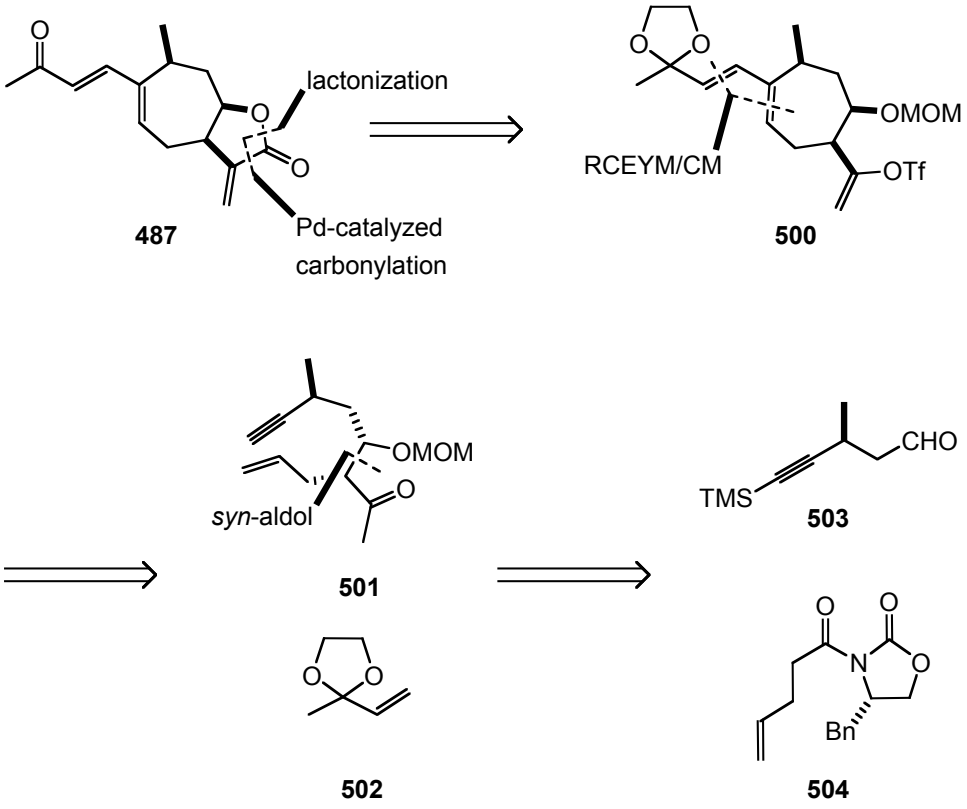
The Oshima-Utimoto protocol to prepare tetrahydrofurans was utilized to generate **496** from the allylic alcohol **494** in good yield and with high diastereoselectivity via the proposed chair-like transition state structure **495**. A series of seven subsequent chemical operations provided the enyne **497**. Exposure of **497** to the Grubbs second-generation catalyst **48** produced the *trans*-disubstituted lactone **498**. Alkylation of the lithium enolate of **498** with MeI afforded **499** with >20:1 diastereoselectivity. The synthesis of **492** was completed upon successful CM of **499** with methyl vinyl ketone

(MVK). Morken's synthesis of **492** was achieved in nineteen steps and 5.5% overall yield from **493** and constituted the first reported preparation of any xanthanolide natural product.

4.3 SYNTHETIC STRATEGY

Prior to Morken's reported synthesis of **492**, we were intrigued by the possibility of assembling the fully functionalized *seco*-guaianolide cores of the xanthanolide antibiotics using a tandem RCEYM-CM strategy. We were particularly interested in preparing 8-*epi*-xanthatin (**487**), as this xanthanolide has emerged as a potentially useful cytotoxic antibiotic for the treatment of various cancers. Toward this end, we envisioned that the preparation of **487** would transpire according to the proposed retrosynthesis outlined in Scheme 124.

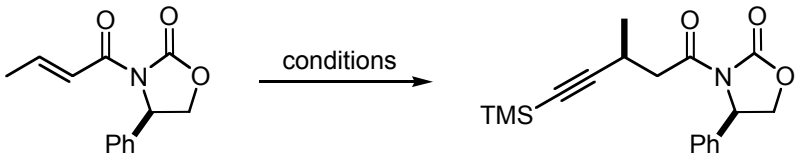
Scheme 124



The natural product would be obtained following the palladium-catalyzed carbonylation of the enol triflate **500** followed by an *in situ* intramolecular lactonization. Intermediate **500** was to be generated from the enyne **501** via a tandem intramolecular RCEYM followed by an *in situ* CM with the vinyldioxolane **502**. The key metathesis precursor **501** in turn would result from the *syn*-aldol coupling of the oxazolidinone **504** with the chiral aldehyde **503**.

4.3.1 Conjugate Alkynylation Experiments

In accord with our proposed retrosynthesis, we embarked upon the construction of the aldehyde **503** using the shortest sequence possible. However, there were no reported syntheses of **503** in the literature. As such, we were intrigued by the possibility of generating **503** through the implementation of a diastereoselective conjugate addition of an alkynylmetal species to a chiral *N*-enoyloxazolidinone. At the onset of our undertaking the synthesis of **487**, there were no examples of the conjugate addition of alkynyl nucleophiles to chiral *N*-enoyloxazolidinones.[216,217] This is in part due to the inability to transfer alkynyl groups efficiently via the cuprate-based strategies that are typically employed for conjugate additions to imides.[218,219] Zinc[220] and boron acetylides,[221] which are sometimes in the conjugate additions of alkynes to α,β-unsaturated ketones, have yet to be utilized in conjunction with the less reactive *N*-enoyloxazolidinone Michael acceptors. Undeterred by these findings, we set out to effect the conjugate alkynylation of the α,β-unsaturated imide **505** with various metal acetylides in a diastereoselective fashion. The results of these trials are provided in Table 18.



505 **506**

Table 18

Entry	Conditions	Yield [a] **506** (%)	*dr*[b]
1	$Zn(OTf)_2$ (60 mol%) TMSC≡CH, Et_3N CH_2Cl_2, rt	0	–
2	TMSC≡CB(O*i*-Pr)$_2$ PhMe, rt → 40 °C	0	–
3	$Et_2AlC{\equiv}CTMS$ PhMe, −78 °C	0	–
4	$Et_2AlC{\equiv}CTMS$ PhMe, 0 °C	90	1.6:1
5	$Ni(acac)_2$ (22 mol%) DIBAL-H (20 mol%) $Me_2AlC{\equiv}CTMS$ PhMe, Et_2O, −15 °C → 0 °C	75	8.7:1

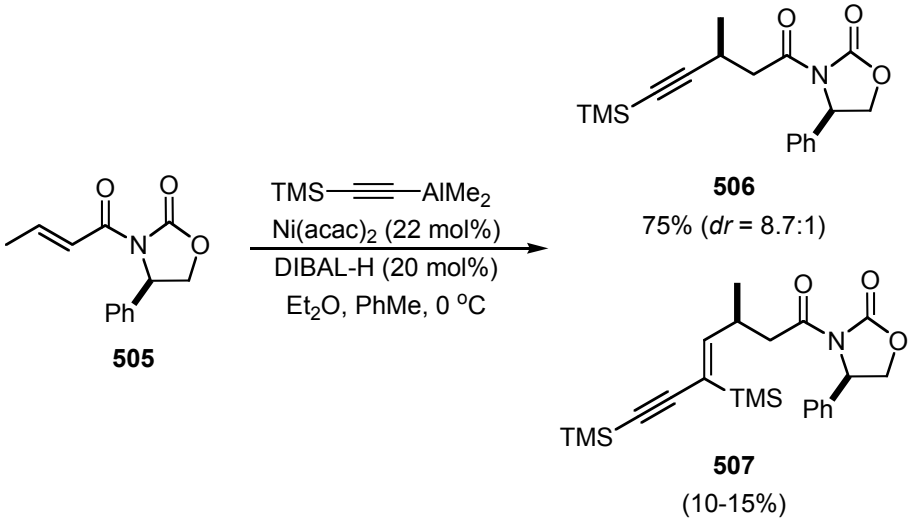
[a] Isolated yields following chromatography.
[b] Determined by integration of the methyl resonances in the crude ^{1}H-NMR, and verified by isolation of the pure diastereomers.

We began our investigation with the $Zn(OTf)_2$-catalyzed conjugate alkynylations recently reported by Carreira and coworkers.[220b] In accord with Carreira's findings that zinc acetylides react only with doubly activated Michael acceptors, these conditions failed to provide any of the desired conjugate addition adduct **506**, resulting in complete recovery of **505** (entry 1). We did find that the conjugate addition could be effected using the corresponding aluminum acetylide[222] to afford an excellent yield of **506** but with poor diastereoselection (entry 4).[223] Although the diastereomers were readily

separable by flash chromatography, we wished to improve upon the selectivity obtained during this addition.

A survey of the literature revealed that Schwartz had reported an efficient nickel(I)-catalyzed conjugate addition of aluminum acetylides to achiral enones.[224,225] We wondered whether the same process could be applied to chiral *N*-enoyloxazolidinones and whether the nickel acetylide species might improve upon the observed diastereo-selection. Application of the Schwartz protocol to our system in the absence of added ligands resulted in the formation of **506** in good yield and diastereoselectivity along with a small amount (10-15%) of the enyne **507**, presumably resulting from the coupling of an intermediate vinyl nickel species with excess aluminum acetylide (Scheme 125).

Scheme 125

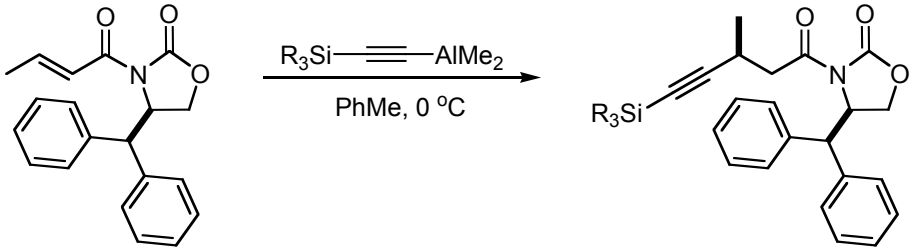


Unfortunately, this reaction was plagued with irreproducible yields and diastereoselectivity. Attempts to optimize this tedious protocol met with little success, and seemed to be highly dependent on the origins of the nickel(II) acetylacetonate [$Ni(acac)_2$] employed.[226] Taking this factor into consideration, it seemed wise not to rely

upon an experimental protocol that could potentially be so heavily dependent upon the source and quality of a particular organometallic reagent, as this would undoubtedly detract from the generality of the method and lead to difficulties in the hands of other researchers. However, the asymmetric variant developed by Corey may still be worth investigating for the preparation of **506**.[225]

As a result of the variable yields and diastereoselection obtained with the nickel-catalyzed conjugate alkynylation reactions, we returned to our original procedure for the conjugate addition of aluminum acetylides to the chiral imide **505** without nickel catalysis. In an effort to improve upon the low diastereoselectivity that was obtained via this protocol, we turned our attention to the diphenylmethyl auxiliary **508** developed by Sibi.[227] The conjugate addition reactions to **508** were conducted with both TMSC≡CAlMe_2 and TIPSC≡CAlMe_2 in order to determine whether an increase in the steric bulk about the acetylide would serve to further enhance the diastereoselection. The results of these reactions are provided in Scheme 126.

Scheme 126



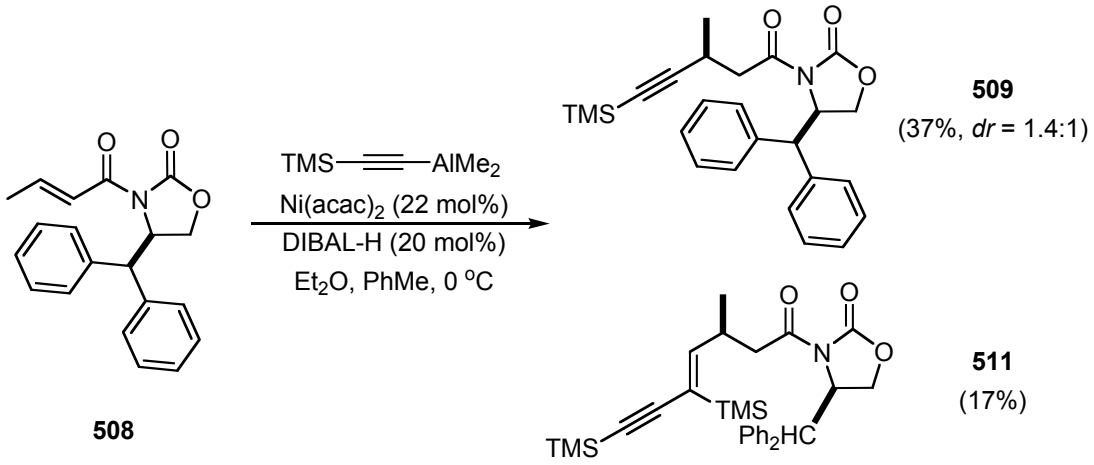
508

509: R = Me (92%, *dr* = 3.4:1)
510: R = *i*-Pr (97%, *dr* = 3.6:1)

An improvement in the diastereoselectivity was evident, and although the yields were excellent, we had hoped to achieve higher levels of diastereoselection. The slight increase in diastereoselection observed in **510** was not substantial enough to warrant the

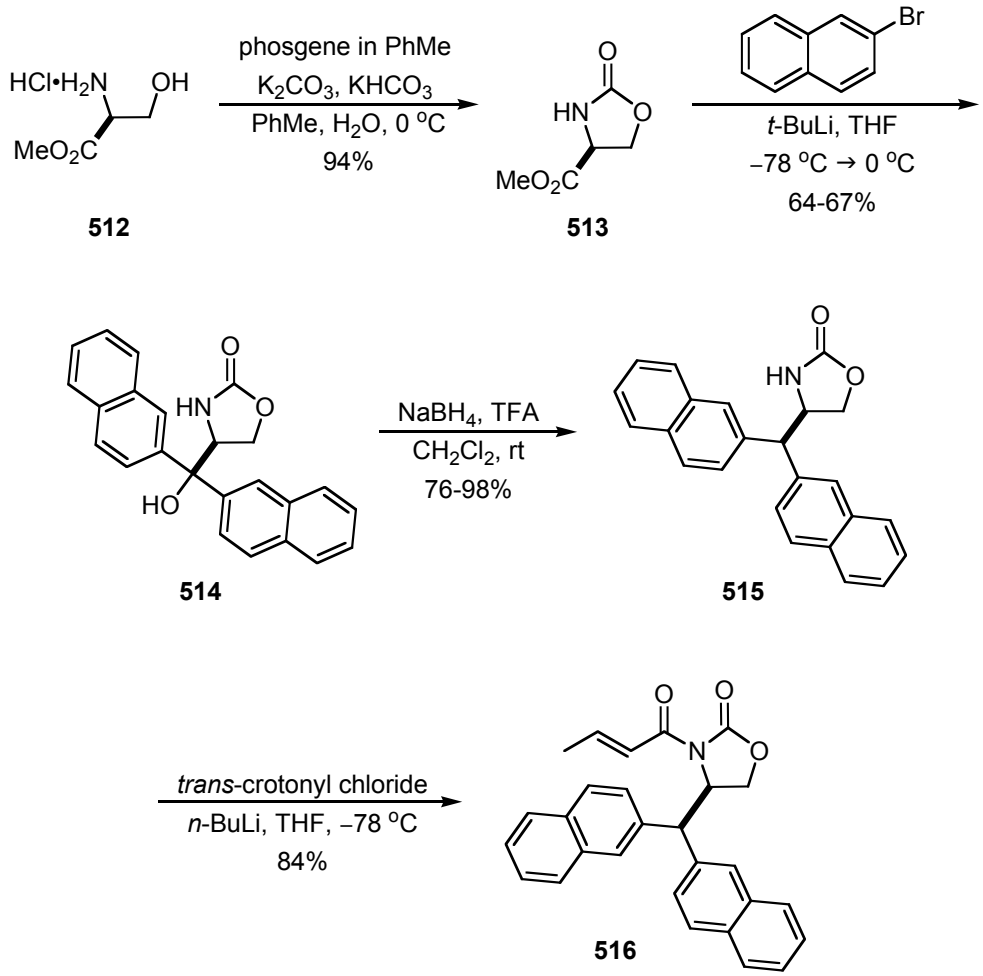
use of the more expensive TIPS-acetylene in further trials. We also subjected **508** to the nickel-catalyzed protocol presented earlier, only to find that the diastereoselectivity of the process was marginal (Scheme 127).

Scheme 127



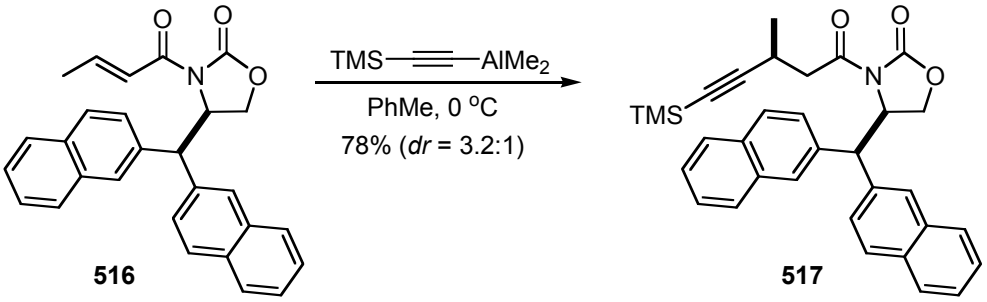
The nickel-catalyzed protocol again proved inferior to the non-catalyzed reactions as evident by the low yield and diastereoselectivity that **509** was obtained in. At this point, we envisioned the creation of a new auxiliary that could improve the diastereoselectivity of our conjugate alkynylation. An adaptation of the Sibi protocol[227] for the preparing **508** was utilized to prepare the new chiral imide **515** from L-serine methyl ester hydrochloride (**512**) according to Scheme 128. The oxazolidinone **513** was treated with an excess of 2-naphthyllithium to afford the tertiary carbinol **514**, which was deoxygenated according to the method of Gribble to afford the oxazolidinone **515**.[228] The imide **516** was then prepared by acylation of the lithium anion of **515** with *trans*-crotonyl chloride. The sequence of reactions utilized for the preparation of **516** has not been optimized.

Scheme 128



With a small quantity of **516** in hand, we subjected it to our conjugate alkynylation protocol. Thus, exposure of **516** to TMSC≡CAlMe$_2$ provided the desired adduct **517** in 78% yield (*dr* = 3.2:1) (Scheme 129). The diastereoselection obtained with **516** was nearly identical to the value obtained using the diphenylmethyl auxiliary **508**, so we began to wonder whether an approach to **503** using a chiral auxiliary was worth further exploration.

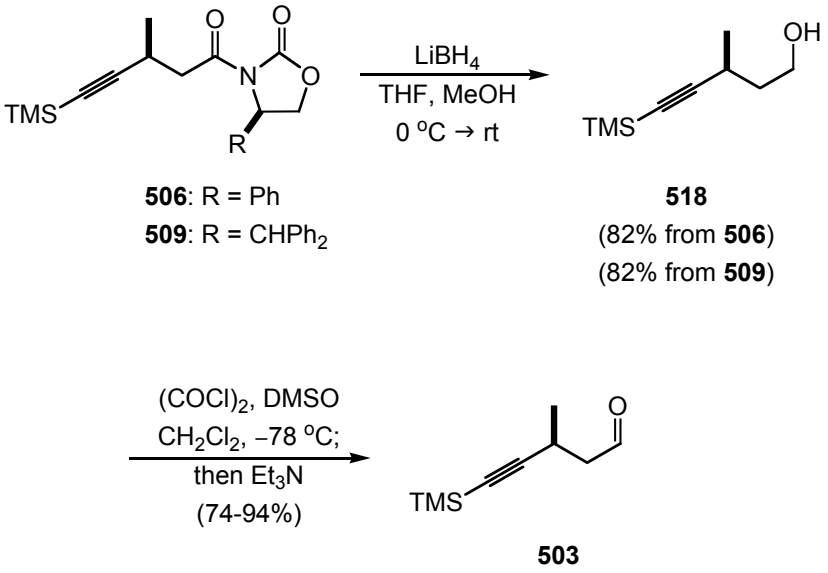
Scheme 129



4.3.2 First Generation Route

During the period we were focused upon the synthesis of **503** via conjugate alkynylation protocols, we obtained suitable quantities of the conjugate addition products **506** and **509**. Hence, we sought to utilize these substrates to prepare **503**. The imides **506** and **509** were thus converted to **503** using standard conditions (Scheme 130).

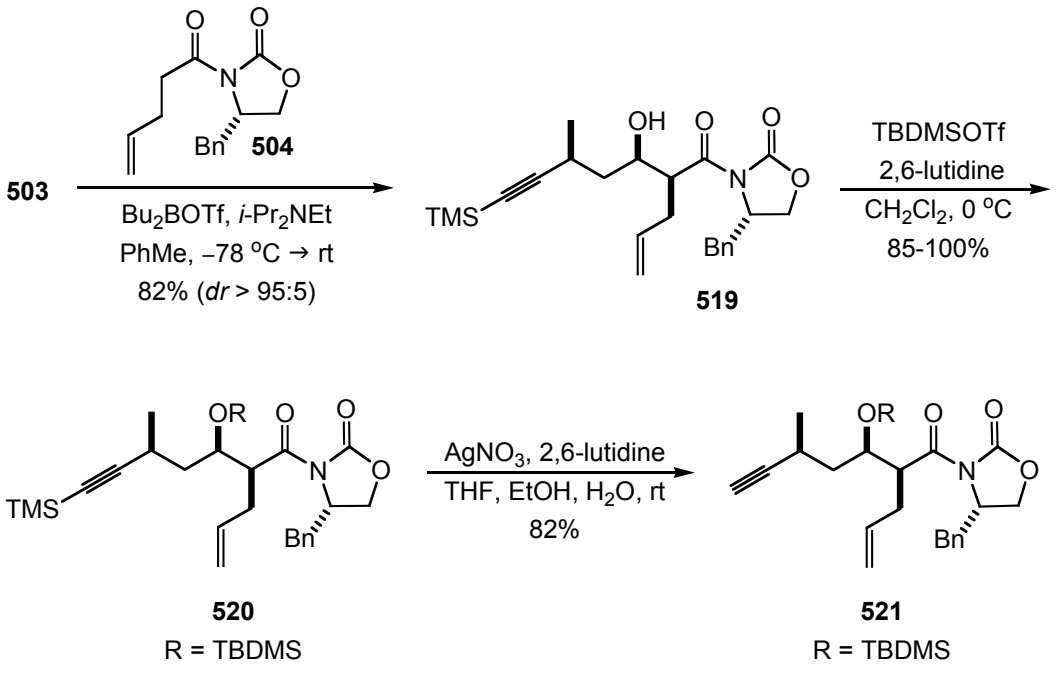
Scheme 130



With the aldehyde **503** in hand, we decided to proceed with the proposed synthetic route to 8-*epi*-xanthatin (**487**). In accordance with our proposed retrosynthesis

of the enyne metathesis precursor **501**, we performed the aldol reaction between **503** and the imide **504** (Scheme 131). We found that conducting the aldol reactions in PhMe as opposed to the more commonly used solvent CH_2Cl_2 significantly improved the yields of the resulting adduct **519**. As expected, the syn-aldol adduct was obtained. The stereochemical assignments were confirmed by the correlation of the ^{1}H-NMR spectrum with the corresponding TIPS-alkyne **544** subsequently prepared by David Kummer utilizing starting materials from the chiral pool (*vide infra*). Protection of the secondary hydroxyl was accomplished without incident to provide **520**. Deprotection of the silylalkyne was best accomplished with silver nitrate ($AgNO_3$) to produce the enyne **521**.[229]

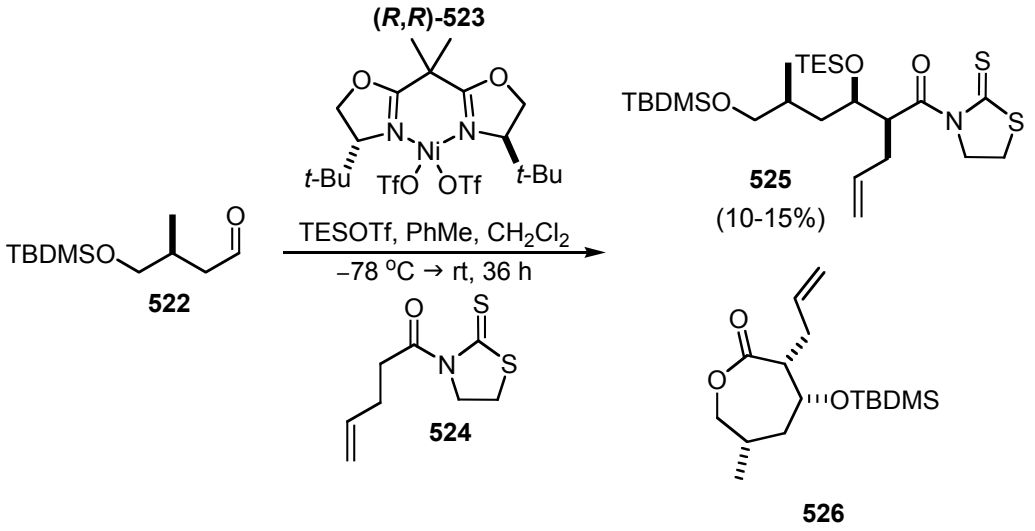
Scheme 131



In conjunction with the original proposed route to 8-*epi*-xanthatin, David Kummer began to explore an alternative route to the enyne metathesis precursor **501**. In

his parallel endeavors, he performed the aldol reaction between the thiazolidinonethione **524** and the aldehyde **522** based on an encouraging report by Evans and coworkers.[230] However, the aldol adduct **525** was produced in meager yield together with an unquantified amount of the lactone **526** as shown in Scheme 132.

Scheme 132

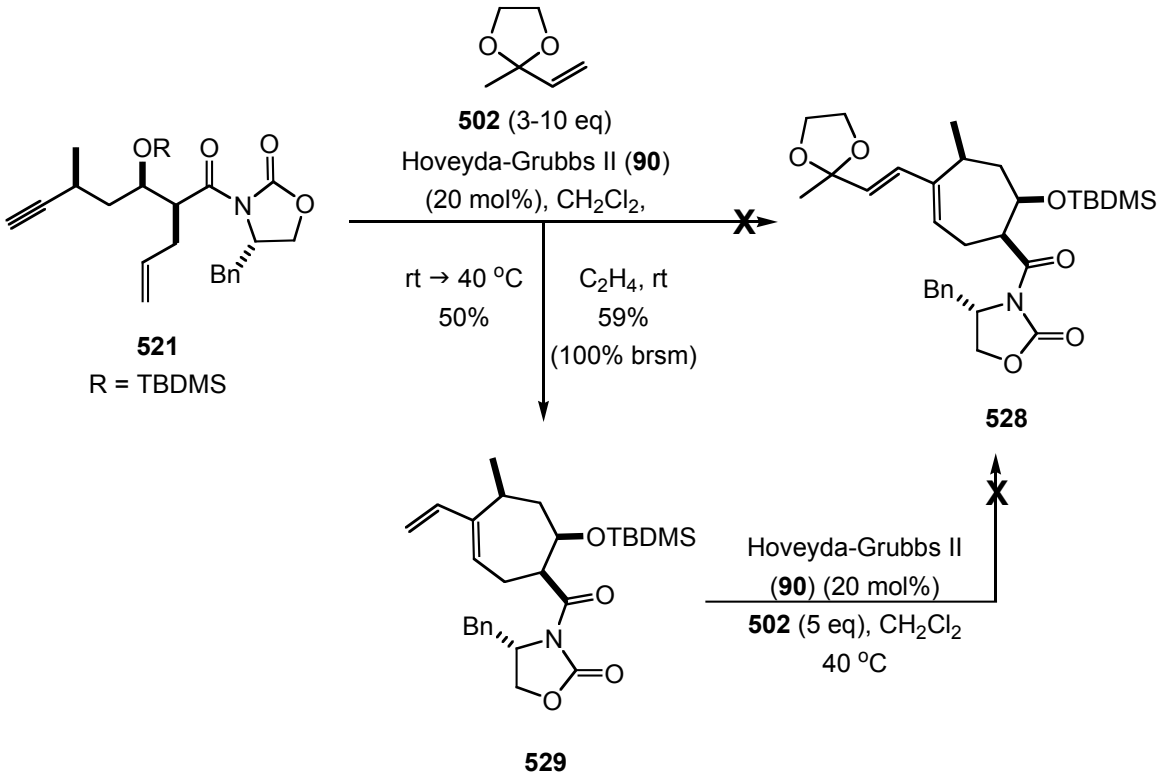


Encouraged by the formation of a small quantity of **525** and the potentially useful lactone **526**, we wondered whether this approach could be optimized to afford useful quantities of the desired aldol adduct **525**, despite having obtained poor yields of **525** in subsequent experiments. Following a series of personal communications with Dr. Andreas Reichelt of the Evans research group regarding the generality of the method, we recognized that this catalytic aldol protocol would require extensive optimization in order to achieve a viable route for the preparation of **525**.

With a suitable quantity of **521** in hand, we began to explore conditions to effect the key tandem RCEYM-CM.[231] Based on literature precedent,[231b] we conducted the metatheses in the presence of the Hoveyda-Grubbs second-generation catalyst **90**. In

accordance with our proposed retrosynthesis, we envisioned the CM reaction occurring with the protected enone **502**, as this alkene has been successfully utilized in simple olefin-olefin CM applications.[232] The results of these trials are presented in Scheme 133.

Scheme 133

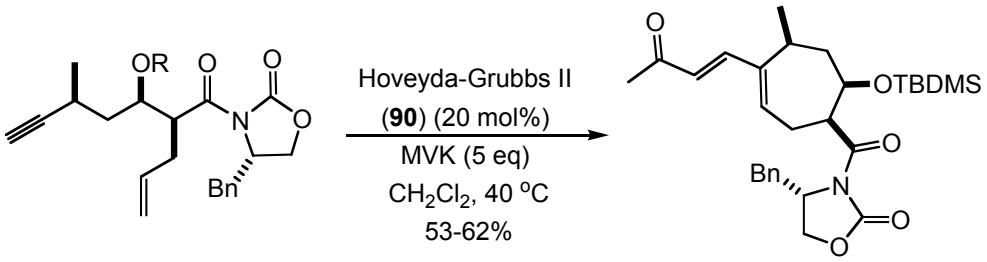


The RCEYM-CM of **521** with the alkene **502** failed to produce any of the desired adduct **528** regardless of the reaction temperature. Rather the simple RCEYM product **529**. In the absence of ethylene, the RCEYM afforded **529** in 50% yield as the only viable reaction product. The remainder of the mass balance was determined by mass spectroscopy to be a dimerization product. The metathesis reaction conducted in the presence of ethylene afforded **529** in 59% yield along with 41% of the recovered enyne **521**. Our inability to perform the tandem RCEYM-CM reaction led us to attempt the

sequential process between the conjugated diene moiety of **529** and the alkene **502**. Unfortunately the CM did not occur at this stage either.

These results of these unsuccessful experiments led us to hypothesize that the alkene coupling partner **502** was either too electron rich or too sterically encumbered to undergo the desired CM reaction. Similar reasoning has been applied to failed tandem RCEYM-CM reactions involving additional electron rich coupling partners such as styrene and allyltrimethylsilane.[231b,233] We therefore sought to perform the tandem process using the more electron deficient coupling partner methyl vinyl ketone (MVK). Exposure of a mixture of **521** and MVK to the Hoveyda-Grubbs second-generation catalyst **90** produced **530** in 62% yield (Scheme 134).

Scheme 134



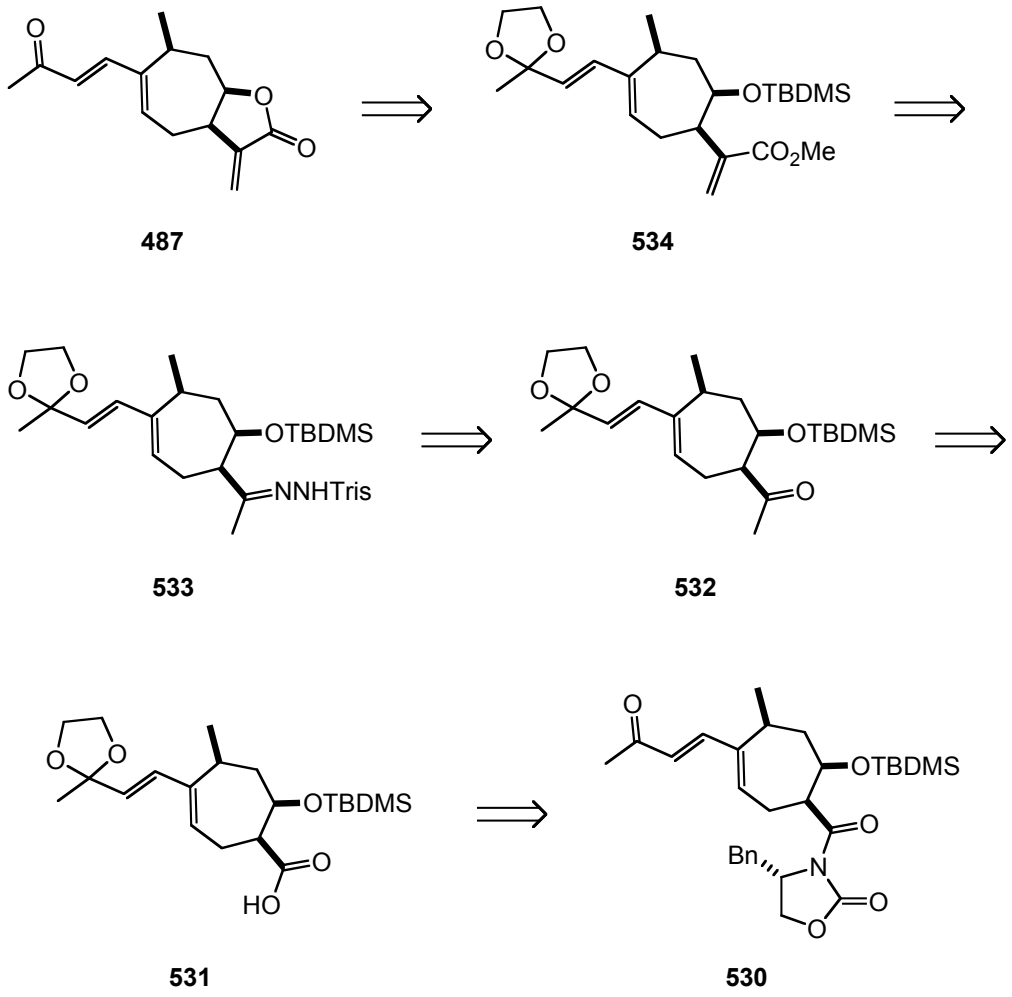
521
R = TBDMS

530

Pleased by our successful generation of a fully functionalized precursor of 8-*epi*-xanthatin, we wished to complete the total synthesis by conducting the cleavage of the oxazolidinone auxiliary to deliver the acid **531** or a related amide. We envisioned the conversion of **531** to the unsaturated ester **534** according to the retrosynthesis provided in Scheme 135. We planned to generate **531** with the enone carbonyl protected as the corresponding ketal, as it was unlikely that this moiety would survive the basic and nucleophilic conditions proposed during the later phases of our planned strategy.

Carboxylic acid **531** would then be elaborated to the methyl ketone **532**. Formation of the trisylhydrazone **533** and a subsequent Shapiro reaction employing Mander's reagent (MeO_2CCN) would deliver **534**. Under optimal conditions, we hoped to achieve the global deprotection of the silyl ether and ketal moieties using conditions that would permit the concomitant intramolecular lactonization to form 8-*epi*-xanthatin.

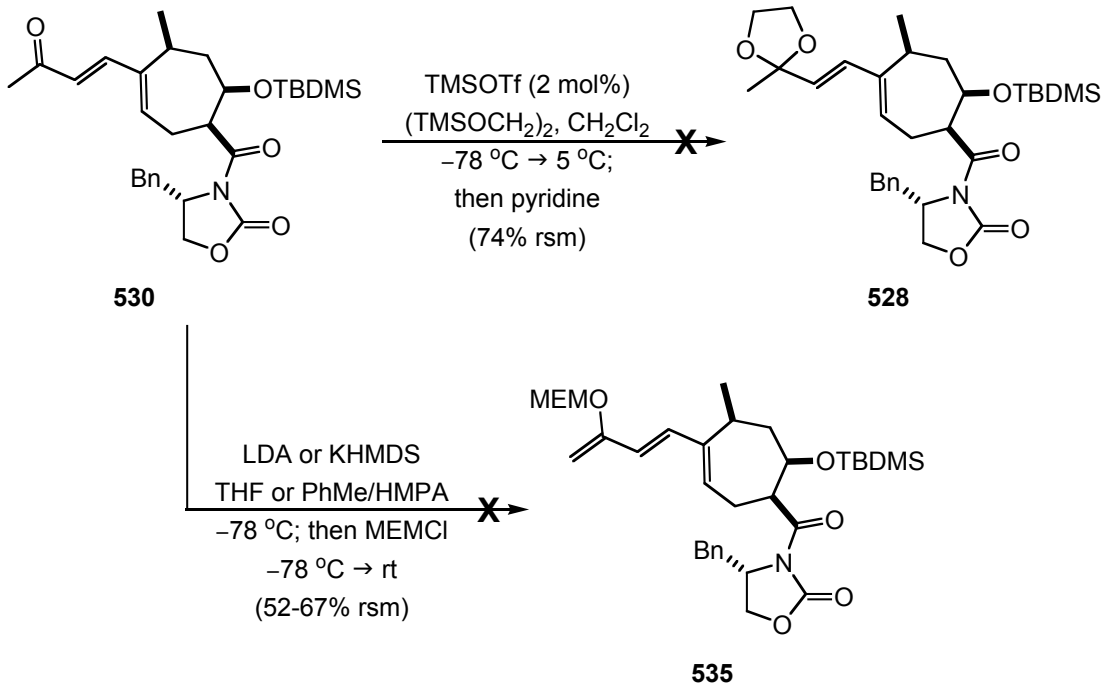
Scheme 135



In line with the proposed strategy for the assembly of **531**, we wished to protect the carbonyl group of the enone in **530** as the ketal. Despite reports in the literature regarding the poor yields generally obtained during the ketalization of conjugated

enones,[234] we attempted to prepare **528** using conditions reported by Hwu[235] for similar systems (Scheme 136). Protection of the enone carbonyl group as the corresponding MEM-enol ether was also attempted.

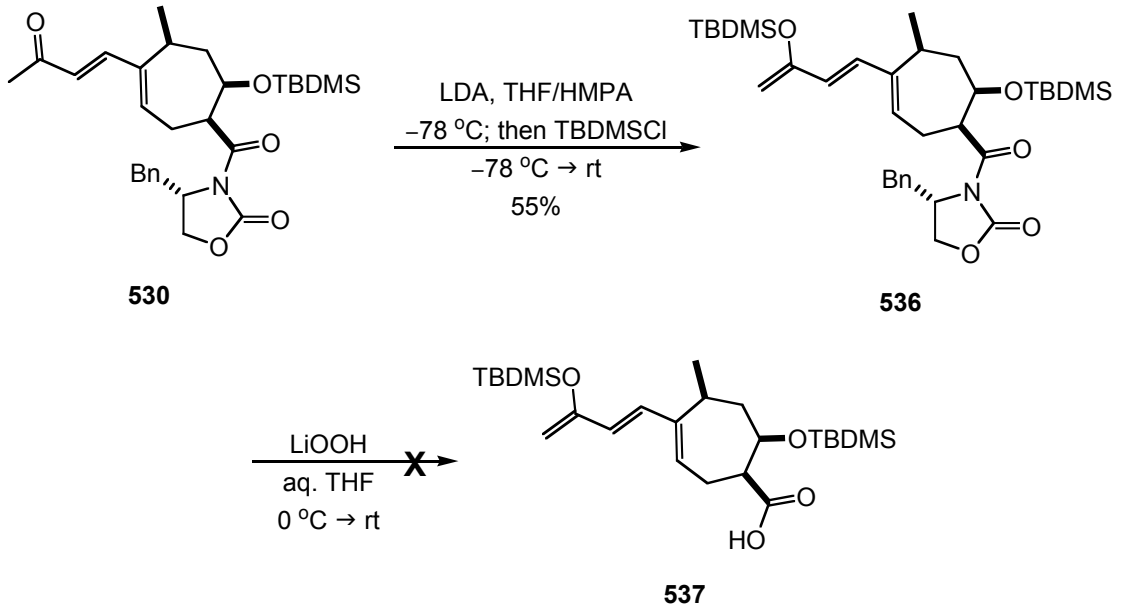
Scheme 136



In both instances, protection of the carbonyl group of the enone present in **524** was unsuccessful, resulting primarily in the recovery of starting material and some highly polar compounds. Although a minimal amount of time was invested trying to effect the protection steps presented in Scheme 136 due to the limited quantities of **530** on hand, we felt the remaining material would have the best chance of being protected as the silyl enol ether **536**. Similar protection of conjugated ketones as silyl enol ethers has been documented,[236] so we prepared **536**, albeit in a modest unoptimized yield, according to Scheme 137. However, attempted removal of the oxazolidinone moiety give the

corresponding acid **537** led to the decomposition of **536** and the formation of an intractable mixture, from which no identifiable compounds could be detected.

Scheme 137



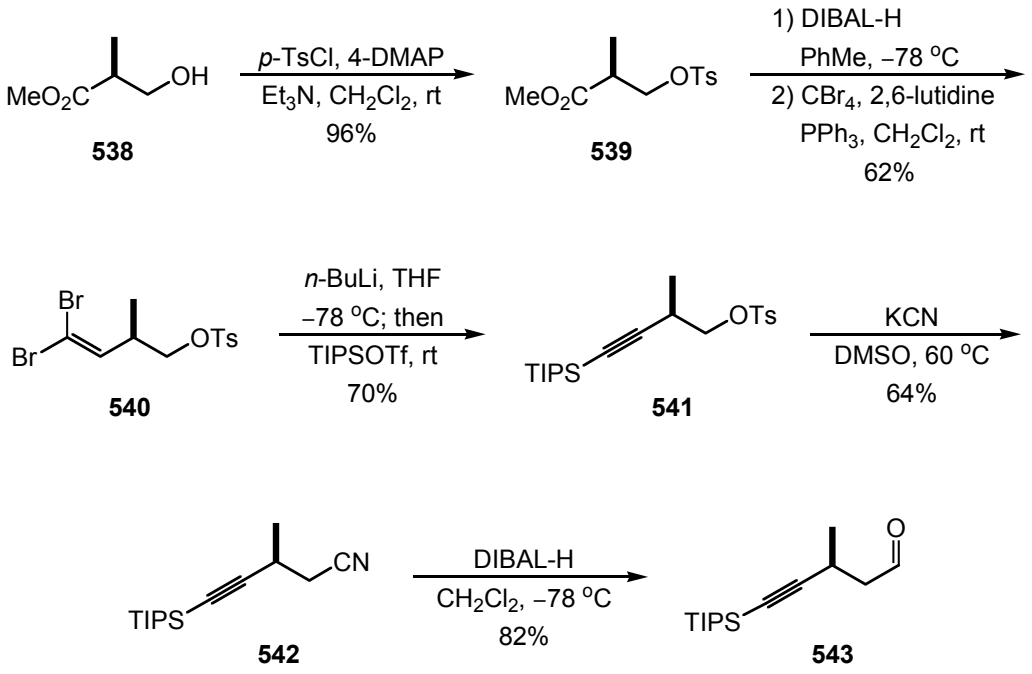
Owing to the decomposition of the small quantity of **536** that had been obtained, and the depletion of any late stage intermediates en route to 8-*epi*-xanthatin, this route was abandoned in favor of the final approach to the natural product.

4.3.4 The Final Route to 8-*epi*-Xanthatin

As mentioned previously, David Kummer began the exploration of an alternative route to 8-*epi*-xanthatin (**469**). In what was to become our final optimized route to the natural product,[237] Kummer began with the conversion of the commercially available ester **538** into the tosylate **539** (Scheme 138). Reduction of the ester moiety and application of the Corey-Fuchs homologation protocol to the resulting aldehyde delivered the vinyl dibromide **540**. Treatment of **540** with *n*-BuLi generated the corresponding lithium acetylide that was trapped with TIPSOTf to produce the alkyne **541**. The TIPS-

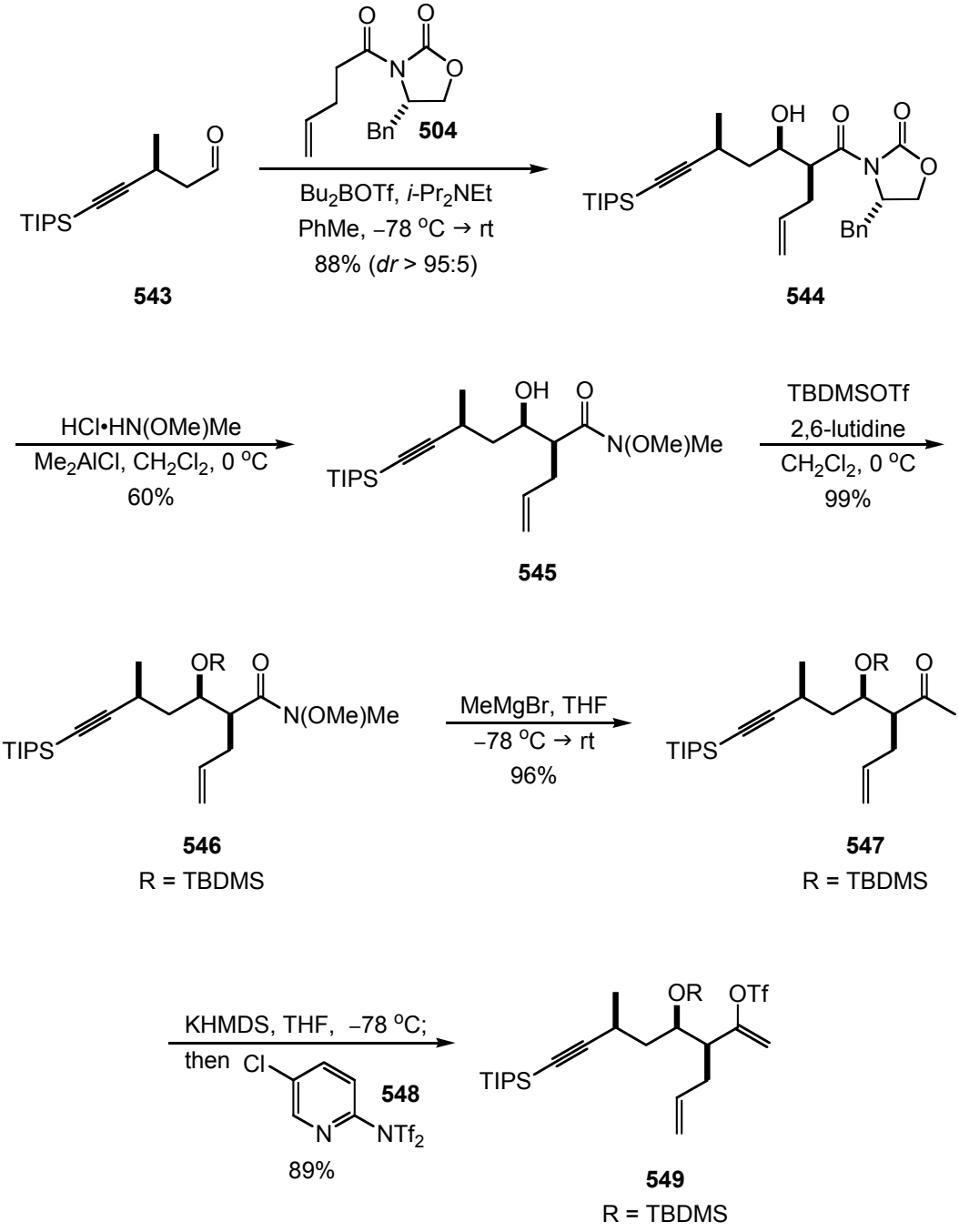
protecting group was utilized in place of the TMS-group in an effort to reduce the volatility of the early stage intermediates. Displacement of the primary tosylate with cyanide afforded the primary nitrile **542** in modest yield owing to competitive elimination of the tosylate under the reaction conditions. The nitrile **542** was then reduced to the aldehyde **543**.

Scheme 138



The aldol coupling reaction between **543** and **504** again proceeded in good yield to afford 5**44** with excellent diastereoselectivity (*dr* > 95:5) (Scheme 139). The *N*,*O*-dimethylamide **545** was prepared using the method of Weinreb.[238] Protection of the secondary alcohol in **544** and nucleophilic addition of MeMgBr to the amide delivered the ketone **547**. Generation of the corresponding enol triflate **549** was accomplished by the quenching of the kinetic enolate generated from **547** with the Comins reagent [*N*-(5-chloro-2-pyridyl)triflimide] (**548**).

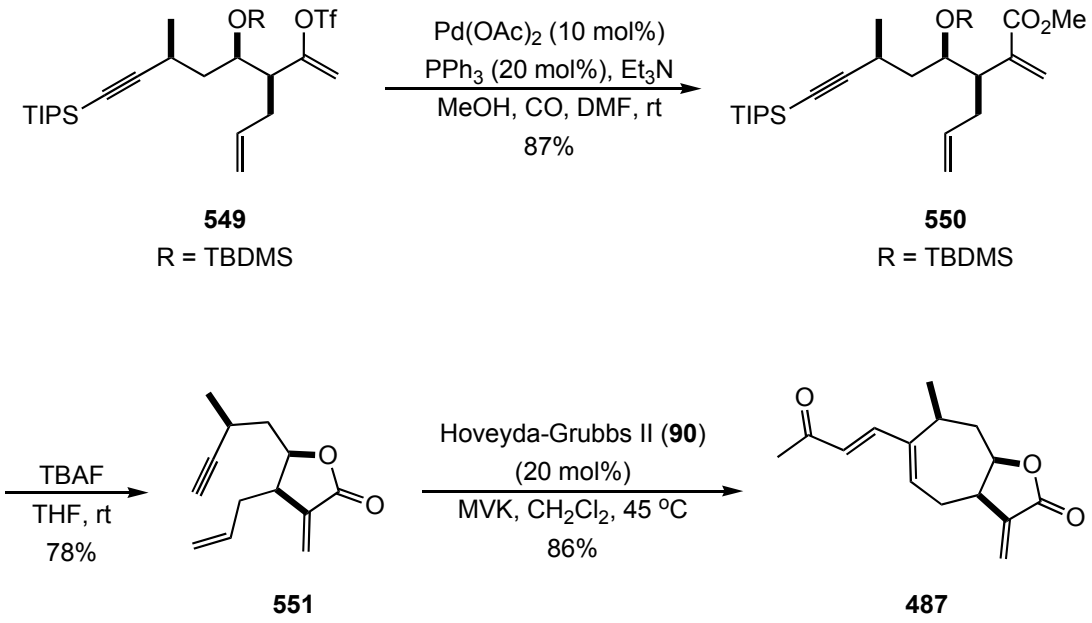
Scheme 139



A palladium-catalyzed carbonylation reaction of **549** delivered the α,β-unsaturated ester **550** in excellent yield (Scheme 140).[239] Of note, this strategy was successfully achieved in the presence of the pendant allyl and alkyne moieties without

competitive CO-insertion into these functionalities. Global deprotection of the silyl protecting groups was effected with tetrabutylammonium fluoride (TBAF) to liberate a secondary alcohol, which spontaneously underwent an intramolecular lactonization to provide **551**.[240] The tandem RCEYM-CM of **551** and MVK was executed in analogous fashion to the preparation of **530** (Scheme 134) to complete the total synthesis of 8-*epi*-xanthatin (**487**).[241]

Scheme 140



We have thus completed the first total synthesis of the cytotoxic xanthanolide **487**[242] in fourteen steps and 5.7% overall yield from commercially available **538**. The synthesis highlighted a tandem RCEYM-CM reaction to assemble the fully functionalized xanthanolide core.

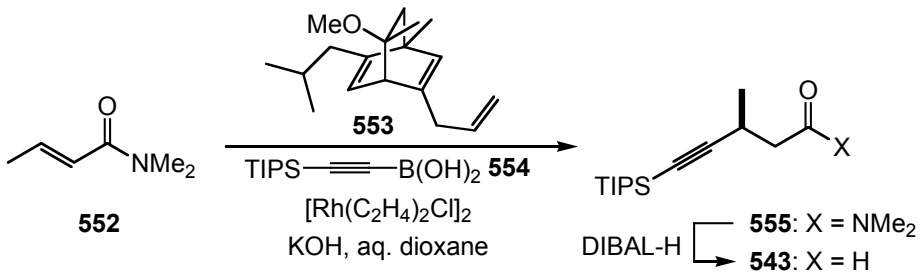
4.4 FUTURE DIRECTIONS

4.4.1 Potential Refinements to the Synthesis

With the total synthesis of 8-*epi*-xanthatin complete, we began to evaluate our synthetic route. Although quite efficient, the six-step sequence required for the conversion of **538** into the aldehyde **543** detracts somewhat from the brevity of our synthesis, especially when compared with the three-step sequence that had previously been used to prepare the related aldehyde **503**. As such, we are of course interested in the development of a synthetic protocol that would deliver **543** in fewer steps and higher overall yield.

A potential solution to this problem may be found in the work of Carreira[243] and Hayashi.[244] Both groups have demonstrated the rhodium catalyzed asymmetric conjugate addition of boronic acids to α,β-unsaturated amides in the presence of chiral dienes. The reactions thus far have been utilized to install aryl moieties, although Carreira does report the addition of a vinyl boronic acid to proceed in high yield and enantioselectivity. We envision the application of this method to the rapid two-step assembly of **543** according to Scheme 141. The rhodium(I)-catalyzed addition of the alkynyl boronic acid **554**[245] to the amide **552** should proceed in the presence of the known ligand **553** to afford the amide **555**. Reduction of the amide to the corresponding aldehyde will produce **543**. By analogy to the examples reported by Carreira and Hiyashi, the addition process should provide **543** with high enantioselectivity (>90% *ee*).

Scheme 141



4.5 SUMMARY

In summary, we have successfully completed the total synthesis of the xanthanolide natural product 8-*epi*-xanthatin (**487**). Our synthesis highlighted the utility of RCEYM in conjunction with CM to prepare the fully functionalized core of the xanthanolides. Furthermore, our approach to **487** constitutes the second and most efficient synthesis of a xanthanolide natural product to date. We hope that this new approach to the xanthanolide skeleton will gain favor in the synthetic community for the preparation of additional natural and non-natural xanthanolide antibiotics with the purpose of obtaining new potent cytotoxic agents for the treatment of various types of cancer.

CHAPTER 5: EXPERIMENTAL PROCUDURES

5.1 GENERAL FOR SYNTHETIC WORK

Unless otherwise indicated, all starting materials were obtained from commercial sources and used without further purification. Dichloromethane (CH_2Cl_2), *N,N,*-diisopropylethylamine (*i*-Pr_2NEt), triethylamine (Et_3N), pyridine, chlorotriethylsilane (TESCl), bis(trimethylsiloxy)ethane ($TMSO(CH_2)_2OTMS$), benzene (PhH), diisopropylamine (*i*-Pr_2NH), and 2,6-lutidine, 2,2,6,6-tetramethylpiperidine (TMP), and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) were distilled from calcium hydride and stored under nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through two columns of neutral alumina and stored under argon. Tetrahydropyran (THP) was dried and distilled from potassium-benzophenone ketyl. Methanol (CH_3OH) and acetonitrile (CH_3CN) was passed through two columns of molecular sieves and stored under argon. Toluene (PhMe) was first passed through a column neutral alumina, then through a column of Q5 reactant and stored under argon. Hexamethylphosphorus triamide (HMPA), dimethylsulfoxide (DMSO) and DMPU were distilled from CaH_2 and stored over sieves under argon. Thiophenol (PhSH), 2-methoxyethoxymethyl chloride (MEMCl) and methyl vinyl ketone (MVK) were distilled prior to use from $CaCl_2$ under reduced pressure. Triethylsilane (Et_3SiH) was purified by passage through a column of neutral Al_2O_3 and subsequent distillation from activated 4Å MS. Cyanotrimethylsilane (TMSCN) was freshly distilled from CaH_2 under an atmosphere of argon. Isopropanol (IPA) and propanol (*n*-PrOH) were distilled from BaO immediately prior to use. Trifluoroacetic anhydride (TFAA), triflic anhydride (Tf_2O), *tert*-butyldimethylsilyl triflate (TBDMSOTf), and triisopropylsilyl triflate (TIPSOTf) were distilled under argon

from P_2O_5. *Trans*-crotonyl chloride, *n*-propyl triflate (*n*-PrOTf), ethyl vinyl ether (EVE) and dibromomethane (CH_2Br_2) were distilled neat under an atmosphere of nitrogen. *N*-methylaniline (PhNHMe) was distilled twice from KOH pellets under an atmosphere of nitrogen. Iodotrimethylsilane (TMSI) was distilled from flame-dried copper powder under an atmosphere of argon, taking special precaution to exclude light from the entire distillation setup. $Ni(acac)_2$ was purified by dissolving in dry Et_2O and filtration through a medium porosity glass frit. The resulting filtrate was concentrated to dryness under reduced pressure and further dried under high vacuum at 100 ^oC. Oxygen (O_2) and carbon monoxide (CO) were dried by passage through a column of Drierite, 4Å molecular sieves, and KOH pellets prior to use. Titanium tetrachloride ($TiCl_4$) was purified by distillation and then volatile impurities were removed by three consecutive freeze-pump-thaw cycles under argon. Ytterbium(III) chloride hexahydrate ($YbCl_3 \cdot 6H_2O$) was pre-dried under reduced pressure (0.5 mm Hg) and 150 ^oC for 15 h. The resulting gray powder was subsequently flamed-dried under reduced pressure (0.5 mm Hg) until a finely divided white powder was obtained. Cerium(III) chloride hexahydrate ($CeCl_3 \cdot 6H_2O$) was pre-dried under reduced pressure (0.5 mm Hg) and 150 ^oC for 15 h.[246] All reactions were performed in flame-dried glassware under argon or nitrogen unless otherwise noted. All metatheses were performed in freshly distilled solvent, and degassed with a continuous stream of argon for a minimum of 15 minutes. All reaction temperatures are reported as the temperature of the surrounding bath.

^1H nuclear magnetic resonance (NMR) spectra were obtained at 500 MHz, 400 MHz or 300 MHz as solutions in $CDCl_3$ unless otherwise noted. ^{13}C NMR spectra were obtained at 125 MHz, 100 MHz or 75 MHz as solutions in $CDCl_3$ unless otherwise noted.

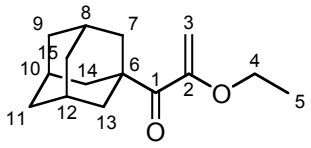
Chemical shifts are reported in parts per million (ppm, δ) and referenced to the solvent. Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s: singlet, d: doublet, t: triplet: q: quartet, m: multiplet, comp m: complex multiplet, br: broad. ^{1}H-NMR and ^{13}C-NMR peak assignments were made based on data obtained from 2D-NMR expirements (COSY and HMQC). Infrared (IR) spectra were obtained using a Perkin-Elmer FTIR 1600 spectrophotometer. IR spectra were taken neat on sodium chloride plates, and reported as wave numbers (cm^{-1}) unless otherwise noted. Low-resolution chemical ionization (CI) mass spectra were obtained with a Finnigan TSQ-70 instrument. High- resolution measurements were made with a VG Analytical ZAB2-E instrument.

Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica gel plates. The plates were visualized with ultraviolet (UV) light, potassium permanganate ($KMnO_4$), ammonium molybdate ceric ammonium nitrate (AmCAN), or ceric ammonium molybdate (CAM/Hanessians stain). Flash chromatography was performed according to the method of Still[247] using ICN Silitech 32-63 D 60A silica gel, Aldrich Activated Brockmann I, standard grade, 150 mesh, neutral or basic alumina.

5.2 α-BRANCHED ENONE PROJECT

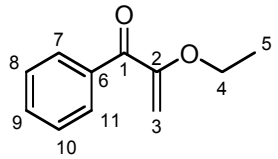
Representative Procedure for the Preparation of 279, 286, 295, and 299a-b: A solution of *tert*-BuLi (1.5 M in pentane) (10.8 mL, 16.2 mmol) was added dropwise to a stirred solution of freshly distilled ethyl vinyl ether (1.28 g, 17.8 mmol) in THF (20 mL) at –78 °C. The resulting bright yellow solution was stirred at –78 °C for 10 min, and then placed into a 0 °C bath. After 5 min, the solution was recooled to –78 °C,

and a solution of **298b** (1.21 g, 5.40 mmol) in THF (27 mL) was added *via* cannula. The reaction mixture was stirred at –78 °C for 2 h, whereupon MeOH (ca. 10 mL) was added and the reaction mixture was warmed to rt by removal of the cooling bath. The reaction mixture was poured onto H_2O (75 mL), and the resulting aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude residue that was purified by flash chromatography eluting with pentane/Et_2O (3:1, containing 2% v/v Et_3N) to afford 1.15 g (91%) of pure enol ether **299b** as a clear oil.



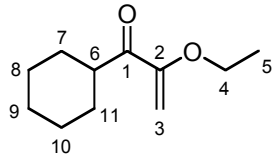
1-Adamantanyl-2-ethoxypropenone (299b). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.79 (d, *J* = 2.3 Hz, 1 H), 4.32 (d, *J* = 2.3 Hz, 1 H), 3.79 (q, *J* = 7.0 Hz, 2 H), 2.01-1.99 (m, 3 H), 1.95 (d, *J* = 2.8 Hz, 6 H), 1.74-1.67 (m, 6 H), 1.38 (t, *J* = 7.0 Hz, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 203.3, 160.4, 89.7, 63.3, 46.0, 37.7, 36.7, 28.1, 14.4; IR (neat) 2909, 1686, 1599, 1296, 1011 cm^{-1}; MS (CI) *m/z* 235.1696 [$C_{15}H_{23}O_2$ (M+1) requires 235.1698], 235 (base).

NMR Assignments. ^{1}H-NMR (500 MHz) δ 4.79 (d, *J* = 2.3 Hz, 1 H, C3-H), 4.32 (d, *J* = 2.3 Hz, 1 H, C3-H), 3.79 (q, *J* = 7.0 Hz, 2 H, C4-H), 2.01-1.99 (m, 3 H, C8-H), 1.95 (d, *J* = 2.8 Hz, 6 H, C7-H), 1.74-1.67 (m, 6 H, C9-H), 1.38 (t, *J* = 7.0 Hz, 3 H, C5-H); ^{13}C-NMR (125 MHz) δ 203.3 (C1), 160.4 (C2), 89.7 (C3), 63.3 (C4), 46.0 (C6), 37.7 (C7), 36.7 (C9), 28.1 (C8), 14.4 (C5).



2-Ethoxy-1-phenylpropenone (279). Purified by flash chromatography eluting with hexanes/EtOAc (9:1, containing 1% v/v Et_3N) to afford **279** as a pale yellow oil (88%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85-7.39 (comp, 5 H), 4.97 (d, *J* = 2.7 Hz, 1 H), 4.76 (d, *J* = 2.7 Hz, 1 H), 3.91 (q, *J* = 6.8 Hz, 2 H), 1.40 (t, *J* = 6.8 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.9, 158.3, 137.0, 132.8, 130.0, 128.3, 95.3, 64.1, 14.5; IR (neat) 2977, 1671, 1604, 1324, 1206, 1060, 982 cm^{-1}; MS (CI) *m/z* 177.0911 [$C_{11}H_{13}O_2$ (M+1) requires 177.0916], 105, 177 (base), 193.

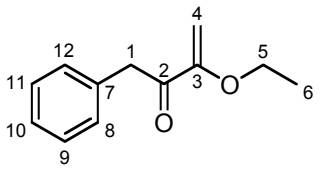
NMR Assignments. ^{1}H-NMR (400 MHz) δ 7.85-7.39 (comp, 5 H, C7-11-H), 4.97 (d, *J* = 2.7 Hz, 1 H, C3-H), 4.76 (d, *J* = 2.7 Hz, 1 H, C3-H), 3.91 (q, *J* = 6.8 Hz, 2 H, C4-H), 1.40 (t, *J* = 6.8 Hz, 3 H, C5-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.9 (C1), 158.3 (C2), 137.0 (C6), 132.8 (C8, C10), 130.0 (C9), 128.3 (C7, C11), 95.3 (C3), 64.1 (C4), 14.5 (C5).



1-Cyclohexyl-2-ethoxypropenone (286). Purified by flash chromatography eluting with hexanes/EtOAc (9:1, containing 2% v/v Et_3N) to afford **286** as a pale yellow oil (88%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.12 (d, *J* = 2.4 Hz, 1 H), 4.37 (d, *J* = 2.4 Hz, 1 H), 3.77 (q, *J* = 6.8 Hz, 2 H), 2.99-2.93 (m, 1 H), 1.79-1.63 (comp, 5 H), 1.35 (t, *J* = 6.8 Hz, 3 H), 1.32-1.16 (comp, 5 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.4, 157.6, 91.0,

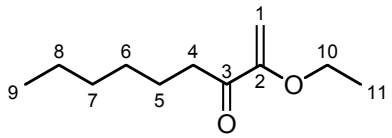
63.8, 45.1, 28.8, 26.8, 26.0, 14.5; IR (neat) 2932, 1702, 1607, 1281, 1061 cm^{-1}; MS (CI) *m/z* 183.1388 [$C_{11}H_{19}O_2$ (M+1) requires 183.1385], 111, 183, 191, 199 (base).

NMR Assignments. ^{1}H-NMR (500 MHz) δ 5.12 (d, *J* = 2.4 Hz, 1 H, C3-H), 4.37 (d, *J* = 2.4 Hz, 1 H, C3-H), 3.77 (q, *J* = 6.8 Hz, 2 H, C4-H), 2.99-2.93 (m, 1 H, C6-H), 1.79-1.63 (comp, 5 H, C7-9-H), 1.35 (t, *J* = 6.8 Hz, 3 H, C5-H), 1.32-1.16 (comp, 5 H, C7-9-H); ^{13}C-NMR (125 MHz) δ 201.4 (C1), 157.6 (C2), 91.0 (C3), 63.8 (C4), 45.1 (C6), 28.8 (C9), 26.8 (C8, C10), 26.0 (C7, C9), 14.5 (C5).



3-Ethoxy-1-phenylbut-3-en-2-one (295). Purified by flash chromatography eluting with hexanes/EtOAc (15:1, containing 2% v/v Et_3N) to afford **295** as a pale yellow oil (80%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.31-7.19 (comp, 5 H), 5.20 (d, *J* = 2.4 Hz, 1 H), 4.39 (d, *J* = 2.4 Hz, 1 H), 3.96 (s, 2 H), 3.78 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 195.3, 157.2, 134.2, 129.7, 128.4, 126.7, 91.3, 63.8, 44.8, 14.3; IR (neat) 2979, 1705, 1610, 1308, 1056 cm^{-1}; MS (CI) *m/z* 191.1069 [$C_{12}H_{15}O_2$ (M+1) requires 191.1072], 191 (base), 207.

NMR Assignments. ^{1}H-NMR (500 MHz) δ 7.31-7.19 (comp, 5 H, C8-12-H), 5.20 (d, *J* = 2.4 Hz, 1 H, C4-H), 4.39 (d, *J* = 2.4 Hz, 1 H, C4-H), 3.96 (s, 2 H, C1-H), 3.78 (q, *J* = 7.2 Hz, 2 H, C5-H), 1.38 (t, *J* = 7.2 Hz, 3 H, C6-H); ^{13}C-NMR (125 MHz) δ 195.3 (C2), 157.2 (C3), 134.2 (C7), 129.7 (C8, C10), 128.4 (C10), 126.7 (C9, C11), 91.3 (C4), 63.8 (C5), 44.8 (C1), 14.3 (C6).

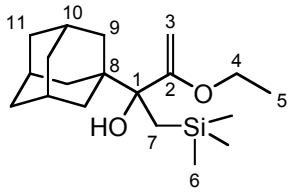


2-Ethoxynon-1-en-3-one (299a). Purified by flash chromatography eluting with hexanes/EtOAc (4:1, containing 1% v/v Et_3N) to afford **299a** as a -ale yellow oil (95%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.14 (d, *J* = 2.4 Hz, 1 H), 4.37 (d, *J* = 2.4 Hz, 1 H), 3.77 (q, *J* = 7.1 Hz, 2 H), 2.64 (t, *J* = 7.5 Hz, 2 H), 1.60-1.54 (m, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.32-1.23 (comp, 6 H), 0.86 (t, *J* = 7.3 Hz, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) 198.3, 157.8, 90.4, 63.6, 37.9, 31.6, 28.9, 23.8, 22.5, 14.3, 14.0; IR (neat) 2926, 1704, 1610, 1288, 1062 cm^{-1}; MS (CI) *m/z* 185.1541 [$C_{11}H_{21}O_2$ (M+1) requires 185.1542], 185 (base), 213, 369, 370.

NMR Assignments. ^{1}H-NMR (500 MHz) δ 5.14 (d, *J* = 2.4 Hz, 1 H, C1-H), 4.37 (d, *J* = 2.4 Hz, 1 H, C1-H), 3.77 (q, *J* = 7.1 Hz, 2 H, C10-H), 2.64 (t, *J* = 7.5 Hz, 2 H, C4-H), 1.60-1.54 (m, 2 H, C5-H), 1.36 (t, *J* = 7.1 Hz, 3 H, C11-H), 1.32-1.23 (comp, 6 H, C6-8-H), 0.86 (t, *J* = 7.3 Hz, 3 H, C9-H); ^{13}C-NMR (125 MHz) 198.3 (C3), 157.8 (C2), 90.4 (C1), 63.6 (C10), 37.9(C4), 31.6 (C7), 28.9 (C6), 23.8 (C5), 22.5 (C8), 14.3 (C11), 14.0 (C9).

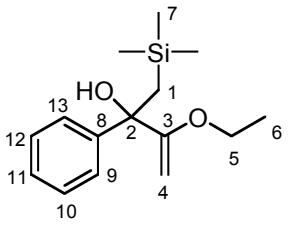
Representative Procedure for the Preparation of 282, 289, 296, and 300a-b: Anhydrous $CeCl_3$ (2.02 g, 8.20 mmol) was suspended in PhMe (41 mL) and the mixture was sonicated for 1 h. The resulting finely divided suspension was cooled to –78 °C, and then treated with a solution of $LiCH_2TMS$ (0.95 M in pentane) (8.4 mL, 8.0 mmol) *via* syringe. The resulting slurry was stirred for 1 h at –78 °C, whereupon a solution of enol ether **299b** (0.914 g, 3.90 mmol) in PhMe (5 mL) was added *via* cannula. The reaction mixture was stirred at –78 °C for 2 h, and then MeOH (ca. 5 mL) was

added. The reaction mixture was allowed to warm to rt by removal of the cooling bath and then filtered through a plug of Celite (1 cm), which was subsequently poured onto H_2O (100 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude residue that was purified by flash chromatography eluting with pentane/Et_2O (4:1, containing 2% v/v Et_3N) to afford 1.25 g (99%) of pure alcohol **300b** as a clear oil.



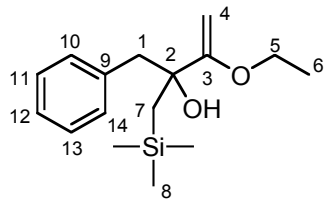
2-Adamantanyl-3-ethoxy-1-trimethylsilanylbut-3-en-2-ol (300b). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.03-4.01 (comp, 2 H), 3.68-3.63 (comp, 2 H), 2.50 (s, 1 H), 1.94 (s, 3 H), 1.67-1.49 (comp, 12 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.11-1.03 (comp, 2 H), -0.04 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 163.9, 82.5, 80.6, 62.8, 40.4, 37.4, 36.6, 29.1, 21.4, 14.8, 0.6; IR (neat) 3580, 2904, 1609, 1247, 1987, 844 cm^{-1}; MS (CI) *m/z* 323.2380 [$C_{19}H_{35}O_2Si$ (M+1) requires 323.2328], 187, 261 (base), 277, 307, 323.

NMR Assignments. ^{1}H-NMR (500 MHz) δ 4.03-4.01 (comp, 2 H, C3-H), 3.68-3.63 (comp, 2 H, C4-H), 2.50 (s, 1 H, -OH), 1.94 (s, 3 H, C10-H), 1.67-1.49 (comp, 12 H, C9, C11-H), 1.29 (t, *J* = 7.0 Hz, 3 H, C5-H), 1.11-1.03 (comp, 2 H, C7-H), -0.04 (s, 9 H, C6-H); ^{13}C-NMR (125 MHz) δ 163.9 (C2), 82.5 (C3), 80.6 (C1), 62.8 (C4), 40.4 (C8), 37.4 (C9), 36.6 (C11), 29.1 (C10), 21.4 (C7), 14.8 (C5), 0.6 (C6).



3-Ethoxy-2-phenyl-1-trimethylsilanylbut-3-en-2-ol (282). Purified by flash chromatography eluting with hexanes/EtOAc (9:1, containing 2% v/v Et_3N) to afford **282** as a pale yellow oil (93%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50-7.17 (comp, 5 H), 4.35 (d, *J* = 2.7 Hz, 1 H) 4.02 (d, *J* = 2.7 Hz, 1 H), 3.72-3.64 (comp, 2 H), 2.83 (s, 1 H), 1.56 (app d, *J* = 14.7 Hz, 1 H), 1.39 (dd, *J* = 14.7, 1.0 Hz, 1 H), 1.20 (t, *J* = 6.9 Hz, 3 H), -0.13 (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.9, 147.3, 127.9, 126.8, 125.5, 81.1, 78.0, 63.5, 30.3, 14.5, 0.3; IR (neat) 3571, 2955, 1621, 1251, 1072 cm^{-1}; MS (CI) *m/z* 265.1575 [$C_{15}H_{25}O_2Si$ (M+1) requires 265.1546], 175, 219, 247 (base), 248, 265.

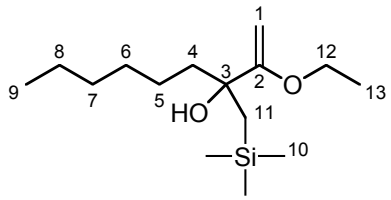
NMR Assignments. ^{1}H-NMR (400 MHz) δ 7.50-7.17 (comp, 5 H, C9-13-H), 4.35 (d, *J* = 2.7 Hz, 1 H, C4-H) 4.02 (d, *J* = 2.7 Hz, 1 H, C4-H), 3.72-3.64 (comp, 2 H, C5-H), 2.83 (s, 1 H, -OH), 1.56 (app d, *J* = 14.7 Hz, 1 H, C1-H), 1.39 (dd, *J* = 14.7, 1.0 Hz, 1 H, C1-H), 1.20 (t, *J* = 6.9 Hz, 3 H, C6-H), -0.13 (s, 9 H, C7-H); ^{13}C-NMR (100 MHz) δ 166.9 (C3), 147.3 (C8), 127.9 (C10, C12), 126.8 (C9, C13), 125.5 (C11), 81.1 (C4), 78.0 (C2), 63.5 (C5), 30.3 (C1), 14.5 (C6), 0.3 (C7).



3-Ethoxy-1-phenyl-2-trimethylsilanylmethylbut-3-en-2-ol (296). Purified by flash chromatography eluting with pentane/Et_2O (15:1, containing 1% v/v Et_3N) to afford **296** as a colorless oil (76%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.26-7.09 (comp, 5 H), 3.98

(d, J = 2.5 Hz, 1 H), 3.82 (d, J = 2.5 Hz, 1 H), 3.68 (app q, J = 7.0 Hz, 2 H), 3.15 (d, J = 13.1 Hz, 1 H), 2.73 (d, J = 13.1 Hz, 1 H), 1.80 (d, J = 1.2 Hz, 1 H), 1.33 (t, J = 7.0 Hz, 3 H), 1.30 (app d, J = 14.8 Hz, 1 H), 1.06 (d, J = 14.8 Hz, 1 H), 0.02 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 165.7, 137.2, 130.4, 128.0, 126.5, 80.3, 76.3, 62.6, 49.3, 29.5, 14.6, 0.1; IR (neat) 3561, 2956, 1617, 1246, 1089 cm^{-1}; MS (CI) *m/z* 279.1791 [$C_{16}H_{27}O_2Si$ (M+1) requires 279.1780], 261 (base), 279, 351.

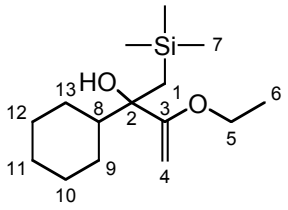
NMR Assignements. ^{1}H-NMR (500 MHz) δ 7.26-7.09 (comp, 5 H, C10-12-H), 3.98 (d, J = 2.5 Hz, 1 H, C4-H), 3.82 (d, J = 2.5 Hz, 1 H, C4-H), 3.68 (app q, J = 7.0 Hz, 2 H, C5-H), 3.15 (d, J = 13.1 Hz, 1 H, C1-H), 2.73 (d, J = 13.1 Hz, 1 H, C1-H), 1.80 (d, J = 1.2 Hz, 1 H, -OH), 1.33 (t, J = 7.0 Hz, 3 H, C6-H), 1.30 (app d, J = 14.8 Hz, 1 H, C7-H), 1.06 (d, J = 14.8 Hz, 1 H, C7-H), 0.02 (s, 9 H, C8-H); ^{13}C-NMR (125 MHz) δ 165.7 (C3), 137.2 (C9), 130.4 (C11, C13), 128.0 (C10, C14), 126.5 (C12), 80.3 (C4), 76.3 (C2), 62.6 (C5), 49.3 (C1), 29.5 (C7), 14.6 (C6), 0.1 (C8).



2-Ethoxy-3-trimethylsilanylmethylnon-1-en-3-ol (300a). Purified by flash chromatography eluting with hexanes/EtOAc (19:1, containing 1% v/v Et_3N) to afford **300a** as a pale yellow oil (94%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.17 (d, J = 2.4 Hz, 1 H), 3.89 (d, J = 2.4 Hz, 1 H), 3.72-3.63 (comp, 2 H), 1.91 (s, 1 H), 1.70-1.64 (m, 1 H), 1.54-1.49 (m, 1 H), 1.29-1.14 (comp, 12 H), 1.02 (d, J = 14.6 Hz, 1 H), 0.85 (t, J = 7.0 Hz, 3 H), 0.00 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 166.7, 79.2, 76.4, 62.8, 42.8, 31.8, 29.8,

29.6, 23.7, 22.6, 14.5, 14.1, 0.1; IR (neat) 3590, 2958, 1246, 1067 cm^{-1}; MS (CI) *m/z* 273.2089 [$C_{15}H_{33}O_2Si$ (M+1) requires 273.2093], 187, 211, 227, 255 (base), 273.

NMR Assignments. ^{1}H-NMR (500 MHz) δ 4.17 (d, *J* = 2.4 Hz, 1 H, C1-H), 3.89 (d, *J* = 2.4 Hz, 1 H, C1-H), 3.72-3.63 (comp, 2 H, C12-H), 1.91 (s, 1 H, -OH), 1.70-1.64 (m, 1 H, C4-H), 1.54-1.49 (m, 1 H, C4-H), 1.29-1.14 (comp, 12 H, C5-8, C11, C13-H), 1.02 (d, *J* = 14.6 Hz, 1 H, C11-H), 0.85 (t, *J* = 7.0 Hz, 3 H, C9-H), 0.00 (s, 9 H, C10-H); ^{13}C-NMR (125 MHz) δ 166.7 (C2), 79.2 (C1), 76.4 (C3), 62.8 (C12), 42.8 (C4), 31.8, 29.8 (C11), 29.6, 23.7, 22.6 (C5-C8), 14.5 (C13), 14.1 (C9), 0.1 (C10).

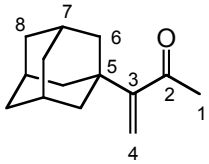


2-Cyclohexyl-3-ethoxy-1-trimethylsilanylbut-3-en-2-ol (289). Purified by flash chromatography eluting with pentane/Et_2O (15:1, containing 1% v/v Et_3N) to afford **289** as a pale yellow oil (81%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.15 (d, *J* = 2.2 Hz, 1 H), 3.92 (d, *J* = 2.2 Hz, 1 H), 3.70-3.61 (comp, 2 H), 1.85 (s, 1 H), 1.85-1.68 (comp, 3 H), 1.62-1.57 (comp, 2 H), 1.49-1.43 (m, 1 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.22-0.92 (comp, 7 H), -0.02, (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.1, 80.2, 78.5, 62.9, 47.9, 27.6, 27.1, 27.0, 26.8, 26.6, 26.5, 14.8, 0.3; IR (neat) 3585, 2930, 1613, 1450, 1244 cm^{-1}; MS (CI) *m/z* 271.2073 [$C_{15}H_{31}O_2Si$ (M+1) requires 271.2015], 181, 225, 253 (base), 271.

NMR Assignments. ^{1}H-NMR (400 MHz) δ 4.15 (d, *J* = 2.2 Hz, 1 H, C4-H), 3.92 (d, *J* = 2.2 Hz, 1 H, C4-H), 3.70-3.61 (comp, 2 H, C5-H), 1.85 (s, 1 H, -OH), 1.85-1.68 (comp, 3 H, ring-H), 1.62-1.57 (comp, 2 H, ring-H), 1.49-1.43 (m, 1 H, C8-H), 1.27 (t, *J* = 7.0 Hz, 3 H, C6-H), 1.22-0.92 (comp, 7 H, C1-H, ring-H), -0.02, (s, 9 H, C7-H); ^{13}C-NMR (100

MHz) δ 166.1 (C3), 80.2 (C4), 78.5 (C2), 62.9 (C5), 47.9 (C8), 27.6 (C11), 27.1 (C12), 27.0 (C10), 26.8 (C9), 26.6 (C13), 26.5 (C1, C9-C13), 14.8 (C6), 0.3 (C7).

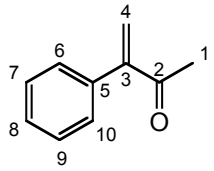
Representative Procedure for the Preparation of 278, 288, 297, and 301a-b: Freshly distilled 2,6-lutidine (1.22 g, 11.4 mmol) in CH_2Cl_2 (60 mL) was cooled to –45 ^oC, whereupon freshly distilled $TiCl_4$ (1.08 g, 5.70 mmol) was added dropwise via syringe. The resulting bright yellow solution was stirred at –45 ^oC for 15 min, and then a solution of **300b** (1.23 g, 3.80 mmol) in CH_2Cl_2 (15 mL) was added via cannula. The resulting dark brown solution was stirred at –45 ^oC for 2.5 h, whereupon a solution of aq. 1 N HCl (ca. 10 mL) was added, and the cooling bath was removed. The mixture was stirred at rt for an additional 10 min, and then washed with H_2O (100 mL). The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a crude residue that was purified by flash chromatography eluting with pentane/Et_2O (4:1) to afford 0.72 g (93%) of pure enone **301b** as a light yellow oil.



3-Adamantanylbut-3-en-2-one (301b). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1 H), 5.23 (s, 1 H), 2.23 (s, 3 H), 2.00-1.96 (m, 3 H), 1.80 (d, J = 2.9 Hz, 6 H), 1.73-1.64 (m, 6 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.4, 159.1, 120.1, 40.9, 37.7, 37.0, 30.3, 28.8; IR (neat) 2906, 1676, 1265, 1135 cm^{-1}; MS (CI) *m/z* 205.1593 [$C_{14}H_{21}O$ (M+1) requires 205.1592], 205 (base), 409.

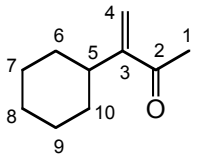
NMR Assignments. ^{1}H-NMR (400 MHz) δ 5.65 (s, 1 H, C4-H), 5.23 (s, 1 H, C4-H), 2.23 (s, 3 H, C1-H), 2.00-1.96 (m, 3 H, C7-H), 1.80 (d, J = 2.9 Hz, 6 H, C6-H), 1.73-1.64

(m, 6 H, C8-H); ^{13}C-NMR (100 MHz) δ 203.4 (C2), 159.1 (C3), 120.1 (C4), 40.9 (C6), 37.7 (C5), 37.0 (C8), 30.3 (C1), 28.8 (C7).



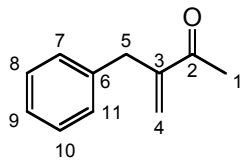
3-Phenyl-but-3-en-2-one (278). Purified by flash chromatography eluting with pentane/Et_2O (9:1) to afford **278** as an unstable pale yellow oil (72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (comp, 5 H), 6.16 (s, 1 H), 5.95 (s, 1 H), 2.43 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.7, 149.7, 137.3, 128.7, 128.4, 128.3, 126.1, 27.7; IR (neat) 3050, 2925, 1687, 1495, 1359, 1172 cm^{-1}; MS (CI) *m/z* 147.0811 [$C_{10}H_{11}O$ (M+1) requires 147.0810], 147 (base).

NMR Assignments. ^{1}H-NMR (400 MHz) δ 7.37-7.28 (comp, 5 H, C6-10-H), 6.16 (s, 1 H, C4-H), 5.95 (s, 1 H, C4-H), 2.43 (s, 3 H, C1-H); ^{13}C-NMR (100 MHz) δ 199.7 (C2), 149.7 (C3), 137.3 (C5), 128.7 (C6, C10), 128.4 (C8), 128.3 (C7, C9), 126.1 (C4), 27.7 (C1).



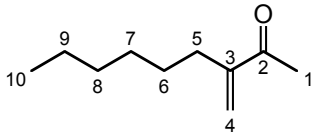
3-Cyclohexyl-but-3-en-2-one (288). Purified by flash chromatography eluting with pentane/Et_2O (9:1) to afford **288** as a clear oil (83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.96 (s, 1 H), 5.66 (s, 1 H), 2.54 (m, 1 H) 2.30 (s, 3 H), 1.75-1.65 (comp, 5 H), 1.39-1.28 (comp, 2 H), 1.18-0.99 (comp, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.2, 154.9, 122.9, 37.4, 32.9 26.8, 26.6, 26.5; IR (neat) 2925, 2852, 1679, 1449, 1358, 1274, 1146 cm^{-1}; MS (CI) *m/z* 153.1276 [$C_{10}H_{17}O$ (M+1) requires 153.1279], 153.

NMR Assignments. ^{1}H-NMR (400 MHz) δ 5.96 (s, 1 H, C4-H), 5.66 (s, 1 H, C4-H), 2.54 (m, 1 H, C5-H) 2.30 (s, 3 H, C1-H), 1.75-1.65 (comp, 5 H, ring-H), 1.39-1.28 (comp, 2 H, ring-H), 1.18-0.99 (comp, 3 H, ring-H); ^{13}C-NMR (100 MHz) δ 200.2 (C2), 154.9 (C3), 122.9 (C4), 37.4 (C5), 32.9 (C6, C10), 26.8 (C7, C9), 26.6 (C8), 26.5 (C1).



3-Benzyl-but-3-en-2-one (297). Purified by flash chromatography eluting with hexanes/EtOAc (15:1) to afford **297** as a clear oil (82%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29-7.14 (comp, 5 H), 6.07 (s, 1 H), 5.63 (t, J = 1.4 Hz, 1 H), 3.58 (s, 2 H), 2.33 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 199.1, 148.6, 139.1, 129.1, 128.4, 126.3, 126.2, 36.7, 25.9; IR (neat) 3015, 2922, 2354, 1675, 1365 cm^{-1}; MS (CI) *m/z* 161.0967 [$C_{11}H_{13}O$ (M+1) requires 161.0966], 161 (base).

NMR Assignments. ^{1}H-NMR (500 MHz) δ 7.29-7.14 (comp, 5 H, C7-9-H), 6.07 (s, 1 H, C4-H), 5.63 (t, J = 1.4 Hz, 1 H, C4-H), 3.58 (s, 2 H, C5-H), 2.33 (s, 3 H, C1-H); ^{13}C-NMR (125 MHz) δ 199.1 (C2), 148.6 (C3), 139.1 (C6), 129.1 (C7, C11), 128.7 (C8, C10), 126.3 (C9), 126.2 (C4), 36.7 (C5), 25.9 (C1).

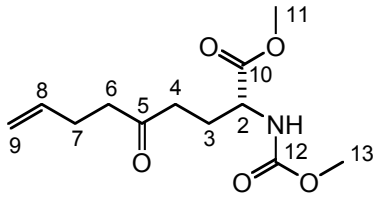


3-Methylene-nonan-2-one (301a). Purified by Kugelrohr distillation at 10 mm Hg (bp = 90-93 ^{o}C) to afford **301a** as a pale yellow oil (86%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.97 (s, 1 H), 5.72 (s, 1 H), 2.31 (s, 3 H), 2.22 (t, J = 7.6 Hz, 2 H), 1.40-1.23 (comp, 8 H), 0.85 (t, J = 6.7 Hz, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 200.2, 149.6,

124.9, 31.9, 30.8, 29.3, 28.6, 26.2, 22.8, 14.3; IR (neat) 2926, 2852, 1683, 1362, 1141 cm^{-1}; MS (CI) *m/z* 155.1441 [$C_{10}H_{19}O$ (M+1) requires 155.1436], 155.

NMR Assignments. ^{1}H-NMR (400 MHz) δ 5.97 (s, 1 H, C4-H), 5.72 (s, 1 H, C4-H), 2.31 (s, 3 H, C1-H), 2.22 (t, *J* = 7.6 Hz, 2 H, C5-H), 1.40-1.23 (comp, 8 H, C6-9-H), 0.85 (t, *J* = 6.7 Hz, 3 H, C10-H); ^{13}C-NMR (100 MHz) δ 200.2 (C2), 149.6 (C3), 124.9 (C4), 31.9 (C8), 30.8 (C5), 29.3 (C7), 28.6 (C6), 26.2 (C9), 22.8 (C1), 14.3 (C10).

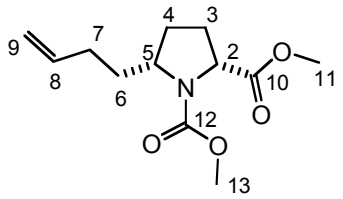
5.3 ANATOXIN-A



(2*R*)-Methoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (313). 4-Bromo-1-butene (72 μL, 0.71 mmol) was added to a stirred mixture of magnesium turnings (202 mg, 8.32 mmol) in THF (8.3 mL) at room temperature. The mixture was stirred for 10 min, and an additional portion of 4-bromo-1-butene (350 μL, 3.45 mmol) was added. The resulting mixture was stirred for an additional 15 min and then transferred via syringe to a flask containing TMEDA (3.8 mL, 25 mmol). The initially cloudy suspension was stirred until all precipitate had disappeared (5 min), whereupon the solution was transferred *via* syringe to a solution of **311**[248] (558 mg, 2.77 mmol) in THF (14 mL) at –78 ^{o}C. The reaction mixture was stirred for 1.5 h at –78 ^{o}C, and MeOH (5 mL) was added. The reaction mixture was then poured into a mixture of 10% H_3PO_4 (50 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash

chromatography (SiO_2) eluting with EtOAc/hexanes (2:1) to provide 465 mg (65%) of **313** as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, J = 16.8, 10.3, 6.5 Hz, 1 H), 5.29 (br s, 1 H), 5.04-4.93 (comp, 2 H), 4.30 (m, 1 H), 3.72 (s, 3 H), 3.65 (s, 3 H), 2.60-2.40 (comp, 4 H), 2.34-2.25 (comp, 2 H), 2.33-2.26 (m, 1 H), 1.96-1.84 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 172.5, 156.6, 136.8, 115.2, 53.2, 52.3, 52.2, 41.6, 38.3, 27.5, 26.0; IR (neat) 3345, 2952, 1713, 1640, 1528, 1443, 1359, 1264, 1219, 1062, 1000, 916, 781 cm^{-1}; mass spectrum (CI) *m/z* 258.1348 [$C_{12}H_{20}NO_5$ (M +1) requires 258.1342], 258, 240 (base), 226, 198.

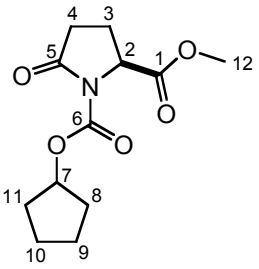
NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, J = 16.8, 10.3, 6.5 Hz, 1 H, C8-H), 5.29 (br s, 1 H, N-H), 5.04-4.93 (comp, 2 H, C9-H), 4.30 (m, 1 H, C2-H), 3.72 (s, 3 H, C13-H), 3.65 (s, 3 H, C11-H), 2.60-2.40 (comp, 4 H, C4-H, C6-H), 2.34-2.25 (comp, 2 H, C7-H), 2.33-2.26 (m, 1 H, C3-H), 1.96-1.84 (m, 1 H, C3-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8 (C5), 172.5 (C10), 156.6 (C12), 136.8 (C8), 115.2 (C9), 53.2 (C2), 52.3 (C11), 52.2 (C6), 41.6 (C4), 38.3 (C7), 27.5 (C3), 26.0 (C13).



(2*R*,5*R*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid dimethyl ester (315). $BF_3{\cdot}OEt_2$ (5.50 mL, 43.2 mmol) was added to a solution of Ph_3SiH (5.63 g, 21.6 mmol) in CH_2Cl_2 (14 mL) at room temperature. The solution was stirred for 5 min, and then transferred via cannula to a stirred solution of **313** (1.85 g, 7.21 mmol) in CH_2Cl_2 (24 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an

additional 2 h. The reaction mixture was recooled to –78 °C and poured into a mixture of sat. aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a clear oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to provide 1.62 g (93%) of **315** as a clear oil (*dr* = 16:1 by GC; major diast. rt = 17.13 min, minor diast. rt = 16.88 min). ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.90-5.78 (m, 1 H), 5.05 (app dd, *J* = 17.3, 1.8 Hz, 1 H), 4.96 (br d, *J* = 9.8 Hz, 1 H), 4.42-4.30 (m, 1 H), 4.01-8.85 (m, 1 H), 3.77-3.63 (comp, 6 H), 2.26-2.16 (m, 1 H), 2.14-1.90 (comp, 5 H), 1.78-1.68 (m, 1 H), 1.58-1.46 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.4, 155.6, 155.0, 138.1, 137.9, 114.7, 114.6, 60.0, 59.6, 58.8, 58.1, 52.4, 52.1, 33.5, 33.1, 30.5, 30.0, 29.3, 29.1, 28.1; IR (neat) 2955, 1754, 1704, 1450, 1385, 1202, 1175, 1112, 1000, 912, 773 cm^{-1}; mass spectrum (CI) *m/z* 242.1388 [$C_{12}H_{20}NO_4$ (M + 1) requires 242.1392], 242 (base), 210, 186, 168.

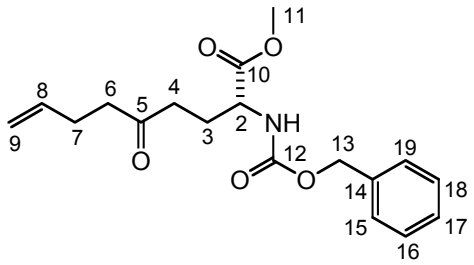
NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.90-5.78 (m, 1 H, C8-H), 5.05 (app dd, *J* = 17.3, 1.8 Hz, 1 H, C9-H), 4.96 (br d, *J* = 9.8 Hz, 1 H, C9-H), 4.42-4.30 (m, 1 H, C2-H), 4.01-8.85 (m, 1 H, C5-H), 3.77-3.63 (comp, 6 H, C11-H, C13-H), 2.26-2.16 (m, 1 H, C3-H), 2.14-1.90 (comp, 5 H, C3-H, C4-H, C6-H, C7-H), 1.78-1.68 (m, 1 H, C6-H), 1.58-1.46 (m, 1 H, C4-H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.4 (C10), 155.6 (C12), 155.0 (C12), 138.1 (C8), 137.9 (C8), 114.7 (C9), 114.6 (C9), 60.0 (C2), 59.6 (C2), 58.8 (C5), 58.1 C(5), 52.4 (C13), 52.1 (C11), 33.5 (C4), 33.1 (C4), 30.5 (C7), 30.0 (C6), 29.3 (C6), 29.1 (C3), 28.1 (C3).



(5*S*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid 1-cyclopentyl ester 2-methyl ester (319e). A 1.8 M solution cyclopentyl chloroformate in toluene (10 mL, 18.9 mmol) was added to a solution of **310** (1.02 g, 7.88 mmol), *i*-Pr_2NEt (1.85 mL, 10.644 mmol), and 4-DMAP (424 mg, 3.47 mmol) in dry CH_3CN (25 mL) at rt. The mixture was stirred for 18 h, whereupon the solvent was removed under reduced pressure. The crude residue was dissolved in EtOAc (10 mL) and poured into brine (40 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:1) to afford 1.185 g (59%) of **319e** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24-5.20 (m, 1 H), 4.62 (dd, *J* = 6.6, 2.8 Hz, 1 H), 3.75 (s, 3 H), 2.61 (dt, *J* = 19.9, 9.6 Hz, 1 H), 2.47 (ddd, *J* = 6.0, 4.6, 3.4 Hz, 1 H), 2.31 (ddt, *J* = 13.3, 10.2, 9.4 Hz, 1 H), 2.03 (ddt, *J* = 13.1, 9.6, 3.4 Hz, 1 H), 1.87-1.53 (comp, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.7, 150.5, 80.2, 58.6, 52.6, 32.6, 32.5, 31.0, 23.5, 23.4, 21.7; IR (neat) 2959, 1791, 1750, 1714, 1439, 1367, 1326, 1296, 1255, 1209, 1036, 995, 959, 775 cm^{-1}; MS (CI) *m/z* 256.1181 [$C_{12}H_{18}NO_5$ (M + 1) requires 256.1185], 284, 256, 188 144 (base).

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24-5.20 (m, 1 H, C7-H), 4.62 (dd, *J* = 6.6, *J* = 2.8 Hz, 1 H, C2-H), 3.75 (s, 3 H, C12-H), 2.61 (dt, *J* = 19.9, 9.6 Hz, C4-H), 2.47 (ddd, *J* = 6.0, 4.6, 3.4 Hz, C4-H), 2.31 (ddt, *J* = 13.3, 10.2, 9.4 Hz, C3-H), 2.03 (ddt,

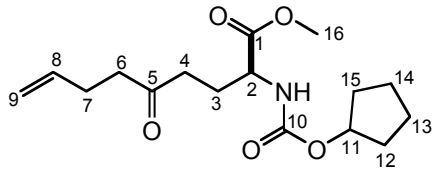
J = 13.1, 9.6, 3.4 Hz, C3-H), 1.87-1.53 (comp, 8 H, C8-H, C9-H, C10-H, C11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9 (C5), 171.7 (C1), 150.5 (C6), 80.2 (C7), 58.6 (C2), 52.6 (C12), 32.6 (C8, C11), 32.5 (C8, C11), 31.0 (C4), 23.5 (C9, C10), 23.4 (C9, C10), 21.7 (C3).



(2*R*)-Benzyloxycarbonylamino-5-oxonon-8-enoic acid methyl ester (320d). 4-Bromo-1-butene (1.0 mL, 9.85 mmol) was added to a stirred mixture of magnesium turnings (3.83 g, 158 mmol) in THF (160 mL) at rt. The mixture was stirred for 20 min, and an additional portion of 4-bromo-1-butene was added (7.0 mL, 69 mmol). The resulting mixture was stirred for an additional 30 min, and transferred via cannula to a flask containing TMEDA (24 mL, 158 mmol). The initially cloudy suspension was stirred until all precipitate had disappeared (5 min), whereupon the solution was transferred via cannula to a solution of **319d**[248] (14.6 g, 52.7 mmol) in THF (260 mL) at –78 ^{o}C. The mixture was stirred for1.5 h at –78 ^{o}C, and *i*-PrOH (35 mL) was added, and the reaction mixture was warmed to rt before pouring into a mixture of 10% H_3PO_4 (300 mL) and Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to provide 11.9 g (73%) of **320d** as a pale-yellow oil. $[\alpha]_D^{26}$ = +14.1 (c = 2.0, MeOH) ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (br d, J = 7.9

Hz, 0.9 H), 7.38-7.24 (comp, 5 H), 5.76 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1 H), 5.02 (s, 2 H), 4.97 (app dq, J = 17.2, 1.8 Hz, 1 H), 4.94-4.90 (m, 1 H), 4.01 (m, 1 H), 3.62 (s, 2.6 H), 3.55 (s, 0.4 H), 2.56-2.43 (comp, 4 H), 2.20-2.15 (comp, 2 H), 1.95-1.88 (m, 1 H), 1.76-1.68 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 208.7, 172.5, 156.0, 137.5, 136.9, 128.3, 127.8, 127.7, 115.0, 65.5, 53.1, 51.8, 40.8, 37.9, 27.2, 24.7; IR (neat) 3342, 2954, 2258, 1712, 1518, 1050, 913, 736 cm^{-1}; MS (CI) *m/z* 334.1642 [$C_{18}H_{24}NO_5$ (M + 1) requires 334.1655], 334, 316, 290 (base), 272, 182, 119.

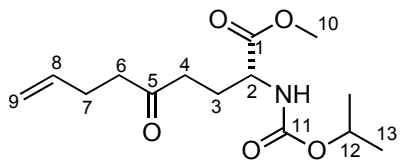
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (br d, *J* = 7.9 Hz, 0.9 H, NH), 7.38-7.24 (comp, 5 H, C15-C19-H), 5.76 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1 H, C8-H), 5.02 (s, 2 H, C13-H), 4.97 (app dq, J = 17.2, 1.8 Hz, 1 H, C9-H(*E*)), 4.94-4.90 (m, 1 H, C9-H(*Z*)), 4.01 (m, 1 H, C2-H), 3.62 (s, 2.6 H, C11-H (major rotamer)), 3.55 (s, 0.4 H, C11-H (minor rotamer)), 2.56-2.43 (comp, 4 H, C6-H, C4-H), 2.20-2.15 (comp, 2 H, C7-H), 1.95-1.88 (m, 1 H, C3-H(*R*), 1.76-1.68 (m, 1 H, C3-H(*S*)); ^{13}C NMR (125 MHz, DMSO-d_6) δ 208.7 (C5), 172.5 (C10), 156.0 (C12), 137.5 (C8), 136.9 (C14), 128.3 (C16,C18), 127.8 (C17), 127.7 (C15,C19), 115.0 (C9), 65.5 (C13), 53.1 (C2), 51.8 (C11), 40.8 (C4), 37.9 (C6), 27.2 (C7), 24.7 (C3).



2-Cyclopentyloxycarbonylamino-5-oxonon-8-enoic acid methyl ester (320e): A 2-neck flask was charged with magnesium turnings (113 mg, 4.65 mmol) and THF (5 mL) under N_2. To this stirred mixture was added a portion of 4-bromo-1-butene (50 μL, 0.49 mmol) at rt. After 25 min, the solution became greenish-black, and additional 4-bromo-1-butene was added (0.19 mL, 1.87 mmol). The resulting yellow solution was

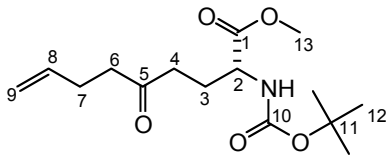
stirred an additional 20 min and then transferred via cannula to a stirred solution of **319e** (297 mg, 1.16 mmol) in THF (5.8 mL) at –78 °C. After 5 h at –78 °C, 10% H_3PO_4 (2 mL) was added, and the reaction mixture was poured into a mixture of brine (40 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to provide 213 mg (59%) of **320e** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 5.15-5.14 (br d, 1 H), 5.06-5.04 (br m, 1 H), 4.97 (dq, *J* = 15.5, 8.4, 1.6 Hz, 2 H), 4.30-4.29 (br m, 1 H), 3.72 (s, 3 H), 2.56-2.42 (comp, 4 H), 2.32-2.28 (comp, 2 H), 2.16-2.08 (m, 1 H), 1.92-1.85 (m, 1 H), 1.84-1.50 (comp, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8 (C5), 172.7, 156.1, 136.9, 115.3, 78.0, 53.2, 52.4, 41.9, 38.5, 32.7, 27.7, 26.5, 23.6; IR (neat) 3346, 2959, 1714, 1525, 1439, 1342, 1260, 1214, 1158, 1051, 913 cm^{-1}; MS (CI) *m/z* 312.1813 [$C_{16}H_{26}NO_5$ requires 312.1811], 312 (base), 294, 244, 182.

NMR Assignments ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.77 (ddt, *J* = 16.9, *J* = 10.2, *J* = 6.6 Hz, 1 H, C8-H), 5.15-5.14 (br d, 1 H, N-H), 5.06-5.04 (br m, 1 H, C11-H), 4.97 (dq, *J* = 15.5, 8.4, 1.6 Hz, 2 H, C9-H), 4.30-4.29 (m, 1 H, C2-H), 3.72 (s, 3 H, C16-H), 2.56-2.42 (comp, 4 H, C4-H, C6-H), 2.32-2.28 (comp, 2 H, C7-H), 2.16-2.08 (m, 1 H, C3-H), 1.92-1.85 (m, 1 H, C3-H), 1.84-1.50 (comp, 8 H, C12-H, C13-H, C14-H, C15-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8 (C5), 172.7 (C1), 156.1 (C10), 136.9 (C8), 115.3 (C9), 78.0 (C11), 53.2 (C2), 52.4 (C16), 41.9 (C6), 38.5 (C4), 32.7 (C12, C15) 27.7 (C7), 26.5 (C3), 23.6 (C13, C14).



(2*R*)-Isopropoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (320f) 4-Bromo-1-butene (0.70 mL, 6.9 mmol) was added to a stirred mixture of magnesium turnings (1.3 g, 52 mmol) in THF (55 mL) at room temperature. The mixture was stirred for 10 min, and an additional portion of 4-bromo-1-butene was added (2.0 mL, 20 mmol). The resulting mixture was stirred for an additional 1 h, whereupon the solution was transferred *via* cannula to a solution of **319f**[248] (2.0 g, 8.7 mmol) in THF (65 mL) at –78 ^{o}C over a 1 h period. Stirring was continued for an additional 1 h at –78 ^{o}C, whereupon a solution of sat. NH_4Cl (10 mL) was added. The reaction mixture was then poured into a mixture of brine (100 mL) and EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to provide 1.9 g (77%) of **320f** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83-5.75 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 5.22 (br d, *J* = 6.6 Hz, 1 H), 5.02 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1 H), 4.97 (ddd, *J* = 10.2, 3.0, 1.4 Hz, 1 H), 4.89 (hept, *J* = 6.0 Hz, 1 H), 4.32 (br d, *J* = 5.0 Hz, 1 H), 3.74 (s, 3 H), 2.59-2.46 (comp, 4 H), 2.35-2.30 (comp, 2 H), 2.20-2.11 (m, 1 H), 1.96-1.88 (m, 1 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 1.21 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$); 208.7, 172.7, 155.8, 136.9, 115.3, 68.6, 53.1, 52.4, 41.8, 38.4, 27.6, 26.4, 22.1, 22.0; IR (neat) 3349, 3077, 2981, 1714, 1642, 1524, 1438, 1375, 1209, 1180, 1112, 1043 cm^{-1}; mass spectrum (CI) *m/z* 286.1652 [$C_{14}H_{24}NO_5$ (M+1) requires 286.1654], 286 (base), 268, 244, 226, 200, 182, 144.

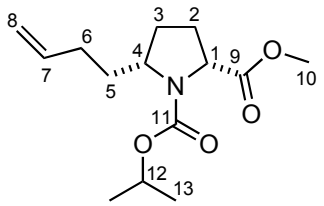
NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83-5.75 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H, C8-H), 5.22 (br d, *J* = 6.6 Hz, 1 H, N-H), 5.02 (ddd, *J* = 17.1, 3.4, 1.6 Hz, 1 H, C9-H), 4.97 (ddd, *J* = 10.2, 3.0, 1.4 Hz, 1 H, C9-H), 4.89 (hept, *J* = 6.0 Hz, 1 H, C12-H), 4.32 (br d, *J* = 5.0 Hz, 1 H, C2-H), 3.74 (s, 3 H, C10-H), 2.59-2.46 (comp, 4 H, C4-H, C6-H), 2.35-2.30 (comp, 2 H, C7-H), 2.20-2.11 (m, 1 H, C3-H), 1.96-1.88 (m, 1 H, C3-H), 1.23 (d, *J* = 6.3 Hz, 3 H, C13-H), 1.21 (d, *J* = 6.3 Hz, 3 H, C13-H); ^{13}C NMR (125 MHz, $CDCl_3$); 208.7 (C5), 172.7 (C1), 155.8 (C11), 136.9 (C8), 115.3 (C9), 68.6 (C12), 53.1 (C2), 52.4 (C10), 41.8 (C6), 38.4 (C4), 27.6 (C7), 26.4 (C3), 22.1 (C13), 22.0 (C13).



(2*R*)-1-*tert*-Butoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (320g). A 2-neck flask was charged with magnesium turnings (200 mg, 8.26 mmol) and THF (8 mL). To this stirred mixture was added a portion of 4-bromo-1-butene (0.10 mL, 0.99 mmol) at room temperature. After 15 min, an additional portion of 4-bromo-1-butene (0.32 mL, 3.15 mmol) was added. The resulting yellow solution was stirred for 10 min and then transferred via cannula to a stirred solution of **319g** (502 mg, 2.06 mmol) in THF (14 mL) at –78 ^{o}C. The mixture was stirred for 3 h at –78 ^{o}C, and then saturated NH_4Cl (5 mL) was added and the reaction mixture was poured into a mixture of H_2O (60 mL) and Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to provide 570 mg (92%) of **320g** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83-5.68 (m, 1 H), 5.12-4.75 (comp, 3 H), 4.28-4.17 (m, 1

H), 3.70-3.67 (comp, 3 H), 2.57-2.37 (comp, 4 H), 2.31-2.24 (comp, 2 H), 2.14-2.03 (m, 1 H), 1.99-1.78 (m, 1 H), 1.40-1.37 (comp, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 173.1, 155.7, 137.2, 115.6, 80.2, 53.1, 52.6, 42.1, 38.7, 28.5, 27.9, 26.7; IR (neat) 3465, 3064, 2984, 1741, 1707, 1392, 1363, 1169, 733 cm^{-1}; mass spectrum (CI) *m/z* 300.1805 [$C_{15}H_{26}NO_5$ (M+1) requires 300.1811], 300, 282, 244 (base), 200, 182.

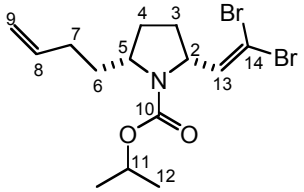
NMR Assignments. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83-5.68 (m, 1 H, C8-H), 5.12-4.75 (comp, 3 H, C9-H, N-H), 4.28-4.17 (m, 1 H, C2-H), 3.70-3.67 (comp, 3 H, C13-H), 2.57-2.37 (comp, 4 H, C4-H, C6-H), 2.31-2.24 (comp, 2 H, C7-H), 2.14-2.03 (m, 1 H, C3-H), 1.99-1.78 (m, 1 H, C3-H), 1.40-1.37 (comp, 9 H, C12-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0 (C5), 173.1 (C1), 155.7 (C10), 137.2 (C8), 115.6 (C9), 80.2 (C11), 53.1 (C2), 52.6 (C13), 42.1 (C6), 38.7 (C4), 28.5 (C12), 27.9 (C7), 26.7 (C3).



(2*R*,5*R*)-1-Isopropyl-2-methyl-5-(but-3-enyl)-pyrrolidine-1,2-dicarboxylate (321). A solution of $BF_3{\cdot}OEt_2$ (2.7 mL, 21 mmol) and Ph_3SiH (2.7 g, 11 mmol) in CH_2Cl_2 (5 mL) was added via syringe to a stirred solution of **320f** (1.0 g, 3.5 mmol) in CH_2Cl_2 (25 mL) at –78 ^{o}C. The reaction mixture was stirred at –78 ^{o}C for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 2 h. The reaction mixture was recooled to –78 ^{o}C and poured into a mixture of sat. aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a clear oil. The

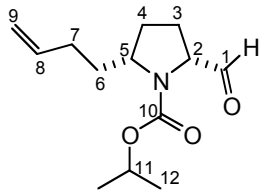
crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:4) to provide 941 mg (99%) of **321** (*dr* >30:1)[249] as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.86-5.79 (m, 1 H), 5.05-5.02 (m, 1 H), 5.00-4.85 (comp, 2 H), 4.40-4.24 (m, 1 H), 3.98-3.83 (m, 1 H), 3.72 (s, 3H), 2.27-1.89 (comp, 6 H), 1.79-1.72 (m, 1 H), 1.59-1.44 (m, 1 H), 1.27-1.12 (comp, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.7, 173.6, 154.8, 154.1, 138.2, 114.5, 68.7, 68.4, 59.8, 59.7, 59.4, 58.5, 57.8, 52.0, 33.7, 33.0, 30.7, 30.5, 30.1, 29.2, 28.9, 28.1, 22.3, 22.2, 22.1, 21.9; IR (neat) 2978, 2952, 1753, 1699, 1640, 1436, 1404, 1385, 1315, 1202, 1175, 1113, 998 cm^{-1}; mass spectrum (CI) *m/z* 270.1709 [$C_{14}H_{24}NO_4$ (M + 1) requires 270.1705], 270 (base), 228, 210, 184, 168, 128.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 5.86-5.79 (m, 1 H, C7-H), 5.05-5.02 (m, 1 H, C6-H), 5.00-4.85 (comp, 2 H, C6-H, C12-H), 4.40-4.24 (m, 1 H, C1-H), 3.98-3.83 (m, 1 H, C4-H), 3.72 (s, 3H, C10-H), 2.27-1.89 (comp, 6 H, C2-H, C3-H, C5-H, C6-H), 1.79-1.72 (m, 1 H, C3-H), 1.59-1.44 (m, 1 H, C2-H), 1.27-1.12 (comp, 6 H, C13-H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 173.7 (C9), 173.6 (C9), 154.8 (C11), 154.1 (C11), 138.2 (C7), 114.5 (C8), 68.7 (C12), 68.4 (C12), 59.8 (C1), 59.7 (C1), 58.5 (C4), 57.8 (C4), 52.0 (C10), 33.7 (C2), 33.0 (C2), 30.7 (C6), 30.5 (C6), 30.1 (C3), 29.2 (C3), 28.9 (C5), 28.1 (C5), 22.3 (C13), 22.2 (C13), 22.1 (C13), 21.9 (C13).



(2*R*,5*R*)-5-But-3-enyl-2-(2,2-dibromovinyl)-pyrrolidine-1-carboxylic acid isopropyl ester (337). A 1.0 M solution of DIBAL-H in toluene (1.6 mL, 1.6 mmol) was

added dropwise to a solution of **321** (393 mg, 1.46 mmol) in toluene (4 mL) at −78 °C. After 1 h at −78 °C, an additional portion of DIBAL-H (1.6 mL, 1.6 mmol) was added, and the mixture was stirred at −78 °C for 15 min. MeOH (0.5 mL) was added, and the mixture was poured into a solution of saturated Rochelle's salt (11 mL) and EtOAc (10 mL), The mixture was stirred at room temperature until the layers separated (1.5 h). The mixture was then poured into brine (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 X 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. The crude product was purified by flash chromatography (neutral Al_2O_3) eluting with EtOAc/hexanes (1:4) to provide 277 mg (79%) of the aldehyde **340** as a pale-yellow oil that was used immediately in the next reaction.

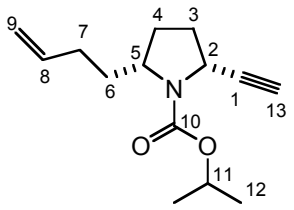


^{1}H-NMR (**340**) (300 MHz, $CDCl_3$) (2 rotamers) δ 9.57-9.37 (m, 1 H), 5.89-5.72 (m, 1 H), 5.07-4.86 (comp, 3 H), 4.31-3.82 (comp, 2 H), 2.22-1.33 (comp, 8 H), 1.30-1.12 (comp, 6 H); mass spectrum (CI) *m/z* 240.1594 [$C_{13}H_{21}NO_3$ (M + 1) requires 240.1599], 240 (base), 226, 198, 154.

NMR Assignments. ^{1}H-NMR (**340**) (300 MHz, $CDCl_3$) (2 rotamers) δ 9.57-9.37 (m, 1 H, C1-H), 5.89-5.72 (m, 1 H, C8-H), 5.07-4.86 (comp, 3 H, C9-H, C11-H), 4.31-3.82 (comp, 2 H, C2-H, C5-H), 2.22-1.33 (comp, 8 H, C3-H, C4-H, C6-H, C7-H), 1.30-1.12 (comp, 6 H, C12-H).

A solution of CBr_4 (420 mg, 1.26 mmol) and PPh_3 (662 mg, 2.52 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 ^oC. After 20 min, a solution of the proceeding aldehyde (151 mg, 0.631 mmol) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred with warming to room temperature for 29 h in the dark. The resulting slurry was concentrated in vacuo, diluted in a minimal amount of CH_2Cl_2 (1 mL), and purified by flash chromatography (neutral Al_2O_3) eluting with Et_2O/pentane (1:4) to provide 217 mg (87%) of **337** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.44-6.20 (m, 1 H), 5.88-5.72 (m, 1 H), 5.07-4.82 (comp, 3 H), 4.52-4.31 (m, 1 H), 3.96-3.76 (m, 1 H), 2.25-1.29 (comp, 8 H), 1.27-1.18 (comp, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 140.9, 138.3, 115.0, 83.3, 68.7, 60.6, 32.3, 30.8, 30.6, 29.4, 22.6, 22.4; mass spectrum (CI) *m/z* 396 (M+1)(base), 382, 354, 340, 294, 210.

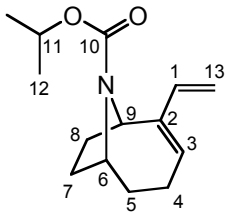
NMR Assignments. ^1H NMR (300 MHz, $CDCl_3$) δ 6.44-6.20 (m, 1 H, C13-H), 5.88-5.72 (m, 1 H, C8-H), 5.07-4.82 (comp, 3 H, C9-H, C11-H), 4.52-4.31 (m, 1 H, C2-H), 3.96-3.76 (m, 1 H, C5-H), 2.25-1.29 (comp, 8 H, C3-H, C4-H, C6-H, C7-H), 1.27-1.18 (comp, 6 H, C12-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3 (C10), 140.9 (C8), 138.3 (C13), 115.0 (C9), 83.3 (C1), 68.7 (C11), 60.6 (C5), 32.3 (C6), 30.8 (C7), 30.6 (C4), 29.4 (C3), 22.6 (C12), 22.4 (C12).



(2*R*)-But-3-enyl-(5*R*)-ethynylpyrrolidine-1-carboxylic acid isopropyl ester (337). A solution of 2.35 M *n*-BuLi in hexanes (218 μL, 0.511 mmol) was added to solution of trimethylsilymethyldiazomethane (295 μL, 0.589 mmol, 2 M in hexanes) in

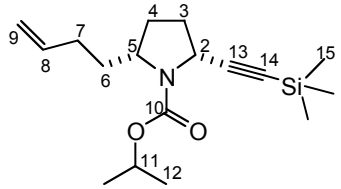
THF (1 mL) at −78 °C. The resulting light-yellow solution was stirred for 0.5 h at −78 °C, whereupon a solution of **340** (94 mg, 0.39 mmol) in THF (0.5 mL) was added, and the reaction mixture was allowed to warm to ambient temperature over 0 °C over a period of 2.5 h. The reaction mixture was quenched upon addition of a saturated solution of aq. NH_4Cl (2 mL) was added, and then poured into a mixture of brine (10 mL) and Et_2O (5 mL). The resulting aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:3) to afford 25 mg (27%) of **337** as a pale-yellow oil. ^{1}H NMR (500 MHz, Acetone-d_6) (2 rotamers) δ 5.89-5.81 (ddt, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.06-5.01 (m, 1 H), 4.93-4.91 (app d, J = 10.2 Hz, 1 H), 4.88-4.81 (m, 1 H), 4.56 (br s, 1 H), 3.83-3.78 (m, 1 H), 2.79 (s, 0.7 H), 2.76 (m, 0.3 H), 2.15-1.79 (comp, 7 H), 1.55 (br s, 1 H), 1.22-1.21 (comp, 6 H); ^{13}C NMR (125 MHz, Acetone-d_6) (2 rotamers) δ 154.7, 139.3, 114.8, 85.8, 71.3, 68.6, 58.7, 49.4, 35.0, 32.8, 30.9, 22.4; mass spectrum (CI) *m/z* 236.1651 [$C_{14}H_{22}NO_2$ (M + 1) requires 236.1651], 236 (base), 222, 194, 180.

NMR Assignments. ^{1}H NMR (500 MHz, Acetone-d_6) (2 rotamers) δ 5.89-5.81 (ddt, J = 17.1, 10.2, 6.6 Hz, 1 H, C8-H), 5.06-5.01 (m, 1 H, C9-H), 4.93-4.91 (app d, J = 10.2 Hz, 1 H, C9-H), 4.88-4.81 (m, 1 H, C11-H), 4.56 (br s, 1 H, C2-H), 3.83-3.78 (m, 1 H, C5-H), 2.79 (s, 0.7 H, C13-H major rotamer), 2.76 (m, 0.3 H, C13-H minor rotamer), 2.15-1.79 (comp, 7 H, C3-H, C4-H, C6-H, C7-H), 1.55 (br s, 1 H, C4-H), 1.22-1.21 (comp, 6 H, C12-H); ^{13}C NMR (125 MHz, Acetone-d_6) (2 rotamers) δ 154.7 (C10), 139.3 (C8), 114.8 (C9), 85.8 (C1), 71.3 (C13), 68.6 (C11), 58.7 (C5), 49.4 (C2), 35.0 (C4), 32.8 (C6), 30.9 (C3), 22.4 (C7).



2-Vinyl-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid isopropyl ester (341). A vial containing **337** (30 mg, 0.128 mmol) and **48** (11 mg, 0.0128 mmol) in dry, degassed toluene under an atmosphere of ethylene was heated with stirring at 80 °C for 3 h. The mixture was cooled to rt, and the solvent was removed in vacuo. The crude residue was purified by flash chromatography (neutral Al_2O_3) eluting with Et_2O/pentane (1:3) to afford 7 mg (25%) of **341** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$, 2 rotamers) δ 6.24 (ddd, *J* = 18.7, 11.2, 8.2 Hz, 1 H), 5.63 (m, 1 H), 5.20 (t, *J* = 16.9 Hz, 1 H), 4.98-4.82 (comp, 3 H), 4.43-4.33 (m, 1 H), 2.28-1.55 (comp m, 8 H), 1.23-1.19 (comp m, 6 H); MS (CI) *m/z* 236.1648 [$C_{14}H_{21}NO_2$ (M + 1) requires 236.1650], 250, 236 (base), 194.

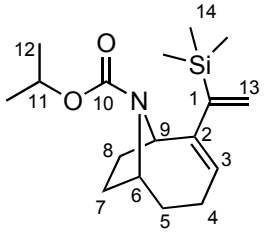
NMR Assignments. ^{1}H NMR (300 MHz, $CDCl_3$, 2 rotamers) δ 6.24 (ddd, *J* = 18.7, 11.2, 8.2 Hz, 1 H, C1-H), 5.63 (m, 1 H, C3-H), 5.20 (t, *J* = 16.9 Hz, 1 H, C9-H), 4.98-4.82 (comp, 3 H, C11-H, C13-H), 4.43-4.33 (m, 1 H, C6-H), 2.28-1.55 (comp m, 8 H, C4-H, C5-H, C8-H), 1.23-1.19 (comp m, 6 H, C12-H).



(2*R*,5*S*)-5-But-3-enyl-2-trimethylsilanylethynyl-pyrrolidine-1-carboxylic acid isopropyl ester (338). A 2.0 M solution of *n*-BuLi (0.44 mL, 8.8 mmol) in hexanes was added to a solution of **342** (165 mg, 0.418 mmol) in THF (5 mL) at –78 °C. The mixture was stirred for 1.5 h at –78 °C, and then TMSCl (60 μL, 0.46 mmol) was added. The

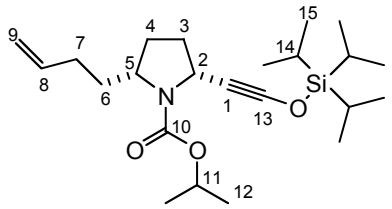
solution was stirred at −78 °C for 4.5 h, and then phosphate buffer (pH 7.4) (1 mL) was added and the reaction was poured into a mixture of brine (10 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a dark-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to provide 59 mg (46%) of **338** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.74 (m, 1 H), 5.06-4.85 (comp, 3 H), 4.61-4.42 (m, 1 H), 3.89-3.76 (m, 1 H), 2.16-1.50 (comp, 8 H), 1.25-1.20 (comp, 6 H), 0.13-0.09 (comp, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 138.4, 114.4, 86.1, 68.3, 57.8, 49.2, 34.1, 32.2, 30.1, 22.3, -0.01; mass spectrum (CI) *m/z* 308 (M+1) (base), 292, 266.

NMR Assignments. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88-5.74 (m, 1 H, C8-H), 5.06-4.85 (comp, 3 H, C9-H, C11-H), 4.61-4.42 (m, 1 H, C2-H), 3.89-3.76 (m, 1 H, C5-H), 2.16-1.50 (comp, 8 H, C3-H, C4-H, C6-H, C7-H), 1.25-1.20 (comp, 6 H, C12-H), 0.13-0.09 (comp, 9 H, C15-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (C10), 138.4 (C8), 114.4 (C9), 86.1 (C13), 68.3 (C11), 57.8 (C14), 49.2 (C5), 34.1 (C2), 32.2 (C6, C7), 30.1 (C3, C4), 22.3 (C12), -0.01 (C15).



2-(1-Trimethylsilanylvinyl)-9-azabicyclo[4.2.1]-non-2-ene-9-caboxylic acid isopropyl ester (339). A solution of **338** (26 mg, 0.085 mmol) in degassed PhMe (0.85 mL) was treated with one portion of solid **48** (4 mg, 4 μmol), and then the solution was

sparged for an additional 10 min. The mixture was then heated to 65 °C for 14 h. After cooling to room temperature, the solution was allowed to stir for 2 h exposed to the atmosphere, and then the solvent was removed under reduced pressure to afford a crude brown oil that was purified by flash chromatography (SiO_2) using gradient elution with hexanes and then EtOAc/hexanes (1:5) to afford 24 mg (91%) of **339** as a pale-yellow oil. ^{1}H NMR (300 MHz, *C*DCl_3) δ 5.60-5.31 (comp, 2 H), 4.97-4.84 (m, 1 H), 4.62-4.38 (br m, 1 H), 3.92-3.72 (br m, 1 H), 2.68-2.45 (m, 1 H), 2.34-2.13 (m, 1 H), 2.12-1.75 (comp, 4 H), 1.66-1.59 (dd, *J* = 6.3, 2.1 Hz, 3 H), 1.26-1.19 (app dd, *J* = 6.4, 3.6 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.4, 148.2, 127.6, 126.5, 68.2, 57.3, 49.5, 36.4, 31.3, 29.7, 22.3, 22.2, 18.0, -0.1; mass spectrum (CI) *m/z* 308 (M+1), 292, 264 (base), 238, 179.

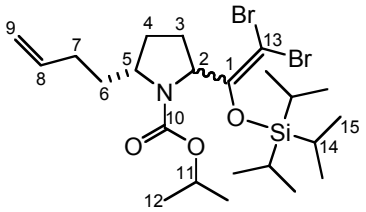


(2*R*,5*S*)-5-But-3-enyl-2-(triisopropylsilanyl-oxyethynyl)pyrrolidine-1-carboxylic acid isopropyl ester (352). A 2.2 M solution of *n*-BuLi in hexanes (0.83 mL, 1.8 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.0 mmol) in THF (3.4 mL) at 0 °C. The resulting light yellow solution was stirred at 0 °C for 5 min, then transferred dropwise via cannula to a solution of **321** (201 mg, 0.746 mmol) and dibromomethane (0.13 mL, 1.9 mmol) in THF (3.3 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h, whereupon 10% citric acid (1 mL) was added. The reaction was immediately poured into H_2O (15 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The

combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/hexanes (1:3) to afford 220 mg (72%) of **348** as an unstable pale-yellow oil. A portion of the product was immediately dissolved in THF under Ar to avoid decomposition and used in the next reaction.

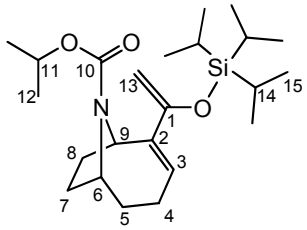
A solution of 2.2 M *n*-BuLi in hexanes (136 μL, 0.294 mmol) was added to solution of 1,1,1,3,3,3-hexamethyldisilazane (68 μL, 0.321 mmol) in THF (1.6 mL) at 0 ^oC. The resulting yellow LiHMDS solution was stirred for 10 min at 0 ^oC, and then transferred via cannula to a solution of **348** (110 mg, 0.268 mmol) in THF (1.4 mL) at –78 ^oC. The reaction mixture was stirred at –78 ^oC for 10 min, whereupon a solution of 1.6 M *t*-BuLi in pentane (0.36 mL, 0.56 mmol) was added. The resulting yellow solution was stirred at –78 ^oC for 1 h, and then freshly distilled TIPSOTf (0.16 mL, 0.59 mmol) was added. After stirring for an additional 10 min, the reaction mixture was diluted with pentane (5 mL) and quenched with saturated $NaHCO_3$ (1 mL) at –78 ^oC. After warming to ambient temperature, the reaction mixture was poured into H_2O (15 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to afford 26 mg (24%) of **352** as a pale-yellow oil along with 21 mg (19%) of **353**. ^1H NMR (500 MHz, PhMe-d_8, 100 ^oC) δ 5.87-5.79 (m, 1 H), 5.05-4.89 (comp, 3 H), 4.68-4.66 (m, 1 H), 3.80-3.78 (m, 1 H), 2.19-2.01 (comp, 2 H), 1.79-1.60 (comp, 4 H), 1.37-1.25 (comp, 2 H), 1.22-1.05 (comp, 27 H); ^{13}C NMR (125 MHz, PhMe-d_8, 100 ^oC) δ 154.5, 139.2, 114.4, 89.2, 68.0, 58.4, 49.4, 35.5, 34.0,

33.7, 30.9, 30.8, 22.5, 20.9, 20.7, 20.6, 20.4, 20.2, 20.1, 19.9, 18.1, 17.7, 12.6; IR (neat) 3058, 2944, 2865, 2262, 1688, 1262, 739 cm^{-1}; mass spectrum (CI) *m/z* 408.2935 [$C_{23}H_{41}NO_3Si$ (M + 1) requires 408.2934], 408 (base), 366, 279.



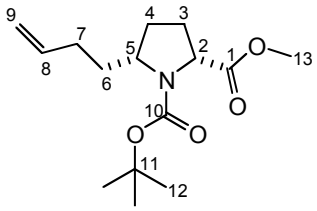
^{1}H NMR (**353**) (500 MHz, d_8-toluene, 363 K) δ 5.84-5.70 (m, 1 H), 5.05-4.88 (comp, 3 H), 4.69-4.66 (dd, *J* = 7.0, 2.2 Hz, 0.5 H), 4.62-4.59 (dd, *J* = 6.9, 2.5 Hz, 0.5 H), 3.79-3.73 (m, 1 H), 2.30-2.17 (m, 1 H), 2.05-1.78 (comp, 3 H), 1.70-1.60 (m, 1 H), 1.59-1.43 (comp, 3 H), 1.42-1.24 (comp, 6 H), 1.21-1.07 (comp, 21 H); mass spectrum (CI) requires *m/z* 567.12 [$C_{23}H_{41}Br_2NO_3Si$]; 568 (base), 524, 488, 446, 408.

NMR Assignments. (500 MHz, d_8-toluene, 363 K) δ 5.84-5.70 (m, 1 H, C8-H), 5.05-4.88 (comp, 3 H, C9-H, C11-H), 4.69-4.66 (dd, *J* = 7.0, 2.2 Hz, 0.5 H, C2-H), 4.62-4.59 (dd, *J* = 6.9, 2.5 Hz, 0.5 H, C2-H), 3.79-3.73 (m, 1 H, C5-H), 2.30-2.17 (m, 1 H, CH_2), 2.05-1.78 (comp, 3 H, CH_2), 1.70-1.60 (m, 1 H, CH_2), 1.59-1.43 (comp, 3 H, C14-H), 1.42-1.24 (comp, 6 H, C12-H), 1.21-1.07 (comp, 21 H, C15-H, ring CH_2).



2-(1-Triisopropylsilanyloxyvinyl)-9-azabicyclo-[4.2.1]non-2-ene-9-carboxylic acid isopropyl ester (363). A screw-capped vial containing **352** (20 mg, 0.049 mmol) and **48** (8 mg, 10 μmol) in PhMe was sparged with ethylene for 10 min. The vial was

then heated with stirring under an atmosphere of ethylene (balloon) at 70 °C for 5 h. The mixture was cooled to room temperature, and then DMSO (1 mL) was added. The solution was stirred for 16 h at room temperature, and then concentrated under reduced pressure. The remaining residue was purified by flash chromatography (neutral Al_2O_3) eluting with Et_2O/pentane (1:3) to afford 11 mg (55%) of **363** as a pale-yellow oil. ^{1}H NMR (500 MHz, PhMe-d_8, 2 rotamers) δ 6.37-6.29 (dt, J = 16.3, 6.0 Hz, 1 H), 5.16-5.15 (d, J = 8.0 Hz, 0.3 H), 5.08-4.98 (m, 1 H), 4.90-4.88 (d, J = 7.6 Hz, 0.7 H), 4.66 (s, 0.3H), 4.52-4.46 (comp, 1.3 H), 4.36 (s, 0.3 H), 4.27-4.22 (comp, 1.2 H), 2.27-2.12 (comp, 1.3 H), 2.11-1.69 (comp, 4 H), 1.69-1.62 (m, 1 H), 1.42-1.04 (comp, 29 H); ^{13}C NMR (125 MHz, PhMe-d_8) δ 156.9, 153.5, 144.2, 127.2, 126.4, 91.0, 89.8, 67.8, 67.5, 57.3, 56.4, 55.7, 55.1, 34.0, 32.5, 32.3, 31.3, 31.1, 29.8, 23.8, 23.6, 22.4, 22.3, 18.4, 13.3; mass spectrum (CI) *m/z* 408.2933 [$C_{23}H_{41}NO_3Si$ (M + 1) requires 408.2934], 448, 436, 408 (base), 394, 364, 348, 322.

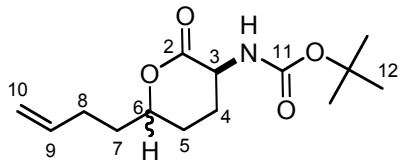


(2*R*,5*R*)-1-*tert*-Butyl-2-methyl-5-(but-3-enyl)-pyrrolidine-1,2-dicarboxylic

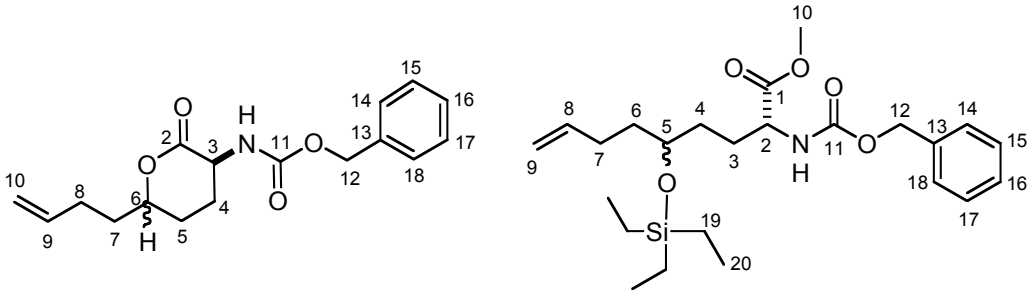
(365) $B(C_6F_5)_3$ (8.2 mg, 0.02 mmol) was added to a solution of Ph_3SiH (92 mg, 0.35 mmol) in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred for 10 min, and then added via cannula to a stirred solution of **320g** (48 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C. The mixture was maintained in a –78 °C bath for 0.5 h, whereupon the cooling-bath was removed, and stirring was continued at room temperature for an additional 2 h. The mixture was then recooled to –78 °C and an additional 1 mL of a pre-

mixed solution of $B(C_6F_5)_3$ (8.2 mg, 0.02 mmol) and Ph_3SiH (92 mg, 0.35 mmol) was added via cannula. The solution was stirred at –78 °C for 10 min, and then the cooling bath was removed and stirring was continued at room temperature for 11 h. Et_3N (0.1 mL) was added and stirring was continued for 20 min. The mixture was poured into a solution of 10% H_3PO_4 (20 mL) and Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 8 mL). The combined organic layers were dried ($MgSO_4$), filtered through a 2 cm plug of SiO_2 with Et_2O (40 mL), and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to provide 44 mg (97%) of **365** (*dr* = >95:5, by ^{1}H NMR) as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1 H), 4.98 (app dq, *J* = 17.2, 1.7 Hz, 1 H), 4.96-4.93 (m, 1 H), 4.21 (t, *J* = 7.5 Hz, 1 H), 3.82-3.77 (m, 1 H), 3.65-3.61 (comp, 3 H), 2.20-1.83 (comp, 6 H), 1.70-1.65 (m, 1 H), 1.52-1.44 (m, 1 H), 1.38 (s, 9 H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 °C) δ 172.6, 152.7, 138.0, 113.8, 78.4, 59.1, 57.3, 50.9, 32.7, 29.4, 28.7, 27.6; IR (neat) 2974, 1754, 1697, 1390, 1172, 1115, 710, 513 cm^{-1}; mass spectrum (CI) *m/z* 284.1860 [$C_{15}H_{26}NO_4$ (M + 1) requires 284.1862], 284 (base), 228, 184.

NMR Assignments ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1 H, C8-H)), 4.98 (app dq, *J* = 17.2, 1.7 Hz, 1 H, C9-H), 4.96-4.93 (m, 1 H, C9-H), 4.21 (t, *J* = 7.5 Hz, 1 H, C2-H), 3.82-3.77 (m, 1 H, C5-H), 3.65-3.61 (comp, 3 H, C13-H), 2.20-1.83 (comp, 6 H, C3-H, C4-H, C6-H, C7-H), 1.70-1.65 (m, 1 H, C4-H), 1.52-1.44 (m, 1 H, C6-H), 1.38 (s, 9 H, C12-H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 °C) δ 172.6 (C1), 152.7 (C10), 138.0 (C8), 113.8 (C9), 78.4 (C11), 59.1 (C2), 57.3 (C5), 50.9 (C13), 32.7 (C6), 29.4 (C7), 28.7 (C4), 27.6 (C3, C12).



(6-But-3-enyl-2-oxotetrahydropyranyl)-(3*S*)-carbamic acid *tert*-butyl ester (391). A mixture of $B(C_6F_5)_3$ (5 mg, 0.02 mmol) and purified Et_3SiH (64 μL, 0.802 mmol) in CH_2Cl_2 (0.4 mL) was added via cannula to a solution of **320g** (60 mg, 0.20 mmol) in CH_2Cl_2 (0.7 mL) at –78 °C, then stirring was continued for an additional 20 min at –78 °C before the cooling bath was removed. The mixture was stirred at rt for 1 h, whereupon the reaction was returned to a –78 °C bath and treated with an additional solution of $B(C_6F_5)_3$ (5 mg, 0.02 mmol) and purified Et_3SiH (64 μL, 0.802 mmol) in CH_2Cl_2 (0.4 mL). The reaction was stirred at –78 °C for 20 min, then at rt for 14 h, whereupon Et_3N (50 μL) was added via syringe and the solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 51 mg (90%) of **365** (previously reported) as a clear oil along with 3 mg (6%) of two separable diastereomers of **391** (*dr* = 2:1) as white solids. MS (CI +) *m/z* 270 (M + 1), 214 (M – *tert*-butyl + 1) (base).



(6-But-3-enyl-2-oxotetrahydropyranyl)-(3*S*)-carbamic acid benzyl ester (393), (2*R*)-Benzyloxycarbonylamino-5-triethylsilanyloxynon-8-enoic acid methyl ester (394). A mixture of $B(C_6F_5)_3$ (4 mg, 8 μmol) and purified Et_3SiH (50 μL, 0.31 mmol) in CH_2Cl_2 (0.4 mL) was added via cannula to a solution of **320d** (52 mg, 0.16

mmol) in CH_2Cl_2 (0.5 mL) at –78 °C, then stirring was continued for an additional 25 min at –78 °C before the cooling bath was removed. The mixture was stirred at rt for 1 h, whereupon the reaction was returned to a –78 °C bath and treated with an additional solution of $B(C_6F_5)_3$ (4 mg, 8 μmol) and purified Et_3SiH (50 μL, 0.31 mmol) in CH_2Cl_2 (0.4 mL). The reaction was stirred at –78 °C for 25 min, then at rt for 20 h, whereupon Et_3N (100 μL) was added via syringe and the solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to afford 19 mg (38%) of **392** as a clear oil (previously described) along with 12 mg (16%) of **394** as a pale yellow oil and two separable diastereomers of **393** (20 mg) (43%, *dr* = 4:1) as white solids. ^{1}H-NMR (400 MHz, $CDCl_3$) (**394**) δ 7.37-7.26 (comp, 5 H), 5.83-5.71 (m, 1 H), 5.38 (br d, *J* = 8.0 Hz, 1 H), 5.09 (s, 2 H), 5.02-4.89 (comp, 2 H), 4.40-4.31 (m, 1 H), 3.77-3.58 (comp, 4 H), 2.12-1.94 (comp, 2 H), 1.93-1.81 (m, 1 H), 1.79-1.65 (m, 1 H), 1.57-1.32 (comp, 4 H), 0.93 (t, *J* = 10.8 Hz, 9 H), 0.62-0.52 (comp, 6 H).

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (**394**) δ 7.37-7.26 (comp, 5 H, C14-C18-H), 5.83-5.71 (m, 1 H, C8-H), 5.38 (br d, *J* = 8.0 Hz, 1 H, NH), 5.09 (s, 2 H, C12-H), 5.02-4.89 (comp, 2 H, C9-H), 4.40-4.31 (m, 1 H, C2-H), 3.77-3.58 (comp, 4 H, C5-H, C10-H), 2.12-1.94 (comp, 2 H, C7-H), 1.93-1.81 (m, 1 H, C3-H), 1.79-1.65 (m, 1 H, C3-H), 1.57-1.32 (comp, 4 H, C4-H, C6-H), 0.93 (t, *J* = 10.8 Hz, 9 H, C20-H), 0.62-0.52 (comp, 6 H, C19-H).

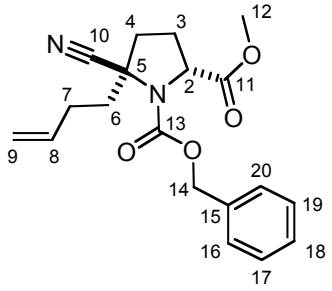
^{1}H-NMR (400 MHz, $CDCl_3$) (**393-major**) δ 7.39-7.26 (comp, 5 H), 5.82-5.70 (m, 1 H), 5.67-5.80 (br m, 1 H), 5.11 (s, 2 H), 5.07-4.97 (comp, 2 H), 4.52-4.33 (comp, 2 H), 2.67-

2.54 (m, 1 H), 2.29-2.10 (comp, 2 H), 2.07-1.94 (m, 1 H), 1.86-1.48 (comp, 4 H); MS (CI –) m/z 340 (M + Cl), 338 (M + Cl) (base), 304 (M + 1).

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (**393-major**) δ 7.39-7.26 (comp, 5 H, C14-C18-H), 5.82-5.70 (m, 1 H, C9-H), 5.67-5.80 (br m, 1 H, NH), 5.11 (s, 2 H, C12-H), 5.07-4.97 (comp, 2 H, C10-H), 4.52-4.33 (comp, 2 H, C3-H, C6-H), 2.67-2.54 (m, 1 H, C4-H), 2.29-2.10 (comp, 2 H, C8-H), 2.07-1.94 (m, 1 H, C5-H), 1.86-1.48 (comp, 4 H, C4-H, C5-H, C7-H).

^{1}H-NMR (400 MHz, $CDCl_3$) (**393-minor**) δ 7.38-7.27 (comp, 5 H), 5.77 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H), 5.50 (br s, 1 H), 5.11 (s, 2 H), 5.08-4.96 (comp, 2 H), 4.38 (app br s, 1 H), 4.13 (m, 1 H), 2.54-2.43 (m, 1 H), 2.30-2.10 (comp, 2 H), 2.08-1.95 (m, 1 H), 1.88-1.62 (comp, 4 H).

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (**393-minor**) δ 7.38-7.27 (comp, 5 H, C14-C18-H), 5.77 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H, C9-H), 5.50 (br s, 1 H, NH), 5.11 (s, 2 H, C12-H), 5.08-4.96 (comp, 2 H, C10-H), 4.38 (app br s, 1 H, C3-H), 4.13 (m, 1 H, C6-H), 2.54-2.43 (m, 1 H, C4-H), 2.30-2.10 (comp, 2 H, C8-H), 2.08-1.95 (m, 1 H, C5-H), 1.88-1.62 (comp, 4 H, C4-H, C5-H, C7-H).

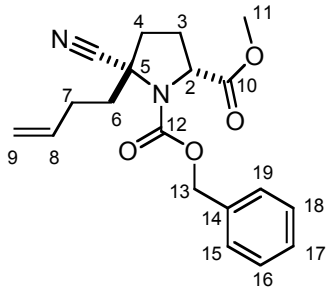


5-But-3-enyl-5-cyanopyrrolidine-1-benzyloxycarbonyl-(2*R*)-methyl ester (397). A mixture of $B(C_6F_5)_3$ (6 mg, 12 μmol) and TBDMSCN (40 mg, 0.28 mmol) in CH_2Cl_2 (0.4 mL) was added via cannula to a solution of **320d** (48 mg, 0.14 mmol) in

CH_2Cl_2 (0.5 mL) at –78 °C, then stirring was continued for an additional 25 min at –78 °C before the cooling bath was removed. The mixture was stirred at rt for 1 h, whereupon the reaction was returned to a –78 °C bath and treated with an additional solution of $B(C_6F_5)_3$ (6 mg, 12 μmol) and TBDMSCN (40 mg, 0.28 mmol) in CH_2Cl_2 (0.4 mL). The reaction was stirred at –78 °C for 25 min, then at rt for 20 h, whereupon Et_3N (100 μL) was added via syringe and the solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to afford 24 mg (49%) of ***cis*-397** as a clear oil and 23 mg (47%) of ***trans*-397** also as a clear oil. ^{1}H-NMR (500 MHz, DMSO-d_6, 100 °C) (***cis*-397**) δ 7.38-7.29 (comp, 5 H), 5.83 (ddt, J = 16.8, 10.3, 6.5 Hz, 1 H), 5.15 (app q, J = 12.6 Hz, 2 H), 5.06 (app dd, J = 17.2, 1.7 Hz, 1 H), 4.99 (app dd, J = 10.2, 1.6 Hz, 1 H), 4.59 (dd, J = 8.8, 2.8 Hz, 1 H), 3.62 (s, 3 H), 2.51-2.42 (comp, 2 H), 2.38-2.29 (m, 1 H), 2.24-2.17 (comp, 3 H), 2.09-2.04 (m, 1 H), 1.98-1.91 (m, 1 H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.2, 152.2, 136.4, 135.5, 127.8, 127.4, 126.9, 119.2, 114.9, 66.6, 60.4, 60.0, 51.5, 35.9, 35.1, 27.6, 26.7.

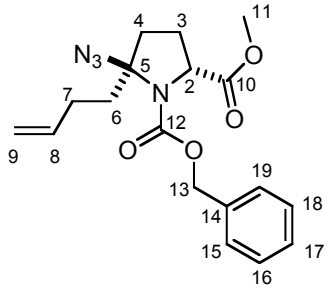
NMR Assignments. ^{1}H-NMR (500 MHz, DMSO-d_6, 100 °C) (***cis*-397**) δ 7.38-7.29 (comp, 5 H, C16-C20-H), 5.83 (ddt, J = 16.8, 10.3, 6.5 Hz, 1 H, C8-H), 5.15 (app q, J = 12.6 Hz, 2 H, C14-H), 5.06 (app dd, J = 17.2, 1.7 Hz, 1 H, C9-H), 4.99 (app dd, J = 10.2, 1.6 Hz, 1 H, C9-H), 4.59 (dd, J = 8.8, 2.8 Hz, 1 H, C2-H), 3.62 (s, 3 H, C12-H), 2.51-2.42 (comp, 2 H, C6-H, C4-H), 2.38-2.29 (m, 1 H, C3-H), 2.24-2.17 (comp, 3 H, C4-H, C7-H), 2.09-2.04 (m, 1 H, C3-H), 1.98-1.91 (m, 1 H, C6-H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.2 (C11), 152.2 (C13), 136.4 (C8), 135.5 (C15), 127.8 (C17,

C19), 127.4 (C18), 126.9 (C16, C20), 119.2 (C10), 114.9 (C9), 66.6 (C14), 60.4 (C5), 60.0 (C2), 51.5 (C12), 35.9 (C4), 35.1 (C6), 27.6 (C7), 26.7 (C3).



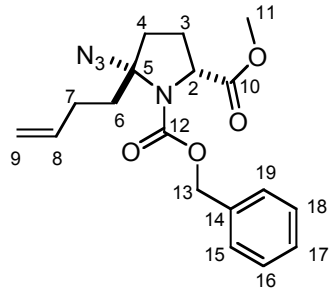
^{1}H-NMR (400 MHz, $CDCl_3$) (***trans*-397**) δ 7.43-7.38 (m, 1 H), 7.37-7.26 (comp, 4 H), 5.82-5.58 (m, 1 H), 5.12 (app d, *J* = 12.3 Hz, 0.4 H), 5.20 (app d, *J* = 12.3 Hz, 1 H), 5.12-4.93 (comp, 2.6 H), 4.49 (dd, *J* = 8.2, 2.7 Hz, 0.4 H), 4.43 (dd, *J* = 7.9, 2.7 Hz, 0.6 H), 3.74 (s, 1 H, rotameric CO_2Me signal), 3.57 (s, 2 H, rotameric CO_2Me signal), 2.60-2.41 (comp, 2 H), 2.39-1.95 (comp, 5 H), 1.86-1.76 (m, 1 H); MS (CI) m/z 343.1646 [$C_{19}H_{23}N_2O$ (M + 1) requires 343.1658], 343, 316 (base), 272.

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (***trans*-397**) δ 7.43-7.38 (m, 1 H, C16-H or C18-H), 7.37-7.26 (comp, 4 H, C15-C19-H), 5.82-5.58 (m, 1 H, C8-H), 5.12 (app d, *J* = 12.3 Hz, 0.4 H, C13-H), 5.20 (app d, *J* = 12.3 Hz, 1 H, C13-H), 5.12-4.93 (comp, 2.6 H, C9-H, C13-H), 4.49 (dd, *J* = 8.2, 2.7 Hz, 0.4 H, C2-H), 4.43 (dd, *J* = 7.9, 2.7 Hz, 0.6 H, C2-H), 3.74 (s, 1 H, rotameric CO_2Me signal, C11-H), 3.57 (s, 2 H, rotameric CO_2Me signal, C11-H), 2.60-2.41 (comp, 2 H, C4-H, C6-H), 2.39-1.95 (comp, 5 H, C3-H, C4-H, C7-H), 1.86-1.76 (m, 1 H, C6-H).



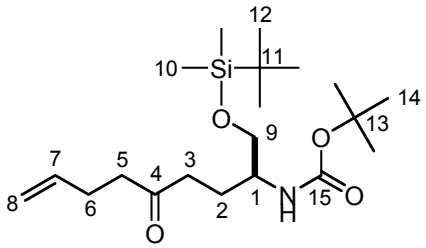
5-Azido-5-but-3-enylpyrrolidine-1-benzyloxycarbonyl-(2*R*)-methyl ester (398). A mixture of $B(C_6F_5)_3$ (6 mg, 12 μmol) and $TMSN_3$ (40 μL, 0.30 mmol) in CH_2Cl_2 (0.4 mL) was added via cannula to a solution of **320d** (50 mg, 0.15 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C, then stirring was continued for an additional 25 min at –78 °C before the cooling bath was removed. The mixture was stirred at rt for 1 h, whereupon the reaction was returned to a –78 °C bath and treated with an additional solution of $B(C_6F_5)_3$ (6 mg, 12 μmol) and $TMSN_3$ (40 μL, 0.30 mmol) in CH_2Cl_2 (0.4 mL). The reaction was stirred at –78 °C for 25 min, then at rt for 14 h, whereupon Et_3N (100 μL) was added via syringe and the solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 30 mg (56%) of ***cis*-398** as a clear oil and 15 mg (28%) of ***trans*-398** as a clear oil along with 4 mg (8%) of recovered **320d**. ^{1}H-NMR (400 MHz, $CDCl_3$) (***cis*-398**) δ 7.41-7.20 (comp, 5 H), 5.91-5.77 (m, 0.6 H), 5.77-5.61 (m, 0.4 H), 5.31-4.86 (comp, 4 H), 4.60-4.46 (m, 1 H), 3.74-3.59 (app br d, 3 H, rotameric CO_2Me signals), 2.79-2.65 (m, 1 H), 2.42-2.03 (comp, 5 H), 1.97-1.86 (comp, 2 H);

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (***cis*-398**) δ 7.41-7.20 (comp, 5 H, C15-C19-H), 5.91-5.77 (m, 0.6 H, C8-H), 5.77-5.61 (m, 0.4 H, C8-H), 5.31-4.86 (comp, 4 H, C9-H, C13-H), 4.60-4.46 (m, 1 H, C2-H), 3.74-3.59 (app br d, 3 H, rotameric CO_2Me signals, C11-H), 2.79-2.65 (m, 1 H, C3-H), 2.42-2.03 (comp, 5 H, C3-H, C4-H, C7-H), 1.97-1.86 (comp, 2 H, C6-H).



^{1}H-NMR (400 MHz, $CDCl_3$) (***trans*-398**) δ 7.40-7.25 (comp, 5 H), 5.79 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 0.6 H), 5.66-5.54 (m, 0.4 H), 5.30 (d, *J* = 12.0 Hz, 0.4 H), 5.18 (d, *J* = 12.0 Hz, 0.6 H), 5.12-4.84 (comp, 3 H), 4.46-4.32 (m, 1 H), 3.75 (s, 1 H, rotameric CO_2Me signal), 3.51 (s, 2H, rotameric CO_2Me signal), 2.60-2.50 (m, 0.6 H), 2.32-2.23 (m, 0.4 H), 2.22-1.82 (comp, 7 H).

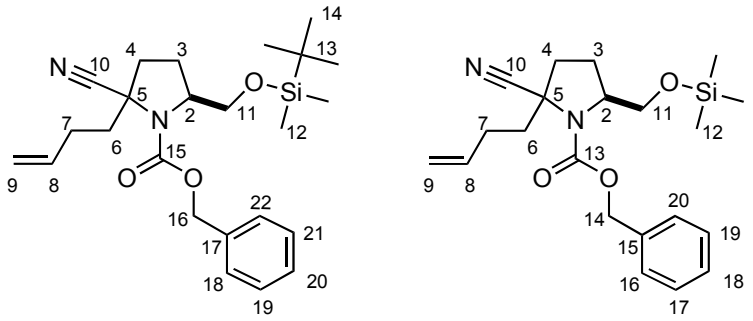
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) (***trans*-398**) δ 7.40-7.25 (comp, 5 H, C15-C19-H), 5.79 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 0.6 H, C8-H), 5.66-5.54 (m, 0.4 H, C8-H), 5.30 (d, *J* = 12.0 Hz, 0.4 H, C9-H), 5.18 (d, *J* = 12.0 Hz, 0.6 H, C9-H), 5.12-4.84 (comp, 3 H, C9-H, C13-H), 4.46-4.32 (m, 1 H, C2-H), 3.75 (s, 1 H, rotameric CO_2Me signal, C11-H), 3.51 (s, 2H, rotameric CO_2Me signal, C11-H), 2.60-2.50 (m, 0.6 H, C3-H), 2.32-2.23 (m, 0.4 H, C3-H), 2.22-1.82 (comp, 7 H, C4-H, C6-H, C7-H).



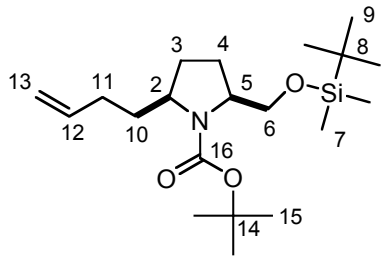
[1*S*-(*tert*-butyldimethylsilanoxymethyl)-4-oxooct-7-enyl]carbamic acid *tert*-butyl ester (399). 4-bromo-1-butene (19 μL, 0.187 mmol) was added to a stirred mixture of magnesium turnings (28 mg, 1.16 mmol) in THF (1.2 mL) at rt. After 10 min, an additional portion of 4-bromo-1-butene was added (40 μL, 0.394 mmol). The resulting

mixture was stirred for an additional 15 min and then transferred via syringe to a stirred solution of **367** (96 mg, 0.290 mmol) in THF (1.5 mL) at –78 °C. After 1 h at –78 °C, saturated $NaHCO_3$ (3 mL) was added, and the reaction mixture was allowed to warm to rt before pouring into a mixture of H_2O (30 mL) and Et_2O (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:4) to provide 112 mg (100%) of **399** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1 H), 5.00 (dq, *J* = 15.5, 1.6 Hz, 1 H), 4.94 (dq, *J* = 8.4 Hz, 1.4 Hz, 1 H), 4.61 (br d, *J* = 7.0 Hz, 1 H), 3.58-3.53 (comp, 3 H), 2.54-2.40 (comp, 4 H), 2.33-2.27 (comp, 2 H), 1.82-1.65 (comp, 2 H), 1.41 (s, 9 H), 0.87 (s, 9 H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 155.8, 137.2, 115.2, 79.1, 65.3, 51.6, 41.9, 39.4, 28.4, 27.8, 25.9, 18.3, -5.5; IR (neat) 3348, 3373, 2935, 2240, 1709, 1496, 1367, 1255, 1171, 1112, 909, 840, 776, 733 cm^{-1}; MS (CI) *m/z* 386.2718 [$C_{20}H_{40}NO_4Si$ requires 386.2726], 386 (base), 368.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1 H, C7-H), 5.00 (dq, *J* = 15.5, 1.6 Hz, 1 H, C8-H), 4.94 (dq, *J* = 8.4 Hz, 1.4 Hz, 1 H, C8-H), 4.61 (br d, *J* = 7.0 Hz, 1 H, NH), 3.58-3.53 (comp, 3 H, C1-H, C9-H), 2.54-2.40 (comp, 4 H, C3-H, C5-H), 2.33-2.27 (comp, 2 H, C6-H), 1.82-1.65 (comp, 2 H, C2-H), 1.41 (s, 9 H, C14-H), 0.87 (s, 9 H, C12-H), 0.24 (s, 6H, C10-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9 (C4), 155.8 (C15), 137.2 (C7), 115.2 (C8), 79.1 (C13), 65.3 (C9), 51.6 (C1), 41.9 (C5), 39.4 (C3), 28.4 (C14), 27.8 (C6), 25.9 (C12, C2), 18.3 (C11), -5.5 (C10).



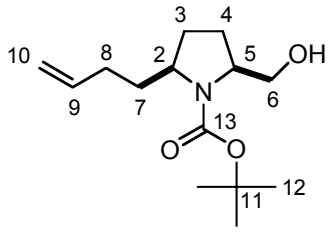
5-But-3-enyl-2(*S*)-(*tert*-butyldimethylsilanyloxymethyl)-5-cyanopyrrolidine-1-benzyloxycarbonyl (400) and 5-But-3-enyl-5-cyanopyrrolidine-2(*S*)-trimethylsilanyloxymethyl-1-benzyloxycarbonyl (401). A mixture of $B(C_6F_5)_3$ (6 mg, 12 μmol) and freshly distilled TMSCN (43 μL, 32 mg, 0.32 mmol) in CH_2Cl_2 (0.3 mL) was added via cannula to a solution of **399** (62 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) at –78 °C. Stirring was continued for an additional 15 min at –78 °C, and then the cooling bath was removed. The mixture was stirred at rt for 1 h, whereupon the reaction was recooled to –78 °C, and a solution of $B(C_6F_5)_3$ (6 mg, 12 μmol) and TMSCN (43 μL, 32 mg, 0.32 mmol) in CH_2Cl_2 (0.3 mL) was added. The reaction was stirred at –78 °C for 25 min, and at rt for 18 h, whereupon Et_3N (100 μL) was added via syringe. The solution was concentrated under reduced pressure, and the crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to afford 34 mg (54%) of **400** as a pale-yellow oil and 6 mg (11%) of **401** also as a pale-yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) (**400**) δ 5.82-5.72 (m, 1 H), 5.06-4.96 (comp, 2 H), 4.14-3.82 (br m, 1 H), 3.77-3.44 (comp, 2 H), 2.79-1.68 (comp, 8 H), 1.64-1.32 (comp, 9 H), 0.86 (s, 9 H), 0.02 (app d, J = 4.8 Hz, 6 H). ^{1}H-NMR (400 MHz, $CDCl_3$) (**401**) δ 5.83-5.73 (m, 1 H), 5.07-4.98 (comp, 2 H), 4.13-3.85 (br m, 1 H), 3.71-3.40 (comp, 2 H), 2.69-1.54 (comp, 8 H), 1.53-1.33 (comp, 9 H), 0.08 (s, 9 H).



(2*S*)-But-3-enyl-(5*S*)-(*tert*-butyldimethylsilanoxylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (368). 4-Bromo-1-butene (18 μL, 0.18 mmol) was added to a stirred mixture of magnesium turnings (26 mg, 1.1 mmol) in THF (1.1 mL) at room temperature. After 20 min, an additional portion of 4-bromo-1-butene (40 μL, 0.35 mmol) was added. The resulting solution was stirred an additional 20 min and then transferred via cannula to a stirred solution of **399** (89 mg, 0.27 mmol) in THF (1.4 mL) at –78 °C. The mixture was stirred for 1 h at –78 °C, and then a mixture of $BF_3{\cdot}OEt_2$ (0.22 mL, 1.7 mmol) and 1 M L-Selectride in THF (0.57 mL, 0.57 mmol) (mixed at room temperature) was added via syringe. The resulting solution was stirred at –78 °C for 1 h, and then the solution was allowed to slowly warm to room temperature before quenching with MeOH (2.5 mL) and H_2O (3 mL). The reaction mixture was then poured into a mixture of saturated $NaHCO_3$ (30 mL) and Et_2O/pentane (1:1) (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O/pentane (1:1) (3 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:5) to provide 79 mg (79%) of **368** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1 H), 5.00 (dq, *J* = 17.4, 1.7 Hz, 1 H), 4.94 (app d, *J* = 9.9 Hz, 1 H), 3.76-3.36 (comp, 4 H), 2.14-1.72 (comp, 6 H), 1.68-1.52 (m, 2 H), 1.44 (s, 9 H), 0.87 (s, 9 H), 0.03 (d, *J* = 3.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.6, 114.6,

79.5, 60.4, 57.1, 40.6, 31.6, 29.4, 26.8, 26.5, 19.2, -4.2; IR (neat) 3446, 2941, 1696, 1460, 1393, 1365, 1258, 1174, 1101, 837, 776 cm^{-1}; mass spectrum (CI) *m/z* 370.2777 [$C_{20}H_{40}NO_3Si$ (M + 1) requires 370.2778], 370, 314, 298, 270 (base), 256.

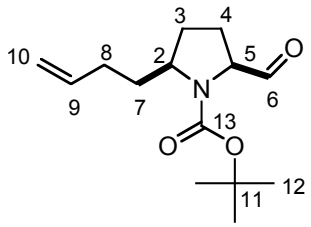
NMR Assignments. ^1H NMR (400 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1 H, C12-H), 5.00 (dq, *J* = 17.4, 1.7 Hz, 1 H, C13-H), 4.94 (app d, *J* = 9.9 Hz, 1 H, C13-H), 3.76-3.36 (comp, 4 H, C2-H, C5-H, C6-H), 2.14-1.72 (comp, 6 H, C3-H, C4-H, C10-H, C11-H), 1.68-1.52 (m, 2 H, C10-H, C3-H), 1.44 (s, 9 H, C15-H), 0.87 (s, 9 H, C9-H), 0.03 (d, *J* = 3.1 Hz, 6 H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (C16), 138.6 (C12), 114.6 (C13), 79.5 (C14), 60.4 (C6), 57.1 (C2), 40.6 (C5), 34.4 (C10), 31.6 (C3), 29.4 (C11), 28.6 (C15), 26.8 (C9), 26.5 (C4), 19.2 (C8), -4.2 (C7).



(2*S*)-But-3-enyl-(5*S*)-hydroxymethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (369) A 1 M solution of TBAF in THF (6.2 mL, 6.20 mmol) was added to a stirred solution of crude **368** (521 mg, 1.41 mmol) in THF (8 mL). After 2 h, the reaction mixture was poured into 10% H_3PO_4 (50 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an orange oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:3) to afford 250 mg (70%) of **369** as a pale-yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H), 5.00 (dq, *J* = 15.5, 1.6 Hz, 1 H), 4.94 (br dq, *J* = 8.4, 1.8 Hz, 1

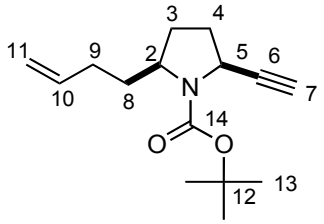
H), 3.96-3.90 (m, 1 H), 3.87-3.81 (m, 1 H), 3.65 (br dd, *J* = 8.6, 2.4 Hz, 1 H), 3.49 (dd, *J* = 11.2, 7.9 Hz, 1 H), 2.11-1.93 (comp, 3 H), 1.90-1.80 (m, 1 H), 1.77-1.50 (comp, 3H), 1.45 (s, 9H), 1.42-1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 114.8, 80.4, 68.8, 61.1, 58.8, 34.6, 30.7, 28.9, 28.5, 26.9; IR (neat) 3416, 3074, 2967, 1693, 1661, 1399, 1255, 1170, 1116, 1047, 908, 855, 775, 737 cm^{-1}; MS (CI) *m/z* 256.1919 [$C_{14}H_{26}NO_3$ (M + 1) requires 256.1913], 511, 411, 379, 256 (base), 224, 200, 184, 156.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1 H, C9-H), 5.00 (dq, *J* = 15.5, 1.6 Hz, 1 H, C10-H), 4.94 (br dq, *J* = 8.4, 1.8 Hz, 1 H, C10-H), 3.96-3.90 (m, 1 H, C5-H), 3.87-3.81 (m, 1 H, C2-H), 3.65 (br dd, *J* = 8.6, 2.4 Hz, 1 H, C6-H), 3.49 (dd, *J* = 11.2, 7.9 Hz, 1 H, C6-H), 2.11-1.93 (comp, 3 H, C4-H, C3-H), 1.90-1.80 (m, 1 H, C3-H), 1.77-1.50 (comp, 3 H, C7-H, C8-H), 1.45 (s, 9 H, C12-H), 1.42-1.29 (m, 1 H, C7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1 (C9), 114.8 (C10), 80.4 (C11), 68.8 (C6), 61.1 (C5), 58.8 (C2), 34.6 (C7), 30.7 (C3), 28.9 (C8), 28.5 (C12), 26.9 (C4).



(2*S*)-But-3-enyl-(5*S*)-formylpyrrolidine-1-carboxylic acid *tert*-butyl ester. TPAP (33 mg, 0.094 mmol) was added to a solution of **5** (239 mg, 0.936 mmol), NMO (165 mg, 1.40 mmol), and powdered 4 Å molecular sieves (300 mg) in CH_2Cl_2 (31 mL) at room temperature. The reaction was stirred for 2 h, and then the solvent was removed under reduced pressure to afford a black residue. The residue was suspended in Et_2O (2 mL), and filtered through a short plug of SiO_2 eluting with Et_2O/pentane (2:1) (175 mL).

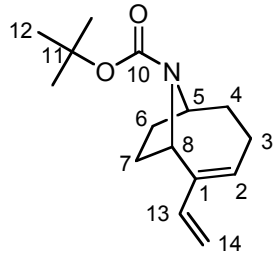
Removal of the solvent under reduced pressure afforded 216 mg (91%) of the corresponding aldehyde as a pale-yellow oil that was used immediately in the next reaction. ^{1}H NMR (500 MHz, PhMe-d_8, 100 ^{o}C) δ 9.35 (d, J = 2.4Hz, 1 H), 5.73 (ddt, J = 16.7, 10.2, 6.3 Hz, 1 H), 4.97 (dq, J = 17.1, 1.7 Hz, 1 H), 4.91-4.88 (m, 1 H), 3.93-3.90 (m, 1 H), 3.78-3.71 (m, 1 H), 2.02-1.81 (comp, 3 H), 1.60-1.42 (comp, 3 H), 1.37 (s, 9H), 1.30-1.19 (comp, 2H); ^{13}C NMR (125 MHz, PhMe-d_8, 100 ^{o}C) δ 199.1, 154.7, 138.6, 114.8, 80.2, 66.6, 58.8, 35.0, 30.9, 30.0, 28.6, 25.4; IR (neat) 2974, 1739, 1696, 1455, 1382, 1258, 1168, 1112, 910, 776 cm^{-1}; mass spectrum (CI) *m/z* 254.1765 [$C_{14}H_{24}NO_3$ (M + 1) requires 254.1756], 254, 238, 226, 224, 198 (base), 182, 180, 155, 136, 124.



(2*S*)-But-3-enyl-(5*S*)-ethynylpyrrolidine-1-carboxylic acid *tert*-butyl ester (372). A solution of the proceeding aldehyde (207 mg, 0.817 mmol) in anhydrous MeOH (1 mL) was added via syringe to a solution of **241** (188 mg, 0.981 mmol) and K_2CO_3 (226 mg, 1.63 mmol) in anhydrous MeOH (6 mL) at room temperature. The reaction was stirred for 3 h, and then diluted with Et_2O (6 mL) and poured into a mixture of saturated $NaHCO_3$ (25 mL) and Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4 x 15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:6) to afford 155 mg (76%) of **372** as a clear oil along with 2% of the separable *trans*-isomer. ^{1}H-NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, J = 16.8, 10.2, 6.5 Hz, 1 H), 5.03

(dq, J = 17.2, 1.7 Hz, 1 H), 4.96-4.92 (m, 1 H), 4.47-4.43 (m, 1 H), 3.77-3.72 (m, 1 H), 2.89 (d, J = 2.1 Hz, 1 H), 2.13-1.96 (comp, 4 H), 1.93-1.85 (comp, 2 H), 1.78-1.71 (m, 1 H), 1.57-1.49 (m, 1 H), 1.43 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.7, 137.8, 113.8, 84.9, 78.3, 71.0, 57.0, 47.7, 33.4, 31.1, 29.0, 28.9, 27.6; IR (neat) 3302, 3059, 2978, 1685, 1639, 1390, 1263, 1170, 1107, 916, 737, 650 cm^{-1}; mass spectrum (CI) *m/z* 250.1807 [$C_{15}H_{24}NO_2$ (M + 1) requires 250.1807], 499, 444, 399, 343, 250 (base), 194.

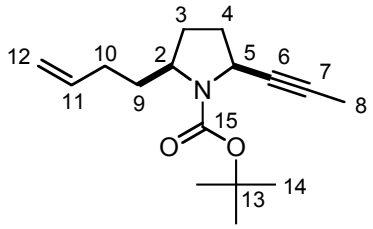
NMR Assignments. δ 5.84 (ddt, J = 16.8, 10.2, 6.5 Hz, 1 H. C10-H), 5.03 (dq, J = 17.2, 1.7 Hz, 1 H, C11-H), 4.96-4.92 (m, 1 H, C11-H), 4.47-4.43 (m, 1 H, C5-H), 3.77-3.72 (m, 1 H, C2-H), 2.89 (d, J = 2.1 Hz, 1 H, C7-H), 2.13-1.96 (comp, 4 H, C4-H, C9-H), 1.93-1.85 (comp, 2 H, C3-H, C8-H), 1.78-1.71 (m, 1 H, C8-H), 1.57-1.49 (m, 1 H, C3-H), 1.43 (s, 9 H, C13-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.7 (C14), 137.8 (C10), 113.8 (C11), 84.9 (C6), 78.3 (C12), 71.0 (C7), 57.0 (C2), 47.7 (C5), 33.4 (C8), 31.1 (C4), 29.0 (C9), 28.9 (C3), 27.6 (C13).



2-Vinyl-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (373)

To a solution of **372** (18 mg, 72 μmol) in dry degassed CH_2Cl_2 (8 mL) was added **47** (7 mg, 0.008 mmol) in one portion. The mixture was stirred at room temperature for 22 h, and then DMSO (1 mL) was added to decompose the catalyst, and stirring was continued for an additional 2 h. The solvent was removed under reduced pressure, and the residue

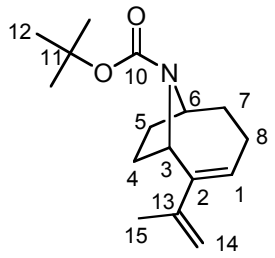
was purified by flash chromatography (SiO_2) using gradient elution Et_2O/pentane (1:5 → 1:3) to afford 14 mg (78%) of **373** as a pale-yellow oil. ^1H NMR (500 MHz, $CDCl_3$) (2 rotamers) δ 6.23 (dd, *J* = 17.6, 6.6 Hz, 1 H), 5.65-5.60 (m, 1 H), 5.14 (t, *J* = 17.1 Hz, 1 H), 4.98-4.90 (comp, 1.4 H), 4.80-4.77 (m, 0.6 H), 4.40-4.37 (m, 0.6 H), 4.28-4.24 (m, 0.4 H), 2.32-2.02 (comp, 5 H), 1.77-1.65 (comp, 2 H), 1.62-1.51 (comp, 2 H), 1.44 (s, 4 H), 1.39 (s, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) (2 rotamers) δ 153.5, 153.3, 145.9, 143.8, 139.0, 138.8, 131.2, 130.8, 111.3, 110.5 79.1, 79.0, 55.2, 54.8, 54.3, 33.9, 31.9, 31.4, 31.0, 30.4, 30.3, 29.6, 28.6, 28.5, 23.8, 23.6; IR (neat) 3437, 2978, 2252, 1683, 1420, 1405, 1367, 1250, 1170, 1116, 994, 908, 737, 652 cm^{-1}; mass spectrum (CI) *m/z* 250.1803 [$C_{15}H_{24}NO_2$ (M + 1) requires 250.1807], 250 (base), 222, 200, 195, 152.



(2*S*)-But-3-enyl-(5*S*)-prop-1-ynylpyrrolidine-1-carboxylic acid *tert*-butyl ester (377) A solution of 2.3 M *n*-BuLi in hexanes (154 μL, 0.349 mmol) was added to solution of diisopropylamine (51 μL, 0.361 mmol) in THF (720 μL) at −78 °C. The resulting solution was stirred for 10 min at −78 °C and then at −5 °C for 15 min before recooling to −78 °C. To this mixture was added a solution of **372** (29 mg, 0.116 mmol) in THF (280 μL). The resulting yellow solution was stirred for 1 min before the addition of HMPA (100 μL, 0.582 mmol). The resulting brown solution was stirred for 5 min, and MeI (22 μL, 0.349 mmol) was then added. The cooling bath was allowed to warm to ambient temperature over 2 h, and stirring was continued for an additional 22 h. The reaction mixture was poured into H_3PO_4 (15 mL) and Et_2O (5 mL), and the layers were

separated. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:8) to afford 23 mg (75%) of **377** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$,) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.00 (dq, *J* = 15.5, 1.8 Hz, 1 H), 4.93-4.91 (m, 1 H), 4.46 (br s, 1 H), 3.73 (br s, 1 H), 2.12-1.86 (comp, 6 H), 1.79-1.74 (comp, 4 H), 1.56-1.47 (m, 1 H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 138.5, 114.4, 79.4, 57.7, 48.9, 34.3, 32.3, 30.4, 28.5, 26.9, 3.6; IR (neat) 2974, 2920, 1696, 1391, 1256, 1171, 1108, 1047, 910, 766 cm^{-1}; MS (CI) *m/z* 264.1968 [$C_{16}H_{26}NO_2$ (M + 1) requires 264.1964], 264 (base), 208, 200, 164, 108.

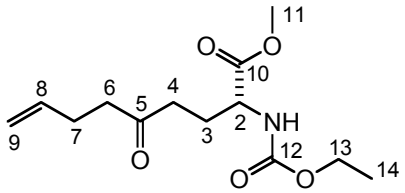
NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H, C11-H), 5.00 (dq, *J* = 15.5, 1.8 Hz, 1 H, C12-H), 4.93-4.91 (m, 1 H, C12-H), 4.46 (br s, 1 H, C5-H), 3.73 (br s, 1 H, C2-H), 2.12-1.86 (comp, 6 H, C10-H, C4-H, C3-H), 1.79-1.74 (comp, 4 H, C8-H, C9-H), 1.56-1.47 (m, 1 H, C9-H), 1.44 (s, 9H, C14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 (C15), 138.5 (C11), 114.4 (C12), 80.2 (C6), 79.4 (C7), 57.7 (C2), 48.9 (C5), 34.3 (C9), 32.3, 30.4, 28.5 (C14), 26.9 (C4), 3.6 (C8).



2-Isopropenyl-9-azabicyclo[4.2.1]non-2-ene-carboxylic acid *tert*-butyl ester (378). To a solution of **377** (20 mg, 0.0759 mmol) in CH_2Cl_2 (7.6 mL) degassed with C_2H_4, was added **48** (6 mg, 7.59 μmol). After 22 h at rt, DMSO (1 mL) was added to

decompose the catalyst, and stirring was continued for an additional 2 h. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:4) to afford 18 mg (90%) of **378** as a yellow-oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.72 (t, J = 6.0 Hz, 1 H), 4.99 (s, 1 H), 4.87 (s, 1 H), 4.78 (d, J = 8.6 Hz, 1 H), 4.27-4.24 (m, 1 H), 2.24 (q, J = 6.2 Hz, 2 H), 2.21-2.19 (m, 1 H), 2.18-1.95 (comp, 2 H), 1.84 (d, J = 0.7 Hz, 3H), 1.75-1.64 (comp, 2 H), 1.60-1.52 (m, 1 H), 1.38 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 151.9, 146.7, 142.6, 124.9, 110.2, 77.6, 55.2, 54.3, 31.8, 30.5, 29.2, 27.6, 22.7, 20.7; IR (neat) 2972, 1694, 1403, 1365, 1246, 1176, 1110 cm^{-1}; MS (CI) *m/z* 264.1952 [$C_{16}H_{26}NO_2$ (M + 1) requires 264.1964], 527, 264, 208 (base), 200, 164.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.72 (t, J = 6.0 Hz, 1 H, C1-H), 4.99 (s, 1 H, C14-H), 4.87 (s, 1 H, C14-H), 4.78 (d, J = 8.6 Hz, 1 H, C3-H), 4.27-4.24 (m, 1 H, C6-H), 2.24 (q, J = 6.2 Hz, 2 H, C8-H), 2.21-2.19 (m, 1 H, C4-H), 2.18-1.95 (comp, 2 H, C5-H, C7-H)), 1.84 (d, J = 0.7 Hz, 3H, C15-H), 1.75-1.64 (comp, 2 H, C4-H, C5-H), 1.60-1.52 (m, 1 H, C7-H), 1.38 (s, 9 H, C12-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 151.9 (C10), 146.7 (C13), 142.6 (C2), 124.9 (C1), 110.2 (C14), 77.6 (C11), 55.2 (C3), 54.3 (C6), 31.8 (C7), 30.5 (C4), 29.2 (C5), 27.6 (C12), 22.7 (C8), 20.7 (C15).

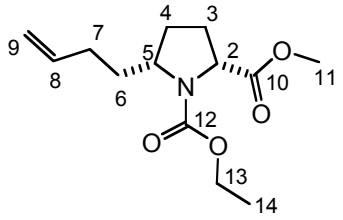


(2*R*)-Ethoxycarbonylamino-5-oxonon-8-enoic acid methyl ester (403). 4-Bromo-1-butene (0.73 mL, 7.2 mmol) was added to a stirred mixture of magnesium

turnings (3.70 g, 152 mmol) in THF (152 mL) at rt. The mixture was stirred for 20 min, and an additional portion of 4-bromo-1-butene was added (7.0 mL, 69 mmol). The resulting mixture was stirred for an additional 30 min and then transferred via cannula to a flask containing TMEDA (23 mL, 152 mmol). The initially cloudy suspension was stirred until all precipitate had disappeared (10 min), whereupon the solution was transferred via cannula to a solution of **402**[248] (13.7 g, 50.7 mmol) in THF (254 mL) at –78 °C. The mixture was stirred for 1 h at –78 °C, and *i*-PrOH (20 mL) was added, and the reaction mixture was warmed to rt. The reaction was poured into a mixture of sat. aqueous NH_4Cl (250 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to provide 11.9 g (88%) of **403** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1 H), 5.22 (br d, *J* = 6.0 Hz, 1 H), 5.00 (dq, *J* = 17.1, 1.6 Hz, 1 H), 4.96 (dq, *J* = 10.0, 1.6 Hz, 1 H), 4.30 (app q, *J* = 5.0 Hz, 1 H), 4.09 (q, *J* = 7.0 Hz, 2 H), 3.72 (t, *J* = 5.0 Hz, 3 H), 2.57-2.43 (comp, 4 H), 2.32-2.27 (comp, 2 H), 2.16-2.09 (m, 1 H), 1.93-1.86 (m, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 172.6, 156.2, 136.9, 115.3, 61.2, 53.3, 52.4, 41.9, 38.5, 27.7, 26.4, 14.5; IR (neat) 3347, 2968, 2357, 1715, 1531, 1262, 1215, 1057 cm^{-1}; MS (CI) *m/z* 272.1494 [$C_{13}H_{22}NO_5$ (M + 1) requires 272.1498], 272 (base), 254, 162.

NMR Assignments. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1 H, C8-H), 5.22 (br d, *J* = 6.0 Hz, 1 H, N-H), 5.00 (dq, *J* = 17.1, 1.6 Hz, 1 H, C9-H(*E*)), 4.96 (dq, *J* = 10.0, 1.6 Hz, 1 H, C9-H(*Z*)), 4.30 (app q, *J* = 5.0 Hz, 1 H, C2-H), 4.09 (q, *J*

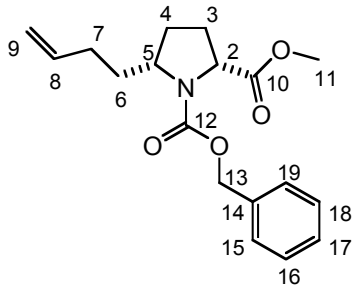
= 7.0 Hz, 2 H, C13-H), 3.72 (t, *J* = 5.0 Hz, 3 H, C11-H), 2.57-2.43 (comp, 4 H, C6-H, C4-H), 2.32-2.27 (comp, 2 H, C7-H), 2.16-2.09 (m, 1 H, C3-H(*R*)), 1.93-1.86 (m, 1 H, C3-H(*S*)), 1.22 (t, *J* = 7.1 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7 (C5), 172.6 (C10), 156.2 (C12), 136.9 (C8), 115.3 (C9), 61.2 (C13), 53.3 (C2), 52.4 (C11), 41.9 (C6), 38.5 (C4), 27.7 (C7), 26.4 (C3), 14.5 (C14).



(2*R*,5*R*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid 1-ethyl ester 2-methyl ester (404). BF_3•OEt_2 (29.0 mL, 229 mmol) was added to a solution of Ph_3SiH (29.9 g, 115 mmol) in CH_2Cl_2 (80 mL) at rt. The solution was stirred for 5 min, then transferred via cannula to a stirred solution of **403** (10.4 g, 38.2 mmol) in CH_2Cl_2 (125 mL) at –78 ^{o}C. The reaction mixture was kept in a –78 ^{o}C bath for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at rt for an additional 2 h. The reaction mixture was then recooled to –78 ^{o}C, and poured into a solution of sat. aqueous $NaHCO_3$ (300 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a clear oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to provide 9.54 g (92.3%) of **404** as a clear oil along with 5.7% of the corresponding *trans*-isomer (by NMR and GC). ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H), 5.03 (app dq, *J* = 17.2, 1.7 Hz, 1 H), 4.96-4.93 (m, 1 H), 4.30-4.26 (m, 1 H), 4.03 (q, *J* = 7.1 Hz, 2 H), 3.88-3.83 (m, 1 H), 3.65 (s, 2.85 H), 3.64 (s, 0.17 H), 2.22-1.86 (comp, 6 H), 1.73-1.66 (m, 1 H), 1.54-1.46 (m, 1 H), 1.17

(t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 172.3, 153.6, 137.9, 113.8, 59.8, 59.1, 57.5, 51.0, 32.6, 29.2, 28.8, 27.6, 13.7; IR (neat) 2968, 1752, 1704, 1415, 1383, 1346, 1204, 1172, 1109, 1030, 914, 772 cm^{-1}; MS (CI) *m/z* 256.1549 [$C_{13}H_{22}NO_4$ (M + 1) requires 256.1549], 256 (base).

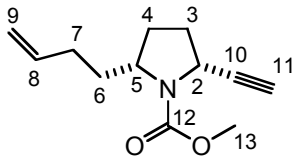
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, J = 17.0, 10.2, 6.5 Hz, 1 H, C8-H), 5.03 (app dq, J = 17.2, 1.7 Hz, 1 H, C9-H(*E*)), 4.96-4.93 (m, 1 H, C9-H(*Z*)), 4.30-4.26 (m, 1 H, C2-H), 4.03 (q, J = 7.1 Hz, 2 H, C13-H), 3.88-8.83 (m, 1 H, C5-H), 3.65 (s, 2.85 H, C11-H (major diastereomer)), 3.64 (s, 0.15 H, C11-H (minor diastereomer)), 2.22-1.86 (comp, 6 H, C3-H, C7-H, C6-H, C4-H), 1.73-1.66 (m, 1 H, C4-H), 1.54-1.46 (m, 1 H, C6-H), 1.17 (t, J = 7.1 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 172.3 (C10), 153.6 (C12), 137.9 (C8), 113.8 (C9), 59.8 (C13), 59.1 (C2), 57.5 (C5), 51.0 (C11), 32.6 (C6), 29.2 (C7), 28.8 (C4), 27.6 (C3), 13.7 (C14).



(2*R*,5*R*)-But-3-enylpyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (392). BF_3•OEt_2 (15.2 mL, 120 mmol) was added to a solution of Ph_3SiH (15.7 g, 60.1 mmol) in CH_2Cl_2 (40 mL) at rt. The solution was stirred for 10 min, then added via cannula to a stirred solution of **320d** (10.0 g, 30.0 mmol) in CH_2Cl_2 (100 mL) at –78 ^{o}C. The reaction mixture was kept in a –78 ^{o}C bath for 0.5 h, whereupon the cooling-bath was removed and stirring was continued at rt for an additional 2 h. The reaction mixture was then recooled to –78 ^{o}C and poured into a solution of saturated aq. $NaHCO_3$ (350

mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to provide 9.37 g (98%) of **392** (*dr* = >95:5, by integration of the methyl ester signals in the ^1H NMR at 100 ^oC) as a clear oil. ^1H NMR (500 MHz, DMSO-d_6, 100 ^oC) δ 7.38-7.27 (comp, 5 H), 5.81 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1 H), 5.15-4.98 (comp, 3 H), 4.94-4.91 (m, 1 H), 4.36-4.33 (m, 1 H), 3.93-3.87 (m, 1 H), 3.61 (s, 3 H), 3.58 (s, 0.05 H), 2.24-2.17 (m, 1 H), 2.14-1.86 (comp, 5 H), 1.74-1.66 (m, 1 H), 1.56-1.47 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^oC) δ 172.2, 153.4, 137.8, 136.3, 127.6, 127.1, 126.7, 113.8, 65.6, 59.1, 57.8, 51.0, 32.6, 29.2, 28.8, 27.6; IR (neat) 2954, 1752, 1707, 1410, 1204, 1176, 1107, 1005, 913, 748, 696 cm^{-1}; MS (CI) *m/z* 318.1695 [$C_{18}H_{24}NO_4$ (M + 1) requires 318.1705], 318 (base), 274, 182.

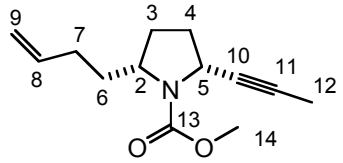
NMR Assignments. ^1H NMR (500 MHz, DMSO-d_6, 100 ^oC) δ 7.38-7.27 (comp, 5 H, C15-C19-H), 5.81 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1 H, C8-H), 5.15-4.98 (comp, 3 H, C13-H, C9-H(*E*)), 4.94-4.91 (m, 1 H, C9-H(*Z*)), 4.36-4.33 (m, 1 H, C2-H), 3.93-3.87 (m, 1 H, C5-H), 3.61 (s, 3 H, C11-H (major diastereomer)), 3.58 (s, 0.05 H, C11-H (minor diastereomer)), 2.24-2.17 (m, 1 H, C3-H), 2.14-1.86 (comp, 5 H, C7-H, C4-H, C3-H, C6-H), 1.74-1.66 (m, 1 H, C4-H), 1.56-1.47 (m, 1 H, C6-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^oC) δ 172.2 (C10), 153.4 (C12), 137.8 (C8), 136.3 (C14), 127.6 (C16,C18), 127.1 (C17), 126.7 (C15, C19), 113.8 (C9), 65.6 (C13), 59.1 (C2), 57.8 (C5), 51.0 (C11), 32.6 (C6), 29.2 (C7), 28.8 (C4), 27.6 (C3).



(2*R*,5*R*)-But-3-enyl-5-ethynylpyrrolidine-1-carboxylic acid methyl ester (405). A solution of 1.0 M DIBAL-H in PhMe (1.23 mL) was added to a solution of **315** (110 mg, 0.456 mmol) in PhMe (2.3 mL) at –78 °C. The resulting solution was stirred at –78 °C for 2 h, whereupon MeOH (1.3 mL) was slowly added via syringe. The cooling bath was removed, and solid NaOMe (148 mg, 2.74 mmol) was added in one portion. After approximately 1 min, a solution of **241** (175 mg, 0.912 mmol) in MeOH (3.7 mL) was added via cannula. The resulting yellow solution was stirred at rt for 2 h, whereupon a mixture of sat. aqueous Rochelles salt solution (5 mL) and Et_2O (5 mL) were added. The mixture was vigorously stirred for 1 h, and then poured into H_2O (30 mL). The resulting layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to provide 61 mg (65%) of **405** as a clear oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.81 (ddt, J = 17.0, 10.1, 6.5 Hz, 1 H), 5.03 (app dq, J = 17.2, 1.7 Hz, 1 H), 4.96-4.92 (m, 1 H), 4.45-4.44 (m, 1 H), 3.81-3.76 (m, 1 H), 3.62 (s, 3 H), 2.90 (app d, J = 2.1 Hz, 1 H), 2.20-1.94 (comp, 4 H), 1.90-1.83 (m, 1 H), 1.81-1.72 (comp, 2 H), 1.44-1.35 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.6, 137.6, 113.9, 83.9, 71.3, 56.3, 51.2, 48.0, 31.8, 30.2, 29.3, 27.3; IR (neat) 3296, 3248, 2951, 1698, 1449, 1384, 1194, 1111, 998, 915, 772 cm^{-1}; MS (CI) *m/z* 208.1332 [$C_{12}H_{18}NO_2$ (M + 1) requires 208.1337], 208 (base), 152.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.81 (ddt, J = 17.0, 10.1, 6.5 Hz, 1 H, C8-H), 5.03 (app dq, J = 17.2, 1.7 Hz, 1 H, C9-H(*E*)), 4.96-4.92 (m, 1 H, C9-H(*Z*)), 4.45-4.44 (m, 1 H, C2-H), 3.81-3.76 (m, 1 H, C5-H), 3.62 (s, 3 H, C13-H),

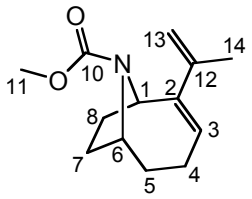
2.90 (app d, J = 2.1 Hz, 1 H, C11-H), 2.20-1.94 (comp, 4 H, C4-H, C3-H, C7-H), 1.90-1.83 (m, 1 H, C4-H), 1.81-1.72 (comp, 2 H, C3-H, C6-H), 1.44-1.35 (m, 1 H, C6-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 153.6 (C12), 137.6 (C8), 113.9 (C9), 83.9 (C10), 71.3 (C11), 56.3 (C5), 51.2 (C13), 48.0 (C2), 31.8 (C6), 30.2 (C3), 29.3 (C7), 27.3 (C4).



(2*R*)-But-3-enyl-(5*R*)-prop-1-ynylpyrrolidine-1-carboxylic acid methyl ester (406). A solution of 2.5 M *n*-BuLi in hexanes (4.30 mL, 10.7 mmol) was added to a solution of diisopropylamine (1.6 mL, 11.1 mmol) in THF (22 mL) at −78 ^{o}C. The resulting solution was stirred for 10 min at −78 ^{o}C, at -5 ^{o}C for 15 min, and then recooled to −78 ^{o}C. To this mixture was added a solution of **405** (742 mg, 3.58 mmol) in THF (3.6 mL). The resulting yellow solution was stirred for 1 min, and then HMPA (3.1 mL, 17.9 mmol) was added. The resulting brown solution was stirred for 5 min, and then MeI (670 μL, 10.7 mmol) was added. The resulting yellow solution was allowed to warm to ambient temperature, and stirring was continued for an additional 20 h. The reaction mixture was poured into 10% H_3PO_4 (80 mL) and Et_2O (30 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellowish-brown oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 706 mg (88%) of **406** as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers) δ 5.82 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 5.03 (app dd, J = 17.1, 1.0 Hz, 1 H), 4.93 (app d, J = 9.9 Hz, 1 H), 4.53 (br s, 1 H), 3.77 (br s, 1 H), 3.71 (s, minor rotamer, 0.3 H), 3.69 (s, major rotamer, 3 H) 2.13-1.89 (comp, 5.4 H),

1.85-1.76 (comp, 4 H), 1.59-1.45 (comp, 1.6 H); IR (neat) 3479, 3365, 2954, 1787, 1707, 1530, 1296, 1050, 919, 782 cm^{-1}; MS (CI) *m/z* 222.1483 [$C_{13}H_{20}NO_2$ (M + 1) requires 222.1494], 222, 198 (base).

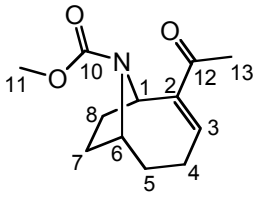
NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$, 2 rotamers) δ 5.82 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H, C8-H), 5.03 (app dd, *J* = 17.1, 1.0 Hz, 1 H, C9-H(*E*)), 4.93 (app d, *J* = 9.9 Hz, 1 H, C9-H(*Z*)), 4.53 (br s, 1 H, C5-H), 3.77 (br s, 1 H, C2-H), 3.71 (s, 0.3 H, C14-H (minor rotamer)), 3.69 (s, 3 H, C14-H (major rotamer)), 2.13-1.89 (comp, 5.4 H, C3-H, C4-H, C6-H, C7-H), 1.85-1.76 (comp, 4 H, C12-H, C3-H), 1.59-1.45 (comp, 1.6 H, C6-H).



(+)-(1*R*)-2-Isopropenyl-9-methoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (407). Solid catalyst **47** (8.4 mg, 0.0102 mmol) was added in one-portion to a solution of **406** (23 mg, 1.02 mmol) in CH_2Cl_2 (21 mL) saturated with ethylene. The mixture was stirred at rt under a blanket of ethylene for 15 h, then DMSO (0.5 mL) was added to decompose the catalyst, and stirring was continued for an additional 3 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:1) to afford 16 mg (70%) of **407** as a yellow oil along with 7 mg (28%) of **408**. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.74-5.71 (m, 1 H), 5.01 (app `s, 1 H), 4.88 (m, 1 H), 4.83 (d, *J* = 8.7 Hz, 1 H), 4.33-4.29 (m, 1 H), 3.57 (s, 3 H), 2.29-2.14 (comp, 3 H), 2.11-1.95 (comp, 2 H), 1.84 (s, 3 H), 1.76-1.67 (comp, 2 H), 1.63-1.55 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.9,

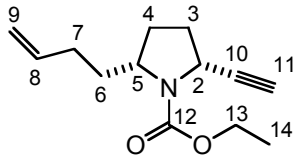
146.3, 142.5, 125.2, 110.5, 56.5, 54.6, 51.1, 31.9, 30.6, 29.2, 22.7, 20.8; IR (neat) 2945, 1702, 1453, 1402, 1193, 1116, 764 cm^{-1}; MS (CI) *m/z* 222.1493 [$C_{13}H_{20}NO_2$ (M + 1) requires 222.1494], 222 (base), 190, 147.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.74-5.71 (m, 1 H, C3-H), 5.01 (app s, 1 H, C13-H), 4.88 (m, 1 H, C13-H), 4.83 (d, *J* = 8.7 Hz, 1 H, C1-H), 4.33-4.29 (m, 1 H, C6-H), 3.57 (s, 3 H, C11-H), 2.29-2.14 (comp, 3 H, C4-H, C8-H), 2.11-1.95 (comp, 2 H, C5-H, C7-H), 1.84 (s, 3 H, C14-H), 1.76-1.67 (comp, 2 H, C7-H, C8-H), 1.63-1.55 (m, 1 H, C5-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.9 (C10), 146.3 (C2), 142.5 (C12), 125.2 (C3), 110.5 (C13), 56.5 (C1), 54.6 (C6), 51.1 (C11), 31.9 (C5), 30.6 (C8), 29.2 (C7), 22.7 (C4), 20.8 (C14).



(+)-(1*R*)-2-Acetyl-9-methoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (409). To a solution of K_2CO_3 (179 mg, 1.29 mmol), $K_3Fe(CN)_6$ (427 mg, 1.29 mmol), and $(DHQD)_2PHAL$ (17 mg, 0.022 mmol) in 50% aqueous *t*-BuOH (4.3 mL) was added solid $K_2OsO_2(OH)_4$ (2 mg, 4 μmol). The solution was cooled to 0 ^{o}C for 10 min, during which time an orange slurry formed. To this slurry was added a solution of **407** (97 mg, 0.43 mmol) in 50% aqueous *t*-BuOH (1.3 mL). The reaction mixture was allowed to slowly warm to rt with vigorous stirring over a 2 h period. Stirring was continued at rt for an additional 16 h, and then solid Na_2SO_3 (327 mg, 2.59 mmol) was added. Stirring was continued for 1.5 h, and then Et_2O (2 mL) was added and the mixture was poured into brine (15 mL). The layers were separated and the aqueous phase was extracted with Et_2O

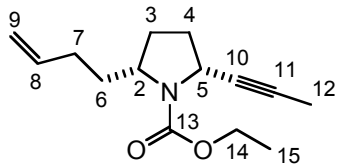
(3 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (4:1) to afford 69 mg (58%) of **409** as a yellow oil contaminated with (12%) of **410**. Data for **409** in agreement with the literature. ^{1}H NMR (400 MHz, $CDCl_3$, only **409** provided) δ 6.79 (m, 1 H), 5.18 (m, 1 H), 4.46-4.30 (m, 1 H), 4.12-3.92 (comp, 3 H), 2.45-2.34 (m, 2 H), 2.30-1.72 (comp, 6 H), 1.70-1.56 (comp, 3 H); IR (neat) cm^{-1}; MS (CI) *m/z* 429, 238 (base), 192.



(2*R*,5*R*)-But-3-enyl-5-ethynylpyrrolidine-1-carboxylic acid ethyl ester (412). A solution of 1.0 M DIBAL-H in PhMe (0.99 mL) was added to a solution of **404** (101 mg, 0.396 mmol) in PhMe (2.0 mL) at –78 ^{o}C. The resulting solution was stirred at –78 ^{o}C for 2.5 h, whereupon EtOH (3 mL) was slowly added via syringe. The cooling bath was removed, and solid Cs_2CO_3 (773 mg, 2.37 mmol) was added in one portion. After approximately 1 min, a solution of **241** (152 mg, 0.791 mmol) in EtOH (1 mL) was added via cannula. The resulting light-green solution was stirred at rt for 27 h, whereupon a mixture of sat. aqueous Rochelles salt solution (10 mL) and EtOAc (5 mL) were added. The mixture was vigorously stirred for 1.5 h, and then poured into H_2O (25 mL). The resulting layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a greenish-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to provide 58 mg (67%) of **412** as a pale-yellow oil along with 4 mg (5%) of the corresponding *trans*-isomer. ^{1}H NMR (500 MHz, DMSO-d_6, 100

^{o}C) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H), 5.03 (app dq, *J* = 17.2, 1.7 Hz, 1 H), 4.97-4.93 (m, 1 H), 4.52-4.49 (m, 1 H), 4.16-4.02 (comp, 2 H), 3.83-3.77 (m, 1 H), 2.93 (app d, *J* = 2.2 Hz, 1 H), 2.14-1.99 (comp, 4 H), 1.95-1.87 (comp, 2 H), 1.81-1.73 (m, 1 H), 1.58-1.50 (m, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 153.5, 137.7, 113.9, 84.6, 71.4, 59.8, 57.2, 47.8, 33.3, 31.2, 29.0, 28.9, 13.8; IR (neat) 3295, 3242, 2979, 1694, 1409, 1378, 1336, 1183, 1025, 909, 835, 772, 667 cm^{-1}; MS (CI) *m/z* 222.1487 [$C_{13}H_{20}NO_2$ (M + 1) requires 222.1494], 222 (base), 166.

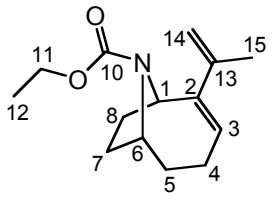
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H, C8-H), 5.03 (app dq, *J* = 17.2, 1.7 Hz, 1 H, C9-H(*E*)), 4.95 (m, 1 H, C9-H(*Z*)), 4.52-4.49 (m, 1 H, C2-H), 4.07 (comp, 2 H, C13-H), 3.83-3.77 (m, 1 H, C5-H), 2.93 (app d, *J* = 2.2 Hz, 1 H, C11-H), 2.14-1.99 (comp, 4 H, C3-H, C4-H, C7-H), 1.95-1.87 (comp, 2 H, C3-H, C6-H), 1.81-1.73 (m, 1 H, C4-H), 1.58-1.50 (m, 1 H, C6-H), 1.21 (t, *J* = 7.0 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 153.5 (C12), 137.7 (C8), 113.9 (C9), 84.6 (C10), 71.4 (C11), 59.8 (C13), 57.2 (C5), 47.8 (C2), 33.3 (C6), 31.2 (C3), 29.0 (C7), 28.9 (C4), 13.8 (C14).



(2*R*)-But-3-enyl-(5*R*)-prop-1-ynylpyrrolidine-1-carboxylic acid ethyl ester (413). A solution of 2.25 M *n*-BuLi in hexanes (10.5 mL, 23.7 mmol) was added to a solution of *i*-Pr_2NH (3.44 mL, 24.5 mmol) in THF (50 mL) at −78 ^{o}C. The resulting solution was stirred for 10 min at −78 ^{o}C, at −5 ^{o}C for 15 min, and then recooled to −78 ^{o}C. To this mixture was added a solution of **412** (1.75 g, 7.91 mmol) in THF (8 mL). The resulting yellow solution was stirred for 2 min, and then HMPA (6.90 mL, 39.5 mmol)

was added. The resulting brown solution was stirred for 5 min, and then MeI (1.50 mL, 23.7 mmol) was added. The resulting yellow solution was allowed to warm to ambient temperature, and stirring was continued for an additional 14 h. The reaction mixture was poured into 10% H_3PO_4 (100 mL) and Et_2O (30 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (4 x 50 mL) and the combined organic extracts were dried ($MgSO_4$), filtered through SiO_2, and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 1.73 g (93%) of **413** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 5.03 (app dq, J = 17.2, 1.7 Hz, 1 H), 4.97-4.93 (m, 1 H), 4.49-4.46 (m, 1 H), 5.01-4.01 (comp, 2 H), 3.80-3.75 (m, 1 H), 2.12-1.96 (comp, 4 H), 1.94-1.83 (comp, 2 H), 1.79-1.72 (comp, 4 H), 1.57-1.49 (m, 1 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 153.5, 137.8, 113.8, 79.9, 76.9, 59.7, 57.1, 48.2, 33.4, 31.5, 29.0, 13.9, 2.2; IR (neat) 3074, 2979, 1699, 1641, 1409, 1378, 1336, 1183, 1109, 1025 cm^{-1}; MS (CI) *m/z* 236.1658 [$C_{14}H_{22}NO_2$ (M + 1) requires 236.1651], 236(base), 180.

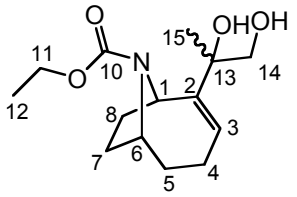
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.84 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H, C8-H), 5.03 (app dq, J = 17.2, 1.7 Hz, 1 H, C9-H(*E*)), 4.97-4.93 (m, 1 H, C9-H(*Z*)), 4.49-4.46 (m, 1 H, C5-H), 5.01-4.01 (comp, 2 H, C14-H), 3.80-3.75 (m, 1 H, C2-H), 2.12-1.96 (comp, 4 H, C3-H, C4-H, C7-H), 1.94-1.83 (comp, 2 H, C6-H, C7-H), 1.79-1.72 (comp, 4 H, C3, C12-H), 1.57-1.49 (m, 1 H, C6-H), 1.20 (t, J = 7.1 Hz, 3 H, C15-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 153.5 (C13), 137.8 (C8), 113.8 (C9), 79.9 (C10), 76.9 (C11), 59.7 (C14), 57.1 (C2), 48.2 (C5), 33.4 (C6), 31.5 (C7), 29.0 (C3, C4), 13.9 (C15), 2.2 (C12).



(+)-(1*R*)-2-Isopropenyl-9-ethoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (414). To a degassed solution of **413** (260 mg, 1.11 mmol) in CH_2Cl_2 (221 mL) was added solid **48** (94 mg, 0.11 mmol) in one portion. The mixture was stirred at rt under a blanket of argon for 23 h, then DMSO (4 mL) was added to decompose the catalyst, and stirring was continued for an additional 21 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 254 mg (98%) of **414** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.74-5.71 (m, 1 H), 5.01 (app s, 1 H), 4.88 (m, 1 H), 4.83 (d, J = 8.8 Hz, 1 H), 4.33-4.29 (m, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 2.30-2.14 (comp, 3 H), 2.11-1.96 (comp, 2 H), 1.84 (s, 3 H), 1.75-1.67 (comp, 2 H), 1.62-1.55 (m, 1 H), 1.16 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.5, 146.5, 142.6, 125.1, 110.4, 59.4, 56.3, 54.5, 30.6, 30.0, 29.1, 22.7, 20.7, 13.9; IR (neat) 2968, 1694, 1425, 1330, 1114, 1025, 883, 841, 767, 735 cm^{-1}; MS (CI) *m/z* 236.1646 [$C_{14}H_{22}NO_2$ (M + 1) requires 236.1651], 236 (base).

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.74-5.71 (m, 1 H, C3-H), 5.01 (app s, 1 H, C14-H), 4.88 (m, 1 H, C14-H), 4.83 (d, J = 8.8 Hz, 1 H, C1-H), 4.33-4.29 (m, 1 H, C6-H), 4.02 (q, J = 7.1 Hz, 2 H, C11-H), 2.30-2.14 (comp, 3 H, C4-H, C8-H), 2.11-1.96 (comp, 2 H, C5-H, C7-H), 1.84 (s, 3 H, C15-H), 1.75-1.67 (comp, 2 H, C7-H, C8-H), 1.62-1.55 (m, 1 H, C5-H), 1.16 (t, J = 7.1 Hz, 3 H, C12-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.5 (C10), 146.5 (C2), 142.6 (C13), 125.1 (C3), 110.4

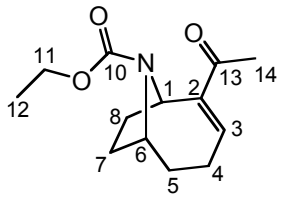
(C14), 59.4 (C11), 56.3 (C1), 54.5 (C6), 30.6 (C5), 30.0 (C8), 29.1 (C7), 22.7 (C4), 20.7 (C15), 13.9 (C12).



(+)-(1*R*)-2-(1,2-Dihydroxy-1-methylethyl)-9-ethoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (417). To a solution of OsO_4 (459 mg, 1.80 mmol) in THF (13 mL) at –78 °C was added TMEDA (372 μL, 2.46 mmol). The resulting red-orange solution was stirred for 5 min, and a solution of **414** (386 mg, 1.64 mmol) in THF (3.4 mL) was added. The resulting brown reaction mixture was stirred and allowed to warm slowly to rt over a period of 3 h. A solution of sat. $NaHSO_3$ (20 mL) was added, and the resulting solution was heated under reflux in a 95 °C oil bath for 2 h. The mixture was allowed to cool to rt, and EtOAc (30 mL) was added. The mixture was poured into a solution of sat. aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a dark-brown oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (9:1) to afford 402 mg (91%) of **417** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.64-5.60 (m, 1 H), 4.65-4.61 (m, 1 H), 4.36-4.32 (m, 1 H), 4.08-4.00 (comp, 2 H), 3.91 (app t, J = 6.0 Hz, 2 H), 3.39 (dd, J = 10.8, 5.9 Hz, 1 H), 3.32 (br dd, J = 10.8, 5.8 Hz, 1 H), 2.29-2.12 (comp, 3 H), 2.02-1.93 (m, 1 H), 1.87-1.79 (comp, 2 H), 1.73-1.66 (m, 1 H), 1.60-1.54 (m, 1 H), 1.23 (s, 3H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 152.4, 151.4, 122.0, 73.8, 68.0, 59.5, 55.2, 54.6, 31.7, 30.9, 27.9,

24.2, 22.6, 13.9; IR (neat) 3429, 2969, 1681, 1252, 1113, 1047, 926, 835, 732 cm^{-1}; MS (CI) *m/z* 270.1698 [$C_{14}H_{24}NO_4$ (M + 1) requires 270.1705], 270, 252 (base).

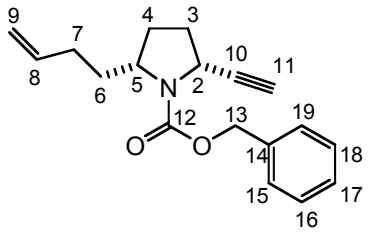
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.64-5.60 (m, 1 H, C3-H), 4.65-4.61 (m, 1 H, C1-H), 4.36-4.32 (m, 1 H, C6-H), 4.08-4.00 (comp, 2 H, C11-H), 3.91 (app t, *J* = 6.0 Hz, 2 H, C13-OH, C14-OH), 3.39 (dd, *J* = 10.8, 5.9 Hz, 1 H, C14-H), 3.32 (br dd, *J* = 10.8, 5.8 Hz, 1 H, C14-H), 2.29-2.12 (comp, 3 H, C4-H, C8-H), 2.02-1.93 (m, 1 H, C7-H), 1.87-1.79 (comp, 2 H, C5-H, C8-H), 1.73-1.66 (m, 1 H, C7-H), 1.60-1.54 (m, 1 H, C5-H), 1.23 (s, 3H, C15-H), 1.18 (t, *J* = 7.1 Hz, 3 H, C12-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.4 (C10), 151.4 (C2), 122.0 (C3), 73.8 (C13), 68.0 (C14), 59.5 (C11), 55.2 (C1), 54.6 (C6), 31.7 (C8), 30.9 (C5), 27.9 (C7), 24.2 (C15), 22.6 (C4), 13.9 (C12).



(+)-(1*R*)-2-Acetyl-9-ethoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (415). Solid $NaIO_4$ (851 mg, 3.98 mmol) was added to a rt solution of **417** (357 mg, 1.33 mmol) in 50% aqueous THF (26 mL). The reaction mixture was stirred for 45 min at rt, then diluted with H_2O (5 mL) and poured into a mixture of H_2O (40 mL) and Et_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered through a short plug of SiO_2, and concentrated under reduced pressure to afford 305 mg (97%) of **415** as a viscous, pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 6.88-6.85 (m, 1 H), 5.06 (br d, *J* = 9.1 Hz, 1 H), 4.34-4.29 (m, 1 H), 3.99 (q, *J* = 7.1 Hz, 2 H), 2.48-2.35 (comp, 2 H),

2.23 (s, 3 H), 2.21-2.04 (comp, 2 H), 2.02-1.94 (m, 1 H), 1.75-1.58 (comp, 3 H), 1.13 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 196.7, 152.3, 147.8, 141.3, 59.5, 54.9, 53.0, 30.4, 30.3, 27.9, 24.7, 23.1, 13.9; IR (neat) 3541, 2971, 1693, 1260, 1112, 1027, 838, 768 cm^{-1}; MS (CI) *m/z* 238.1434 [$C_{13}H_{20}NO_3$ (M + 1) requires 238.1443], 238 (base), 224, 192.

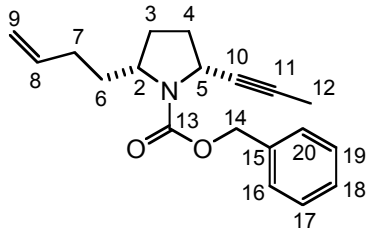
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 6.88-6.85 (m, 1 H, C3-H), 5.06 (br d, J = 9.1 Hz, 1 H, C1-H), 4.34-4.29 (m, 1 H, C6-H), 3.99 (q, J = 7.1 Hz, 2 H, C11-H), 2.48-2.35 (comp, 2 H, C4-H), 2.23 (s, 3 H, C14-H), 2.21-2.04 (comp, 2 H, C7-H, C8-H), 2.02-1.94 (m, 1 H, C5-H), 1.75-1.58 (comp, 3 H, C5-H, C7-H, C8-H)), 1.13 (t, J = 7.0 Hz, 3 H, C12-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 196.7 (C13), 152.3 (C10), 147.8 (C2), 141.3 (C3), 59.5 (C11), 54.9 (C6), 53.0 (C1), 30.4 (C5), 30.3 (C7), 27.9 (C8), 24.7 (C14), 23.1 (C4), 13.9 (C12).



(2*R*,5*R*)-But-3-enyl-5-ethynylpyrrolidine-1-carboxylic acid benzyl ester (419). A solution of 1.0 M DIBAL-H in PhMe (66 mL) was added to a solution of **392** (10.47 g, 32.99 mmol) in PhMe (160 mL) at –78 ^{o}C. The resulting solution was stirred at –78 ^{o}C for 3 h, whereupon *i*-PrOH (160 mL) was slowly added via cannula. The cooling bath was removed, and the reaction mixture was warmed to rt. To the resulting cloudy-white solution was added solid Cs_2CO_3 (43 g, 132 mmol) in one portion. After approximately 0.5 h, a solution of **241** (11.76 g, 61.22 mmol) in *i*-PrOH (40 mL) was added via cannula. The resulting yellow solution was stirred at rt for 17 h, whereupon a mixture of sat.

aqueous Rochelles salt solution (100 mL), and H_2O (100 mL), and EtOAc (100 mL) were added. The reaction mixture was vigorously stirred for 7 h, and then poured into brine (300 mL). The resulting layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to provide 6.69 g (72%) of **419** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40-7.27 (comp, 5 H,), 5.80 (ddt, J =17.0, 10.2, 6.5 Hz, 1 H), 5.11 (s, 2 H), 5.01 (app dq, J = 17.2, 1.7 Hz, 1 H), 4.95-4.91 (m, 1 H), 4.58-4.55 (m, 1 H), 3.88-3.81 (m, 1 H), 2.95 (app d, J = 2.2 Hz, 1 H), 2.17-1.87 (comp, 6 H), 1.82-1.75 (m, 1 H), 1.60-1.51 (m, 1 H); ^{13}C NMR 153.3, 137.6, 136.5, 127.7, 127.0, 126.7, 113.9, 84.5, 71.6, 65.6, 57.4, 48.0, 33.2, 31.2, 28.9; IR (neat) 3307, 2955, 2355, 2250, 1696, 1408, 1355, 1185, 1102 cm^{-1}; MS (CI) *m/z* 284.1639 [$C_{18}H_{22}NO_2$ (M + 1) requires 284.1651], 284 (base), 240.

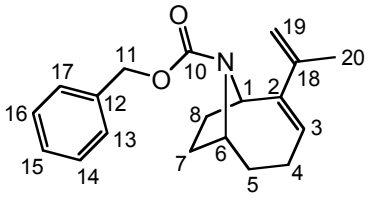
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.40-7.27 (comp, 5 H, C15-C19-H), 5.80 (ddt, J =17.0, 10.2, 6.5 Hz, 1 H, C8-H), 5.11 (s, 2 H, C13-H), 5.01 (app dq, J = 17.2, 1.7 Hz, 1 H, C9-H(*E*)), 4.95-4.91 (m, 1 H, C9-H(*Z*)), 4.58-4.55 (m, 1 H, C2-H), 3.88-3.81 (m, 1 H, C5-H), 2.95 (app d, J = 2.2 Hz, 1 H, C11-H), 2.17-1.87 (comp, 6 H, C3-H, C4-H, C6-H, C7-H), 1.82-1.75 (m, 1 H, C4-H), 1.60-1.51 (m, 1 H, C6-H); ^{13}C NMR 153.3 (C12), 137.6 (C8), 136.5 (C14), 127.7 (C16, C18), 127.0 (C17), 126.7 (C15, C19), 113.9 (C9), 84.5 (C10), 71.6 (C11), 65.6 (C13), 57.4 (C5), 48.0 (C2), 33.2 (C6), 31.2 (C3), 28.9 (C4, C7).



(2*R*)-But-3-enyl-(5*R*)-prop-1-ynylpyrrolidine-1-carboxylic acid benzyl ester (420). A solution of **419** (765 mg, 2.69 mmol) in THF (13 mL) was added to a solution of 1.0 M NaHMDS in THF (8.0 mL, 8.0 mmol) at –78 °C. The resulting solution was stirred for 5 min at -78 °C, and MeOTf (1.53 mL, 13.5 mmol) was added. After stirring for 2 h at –78 °C, the reaction mixture was poured into a mixture of sat. aqueous $NaHCO_3$ (90 mL) and Et_2O (20 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with 1 N HCl (2 x 70 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 781 mg (97%) of **420** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39-7.33 (comp, 4 H), 7.32-7.27 (m, 1 H), 5.80 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 5.10 (dd, J = 24.0, 12.9 Hz, 1 H), 5.03-4.98 (m, 1 H), 4.94-4.90 (m, 1 H), 4.55-4.51 (m, 1 H), 3.85-3.79 (m, 1 H), 2.15-1.96 (comp, 4 H), 1.95-1.84 (comp, 2 H), 1.82-1.72 (comp, 4 H), 1.58-1.51 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) 153.3, 137.7, 136.6, 127.6, 127.0, 126.7, 113.8, 79.8, 77.2, 65.4, 57.3, 48.3, 33.3, 31.5, 29.0, 28.9, 2.3; IR (neat) 2955, 1702, 1402, 1343, 1208, 1097 cm^{-1}; MS (CI) *m/z* 298.1800 [$C_{19}H_{24}NO_2$ (M + 1) requires 298.1807], 298 (base).

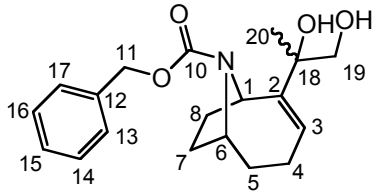
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39-7.33 (comp, 4 H, C16-H, C17-H, C19-H, C20-H), 7.32-7.27 (m, 1 H, C18-H), 5.80 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H, C8-H), 5.10 (dd, J = 24.0, 12.9 Hz, 1 H, C14-H), 5.03-4.98 (m, 1 H, C9-H(*E*)),

4.94-4.90 (m, 1 H, C9-H(*Z*)), 4.55-4.51 (m, 1 H, C5-H), 3.85-3.79 (m, 1 H, C2-H), 2.15-1.96 (comp, 4 H, C3-H, C4-H, C7-H), 1.95-1.84 (comp, 2 H, C3-H, C6-H), 1.82-1.72 (comp, 4 H, C4-H, C12-H), 1.58-1.51 (m, 1 H, C6-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 153.3 (C13), 137.7 (C8), 136.6 (C15), 127.6 (C17, C19), 127.0 (C18), 126.7 (C16, C20), 113.8 (C9), 79.8 (C10), 77.2 (C11), 65.4 (C14), 57.3 (C2), 48.3 (C5), 33.3 (C6), 31.5 (C3), 29.0 (C7), 28.9 (C4), 2.3 (C12).



(+)-(1*R*)-2-Isopropenyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (421). To a degassed solution of **48** (212 mg, 0.250 mmol) in CH_2Cl_2 (500 mL) was added a solution **420** (744 mg, 2.50 mmol) in degassed CH_2Cl_2 (30 mL). The mixture was stirred under a blanket of argon for 16 h, then DMSO (0.89 mL) was added to decompose the catalyst, and stirring was continued for an additional 23 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 623 mg (84%) of **421** as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.36-7.25 (comp, 5 H), 5.74-5.71 (m, 1 H), 5.10-4.96 (comp, 3 H), 4.91-4.84 (comp, 2 H), 4.39-4.34 (m, 1 H), 2.29-2.16 (comp, 3 H), 2.13-1.97 (comp, 2 H), 1.82 (s, 3 H), 1.77-1.68 (comp, 2 H), 1.64-1.57 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 152.3, 146.3, 142.4, 136.8, 127.6, 127.0, 126.7, 125.2, 110.5, 65.2, 56.5, 54.7, 31.8, 30.6, 29.2, 22.7, 20.7; IR (neat) 2931, 1701, 1421, 1330, 1107, 1005 cm^{-1}; MS (CI) *m/z* 298.1799 [$C_{19}H_{24}NO_2$ (M + 1) requires 298.1807], 298 (base), 254.

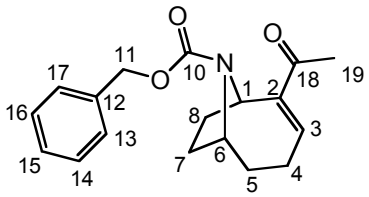
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.36-7.25 (comp, 5 H, C13-C17-H), 5.74-5.71 (m, 1 H, C3-H), 5.10-4.96 (comp, 3 H, C11-H, C19-H), 4.91-4.84 (comp, 2 H, C6-H, C19-H), 4.39-4.34 (m, 1 H, C1-H), 2.29-2.16 (comp, 3 H, C4-H, C5-H), 2.13-1.97 (comp, 2 H, C7-H, C8-H), 1.82 (s, 3 H, C20-H), 1.77-1.68 (comp, 2 H, C7-H, C5-H), 1.64-1.57 (m, 1 H, C8-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 152.3 (C10), 146.3 (C2), 142.4 (C18), 136.8 (C12), 127.6 (C13, C17), 127.0 (C15), 126.7 (C14, C16), 125.2 (C3), 110.5 (C19), 65.2 (C11), 56.5 (C6), 54.7 (C1), 31.8 (C8), 30.6 (C5), 29.2 (C7), 22.7 (C4), 20.7 (C20).



(+)-(1*R*)-2-(1,2-Dihydroxy-1-methylethyl)-9-benzyloxycarbonyl-9-aza-bicyclo[4.2.1]-2-nonene (422). Et_3N (74 μL, 0.53 mmol) was added to a solution of OsO_4 (108 mg, 0.424 mmol) in THF (2.1 mL) at room temperature. The resulting brown solution was stirred for 5 min and then cooled to –78 ^{o}C. To this mixture was added a solution **421** (87 mg, 0.29 mmol) in THF (2 mL). The resulting mixture was allowed to warm slowly to room temperature over 2 h, and stirring was continued for 20 h at room temperature. A solution of sat. aqueous $NaHSO_3$ (5 mL) was added, and the mixture was heated to reflux for 2.5 h. The resulting black mixture was cooled to room temperature, diluted with EtOAc (10 mL), and then filtered through a plug of SiO_2, eluting with EtOAc. The filtrate was concentrated under reduced pressure to provide a crude oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (3:1) to afford 89 mg (76%) of **422** as a pale-yellow oil and 15 mg (13%) of the undesired cyclic diol

423 (mp 94-95 °C). ^{1}H NMR (**422**) (500 MHz, DMSO-d_6, 100 °C) δ 7.36-7.27 (comp, 5 H), 5.64-5.61 (m, 1 H), 5.06 (app q, J = 12.6 Hz, 2 H), 4.68-4.66 (m, 1 H), 4.41-4.37 (m, 1 H), 4.02-3.93 (comp, 2 H), 3.39-3.25 (comp, 2 H), 2.28-2.12 (comp, 3 H), 2.03-1.95 (m, 1 H), 1.86-1.80 (comp, 2 H), 1.73-1.67 (m, 1 H), 1.61-1.55 (m, 1 H), 1.26-1.15 (comp, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.4, 136.7, 127.7, 127.1, 127.0, 122.1, 73.9, 68.0, 65.3, 55.5, 54.9, 31.1, 28.0, 24.2, 22.6; IR (neat) 3401, 2931, 1672, 1426, 1326, 1114, 914, 732 cm^{-1}; mass spectrum (CI) *m/z* 332.1854 [$C_{19}H_{26}NO_4$ (M + 1) requires 332.1862], 332, 314 (base).

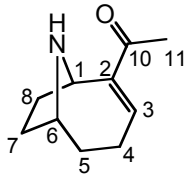
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.36-7.27 (comp, 5 H, C13-C17-H), 5.64-5.61 (m, 1 H, C3-H), 5.06 (app q, J = 12.6 Hz, 2 H, C11-H), 4.68-4.66 (m, 1 H, C1-H), 4.41-4.37 (m, 1 H, C6-H), 4.02-3.93 (comp, 2 H, C18-OH, C19-OH), 3.39-3.25 (comp, 2 H, C19-H), 2.28-2.12 (comp, 3 H, C4-H, C8-H), 2.03-1.95 (m, 1 H, C7-H), 1.86-1.80 (comp, 2 H, C5-H, C8-H), 1.73-1.67 (m, 1 H, C7-H), 1.61-1.55 (m, 1 H, C5-H), 1.26-1.15 (comp, 3 H, C20-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2 (C10), 151.4 (C2), 136.7 (C12), 127.7 (C14, C16), 127.1 (C15), 127.0 (C13, C17), 122.1 (C3), 73.9 (C18), 68.0 (C19), 65.3 (C11), 55.5 (C6), 54.9 (C1), 31.1 (C5), 28.0 (C7), 24.2 (C20), 22.6 (C4, C8).



(+)-(1*R*)-2-Acetyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (103). Solid $NaIO_4$ (140 mg, 0.655 mmol) was added to a solution of **422** (70 mg, 0.21 mmol) in 50% aqueous THF (4 mL) at room temperature. The reaction mixture was stirred for 1.5

h, and then diluted with H_2O (2 mL). The solution was poured into a mixture of H_2O (15 mL) and Et_2O (5 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (8:1) to afford 60 mg (95%) of **103** as a pale-yellow oil. All data in agreement with the literature.[32b] $[\alpha]^{26}_D$ – 36.1 (*c* 1.42, CH_3OH) (lit[32b] $[\alpha]^{22}_D$ –37.5 (*c* 1.12, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (comp, 5 H), 6.83-6.75 (m, 1 H), 5.27 (d, *J* = 8.9 Hz, 1 H), 5.16-4.98 (comp, 2 H), 4.52-4.38 (m, 1 H), 2.47-2.00 (comp, 8 H), 1.74-1.61 (comp, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 153.4, 149.3, 142.3, 136.8, 128.4, 127.9, 127.7, 66.3, 56.0, 53.0, 31.6, 30.4, 28.5, 25.3, 24.1; IR (neat) 3538, 2951, 1700, 1665, 1418, 1106 cm^{-1}; mass spectrum (CI) *m/z* 300.1587 [$C_{18}H_{22}NO_3$ (M + 1) requires 300.1600], 300 (base), 256, 192.

NMR Assignments. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (comp, 5 H, C13-C17-H), 6.83-6.75 (m, 1 H, C3-H), 5.27 (d, *J* = 8.9 Hz, 1 H, C1-H), 5.16-4.98 (comp, 2 H, C11-H), 4.52-4.38 (m, 1 H, C6-H), 2.47-2.00 (comp, 8 H, C4-H, C5-H, C7-H, C8-H), 1.74-1.61 (comp, 3 H, C19-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8 (C18), 153.4 (C10), 149.3 (C2), 142.3 (C12), 136.8 (C3), 128.4 (C14, C16), 127.9 (C15), 127.7 (C13, C17), 66.3 (C11), 56.0 (C6), 53.0 (C1), 31.6 (C5), 30.4 (C7), 28.5 (C8), 25.3 (C19), 24.1 (C4).

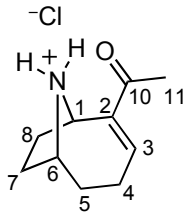


(+)-(1*R*)-2-Acetyl-9-azabicyclo[4.2.1]-2-nonene (1) ((+)-anatoxin-a) [(+)-4].

Freshly distilled TMSI (122 μL, 0.856 mmol) was added to a solution of **103** (122 mg, 0.408 mmol) in CH_3CN (1.4 mL) at –10 ^oC. The resulting solution was allowed to stir for 20 min in the absence of light, and then quenched with a solution of 1.25 M methanolic HCl (1 mL). The resulting solution was maintained in the dark and allowed to warm to rt, then concentrated under reduced pressure. The resulting solid was dissolved in H_2O (10 mL) and the aqueous solution was extracted with CH_2Cl_2 (2 x 4 mL). The aqueous phase was basified to pH=12 with NH_4OH and extracted with CH_2Cl_2 (2 x 4 mL) and then 3:1 CH_2Cl_2/*i*-PrOH (2 x 5 mL). The combined organics were rapidly dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The light-sensitive free-base was dried at 0.1 mm Hg for 1 h to afford 67 mg (99%) of **(+)-4** as a pale-yellow oil. The ^1H and ^{13}C NMR data were consistent with those reported in the literature. ^1H-NMR (400 MHz, $CDCl_3$) δ 6.89-6.84 (m, 1 H), 4.66 (app d, *J* = 8.9 Hz, 1 H), 3.82-3.75 (m, 1 H), 3.13 (br s, 1 H), 2.52-2.34 (comp, 2 H), 2.25 (s, 3 H), 2.21-2.09 (m, 1 H), 2.01-1.92 (m, 1 H), 1.82-1.57 (comp, 4 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.9, 152.4, 143.6, 58.1, 54.3, 33.5, 33.1, 30.5, 25.8, 25.2; IR (neat) 3392, 2933, 1663, 1433, 1397, 1361, 1258, 1228, 847 cm^{-1}; mass spectrum (CI) *m/z* 166.1234 [$C_{10}H_{16}NO$ (M + 1) requires 166.1232], 166 (base), 149.

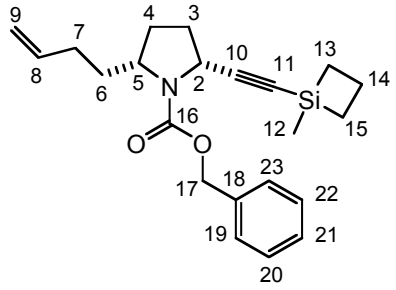
NMR Assignments. ^1H-NMR (400 MHz, $CDCl_3$) δ 6.89-6.84 (m, 1 H, C3-H), 4.66 (app d, *J* = 8.9 Hz, 1 H, C1-H), 3.82-3.75 (m, 1 H, C6-H), 3.13 (br s, 1 H, NH), 2.52-2.34 (comp, 2 H, C4-H), 2.25 (s, 3 H, C11-H), 2.21-2.09 (m, 1 H, C8-H), 2.01-1.92 (m, 1 H, C7-H), 1.82-1.57 (comp, 4 H, C5-H, C7-H, C8-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.9

(C10), 152.4 (C2), 143.6 (C3), 58.1 (C6), 54.3 (C1), 33.5 (C5), 33.1 (C7), 30.5 (C8), 25.8 (C11), 25.2 (C4).



(+)-(1*R*)-2-Acetyl-9-azabicyclo[4.2.1]-2-nonene hydrochloride [(+)-4·HCl]. A solution of 1.25 M HCl in MeOH (1 mL) was added to a solution of **(+)-4** (48 mg, 0.16 mmol) in dry MeOH (1 mL) at 0 °C. The solvent was removed under reduced pressure, and the crude oil was dried under vacuum (0.3 mm Hg) for 15 h. The resulting off-white foam was azeotropically dried with PhH (2 x 0.3 mL) and then under vacuum (0.3 mm Hg) for 2 h. The resulting foam was dissolved in a solution of 6% MeOH/Et_2O (2 mL), at 50 °C. The solution was cooled to room temperature and placed in a 4 °C refrigerator for 5 d. The resulting colorless prisms were collected by vacuum filtration, rinsing with cold Et_2O (5 mL), and dried at 0.3 mm Hg for 2 d to afford 32 mg (100%) of **(+)-4·HCl**. All spectra in agreement with the literature. $[\alpha]^{27}_D$ +37.3 (c 2.08, abs. EtOH) [(lit[31] $[\alpha]^{24}_D$ +43.2 (c 0.676, abs. EtOH), (lit[20] $[\alpha]^{24}_D$ +36 (c 0.85, EtOH)]; mp 151-153 °C (lit[31] mp 152-153 °C). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.02 (br s, 1 H), 9.42 (br s, 1 H), 7.11 (dd, *J* = 8.2, 3.4 Hz, 1 H), 5.23-5.19 (m, 1 H), 4.37-4.29 (m, 1 H), 2.65-2.58 (m, 1 H), 2.56-2.47 (comp, 2 H), 2.42-2.30 (comp, 5 H), 1.94-1.78 (comp, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 196.4, 145.4, 143.9, 58.3, 52.1, 30.2, 27.7, 27.5, 25.2, 23.6; IR (neat) 3417, 2924, 1661, 1471, 1432, 1403, 1364, 1269, 1230, 911, 743 cm^{-1}; mass spectrum (CI) *m/z* 200.0835 [$C_{10}H_{15}NOCl$ (M - 1) requires 200.0842], 216, 202, 200 (base), 179.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 10.02 (br s, 1 H, NH), 9.42 (br s, 1 H, NH), 7.11 (dd, *J* = 8.2, 3.4 Hz, 1 H, C3-H), 5.23-5.19 (m, 1 H, C1-H), 4.37-4.29 (m, 1 H, C6-H), 2.65-2.58 (m, 1 H, C4-H), 2.56-2.47 (comp, 2 H, C4-H, C8-H), 2.42-2.30 (comp, 5 H, C5-H, C7-H, C11-H), 1.94-1.78 (comp, 3 H, C8-H, C7-H, C5-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ196.4 (C10), 145.4 (C3), 143.9 (C2), 58.3 (C6), 52.1 (C1), 30.2 (C8), 27.7 (C7), 27.5 (C5), 25.2 (C11), 23.6 (C4).

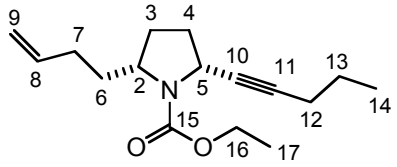


(2*R*,5*R*)-But-3-enyl-2-(1-methylsiletan-1-ylethynyl)pyrrolidine-1-carboxylic acid benzyl ester (427). A solution of **419** (302 mg, 1.07 mmol) in THF (11 mL) was added via cannula to a solution of KHMDS (4.3 mL, 2.1 mmol, 0.5 M in PhMe) in THF (4.3 mL) at –78 ^{o}C. The mixture was stirred at –78 ^{o}C for 10 min, and then **426** (0.52 mL, 514 mg, 4. 3 mmol) was added via syringe. Stirring was continued at –78 ^{o}C for 5 h, whereupon the reaction was poured into a mixture of 1 N HCl (40 mL) and Et_2O (10 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a crude oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:3) to afford 309 mg (79%) of **427** as a colorless oil along with 15% recovered **419**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (comp, 5 H), 5.80 (br s, 1 H), 5.27-4.88 (comp, 4 H), 4.64 (br s, 1 H), 3.96-3.80 (m, 1 H), 2.18-1.80 (comp, 9 H), 1.68-1.56 (m, 1 H), 1.24-1.10 (comp, 2 H), 1.07-0.96 (comp, 2

H), 0.38 (s, 3 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.3, 137.7, 136.5, 127.7, 127.1, 126.8, 114.0, 84.5, 71.7, 65.6, 57.4, 48.8, 48.0, 33.2, 31.2, 28.9, 17.2, 15.4, 14.5, -0.8; IR (neat) 3067, 3034, 2931, 2711, 1705, 1641, 1496, 1449, 1406, 1355, 1308, 1252, 1184, 1107, 996, 911, 872 cm^{-1}; MS (CI) *m/z* 368.2053 [$C_{22}H_{30}NOSi$ (M + 1) requires 368.2046], 368 (base), 324, 284.

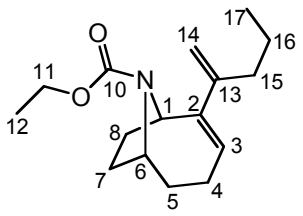
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (comp, 5 H, C19-C23-H), 5.80 (br s, 1 H, C8-H), 5.27-4.88 (comp, 4 H, C9-H, C12-H), 4.64 (br s, 1 H, C2-H), 3.96-3.80 (m, 1 H, C5-H), 2.18-1.80 (comp, 9 H, C7-H, C6-H, C4-H, C3-H, C14-H), 1.68-1.56 (m, 1 H, C6-H), 1.24-1.10 (comp, 2 H, C15-H), 1.07-0.96 (comp, 2 H, C13-H), 0.38 (s, 3 H, C12-H); ^{13}C-NMR Assignments could not be made due to decomposition of the sample during VT-NMR work conducted at 100 °C.

5.4 PINNAMINE



(2*R*)-But-3-enyl-(5*R*)-pent-1-ynylpyrrolidine-1-carboxylic acid ethyl ester (430). A solution of 2.4 M *n*-BuLi in hexanes (292 μL, 0.699 mmol) was added to a solution of diisopropylamine (101 μL, 0.723 mmol) in THF (1.5 mL) at −78 °C. The resulting solution was stirred for 10 min at −78 °C, at −5 °C for 15 min and then recooled to −78 °C. To this mixture was added a solution of **412** (52 mg, 0.23 mmol) in THF (1 mL). The resulting yellow solution was stirred for 2 min, then HMPA (203 μL, 1.17 mmol) was added. The resulting yellow-brown solution was stirred for 3 min, and n-PrOTf (270 mg, 1.40 mmol) was added. The reaction mixture was allowed to warm to ambient temperature, and stirring was continued for an additional 18 h. The mixture was

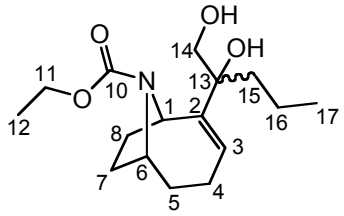
poured into 10% H_3PO_4 (20 mL) and Et_2O (5 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 37 mg (61%) of **413** as a pale-yellow oil and 4 mg (7%) of recovered **412**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.03 (app dd, *J* = 17.1, 1.7 Hz, 1 H), 4.93 (app d, *J* = 9.9 Hz, 1 H), 4.55 (br s, 1 H), 4.20-4.06 (comp, 2 H), 3.79 (br s, 1 H), 2.15-1.88 (comp, 6 H), 1.86-1.74 (m, 1 H), 1.59-1.37 (comp, 4 H), 1.36-1.21 (comp, 4 H), 0.94 (t, *J* = 7.5 Hz, 3 H); IR (neat) 3501, 3078, 2945, 1699, 1639, 1409, 1379, 1337, 1180, 1107, 1029, 908, 769 cm^{-1}; MS (CI) *m/z* 264.1957 [$C_{16}H_{26}NO_2$ (M + 1) requires 264.1964], 264 (base).



(+)-(1*R*)-2-(1-Methylenebutyl)-9-ethoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (431). A solution of **430** (187 mg, 0.710 mmol) in degassed CH_2Cl_2 (12 mL) was added via cannula to a degassed solution of **48** (91 mg, 0.11 mmol) in CH_2Cl_2 (130 mL). The resulting mixture was stirred at rt under a blanket of argon for 20 h, then DMSO (2.52 mL, 35.5 mmol) was added to destroy any remaining catalyst. After an additional 5 h of stirring, the solvent was removed under reduced pressure and the remaining crude brown oil was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 142 mg (76%) of **431** as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.65 (t, *J* = 5.9 Hz, 1 H), 4.98 (app s, 1 H), 4.82 (app d, *J* = 1.2 Hz,

1 H), 4.72 (d, J = 8.7 Hz, 1 H), 4.34-4.29 (m, 1 H), 4.06-3.97 (comp, 2 H), 2.25-2.20 (comp, 2 H), 2.19-2.11 (comp, 3 H), 2.10-2.03 (m, 1 H), 2.02-1.95 (ddt, J = 13.4, 7.8, 5.5 Hz, 1 H), 1.75-1.67 (comp, 2 H), 1.62-1.55 (m, 1 H), 1.48-1.36 (comp, 2 H), 1.16 (t, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.5, 148.0, 146.3, 124.5, 109.8, 59.4, 56.9, 54.5, 35.8, 31.8, 30.5, 28.9, 22.7, 20.5, 13.9, 12.8; IR (neat) 2957, 1699, 1427, 1331, 1007 cm^{-1}; MS (CI) *m/z* 264.1962 [$C_{16}H_{26}NO_2$ (M + 1) requires 264.1963], 264 (base).

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 5.65 (t, J = 5.9 Hz, 1 H, C3-H), 4.98 (app s, 1 H, C14-H), 4.82 (app d, J = 1.2 Hz, 1 H, C14-H), 4.72 (d, J = 8.7 Hz, 1 H, C1-H), 4.34-4.29 (m, 1 H, C6-H), 4.06-3.97 (comp, 2 H, C11-H), 2.25-2.20 (comp, 2 H, C4-H), 2.19-2.11 (comp, 3 H, C8-H, C15-H), 2.10-2.03 (m, 1 H, C7-H), 2.02-1.95 (ddt, J = 13.4, 7.8, 5.5 Hz, 1 H, C5-H), 1.75-1.67 (comp, 2 H, C7-H, C8-H), 1.62-1.55 (m, 1 H, C5-H), 1.48-1.36 (comp, 2 H, C16-H), 1.16 (t, J = 7.0 Hz, 3 H, C12-H), 0.88 (t, J = 7.4 Hz, 3 H, C17-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.5 (C10), 148.0 (C13), 146.3 (C2), 124.5 (C3), 109.8 (C14), 59.4 (C11), 56.9 (C1), 54.5 (C6), 35.8 (C15), 31.8 (C5), 30.5 (C8), 28.9 (C7), 22.7 (C4), 20.5 (C16), 13.9 (C12), 12.8 (C17).

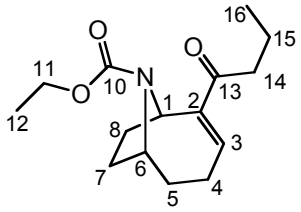


(+)-(1*R*)-2-(1-Hydroxy-1-hydroxymethylbutyl)-9-ethoxycarbonyl-9-azabicyclo-[4.2.1]-2-nonene (434). Solid quinuclidine (39 mg, 0.35 mmol) was added to a solution of OsO_4 (81 mg, 0.32 mmol) in THF (3.2 mL) at rt. The resulting red-orange

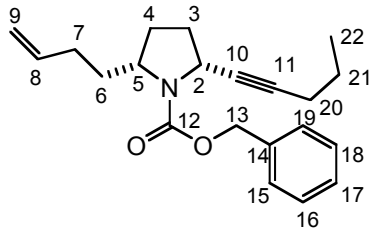
solution was stirred for 5 min, then cooled to −78 °C. To this mixture was added a solution **431** (76 mg, 0.29 mmol) in THF (1 mL). The resulting red-orange reaction mixture was allowed to slow warming to rt over a period of 3 h. The resulting dark-green solution was allowed to stir for an additional 14 h at rt, and then diluted with THF (4 mL) and sat. aqueous $NaHSO_3$ (4 mL). The mixture was then heated under reflux in an 80 °C oil bath for 2 h, then cooled to rt, and poured into a mixture of EtOAc (6 mL) and sat. aqueous $NaHCO_3$ (30 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a brown oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (7:1) to afford 68 mg (79%) of **434** as a clear oil and 4 mg (5%) of undesired cyclic diol **435** as an off-white solid. ^{1}H NMR (**434**) (500 MHz, DMSO-d_6, 100 °C) δ 5.57 (m, 1 H), 4.67-4.63 (m, 1 H), 4.37-4.32 (m, 1 H), 4.03 (comp, 2 H), 3.88 (br t, J = 5.6 Hz, 1 H), 3.74 (br s, 1 H), 3.43 (dd, J = 10.9, 5.8 Hz, 1 H), 3.32 (dd, J = 10.8, 5.6 Hz, 1 H), 2.30-2.10 (comp, 3 H), 2.01-1.93 (m, 1 H), 1.87-1.79 (comp, 2 H), 1.73-1.66 (m, 1 H), 1.62-1.54 (comp, 2 H), 1.52-1.45 (m, 1 H), 1.32-1.23 (comp, 2 H), 1.18 (t, J = 7.1 Hz, 3 H), 0.85 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 152.5, 149.6, 122.8, 76.1, 67.0, 59.6, 55.2, 54.5, 37.8, 31.1, 28.0, 22.6, 15.5, 13.9, 13.8; IR (neat) 3406, 2953, 1668, 1433, 1329, 1116, 768, 733 cm^{-1}; MS (CI) *m/z* 298.2013 [$C_{16}H_{28}NO_4$ (M + 1) requires 298.2018], 298 (base), 280.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 5.57 (m, 1 H, C3-H), 4.67-4.63 (m, 1 H, C1-H), 4.37-4.32 (m, 1 H, C6-H), 4.03 (comp, 2 H, C11-H), 3.88 (br t, J = 5.6 Hz, 1 H, C14-OH), 3.74 (br s, 1 H, C13-OH), 3.43 (dd, J = 10.9, 5.8 Hz, 1 H, C14-H), 3.32 (dd, J = 10.8, 5.6 Hz, 1 H, C14-H), 2.30-2.10 (comp, 3 H, C4-H, C8-H),

2.01-1.93 (m, 1 H, C7-H), 1.87-1.79 (comp, 2 H, C5-H, C8-H), 1.73-1.66 (m, 1 H, C7-H), 1.62-1.54 (comp, 2 H, C5-H, C15-H), 1.52-1.45 (m, 1 H, C15-H), 1.32-1.23 (comp, 2 H, C16-H), 1.18 (t, J = 7.1 Hz, 3 H, C12-H), 0.85 (t, J = 7.4 Hz, 3 H, C17-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.5 (C10), 149.6 (C2), 122.8 (C3), 76.1 (C13), 67.0 (C14), 59.6 (C11), 55.2 (C6), 54.5 (C1), 37.8 (C15), 31.1 (C5, C8), 28.0 (C7), 22.6 (C4), 15.5 (C16), 13.9 (C12), 13.8 (C17).

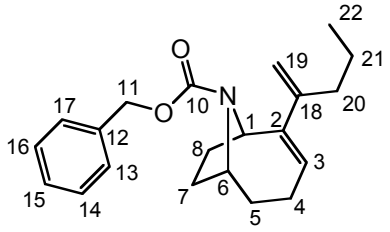


(+)-(1*R*)-2-Butyryl-9-ethoxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (432). Solid $NaIO_4$ (71 mg, 0.33 mmol) was added to a solution of **434** (33mg, 0.11 mmol) in 50% aqueous THF (2.2 mL) at rt. The mixture was stirred for 1 h, then diluted with H_2O (2 mL) and poured into a mixture of H_2O (10 mL) and Et_2O (3 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a clear oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (4:1) to afford 28 mg (95%) of **432** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82-6.71 (m, 1 H), 5.22-5.11 (m, 1 H), 4.48-4.29 (m, 1 H), 4.12-3.95 (comp, 2 H), 2.66-2.50 (comp, 2 H), 2.46-1.96 (comp, 5 H), 1.71-1.53 (comp, 5 H), 1.24-1.08 (comp, 3 H), 0.89 (t, J = 7.2 Hz, 3 H); IR (neat) 3582, 3514, 2954, 2247, 1695, 1667, 1421, 1330, 1113, 1022, 930, 771, 731 cm^{-1}; MS (CI) *m/z* 266.1754 [$C_{15}H_{24}NO_3$ (M + 1) requires 266.1756], 266(base), 238.



(5*R*)-But-3-enyl-(2*R*)-pent-1-ynylpyrrolidine-1-carboxylic acid benzyl ester (437). A solution of **419** (1.06 g, 3.74 mmol) in THF (7.5 mL) was added to a solution of 2.0 M NaHMDS in THF (5.6 mL, 11 mmol) at –78 °C. The resulting solution was stirred for 5 min at –78 °C, and then transferred via cannula to a –40 °C solution of anhydrous $CeCl_3$ (2.95 g, 11.9 mmol) in PhMe (24 mL). The slurry was stirred at –40 °C for 0.5 h, whereupon a solution of *n*-PrOTf (7.2 g, 37 mmol) in PhMe (20 mL) was added via cannula, and the solution was stirred for 0.5 h at –40 °C. The reaction mixture was poured into a mixture of cold 1 N HCl (120 mL) and Et_2O (20 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 40 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a dark-brown oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 955 mg (79%) of **437** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38-7.27 (comp, 5 H), 5.80 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 5.10 (q, J = 12.7 Hz, 2 H), 4.99 (app dq, J = 17.1, 1.7 Hz, 1 H), 4.93-4.90 (m, 1 H), 4.57-4.54 (m, 1 H), 3.85-3.80 (m, 1 H), 2.16-1.98 (comp, 6 H), 1.94-1.85 (comp, 2 H), 1.82-1.74 (m, 1 H), 1.60-1.52 (m, 1 H), 1.47-1.38 (comp, 2 H), 0.92, (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) 153.3, 137.8, 136.7, 127.7, 127.0, 126.7, 113.9, 81.6, 81.1, 65.4, 57.3, 48.3, 33.2, 31.7, 29.0, 21.1, 19.4, 12,4; IR (neat) 2946, 1705, 1409, 1358, 1106, 910, 736, 697 cm^{-1}; MS (CI) *m/z* 326.2119 [$C_{21}H_{28}NO_2$ (M + 1) requires 326.2120], 326 (base), 248.

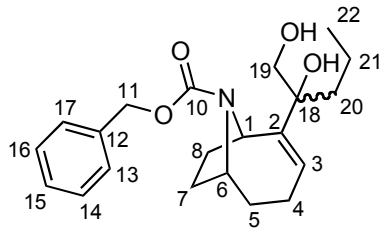
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.38-7.27 (comp, 5 H, C18-C22-H), 5.80 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H, C8-H), 5.10 (q, J = 12.7 Hz, 2 H, C16-H), 4.99 (app dq, J = 17.1, 1.7 Hz, 1 H, C9-H(*E*)), 4.93-4.90 (m, 1 H, C9-H(*Z*)), 4.57-4.54 (m, 1 H, C2-H), 3.85-3.80 (m, 1 H, C5-H), 2.16-1.98 (comp, 6 H, C12-H, C3-H, C4-H, C7-H), 1.94-1.85 (comp, 2 H, C3-H, C6-H), 1.82-1.74 (m, 1 H, C4-H), 1.60-1.52 (m, 1 H, C6-H), 1.47-1.38 (comp, 2 H, C13-H), 0.92, (t, J = 7.3 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 153.3 (C15), 137.8 (C8), 136.7 (C17), 127.7 (C19, C21), 127.0 (C20), 126.7 (C18, C22), 113.9 (C9), 81.6 (C10), 81.1 (C11), 65.4 (C16), 57.3 (C5), 48.3 (C2), 33.2 (C6), 31.7 (C3), 29.0 (C4, C7), 21.1 (C13), 19.4 (C12), 12.4 (C14).



(+)-(1*R*)-2-Isopentenyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (438). To a degassed solution of **48** (270 mg, 0.319 mmol) in CH_2Cl_2 (420 mL) was added a solution of **437** (692 mg, 2.13 mmol) in degassed CH_2Cl_2 (5 mL). The mixture was stirred under a blanket of argon for 4 h. DMSO (1.1 mL) was added (to decompose the catalyst) and stirring was continued for an additional 18 h. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 653 mg (94%) of **438** as a pale orange oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.35-7.26 (comp, 5 H), 5.66 (t, J = 5.9 Hz, 1 H), 5.06 (s, 2 H), 4.96 (br s, 1 H), 4.80-4.76 (comp, 2 H), 4.38-4.34 (m, 1 H), 2.24-1.96 (comp, 7 H), 1.76-1.69 (comp, 2 H), 1.63-1.57 (m, 1 H), 1.44-1.33 (comp, 2 H), 0.84 (t, J

= 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 152.3, 147.8, 146.1, 136.7, 127.6, 127.0, 126.7, 124.6, 109.9, 65.2, 57.1, 54.7, 35.8, 31.9, 30.5, 29.0, 22.7, 20.5, 12.8; IR (neat) 2957, 1700, 1420, 1330, 1106, 736 cm^{-1}; MS (CI) *m/z* 326.2111 [$C_{21}H_{28}NO_2$ (M + 1) requires 326.2120], 326 (base), 282, 218.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.35-7.26 (comp, 5 H, C13-C17-H), 5.66 (t, *J* = 5.9 Hz, 1 H, C3-H), 5.06 (s, 2 H, C11-H), 4.96 (br s, 1 H, C19-H), 4.80-4.76 (comp, 2 H, C19-H, C6-H), 4.38-4.34 (m, 1 H, C1-H), 2.24-1.96 (comp, 7 H, C20-H, C4-H, C5-H, C7-H, C8-H), 1.76-1.69 (comp, 2 H, C5-H, C7-H), 1.63-1.57 (m, 1 H, C8-H), 1.44-1.33 (comp, 2 H, C21-H), 0.84 (t, *J* = 7.3 Hz, 3 H, C22-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) 152.3 (C10), 147.8 (C2), 146.1 (C18), 136.7 (C12), 127.6 (C14, C16), 127.0 (C15), 126.7 (C13, C17), 124.6 (C3), 109.9 (C19), 65.2 (C11), 57.1 (C6), 54.7 (C1), 35.8 (C4), 31.9 (C8), 30.5 (C7), 29.0 (C5), 22.7 (C20), 20.5 (C21), 12.8 (C22).

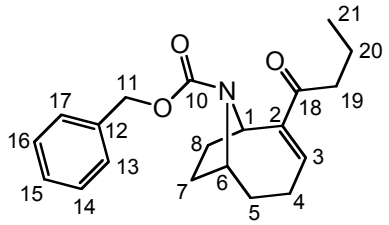


(+)-(1*R*)-2-(1-Hydroxy-1-hydroxymethylbutyl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (439). Freshly distilled Et_3N (434 μL, 315 mg, 3.11 mmol) was added to a solution of OsO_4 (633 mg, 2.49 mmol) in THF (12.4 mL) at rt. The resulting brown solution was stirred for 5 min, and then cooled to –78 ^{o}C. To this mixture was added a solution **438** (675 mg, 2.07 mmol) in THF (10.4 mL). The resulting solution was allowed to slowly warm to rt over a period of 3 h and then stirred at this temperature for an additional 16 h. The reaction was diluted with THF (10 mL) and sat.

aqueous $NaHSO_3$ (20 mL) and the resultant solution was heated under reflux in an 85 ^oC oil bath for 3 h. The mixture was cooled to rt and then filtered through a 2-inch plug of SiO_2 and Celite (1:1) with EtOAc (75 mL). The filtrate was poured into a mixture of EtOAc (15 mL) and brine (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (3:1) to afford 680 mg (91%) of **439** as a pale-yellow oil and 50 mg (7%) of the undesired cyclic diol **440** as a pale-yellow solid that crystallized from hexanes to afford colorless crystals. ^1H NMR (**439**) (500 MHz, DMSO-d_6, 100 ^oC) δ 7.36-7.26 (comp, 5 H), 5.59-5.56 (m, 1 H), 5.11 (app d, J = 12.7 Hz, 1 H), 5.00 (app d, J = 13.0 Hz, 1 H), 4.71-4.68 (m, 1 H), 4.41-4.37 (m, 1 H), 3.93 (br s, 1 H), 3.76 (br s, 1 H), 3.43-3.39 (app dd, J = 10.9, 5.4 Hz, 1 H), 3.32-3.27 (m, 1 H), 2.29-2.11 (comp, 3 H), 2.02-1.94 (m, 1 H), 1.88-1.76 (comp, 2 H), 1.74-1.66 (m, 1 H), 1.62-1.52 (comp, 2 H), 1.50-1.43 (m, 1 H), 1.32-1.17 (comp, 2 H), 0.80 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^oC) δ 152.3, 149.6, 136.8, 127.7, 127.1, 126.8, 122.8, 76.2, 67.1, 65.3, 55.5, 54.7, 37.8, 31.3, 28.2, 22.6, 15.5, 13.8; IR (neat) 3400, 2957, 1671, 1424, 1326, 1112, 753, 698 cm^{-1}; MS (CI) *m/z* 360.2180 [$C_{21}H_{30}NO_4$ (M + 1) requires 360.2175], 360 (base), 342.

NMR Assignments. ^1H NMR (500 MHz, DMSO-d_6, 100 ^oC) δ 7.36-7.26 (comp, 5 H, C13-C17-H), 5.59-5.56 (m, 1 H, C3-H), 5.11 (app d, J = 12.7 Hz, 1 H, C11-H), 5.00 (app d, J = 13.0 Hz, 1 H, C11-H), 4.71-4.68 (m, 1 H, C1-H), 4.41-4.37 (m, 1 H, C6-H), 3.93 (br s, 1 H, C19-OH), 3.76 (br s, 1 H, C18-OH), 3.43-3.39 (app dd, J = 10.9, 5.4 Hz, 1 H, C19-H), 3.32-3.27 (m, 1 H, C19-H), 2.29-2.11 (comp, 3 H, C4-H, C8-H), 2.02-1.94 (m, 1

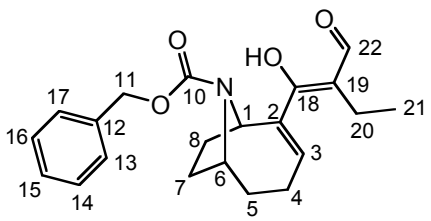
H, C7-H), 1.88-1.76 (comp, 2 H, C5-H, C8-H), 1.74-1.66 (m, 1 H, C7-H), 1.62-1.52 (comp, 2 H, C5-H, C20-H), 1.50-1.43 (m, 1 H, C20-H), 1.32-1.17 (comp, 2 H, C21-H), 0.80 (t, J = 7.5 Hz, 3 H, C22-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 152.3 (C10), 149.6 (C2), 136.8 (C12), 127.7 (C14, C16), 127.1 (C15), 126.8 (C13, C17), 122.8 (C3), 76.2 (C18), 67.1 (C19), 65.3 (C11), 55.5 (C6), 54.7 (C1), 37.8 (C20), 31.3 (C5), 28.2 (C7), 22.6 (C4, C8), 15.5 (C21), 13.8 (C22).



(+)-(1*R*)-2-Butyryl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (441). Solid $NaIO_4$ (11.7 g, 54.8 mmol) was added to a solution of **439** (6.56 g, 18.3 mmol) in 50% aqueous THF (365 mL) at rt. The reaction mixture was stirred for 45 min, diluted with H_2O (300 mL), and poured into a mixture of brine (200 mL) and Et_2O (100 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a pale-yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:3) to afford 5.96 g (99%) of **441** as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.38-7.24 (comp, 5 H), 6.84 (app t, J = 6.4 Hz, 1 H), 5.10 (app d, J = 8.5 Hz, 1 H), 5.06-4.98 (comp, 2 H), 4.39-4.34 (m, 1 H), 2.61-2.32 (comp, 4 H), 2.24-2.16 (m, 1 H), 2.14-2.06 (m, 1 H), 2.01-1.94 (m, 1 H), 1.75-1.59 (comp, 3 H), 1.54-1.44 (comp, 2 H), 0.84 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 199.2, 152.1, 147.5, 140.3, 136.6, 127.7, 127.1, 126.7, 65.3, 55.1, 53.4, 38.1, 30.6, 30.2, 27.9, 23.1, 17.2, 12.9; IR (neat) 2955, 1693,

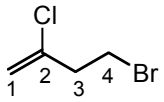
1665, 1413, 1329, 1105, 1016, 691 cm^{-1}; MS (CI) *m/z* 328.1921 [$C_{20}H_{26}NO_3$ (M + 1) requires 328.1913], 328 (base), 284.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.38-7.24 (comp, 5 H, C13-C17-H), 6.84 (app t, *J* = 6.4 Hz, 1 H, C3-H), 5.10 (app d, *J* = 8.5 Hz, 1 H, C1-H), 5.06-4.98 (comp, 2 H, C11-H), 4.39-4.34 (m, 1 H, C6-H), 2.61-2.32 (comp, 4 H, C19-H, C4-H), 2.24-2.16 (m, 1 H, C8-H), 2.14-2.06 (m, 1 H, C7-H), 2.01-1.94 (m, 1 H, C5-H), 1.75-1.59 (comp, 3 H, C7-H, C5-H, C8-H), 1.54-1.44 (comp, 2 H, C20-H), 0.84 (t, *J* = 7.3 Hz, 3 H, C21-H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 199.2 (C18), 152.1 (C10), 147.5 (C2), 140.3 (C3), 136.6 (C12), 127.7 (C13, C17), 127.1 (C15), 126.7 (C14, C16), 65.3 (C11), 55.1 (C6), 53.4 (C1), 38.1 (C19), 30.6 (C8), 30.2 (C5), 27.9 (C7), 23.1 (C4), 17.2 (C20), 12.9 (C21).



(+)-(1*R*)-2-(Formyl-1-hydroxybut-1-enyl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (444). A solution of **441** (44 mg, 0.13 mmol) and $(Me_2N)_3CH$ (70 μL, 0.40 mmol) in DMF (0.25 mL) was heated at 70 ^{o}C for 1.5 h. The solution was cooled to rt and poured into a mixture of brine (2 mL) and EtOAc (1 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 1 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude yellow oil (**442**) was resuspended in a 25% aqueous solution of THF (1 mL) and acidified with TFA (50 μL). The orange reaction mixture was stirred at rt for 10 min, and then poured into a mixture of saturated aq. $NaHCO_3$ (10

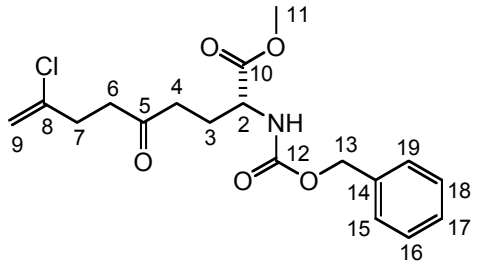
mL) and EtOAc (3 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:1) to afford and undetermined mass of **444** as a pale-yellow oil. ^{1}H-NMR δ 9.45-9.40 (m, 1 H, C22-H) and LRMS (CI +) 356 (base, M + 1) confirm the identity of the aldehyde **444**.



4-Bromo-2-chlorobut-1-ene (454). Iodopropene **452**[250] (6.4 g, 32 mmol) was suspended in a mixture of H_2O (50 mL) and 37% aqueous CH_2O (1.2 mL, 16 mmol), and solid In^o powder (1.8 g, 16 mmol) was added. The reaction flask was wrapped in foil to exclude light and the mixture was vigorously stirred at rt for 23 h, whereupon the mixture was filtered through a plug of Celite, which was then washed with H_2O (70 mL) and CH_2Cl_2 (50 mL). The combined layers were separated and the aqueous phase was extracted with CH_2Cl_2 (6 x 60 mL). The combined organic layers were dried rapidly ($MgSO_4$) and filtered through Celite. Oven-dried 4Å sieves (ca. 5 g) were then added to the filtrate (ca 450 mL), and the mixture was stirred vigorously at rt for 20 min, whereupon Ph_3P (5.8 g, 22 mmol) was added and the reaction mixture was cooled to 5 ^{o}C. Freshly recrystallized NBS (3.4 g, 19 mmol) was slowly added over 1 min, and the resulting yellow solution was maintained at 5 ^{o}C for 10 min. The cooling bath was removed and the mixture was stirred at rt for 2h, whereupon MeOH (1 mL) to destroy excess NBS, and the solvent was removed under reduced pressure (200 mm Hg). The resulting slurry was triturated with pentane (100 mL) and filtered through a plug of SiO_2 with Et_2O/pentane (1:9). The filtrate was concentrated by short-path distillation (60 ^{o}C)

at atmospheric pressure. The residue was purified by bulb-to-bulb distillation (185-190 ^{o}C) at atmospheric pressure to afford 2.34 g (87%) of **454** as a clear pungent-smelling oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.29 (d, *J* = 1.7 Hz, 1 H), 5.26-5.25 (m, 1 H), 3.54 (t, *J* = 6.8 Hz, 2 H), 2.84 (ddd, *J* = 13.7, 6.8, 1.0 Hz, 2 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8, 115.0, 42.1, 28.9; IR (neat) 2969, 1636, 1419, 1279, 1181, 891, 622, 550 cm^{-1}; MS (CI) *m/z* 168.9422 [C_4H_7BrCl (M + 1) requires 169.9420], 173, 172, 171, 170, 169, 168, 154 (base), 89.

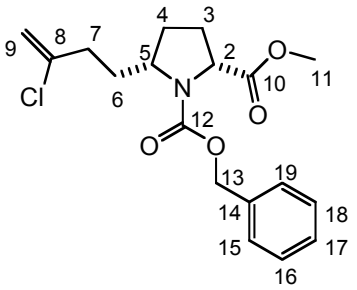
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.29 (d, *J* = 1.7 Hz, 1 H, C4-H(*Z*)), 5.26-5.25 (m, 1 H, C4-H(*E*)), 3.54 (t, *J* = 6.8 Hz, 2 H, C1-H), 2.84 (ddd, *J* = 13.7, 6.8, 1.0 Hz, 2 H, C2-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8 (C3), 115.0 (C4), 42.1 (C2), 28.9 (C1).



(2*R*)-Benzyloxycarbonylamino-8-chloro-5-oxonon-8-enoic acid methyl ester (455d). Dibromoethane (7 μL, 0.08 mmol) was added to a suspension of Mg turnings (37 mg, 1.5 mmol) in THF (2 mL). The mixture was then heated to 40 ^{o}C for 1 h, whereupon it was cooled to –5 ^{o}C and a solution of **454** (144 mg, 0.757 mmol) in THF (2 mL) was added. The reaction was allowed to warm to 0 ^{o}C over a period of 45 min and then added via cannula to a solution of TMEDA (0.46 mL, 3.03 mmol) at rt. The mixture was stirred vigorously for 5 min, and then added via cannula to a solution of **319d** (105 mg, 0.379 mmol) in THF (1.3 mL) at –78 ^{o}C. The reaction mixture was stirred at –78 ^{o}C for 3 h,

and then the solution was then poured into a mixture of saturated aq. NH_4Cl (20 mL) and Et_2O (5 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (4:1) to afford 70 mg (50%) of **455d** as a pale-yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (comp, 5 H), 5.49-5.41 (br m, 1 H), 5.16-5.00 (comp, 4 H), 4.35-4.29 (m, 1 H), 3.70 (s, 3 H), 2.65-2.41 (comp, 6 H), 2.19-2.10 (m, 1 H), 1.92-1.83 (m, 1 H); LRMS (CI +) m/z 368 (M + 1), 350, 324, 306, 288 (base).

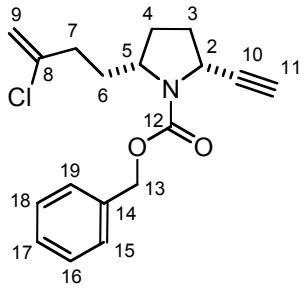
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (comp, 5 H, C15-C19-H), 5.49-5.41 (br m, 1 H, N-H), 5.16-5.00 (comp, 4 H, C9-H, C13-H), 4.35-4.29 (m, 1 H, C2-H), 3.70 (s, 3 H, C11-H), 2.65-2.41 (comp, 6 H, C3-H, C4-H, C6-H, C7-H), 2.19-2.10 (m, 1 H, C7-H), 1.92-1.83 (m, 1 H, C3-H).



(2*R*,5*R*)-(3-Chlorobut-3-enyl)pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (456). BF_3•OEt_2 (145 μL, 1.14 mmol) was added to a solution of Ph_3SiH (149 mg, 0.571 mmol) in CH_2Cl_2 (0.6 mL) at rt. The solution was stirred for 10 min, and then added via cannula to a stirred solution of **455d** (103 mg, 0.280 mmol) in CH_2Cl_2 (1 mL) at –78 °C. The mixture was kept in a –78 °C bath for 0.5 h, whereupon the cooling-bath was removed, and stirring was continued at rt for an additional 2 h. The mixture

was then recooled to –78 ^{o}C and poured into a solution of sat. aqueous $NaHCO_3$ (10 mL) and Et_2O (5 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to provide 89 mg (90%) of **456** (*dr* = 14.5:1, by ^{1}H-NMR) as a pale-yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.37-7.27 (comp, 5 H), 5.26 (s, 1 H), 5.15-5.14 (m, 1 H), 5.07 (dd, *J* = 12.7, 4.5 Hz, 2 H), 4.37-4.33 (m, 1 H), 3.95-3.90 (m, 1 H), 3.62 (s, 3 H), 2.46-2.34 (comp, 2 H), 2.26-2.19 (m, 1 H), 2.09-1.85 (comp, 3 H), 1.74-1.64 (comp, 2 H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 172.3, 153.4, 141.7, 136.3, 127.7, 127.2, 126.8, 111.8, 65.7, 59.2, 57.4, 51.1, 34.9, 31.3, 28.8, 27.6; MS (CI) *m/z* 352.1327 [$C_{18}H_{23}NO_4Cl$ (M + 1) requires 352.1316], 352 (base), 308, 286.

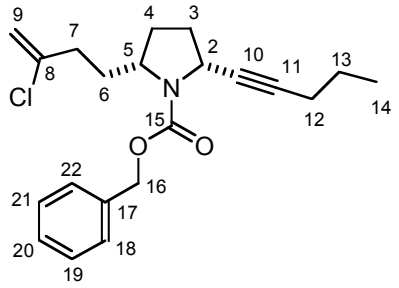
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 100 ^{o}C) δ 7.37-7.27 (comp, 5 H, C15-C19-H), 5.26 (s, 1 H, C9-H), 5.15-5.14 (m, 1 H, C9-H), 5.07 (dd, *J* = 12.7, 4.5 Hz, 2 H, C13-H), 4.37-4.33 (m, 1 H, C2-H), 3.95-3.90 (m, 1 H, C5-H), 3.62 (s, 3 H, C11-H), 2.46-2.34 (comp, 2 H, C7-H), 2.26-2.19 (m, 1 H, C3-H), 2.09-1.85 (comp, 3 H, C6-H, C4-H, C3-H), 1.74-1.64 (comp, 2 H, C4-H, C6-H); ^{13}C-NMR (125 MHz, DMSO-d_6, 100 ^{o}C) δ 172.3 (C10), 153.4 (C12), 141.7 (C8), 136.3 (C14), 127.7 (C16, C18), 127.2 (C17) 126.8 (C15, C19), 111.8 (C9), 65.7 (C13), 59.2 (C2), 57.4 (C5), 51.1 (C11), 34.9 (C7), 31.3 (C6), 28.8 (C4), 27.6 (C3).



(5*S*)-(3-Chlorobut-3-enyl)-(2*R*)-ethynylpyrrolidine-1-benzyloxycarbonyl (457). A solution of 1.0 M DIBAL-H in PhMe (0.89 mL) was added to a solution of **456** (141 mg, 0.402 mmol) in PhMe (2 mL) at –78 ^{o}C. The resulting solution was stirred at –78 ^{o}C for 3 h, whereupon *i*-PrOH (2 mL) was slowly added via cannula over a period of 10 min. The cooling bath was removed, and the reaction mixture was warmed to rt, whereupon solid Cs_2CO_3 (786 mg, 2.41 mmol) was added in one portion followed by the addition of a solution of **241** (154 mg, 0.804 mmol) in *i*-PrOH (0.5 mL). The resulting yellow solution was stirred at rt for 15 h, whereupon a mixture of sat. aqueous Rochelle's salt solution (4 mL) and EtOAc (2 mL) were added. The reaction mixture was vigorously stirred for 3 h and then poured into H_2O (10 mL). The resulting layers were separated, and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to provide 70 mg (55%) of **457** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (comp, 5 H,), 5.22-5.01 (comp, 4 H), 4.61 (br s, 1 H), 3.88 (br s, 1 H), 2.42-1.97 (comp, 7 H), 1.92-1.68 (comp, 2 H).

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.26 (comp, 5 H, C15-C19-H), 5.22-5.01 (comp, 4 H, C9-H, C13-H), 4.61 (br s, 1 H, C2-H), 3.88 (br s, 1 H, C5-H),

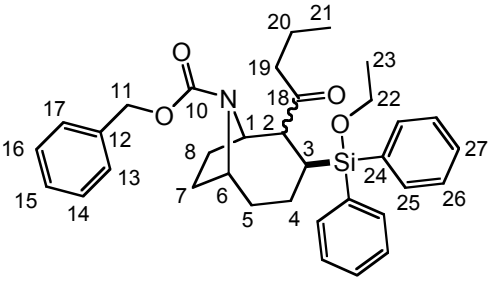
2.42-1.97 (comp, 7 H, C3-H, C4-H, C6-H, C7-H, C11-H), 1.92-1.68 (comp, 2 H, C4-H, C6-H).



(5*S*)-(3-Chlorobut-enyl)-(2*R*)-(pent-1-ynyl)pyrrolidine-1-benzyloxycarbonyl (458). A solution of **457** (62 mg, 0.20 mmol) in THF (0.4 mL) was added to a solution of 2.0 M NaHMDS (0.29 mL, 0.59 mmol) in THF (1.2 mL) at –78 ^{o}C. The resulting solution was stirred for 5 min at –78 ^{o}C, and then transferred via cannula to a –40 ^{o}C suspension of anhydrous $CeCl_3$ (154 mg, 0.624 mmol) in PhMe (1.3 mL). The slurry was stirred at –40 ^{o}C for 0.5 h, whereupon a solution of *n*-PrOTf (375 mg, 1.95 mmol) in PhMe (1 mL) was added via cannula, and the solution was stirred for 1 h at –40 ^{o}C. The reaction mixture was poured into a mixture of cold 1 N HCl (10 mL) and Et_2O (5 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 5 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to afford 55 mg (78%) of **458** as a foul smelling yellow oil and 7 mg of recovered **457** (11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.24 (comp, 5 H), 5.22-5.00 (comp, 4 H), 4.61 (br s, 1 H), 3.87 (br s, 1 H), 2.42-2.27 (comp, 2 H), 2.24-1.70 (comp, 8 H), 1.53-1.42 (comp, 2 H), 0.98-0.89 (comp, 3 H).

NMR Assignments. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.24 (comp, 5 H, C18-C22-H), 5.22-5.00 (comp, 4 H, C9-H, C16-H), 4.61 (br s, 1 H, C2-H), 3.87 (br s, 1 H, C5-H),

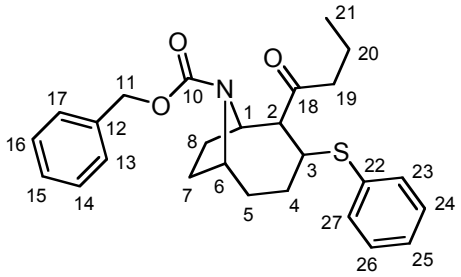
2.42-2.27 (comp, 2 H, C12-H), 2.24-1.70 (comp, 8 H, C3-H, C4-H, C6-H, C7-H), 1.53-1.42 (comp, 2 H, C13-H), 0.98-0.89 (comp, 3 H, C14-H).



(+)-(1*R*)-2-Butyryl-3-ethoxydiphenylsilanyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-2-nonene (464). Freshly cut lithium wire (200 mg) was added to a solution of $Ph_2Si(NEt_2)Cl$ (1 mL, 3.7 mmol) in THF (15 mL). The resulting yellow solution was cooled to 0 ^oC, whereupon a color change from yellow to brown to dark green occurred. The solution was stirred for 2 h at 0 ^oC, and the cooling bath was removed and stirring was continued at rt for 1 h to generate a solution of $Ph_2Si(NEt_2)Li$ (ca. 0.23 M). A portion of the solution of $Ph_2Si(NEt_2)Li$ (0.70 ml, 0.16 mmol) was added via syringe to a solution of Et_2Zn (0.16 mL, 0.16 mmol, 1.0 M in hexanes) in THF (1.1 mL) at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 10 min and then cooled to –78 ^oC, whereupon a solution of **441** (same as **448**) (50 mg, 0.15 mmol) in THF (1 mL) was added via cannula. The mixture was stirred for 10 min at –78 ^oC, and then allowed to warm to rt over a 2 h period, whereupon dry absolute EtOH (3 mL) and solid NH_4Cl (0.5 g) were added sequentially. The resultant slurry was stirred at rt for 19 h before diluting with H_2O (10 mL), and then pouring into a mixture of brine (40 mL) and Et_2O (10 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash

chromatography (SiO_2) eluting with EtOAc/hexanes (1:3) to afford 32 mg (38%) of **464** as a pale-yellow oil.

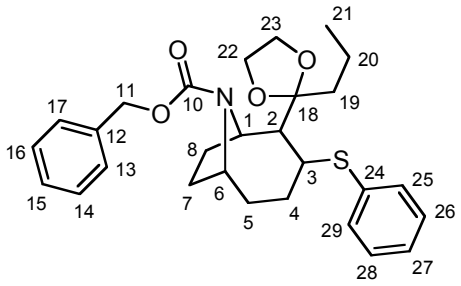
Similarly, a solution of the $Ph_2Si(NEt_2)Li$ (1.6 ml, 0.37 mmol) was added via syringe to a solution of CuBr·DMS (38 mg, 0.18 mmol,) in THF (1.2 mL) at -78 ^oC. The resultant slurry was stirred at –78 ^oC for 10 min, and then warmed to rt over 0.5 h. The rt solution was then recooled to –78 ^oC, whereupon a solution of **441** (same as **448**) (55 mg, 0.17 mmol) in THF (1 mL) was added via cannula. The reaction mixture was stirred with warming to –60 ^oC, and was then quenched at this temperature by the sequential addition of dry absolute EtOH (4 mL) and solid NH_4Cl (0.5 g). The slurry was stirred at rt for 22 h, and then poured into a mixture of H_2O (30 mL) and Et_2O (10 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:2) to afford 51 mg (55%) of **464** as a pale-yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) and LRMS (CI +) indicate formation of **464** as a complex mixture of diastereomers from which individual NMR resonances could not be assigned.



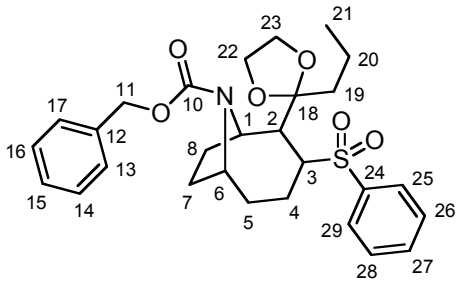
2-Butyryl-3-phenylsufanyl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (468). To a solution of Tf_2NH (35 mg, 0.12 mmol) and PhSH (0.19 mL, 1.8 mmol) in MeCN (4 mL) at rt was added a solution of **448** (402 mg, 1.23 mmol) in MeCN (3 mL).

The resulting pale-yellow solution was stirred for 12 h, whereupon solid Na_2CO_3 (50 mg) was added and the reaction mixture was concentrated under reduced pressure. The residue that was obtained was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 445 mg (83%) of **468** as a mixture of separable diastereomers (ca. 4:1 for the major detectable diastereomers) and as foul smelling pale-yellow oil. Characterization data provided for the major diastereomer only. ^{1}H NMR (500 MHz, DMSO-d_6, 110 ^{o}C) δ 7.45-7.19 (comp, 10 H), 5.24-5.05 (comp, 2 H), 4.50-4.46 (m, 1 H), 4.25-4.21 (app t, J = 7.1 Hz, 1 H), 3.69-3.65 (app t, J = 8.9 Hz, 1 H), 2.45-2.31 (comp, 2 H), 2.21-2.12 (m, 1 H), 2.01-1.82 (comp, 4 H), 1.64-1.31 (comp, 6 H), 0.85-0.68 (comp, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 110 ^{o}C) δ 208.2, 152.2, 136.5, 134.0, 131.9, 130.8, 129.8, 129.2, 128.4, 127.7, 127.6, 127.2, 127.0, 126.4, 65.7, 55.4, 53.8, 45.6, 44.1, 31.0, 29.5, 23.2, 16.0,12.7; IR (neat) 2960, 2360, 1698, 1418, 1338, 1108, 748, 694 cm^{-1}; MS (CI) m/z 438.2099 [$C_{26}H_{32}NO_3S$ (M + 1) requires 438.2103], 438 (M + 1), 420, 328 (base), 294, 284.

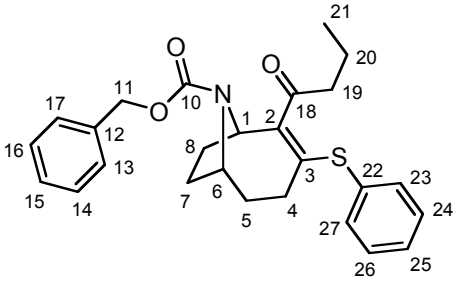
NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 110 ^{o}C) δ 7.45-7.19 (comp, 10 H, C13-C17-H, C23-C27-H), 5.24-5.05 (comp, 2 H, C11-H), 4.50-4.46 (m, 1 H, C1-H), 4.25-4.21 (app t, J = 7.1 Hz, 1 H, C6-H), 3.69-3.65 (app t, J = 8.9 Hz, 1 H, C2-H), 2.45-2.31 (comp, 2 H, C19-H), 2.21-2.12 (m, 1 H, C4-H), 2.01-1.82 (comp, 4 H, C5-H, C7-H, C8-H), 1.64-1.31 (comp, 6 H, C3-H, C4-H, C5-H, C7-H, C20-H), 0.85-0.68 (comp, 3 H, C12-H); ^{13}C NMR (125 MHz, DMSO-d_6, 110 ^{o}C) δ 208.2 (C18), 152.2 (C10), 136.5 (C12), 134.0 (C22), 130.8 (C14, C16), 128.4 (C24, C26), 127.7 (C13, C17), 127.2 (C15), 127.0 (C23, C27), 126.4 (C25), 65.7 (C11), 55.4 (C1), 53.8 (C6), 45.6 (C2), 44.1 (C19), 31.0 (C4, C5), 29.5 (C3, C7), 23.2 (C8), 16.0 (C20), 12.7 (C21).



3-Phenylsulfanyl-2-(2-propyl-[1,3]dioxolan-2-yl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (469). **(**$(TMSOCH_2)_2$ (0.18 mL, 0.74 mmol) was added to a solution of TMSOTf (7 μL, 40 μmol) in CH_2Cl_2 (0.4 mL) at 0 ^oC. The reaction mixture was stirred for 5 min, whereupon a solution of **468** (161 mg, 0.368 mmol) in CH_2Cl_2 (4 mL) was added via cannula, and the reaction was allowed to slowly warm to room temperature over a period of 11 h. The resulting brown solution was quenched by the addition of pyridine (0.2 mL) and poured into a mixture of sat. $NaHCO_3$ (15 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude product was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to afford 154 mg (87%) of **469** as a pale-yellow oil and as a mixture of diastereomers. Could not assign signals due to complexity of the spectrum containing the mixture of diastereomers. IR (neat) 2960, 2363, 1698, 1419, 1334, 1105, 747, 697 cm^{-1}; MS (FAB +) m/z 481.2281 [$C_{28}H_{35}NO_4S$ (M + 1) requires 481.2287], 482 (M + 1), 420, 372 (base), 307, 284.

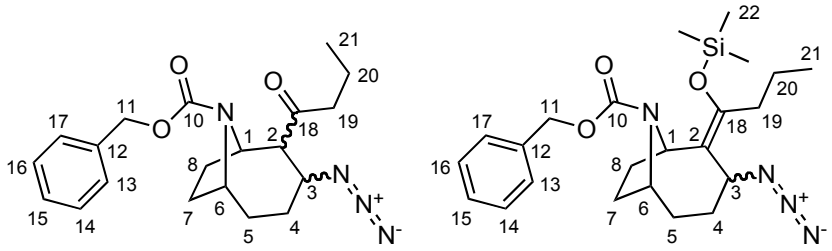


3-Benzenesulfonyl-2-(2-propyl-[1,3]dioxolan-2-yl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (474) A solution of Oxone® (253 mg, 0.411 mmol) in H_2O (1.4 mL) was added in via cannula to a solution of **469** (90 mg, 0.19 mmol) in MeOH (4 mL) at 0 °C. The resulting white slurry was allowed to slowly warm to rt over a period of 17 h, whereupon the solvent was removed under reduced pressure. The remaining residue was diluted with H_2O (10 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude yellow oil was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:1) to afford 82 mg (86%) of **474** as a pale-yellow oil. Assignment of the signals in the ^{1}H-NMR and ^{13}C-NMR spectra could not be done due to the complexity and multitude of signals obtained from the diastereomeric mixture. MS (CI +) *m/z* 514 (M + 1) (base), 470, 388, 372, 328.



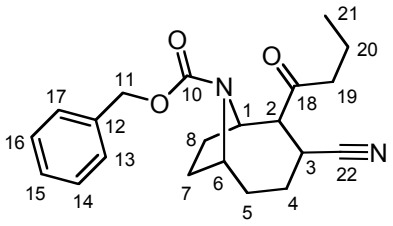
Attempted Synthesis of 471 from 468. Solid NCS (17 mg, 0.13 mmol) was added in one portion to a solution of **468** (53 mg, 0.12 mmol) in CCl_4 (2 mL) at rt. The reaction mixture was heated at 70 °C in an oil bath for 0.5, after which time the solution became yellow and an additional portion of NCS (17 mg, 0.13 mmol) was added and the mixture was heated at 70 °C for a period of 23 h. The solution was cooled to rt and diluted with pentane (3 mL) to precipitate the succinimide. Filtration of the reaction mixture through a plug of glass millifiber filter paper afforded a yellow solution that was concentrated

under reduced pressure and dried under high vacuum for a period of 2 h. A crude ^{1}H-NMR (400 MHz, $CDCl_3$) of the sample appeared consistent with the proposed structure of **472**. The NMR sample was concentrated under reduced pressure and redissolved in PhMe (3 mL). DBU (0.2 mL) was added and the mixture was heated at 100 ^oC for 20 min, whereupon the solution was cooled to rt and poured into1 N HCl (10 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was further dried under high vacuum (20 h). Only a crude ^{1}H-NMR was obtained. Attempts to purify this crude mixture by flash chromatography eventually led to decomposition.

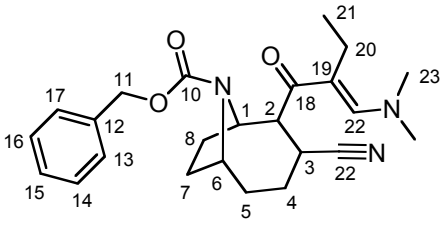


3-Azido-2-Butyryl-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (475) and 3-Azido-2-(1-trimethylsilanyloxybutylidene)-9-benzyloxycarbonyl-9-azabicyclo-[4.2.1]nonane (476). A 1.9 M solution of Et_3Al in PhMe (1.3 mL, 2.5 mmol) was added via syringe to a stirred solution of $TMSN_3$ (0.37 mL, 2.8 mmol) in PhMe (1.7 mL) at rt. The solution was stirred for an additional 5 min, whereupon it was rapidly added via cannula to a solution of **448** (0.41 g, 1.3 mmol) in PhMe (0.8 mL) at rt. The resulting pale-yellow solution was stirred for 20 h at rt and then slowly quenched with a mixture of sat. Rochelle's salt (5 mL) and H_2O (5 mL). The resulting mixture was stirred for 2.5 h, at which time the resulting layers were separated, and the aqueous phases were extracted with Et_2O (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and

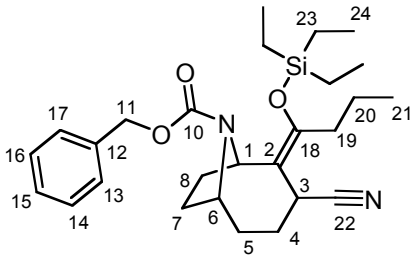
concentrated under reduced pressure to afford a crude pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to provide 274 mg (59%) of **475** as a pale-yellow oil and as a mixture of diastereomers, along with 32 mg (6%) of **476** as a pale-yellow oil and as a mixture of diastereomers (*dr* = 3:1). ^{1}H-NMR assignments could not be made for the diastereomeric product mixtures.



2-Butyryl-3-cyano-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (478). A 1 M solution of Et_2AlCN in PhMe (3.2 mL, 3.2 mmol) was added via syringe to a stirred solution of Tf_2NH (457 mg, 1.63mmol) in PhMe (3 mL) at rt. The solution was stirred for an additional 5 min, and then cooled to 0 ^oC in an ice bath, whereupon it was rapidly added via cannula to a solution of **448** (404 mg, 1.23 mmol) in PhMe (25 mL) at 0 ^oC. The resulting solution was stirred for 45 min at 0 ^oC, and then poured into a mixture of 1 N NaOH (50 mL) and ice. The resulting layers were separated and the organic phase was washed with a solution of sat. Rochelle's salt (30 mL). The resulting layers were separated and the aqueous phases were extracted with CH_2Cl_2 (2 x 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O to provide 408 mg (93%) of **478** as a pale-yellow oil and as a mixture of diastereomers. Could not assign signals in the NMR spectra due to the complex spectra obtained from the diastereomeric mixture. MS (CI +) *m/z* 355 (M + 1), 311 (M – H_2O – CN) (base).

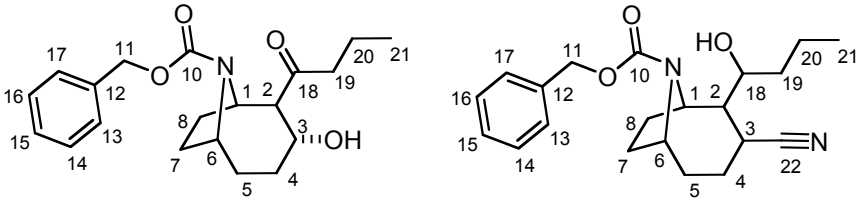


3-Cyano-2-(2-dimethylaminomethylebutyryl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (479). Tris(dimethylamino)methane (120 μL) was added to a solution of **478** (80 mg, 0.23 mmol) in PhMe (1 mL) at rt. The yellow solution was heated at 70 ^{o}C for a period of 2 h, whereupon the solution was cooled to rt and concentrated under reduced pressure to afford the crude vinylogous amide **479**. The crude amide was further dried under high vacuum (3 h) provided 74 mg of a dark yellow oil that was used directly in subsequent reactions. MS (CI +) *m/z* 438 (M + C_2H_5), 410 (M + 1) (base), 383, 356, 312, 249.

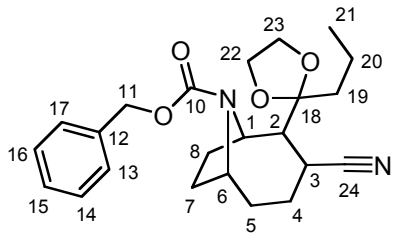


3-Cyano-2-(2-triethylsilanyloxybutylidene)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (482). A 1 M solution of Et_2AlCN in PhMe (0.92 mL, 0.92 mmol) was added via syringe to a solution of **448** (50 mg, 0.15 mmol) in PhMe (3 mL) at –5 ^{o}C. The solution was stirred for 19 h at –2 ^{o}C, whereupon a mixture of freshly distilled TESCl (0.31 mL, 1.8 mmol) and pyridine (0.29 mL, 3.7 mmol) in PhMe (0.5 mL) was added via syringe. The cooling bath was removed and stirring was continued at rt for an additional 2.5 h. The reaction mixture was poured into a solution of saturated Rochelles salt (30 mL) and Et_2O (5 mL). The layers were separated and the aqueous

phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude pale-yellow oil. The crude product was further dried under high vacuum (18 h) to provide 66 mg (92%) of **482** as a foul-smelling unstable pale-yellow oil and as an apparent mixture of two diastereomers that was used directly in the next reaction..

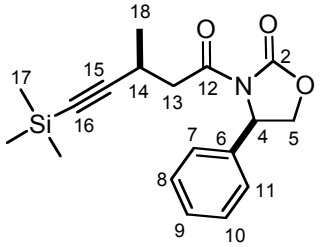


3-Cyano-2-(1-hydroxybutyl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (483). A 0.5 M solution of LDA in THF (0.56 mL, 0.28 mmol) was added via syringe to a solution of **482** (66 mg, 0.14 mmol) in THF (1.4 mL) at –78 ^oC. The mixture was stirred at –78 ^oC for 20 min, and then dry O_2 was bubbled into the reaction mixture over a period of 1.5 h via a balloon fitted with an 18-gauge needle, whereupon MeOH (2 mL) was added via syringe. The reaction mixture was then transferred to an ice bath and solid $NaBH_4$ (210 mg, 5.63 mmol) was added in one portion and stirring was continued for an additional 1 h. The reaction was then poured into a mixture of 3 N HCl (10 mL) and Et_2O (5 mL). The resulting layers were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a crude oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (3:1) to afford 10 mg (20%) of **484** as a mixture of diastereomers and 2 mg (4%) of a oil that appears to be **483** by LRMS (CI). MS data for **484**: MS (CI +) *m/z* 357 (M + 1) (base), 223 (M – Z + 1). MS data for MS (CI +) *m/z* 346 (M + 1), 281 (base).



3-Cyano-2-(2-propyl-[1,3]dioxolan-2-yl)-9-benzyloxycarbonyl-9-azabicyclo[4.2.1]-nonane (485). Solid *p*-TsOH·H_2O (4 mg, 0.02 mmol) was added to a solution of ethylene glycol (0.14 mL, 2.5 mmol) and **478** (402 mg, 1.13 mmol) in C_6H_6 (6 mL) at rt. A Dean-Stark trap was attached to the reaction vessel and the mixture was heated to 95 ^oC for 6 h, whereupon additional portions of *p*-TsOH·H_2O (4 mg, 0.02 mmol) and ethylene glycol (0.14 mL, 2.5 mmol) were added. The reaction mixture was heated under reflux for 18 h, then cooled to rt and poured into a solution of sat. $NaHCO_3$ (40 mL). The resulting layers were separated and aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O to afford 103 mg (23%) of **485** along with 222 mg of recovered **478**. MS data for **485**: MS (CI +) *m/z* 399 (M + 1) (base), 355 (M – C_2H_4O + 1).

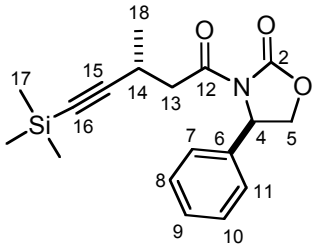
5.5 8-*EPI*-XANTHATIN



(3*S*)-(3-Methyl-5-trimethylsilanylpent-4-ynoyl)-(4*R*)-phenyloxazolidin-2-one (506*S*). A solution of 2.46 M *n*-BuLi in hexanes (4.4 mL, 11 mmol) was added to a

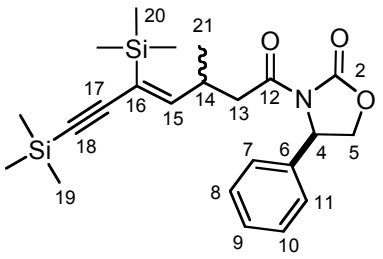
solution of TMSC≡CH (1.5 mL, 11 mmol) in PhMe (80 mL) under Ar at 0 ^{o}C. The reaction was kept at this temperature for 0.5 h, whereupon the cooling bath was removed and stirring was continued at rt for an additional 0.5 h. The resulting solution of TMSC≡CLi was returned to the 0 ^{o}C bath, and a 1 M solution of Me_2AlCl in hexanes (11 mL, 11 mmol) was added via syringe to afford a cloudy solution of the corresponding aluminum acetylide that was incubated at 0 ^{o}C for a period of 0.5 h. To the resulting mixture was added a solution of **505**[251] (998 mg, 4.32 mmol) in PhMe (30 mL), and stirring was continued for a period of 0.5 h. The reaction was then slowly quenched by the addition of a solution of sat. Rochelle's salt (40 mL), and then H_2O (40 mL) and EtOAc (50 mL) were added. The resulting mixture was stirred at rt overnight, and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (2:1) to afford 873 mg (61%) of the desired major diastereomer **506*S*** as a colorless solid (mp 24-25 ^{o}C) and 458 mg (32%) of the undesired adduct **506*R*** as a colorless solid (mp 25-26 ^{o}C) (*dr* = 1.6:1). ^{1}H-NMR (500 MHz, $CDCl_3$) (**506*S***) δ 7.38-7.26 (comp, 5 H), 5.44-5.38 (m, 1 H), 4.69-4.65 (m, 1 H), 4.27-4.24 (m, 1 H), 3.22 (app d, *J* = 6.1 Hz, 1 H), 3.06-2.94 (comp, 2 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 0.07 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.3, 153.6, 138.9, 129.2, 128.7, 125.9, 109.8, 84.5, 70.0, 57.7, 42.4, 22.7, 20.8, 0.1; IR (neat) 2958, 2173, 1784, 1713, 1384, 1197, 843 cm^{-1}; MS (CI +) m/z 330.1542 [$C_{18}H_{24}NO_3Si$ (M + 1) requires 330.1526], 330 (base), 314.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) (**506*S***) δ 7.38-7.26 (comp, 5 H, C7-C11-H), 5.44-5.38 (m, 1 H, C4-H), 4.69-4.65 (m, 1 H, C5-H), 4.27-4.24 (m, 1 H, C5-H), 3.22 (app d, *J* = 6.1 Hz, 1 H, C13-H), 3.06-2.94 (comp, 2 H, C13-H, C14-H), 1.17 (d, *J* = 6.8 Hz, 3 H, C18-H), 0.07 (s, 9 H, C17-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.3 (C12), 153.6 (C2), 138.9 (C6), 129.2 (C8, C10), 128.7 (C9), 125.9 (C7, C11), 109.8 (C15), 84.5 (C16), 70.0 (C5), 57.7 (C4), 42.4 (C13), 22.7 (C14), 20.8 (C18), 0.1 (C17).



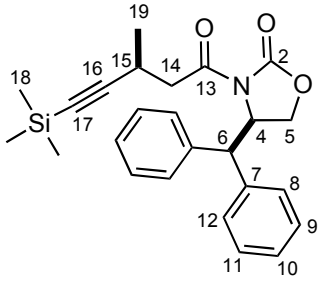
^{1}H-NMR (500 MHz, $CDCl_3$) (**506*R***) δ 7.38-7.26 (comp, 5 H), 5.42 (dd, *J* = 8.8, 3.8 Hz, 1 H), 4.67 (t, *J* = 8.8 Hz, 1 H), 4.26 (dd, *J* = 8.8, 3.8 Hz, 1 H), 3.21-3.14 (m, 1 H), 3.04-2.95 (comp, 2 H), 1.14 (d, *J* = 6.8 Hz, 3 H), 0.08 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.3, 153.7, 139.0, 129.2, 128.7, 125.9, 109.7, 84.7, 70.0, 57.6, 42.2, 23.0, 20.8, 0.1; IR (neat) 2959, 2171, 1786, 1708, 1386, 1198, 843 cm^{-1}; m/z 330.1537 [$C_{18}H_{24}NO_3Si$ (M + 1) requires 330.1526], 330 (base), 314.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) (**506*R***) δ 7.38-7.26 (comp, 5 H, C7-C11-H), 5.42 (dd, *J* = 8.8, 3.8 Hz, 1 H, C4-H), 4.67 (t, *J* = 8.8 Hz, 1 H, C5-H), 4.26 (dd, *J* = 8.8, 3.8 Hz, 1 H, C5-H), 3.21-3.14 (m, 1 H, C13-H), 3.04-2.95 (comp, 2 H, C13-H, C14-H), 1.14 (d, *J* = 6.8 Hz, 3 H, C18-H), 0.08 (s, 9 H, C17-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.3 (C12), 153.7 (C2), 139.0 (C6), 129.2 (C8, C10), 128.7 (C9), 125.9 (C7, C11), 109.7 (C15), 84.7 (C16), 70.0 (C5), 57.6 (C4), 42.2 (C13), 23.0 (C14), 20.8 (C18), 0.1 (C17).



^{1}H-NMR (500 MHz, $CDCl_3$) (**507**) δ 7.41-7.28 (comp, 5 H), 5.99 (d, *J* = 9.0 Hz, 1 H), 5.37 (dd, *J* = 8.6, 3.5 Hz, 1 H), 4.70 (t, *J* = 8.8 Hz, 1 H), 4.26 (dd, *J* = 8.8, 3.4 Hz, 1 H), 3.48-3.39 (m, 1 H), 3.21 (dd, *J* = 15.5, 7.5 Hz, 1 H), 2.82 (dd, *J* = 15.4, 6.9 Hz, 1 H), 1.09 (d, *J* = 6.6 Hz, 3 H), 0.17 (s, 9 H), 0.14 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.9, 155.1, 153.6, 139.2, 129.1, 128.5, 125.8, 124.5, 103.8, 102.9, 69.9, 57.7, 42.1, 33.4, 19.7, 0.1, -2.1; MS (CI +) 429, 428 (M + 1) (base), 412, 236.

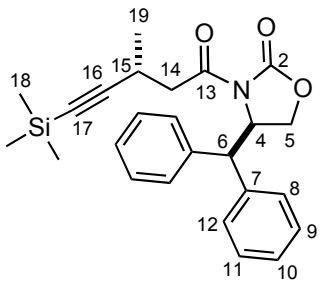
NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) (**507**) δ 7.41-7.28 (comp, 5 H, C7-C11-H), 5.99 (d, *J* = 9.0 Hz, 1 H, C15-H), 5.37 (dd, *J* = 8.6, 3.5 Hz, 1 H, C4-H), 4.70 (t, *J* = 8.8 Hz, 1 H, C6-H), 4.26 (dd, *J* = 8.8, 3.4 Hz, 1 H, C6-H), 3.48-3.39 (m, 1 H, C14-H), 3.21 (dd, *J* = 15.5, 7.5 Hz, 1 H, C13-H), 2.82 (dd, *J* = 15.4, 6.9 Hz, 1 H, C13-H), 1.09 (d, *J* = 6.6 Hz, 3 H, C21-H), 0.17 (s, 9 H, C19-H), 0.14 (s, 9 H, C20-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.9 (C12), 155.1 (C2), 153.6 (C15), 139.2 (C6), 129.1 (C8, C10), 128.5 (C9), 125.8 (C7, C11), 124.5 (C16), 103.8 (C17), 102.9 (C18), 69.9 (C6), 57.7 (C4), 42.1 (C13), 33.4 (C14), 19.7 (C21), 0.1 (C19), -2.1 (C20).



4(*R*)-Benzhydryl-3-(3(*S*)-methyl-5-trimethylsilanylpent-4-ynoyl)oxazolidin-2-one (509*S*) and 4(*R*)-Benzhydryl-3-(3(*R*)-methyl-5-trimethylsilanylpent-4-ynoyl)oxazolidin-2-one (509*R*). A solution of 2.5 M *n*-BuLi in hexanes (340 μL, 0.832 mmol) was added to a solution of TMSC≡CH (120 μL, 83 mg, 0.832 mmol) in PhMe (6 mL) under Ar at 0 ^{o}C. The reaction was maintained at this temperature for 0.5 h before the cooling bath was removed, and stirring was continued at rt for an additional 0.5 h. The resulting mixture containing TMSC≡CLi was recooled to 0 ^{o}C, and a solution of Me_2AlCl (1 M in hexanes) (840 μL, 0.832 mmol) was added via syringe to afford a cloudy solution of the corresponding aluminum acetylide. The mixture was stirred at 0 ^{o}C for 0.5 h, whereupon a solution of **508** (107 mg, 0.333 mmol) in PhMe (2.4 mL) was added via cannula. The resulting pale-yellow mixture was stirred at 0 ^{o}C for 40 min and a solution of saturated aq. Rochelle's salt (10 mL) was added. H_2O (10 mL) was then added, and the biphasic mixture was removed from the cooling bath and stirred at rt for 5 h. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:2) to afford 99 mg (71%) of the desired major diastereomer **509*S*** as a white foam (mp 24-25 ^{o}C) and 28 mg (20%) of the undesired adduct **509*R*** as a white foam (mp 25-26 ^{o}C) (*dr* = 3.4:1 for total reaction). ^{1}H-NMR (500 MHz, $CDCl_3$) (**509*S***) δ 7.34-7.27 (comp, 5 H), 7.26-7.24 (m, 1 H), 7.12-7.10 (comp, 2 H), 7.08-7.06 (comp, 2 H), 5.32-5.29 (m, 1 H), 4.75 (d, *J* = 5.0 Hz, 1 H), 4.46-4.39 (comp, 2 H), 3.11-2.94 (comp, 3 H), 1.19 (app dd, *J* = 6.9, 1.7 Hz, 3 H), 0.14 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.6, 153.3, 139.5, 137.9, 129.4, 128.9, 128.7,

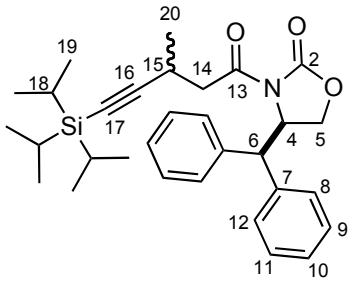
128.3, 127.9, 127.1, 110.2, 84.5, 64.7, 56.2, 50.2, 42.5, 22.6, 20.8, 0.2; IR (neat) 2962, 2165, 1784, 1704, 1389, 1280, 1249, 1212, 838, 756, 697 cm^{-1}; MS (CI +) m/z 420.1986 [$C_{25}H_{30}NO_3Si$ (M + 1) requires 420.1995], 448, 420 (base), 404, 326, 254, 167.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) (**509*S***) δ 7.34-7.27 (comp, 5 H, C9-H, C11-H, C12-H), 7.26-7.24 (m, 1 H, C12-H), 7.12-7.10 (comp, 2 H, C8-H), 7.08-7.06 (comp, 2 H, C10-H), 5.32-5.29 (m, 1 H, C4-H), 4.75 (d, *J* = 5.0 Hz, 1 H, C6-H), 4.46-4.39 (comp, 2 H, C5-H), 3.11-2.94 (comp, 3 H, C14-H, C15-H), 1.19 (app dd, *J* = 6.9, 1.7 Hz, 3 H, C19-H), 0.14 (s, 9 H, C18-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.6 (C13), 153.3 (C2), 139.5 (C7), 137.9 (C7), [129.4, 128.9, 128.7, 128.3, 127.9, 127.1 (C8-12)], 110.2 (C16), 84.5 (C17), 64.7 (C5), 56.2 (C4), 50.2 (C6), 42.5 (C14), 22.6 (C15), 20.8 (C19), 0.2 (C18).



^{1}H-NMR (500 MHz, $CDCl_3$) (**509*R***) δ 7.34-7.26 (comp, 5 H), 7.24-7.20 (m, 1 H), 7.17-7.14 (comp, 2 H), 7.10-7.07 (comp, 2 H), 5.34-5.30 (m, 1 H), 4.67 (d, *J* = 5.8 Hz, 1 H), 4.43-4.36 (comp, 2 H), 3.04 (dd, *J* = 15.9, 6.8 Hz, 3 H), 2.96 (app sext, *J* = 6.7 Hz, 1 H), 2.87 (dd, *J* = 15.9, 6.4 Hz, 1 H), 1.13 (app d, *J* = 6.6 Hz, 3 H), 0.12 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.4, 153.3, 139.5, 138.0, 129.3, 128.9, 128.7, 128.4, 127.9, 127.1, 109.8, 84.9, 65.2, 56.3, 51.0, 42.3, 22.9, 20.9, 0.1; IR (neat) 2966, 2167, 1784, 1702, 1496, 1455, 1390, 1367, 1249, 1208, 1114, 844, 756, 703 cm^{-1}; MS (CI +) m/z 420.1985 [$C_{25}H_{30}NO_3Si$ (M + 1) requires 420.1995], 448, 420 (base), 404, 326, 167.

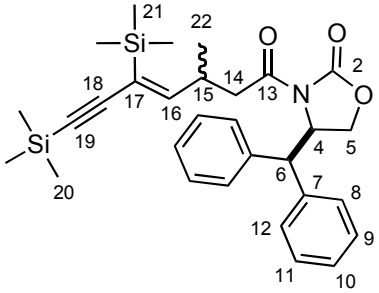
NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) (**509*R***) δ 7.34-7.26 (comp, 5 H, C9-H, C11-H, C12-H), 7.24-7.20 (m, 1 H, C12-H), 7.17-7.14 (comp, 2 H, C8-H), 7.10-7.07 (comp, 2 H, C10-H), 5.34-5.30 (m, 1 H, C4-H), 4.67 (d, *J* = 5.8 Hz, 1 H, C6-H), 4.43-4.36 (comp, 2 H, C5-H), 3.04 (dd, *J* = 15.9, 6.8 Hz, 3 H, C14-H), 2.96 (app sext, *J* = 6.7 Hz, 1 H, C15-H), 2.87 (dd, *J* = 15.9, 6.4 Hz, 1 H, C14-H), 1.13 (app d, *J* = 6.6 Hz, 3 H, C19-H), 0.12 (s, 9 H, C18-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.4 (C13), 153.3 (C2), 139.5 (C7), 138.0 (C7), [129.3, 128.9, 128.7, 128.4, 127.9, 127.1 (C8-C12)], 109.8 (C16), 84.9 (C17), 65.2 (C5), 56.3 (C4), 51.0 (C6), 42.3 (C14), 22.9 (C15), 20.9 (C19), 0.1 (C18).



4(*R*)-Benzhydryl-3-(3-methyl-5-triisopropylsilanylpent-4-ynoyl)oxazolidin-2-one (510). A solution of 2.5 M *n*-BuLi in hexanes (176 μL, 0.434 mmol) was added to a solution of TIPSC≡CH (103 μL, 84 mg, 0.434 mmol) in PhMe (3.1 mL) under Ar at 0 °C. The reaction was maintained at this temperature for 0.5 h, wherupon the cooling bath was removed, and stirring was continued at rt for an additional 0.5 h. The resulting solution of TIPSC≡CLi was recooled to 0 °C, and a solution of Me_2AlCl (1 M in hexanes) (434 μL, 0.434 mmol) was added via syringe to afford a cloudy solution of the corresponding aluminum acetylide. The mixture was stirred at 0 °C for 0.5 h, whereupon a solution of **508** (56 mg, 0.174 mmol) in PhMe (1.2 mL) was added via cannula. The resulting pale-yellow mixture was stirred at 0 °C for 40 min and sat. Rochelle's salt (5 mL) was added.

H_2O (5 mL) was then added and the biphasic mixture was removed from the cooling bath and stirred at rt for 16 h. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude pale-yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford 85 mg (97%) of **510** as a separable mixture of diastereomers (*dr* = 3.6:1) and as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.03 (comp, 10 H), 5.34-5.25 (m, 1 H), 4.76 (d, *J* = 4.8 Hz, 1 H, major diastereomer), 4.70 (d, *J* = 5.5 Hz, 0.28 H, minor diastereomer), 4.49-4.37 (comp, 2 H), 3.16-2.97 (comp, 3 H), 1.23 (app d, *J* = 6.5 Hz, 3 H, major diastereomer), 1.18 (app d, *J* = 6.5 Hz, 0.8 H, minor diastereomer), 1.14-0.96 (comp, 21 H).

NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.03 (comp, 10 H, C8-C12-H), 5.34-5.25 (m, 1 H, C4-H), 4.76 (d, *J* = 4.8 Hz, 1 H, major diastereomer, C6-H), 4.70 (d, *J* = 5.5 Hz, 0.28 H, minor diastereomer, C6-H), 4.49-4.37 (comp, 2 H, C5-H), 3.16-2.97 (comp, 3 H, C14-H, C15-H), 1.23 (app d, *J* = 6.5 Hz, 3 H, major diastereomer, C20-H), 1.18 (app d, *J* = 6.5 Hz, 0.8 H, minor diastereomer, C20-H), 1.14-0.96 (comp, 21 H, C18-H, C19-H).

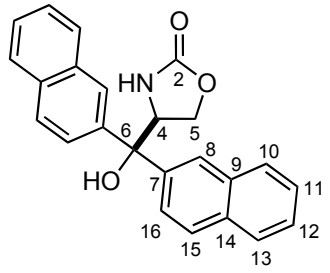


4(*R*)-Benzhydryl-3-[3-methyl-5,7-bis(trimethylsilanyl)hept-4-en-6-ynoyl]oxazolidin-2-one (511). A solution of 2.5 M *n*-BuLi in hexanes (160 μL, 0.389 mmol) was added to a solution of TMSC≡CH (55 μL, 38 mg, 0.389 mmol) in PhMe (2.8

mL) under Ar at 0 °C. The reaction was maintained at this temperature for 0.5 h, whereupon the cooling bath was removed, and stirring was continued at rt for an additional 0.5 h. The resulting solution of TMSC≡CLi was recooled to 0 °C, and a solution of Me_2AlCl (1 M in hexanes) (389 μL, 0.389 mmol) was added via syringe to afford a cloudy solution of the corresponding aluminum acetylide. The mixture was stirred at 0 °C for a period of 1 h. In a separate Schlenk flask, a solution of DIBAL-H (1 M in PhMe) (39 μL, 39 μmol) was added via syringe to a solution of purified $Ni(acac)_2$ (12 mg, 47 μmol) in Et_2O (0.8 mL) at –2 °C. The yellow solution was cooled to –20 °C for 5 min, and then treated via cannula with the previously prepared solution of Me_2AlC≡CTMS. The Schlenk flask containing the resulting brown slurry was stirred at –20 °C for 5 min, whereupon a solution of **508** (50 mg, 0.156 mmol) in Et_2O (1.1 mL) was added rapidly via cannula. The reaction mixture was immediately transferred to a –2 °C bath, and stirring was continued for 22 h. A solution of tris(hydroxymethyl)phosphine (100 mg, 0.778 mmol) in THF (2 mL) was added to remove nickel containging byproducts, and stirring was continued for an additional 1 h with slow warming to rt. The reaction was diluted with H_2O (10 mL) and stirred for an additional 45 min. The biphasic mixture was filtered though a short plug of Celite, which was subsequently rinsed with Et_2O (20 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a brown oil that was repeatedly purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (3:2) to afford 14 mg (17%) of **511** as a brownish-yellow solid along with 24 mg (37%) of **509** as a mixture of diastereomers (*dr* = 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$) (**511**) δ 7.36-7.19

(comp, 6 H), 7.16-7.04 (comp, 4 H), 5.97 (app dd, *J* = 10.6, 8.9 Hz, 1 H), 5.32-5.18 (m, 1 H), 4.74-4.66 (m, 1 H), 4.45-4.32 (comp, 2 H), 3.41-3.27 (m, 1 H), 3.16 (dd, *J* = 15.7, 7.2 Hz, 0.5 H), 3.00 (dd, *J* = 16.4, 6.2 Hz, 0.5 H), 2.77 (dd, *J* = 16.8, 7.5 Hz, 0.5 H), 2.61 (dd, *J* = 15.7, 7.2 Hz, 0.5 H), 1.07 (dd, *J* = 14.0, 6.8 Hz, 3 H), 0.16 (d, *J* = 2.7 Hz, 9 H), 0.11 (d, *J* = 8.9 Hz, 9 H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 170.6, 156.3, 156.2, 153.1, 139.9, 138.7, 129.2, 128.5, 128.3, 127.3, 127.2, 126.7, 123.0, 122.9, 104.4, 104.3, 102.6, 102.4, 64.7, 64.5, 55.7, 50.3, 50.0, 41.0, 40.8, 32.7, 32.6, 19.5, 19.2, 0.1, -2.1; MS (CI +) m/z 518.2543 [$C_{30}H_{40}NO_3Si_2$ (M + 1) requires 518.2547], 518 (base), 502, 326.

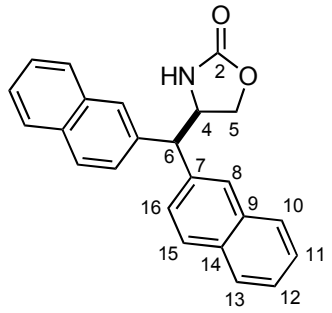
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (comp, 6 H, C9-H, C11-H, C12-H), 7.16-7.04 (comp, 4 H, C10-H, C12-H), 5.97 (app dd, *J* = 10.6, 8.9 Hz, 1 H, C16-H), 5.32-5.18 (m, 1 H, C6-H), 4.74-4.66 (m, 1 H, C4-H), 4.45-4.32 (comp, 2 H, C5-H), 3.41-3.27 (m, 1 H, C15-H), 3.16 (dd, *J* = 15.7, 7.2 Hz, 0.5 H, C14-H), 3.00 (dd, *J* = 16.4, 6.2 Hz, 0.5 H, C14-H), 2.77 (dd, *J* = 16.8, 7.5 Hz, 0.5 H, C14-H), 2.61 (dd, *J* = 15.7, 7.2 Hz, 0.5 H, C14-H), 1.07 (dd, *J* = 14.0, 6.8 Hz, 3 H, C22-H), 0.16 (d, *J* = 2.7 Hz, 9 H, C20-H), 0.11 (d, *J* = 8.9 Hz, 9 H, C21-H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 170.6 (C13), 156.3 (C16), 156.2 (C16), 153.1 (C2), 139.9 (C7), 138.7 (C7), 129.2 (C9, C11), 128.5 (C9, C11), 128.3 (C8, C12), 127.3 (C8, C12), 127.2 (C10), 126.7 (C10), 123.0 (C17), 122.9 (C17), 104.4 (C18), 104.3 (C18), 102.6 (C19), 102.4 (C19), 64.7 (C5), 64.5 (C5), 55.7 (C6), 50.3 (C4), 50.0 (C4), 41.0 (C14), 40.8 (C14), 32.7 (C15), 32.6 (C15), 19.5 (C22), 19.2 (C22), 0.1 (C20), -2.1 (C21).



4(*R*)-[Hydroxy(dinaphthalen-2-yl)methyl]oxazolidin-2-one (514). A solution of 1.7 M *t*-BuLi in pentane (2.8 mL, 4.7 mmol) was added dropwise via syringe to a solution of 2-bromonaphthalene (0.49 g, 2.4 mmol) in THF (5 mL) at –78 ^{o}C. The resulting yellowish-green slurry was stirred at –78 ^{o}C for 10 min, whereupon the mixture was transferred to a –2 ^{o}C bath for a period of 10 min. The greenish slurry was then recooled to –78 ^{o}C and treated with a solution of **513**[227a] (0.11 g, 0.76 mmol) in THF (2 mL) via cannula. The mixture was stirred at –78 ^{o}C for 1 h, whereupon a dilute aqueous solution of NH_4Cl (10 mL) was added and the mixture was removed from the cooling bath. The mixture was poured into brine (30 mL), and the resulting layers were separated. The aqueous phase was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude yellow solid that was dissolved in a minimal volume of DMSO and purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (4:1) to afford 188 mg (67%) of **514** as a white solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.15-8.14 (m, 1 H), 8.10-8.09 (m, 1 H), 7.92 (br t, J = 7.8 Hz, 2 H), 7.83-7.81 (comp, 2 H), 7.77 (dd, J = 9.0, 3.8 Hz, 2 H), 7.70 (br s, 1 H), 7.52-7.45 (comp, 6 H), 6.30 (s, 1 H), 5.29-5.26 (m, 1 H), 4.32 (t, J = 8.8 Hz, 1 H), 4.21 (dd, J = 8.6, 5.0 Hz, 1 H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 159.1, 142.0, 141.9, 132.6, 132.5, 131.9, 131.8, 128.3, 128.2, 127.7, 127.4, 127.3, 127.2, 126.1,

126.0, 125.9, 125.8, 125.4, 125.1, 124.7, 124.3, 77.9, 65.0, 57.5; MS (CI +) m/z 370. 1453 [$C_{24}H_{20}NO_3$ (M + 1) requires 370.1443], 370 (base), 352, 283, 169.

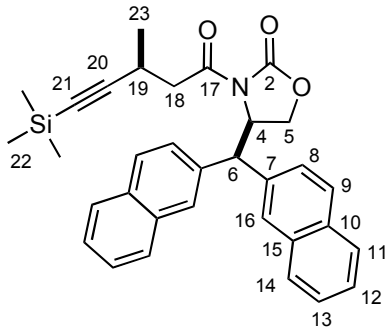
NMR Assignments. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.15-8.14 (m, 1 H, C13-H), 8.10-8.09 (m, 1 H, C13-H), 7.92 (br t, J = 7.8 Hz, 2 H, C16-H), 7.83-7.81 (comp, 2 H, C10-H), 7.77 (dd, J = 9.0, 3.8 Hz, 2 H, C15-H), 7.70 (br s, 1 H, N-H), 7.52-7.45 (comp, 6 H C8-H, C11-H, C12-H), 6.30 (s, 1 H, O-H), 5.29-5.26 (m, 1 H, C4-H)), 4.32 (t, J = 8.8 Hz, 1 H, C5-H), 4.21 (dd, J = 8.6, 5.0 Hz, 1 H, C5-H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 159.1 (C2), 142.0 (C7), 141.9 (C7), 132.6 (C9), 132.5 (C9), 131.9 (C14), 131.8 (C14), 128.3 (C16), 128.2 (C16), 127.7 (C15), 127.4 (C15), 127.3 (C10), 127.2 (C10), 126.1 (C8), 126.0 (C8), 125.9 (C11), 125.8 (C11), 125.4 (C12), 125.1 (C12), 124.7 (C13), 124.3 (C13), 77.9 (C6), 65.0 (C5), 57.5 (C4).



4(*R*)-[(Dinaphthalen-2-yl)methyl]oxazolidin-2-one (515). TFA (3 mL) was added dropwise via syringe to a slurry of **514** (185 mg, 0.501 mmol) and $NaBH_4$ (95 mg, 2.5 mmol) in CH_2Cl_2 (7 mL) at rt, during which time a vigorous evolution of H_2 was observed. The reaction mixture was stirred at rt for 21 h, and then diluted with H_2O (10 mL) and neutralized (pH = 7) by the addition of solid KOH pellets. The resulting layers were separated, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a crude yellow solid that was purified by recrystallization from

MeOH-hexanes. The resulting crystals were collected by vacuum filtration, rinsed with cold hexanes (2 x 5 mL), and dried under reduced pressure to afford 173 mg (98%) of **515** as an off-white crystalline solid. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.98 (br d, J = 3.6 Hz, 2 H), 7.91-7.86 (comp, 3 H), 7.84-7.80 (comp, 4 H), 7.53-7.42 (comp, 6 H), 5.06-5.01 (m, 1 H), 4.40-4.36 (comp, 2 H), 4.04-3.98 (m, 1 H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 158.7, 139.0, 138.6, 133.1, 133.0, 132.0, 131.9, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 126.8, 126.7, 126.6, 126.4, 126.3, 126.1, 125.9, 125.7, 67.9, 56.3, 54.2. IR (neat) 3274, 3053, 1756, 1404, 1239, 1026, 756 cm^{-1}; MS (CI +) *m/z* 354.1492 [$C_{24}H_{20}NO_2$ (M + 1) requires 354.1494], 355 (base), 267, 129.

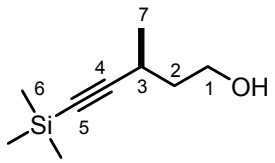
NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.98 (br d, J = 3.6 Hz, 2 H, NH, C13-H), 7.91-7.86 (comp, 3 H, C10-H, C13-H), 7.84-7.80 (comp, 4 H, C8-H, C15-H), 7.53-7.42 (comp, 6 H, C11-H, C12-H, C16-H), 5.06-5.01 (m, 1 H, C4-H), 4.40-4.36 (comp, 2 H, C5-H, C6-H), 4.04-3.98 (m, 1 H, C5-H). ^{13}C-NMR (125 MHz, DMSO-d_6) δ 158.7 (C2), 139.0 (C7), 138.6 (C7), 133.1 (C8), 133.0 (C8), 132.0 (C14), 131.9 (C14), [128.2, 128.1, 127.8, 127.7, 127.5, 127.4, 126.8 (C8, C10, C13, C15)], [126.7, 126.6, 126.4, 126.3, 126.1, 125.9, 125.7 (C11, C12, C13, C16)], 67.9 (C5), 56.3 (C6), 54.2 (C4).



4(*R*)-[(Dinaphthalen-2-yl)methyl]-3-[3(*S*)-methyl-5-trimethylsilanylpent-4-ynoyl]oxazoldin-2-one (517). A solution of 2.4 M *n*-BuLi in hexanes (110 μL, 0.26

mmol) was added to a solution of TMSC≡CH (37 μL, 26 mg, 0.26 mmol) in PhMe (2 mL) under Ar at 0 ^{o}C. The reaction was maintained at this temperature for 0.5 h, whereupon the cooling bath was removed, and stirring was continued at rt for an additional 0.5 h. The resulting solution of TMSC≡CLi was recooled to 0 ^{o}C, and a solution of Me_2AlCl (1 M in hexanes) (260 μL, 0.26 mmol) was added via syringe to afford a cloudy solution of the corresponding aluminum acetylide. The mixture was stirred at 0 ^{o}C for a period of 0.5 h, whereupon a solution of **516** (44 mg, 0.104 mmol) in PhMe (0.8 mL) was added via cannula. The pale-yellow mixture was stirred at 0 ^{o}C for 1 h and then at rt for 1 h. A mixture of sat. Rochelle's salt (4 mL) and H_2O (4 mL) was then added and the biphasic mixture was removed from the cooling bath. The mixture was stirred at rt for 17 h, and then poured into brine (20 mL). The resulting layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (1:1) to afford 42 mg (78%) of **517** as a white foam (mp 24-25 ^{o}C) (*dr* = 3:1). ^{1}H-NMR (500 MHz, DMSO-d_6) (mixture of diastereomers) δ 7.95-7.82 (comp, 6.5 H), 7.76 (br s, 1 H), 7.70 (br s, 1 H), 7.56-7.48 (comp, 4 H), 7.32 (dd, *J* = 8.6, 1.8 Hz, 0.28 H), 7.27 (dd, *J* = 8.5, 1.7 Hz, 0.78 H), 7.21 (overlapping pair of dd, *J* = 8.3, 1.8 Hz for the minor set, and *J* = 8.6, 1.8 Hz for the major set, total integral is 1 H), 5.45-5.50 (m, 1 H), 4.91 (d, *J* = 4.1 Hz, 0.76 H), 4.86 (d, *J* = 5.1 Hz, 0.26 H), 4.78-4.71 (m, 1 H), 4.55 (dd, *J* = 9.2, 2.3 Hz, 0.72 H), 4.51 (dd, *J* = 9.2, 2.3 Hz, 0.25 H), 3.11 (dd, *J* = 16.7, 6.6 Hz, 0.73 H), 2.98-2.82 (comp, 2.23 H), 1.11 (d, *J* = 6.8 Hz, 2.33 H), 0.98 (d, *J* = 6.2 Hz, 0.75 H), 0.13 (s, 6.3 H) , 0.11 (s, 2.1 H); IR (neat) 2962, 2164, 1782, 1704, 1385,

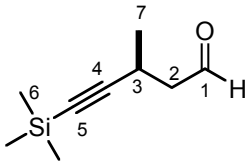
1249, 1212, 842, 759 cm^{-1}; MS (CI +) m/z 520.2306 [$C_{33}H_{34}NO_3Si$ (M + 1) requires 520.2308], 520, 267 (base).



(3*S*)-Methyl-5-trimethylsilanylpent-4-yn-1-ol (518). Solid $LiBH_4$ (49 mg, 2.1 mmol) and dry MeOH (78 μL, 1.9 mmol) were sequentially added to a solution of **506*S*** (637 mg, 1.93 mmol) in THF (19 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, whereupon the cooling bath was removed, and stirring was continued at rt for 8 h. The reaction was poured into a mixture of 25% w/v aq. NaOH (40 mL) and Et_2O (10 mL). The resulting layers were separated, and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated by short-path distillation at atmospheric pressure (70 °C bath). The crude yellow oil obtained was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (4:1) to afford 270 mg (82%) of **518** as a pale-yellow oil after removal of the solvent by short-path distillation (55 °C bath). Alternatively this compound was obtained in identical yield on 1.4 mmol scale from **509** (see IVJB147). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83-3.70 (comp, 2 H), 2.66-2.55 (m, 1 H), 1.93 (br s, 1 H), 1.73-1.58 (comp, 2 H), 1.17 (d, J = 6.8 Hz, 3 H), 0.11 (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 111.2, 85.2, 61.2, 39.3, 23.9, 21.1, 0.1; IR (neat) 3350, 2961, 2167, 1250, 841, 760 cm^{-1}; MS (CI +) *m/z* 171.1207 [$C_9H_{19}OSi$ (M + 1) requires 171.1205], 171 (base), 155, 139.

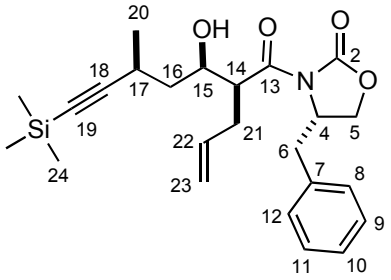
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83-3.70 (comp, 2 H, C1-H), 2.66-2.55 (m, 1 H, C3-H), 1.93 (br s, 1 H, C1-OH), 1.73-1.58 (comp, 2 H, C2-H), 1.17 (d, J =

6.8 Hz, 3 H, C7-H), 0.11 (s, 9 H, C6-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 111.2 (C4), 85.2 (C5), 61.2 (C1), 39.3 (C2), 23.9 (C3), 21.1 (C7), 0.1 (C6).



(3*S*)-Methyl-5-trimethylsilanylpent-4-ynal (503). Distilled DMSO (666 μL, 9.38 mmol) was added via syringe to a solution of oxalyl chloride (406 μL, 4.65 mmol) in CH_2Cl_2 (58 mL) at –78 °C. The mixture was stirred at –78 °C for 15 min, whereupon a solution of **518** (264 mg, 1.55 mmol) in CH_2Cl_2 (4 mL) was added via cannula, and stirring was continued for an additional 1 h. Et_3N (2.6 mL, 19 mmol) was added via syringe and the reaction mixture was transferred to a 0 °C bath for 0.5 h. H_2O (10 mL) was added and the mixture was poured into a solution of 1 N HCl (100 mL). The resulting layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried ($MgSO_4$) and filtered through a 0.5-inch plug of neutral Al_2O_3 with CH_2Cl_2 (100 mL) and Et_2O (50 mL). The solvent was removed by short-path distillation (55 °C bath) at atmospheric pressure until the smell of DMS had disappeared. The resulting crude residue was triturated with pentane (5 mL) and filtered through a plug of glass millifiber filter paper to remove residual ammonium salts. Concentration of the filtrate by short-path distillation afforded 246 mg (94%) of **503** as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.1 Hz, 1 H), 2.97 (sext, J = 6.8 Hz, 1 H), 2.63-2.41 (comp, 2 H), 1.21 (d, J = 6.8 Hz, 3 H), 0.11 (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.1, 109.1, 85.7, 49.8, 21.5, 20.9, 0.1; IR (neat) 2962, 2169, 1714, 1410, 1250, 842, 760 cm^{-1}; MS (CI +) *m/z* 169.1050 [$C_9H_{17}OSi$ (M + 1) requires 169.1049], 169 (base).

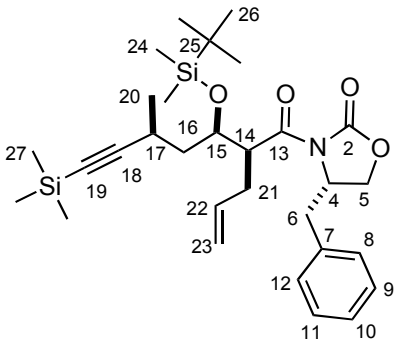
NMR Assignments. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.1 Hz, 1 H, C1-H), 2.97 (sext, *J* = 6.8 Hz, 1 H, C3-H), 2.63-2.41 (comp, 2 H, C2-H), 1.21 (d, *J* = 6.8 Hz, 3 H, C7-H), 0.11 (s, 9 H, C6-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.1 (C1), 109.1 (C4), 85.7 (C5), 49.8 (C2), 21.5 (C3), 20.9 (C7), 0.1 (C6).



3-[(2*S*)-Allyl-(3*R*)-hydroxy-(5*S*)-methyl-7-trimethylsilanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (519). Freshly prepared Bu_2BOTf (0.57 mL, 2.3 mmol) was added via syringe to a solution of **504** (594 mg, 2.29 mmol) in PhMe (12 mL) at 0 °C, followed immediately by the addition of *i*-Pr_2NEt (400 μL, 2.29 mmol). The resulting pale-yellow solution was stirred at 0 °C for 1 h and then cooled to –78 °C, whereupon a solution of **503** (285 mg, 1.69 mmol) in PhMe (2 mL) was added via cannula. The bright-yellow reaction mixture was stirred at –78 °C for 0.5 h. The cooling bath was removed, and stirring was continued at rt for 2 h to afford a brown solution. The mixture was recooled to 0 °C, and a solution of pH = 7 phosphate buffer (1 mL), MeOH (1 mL), and of 30% H_2O_2 (1 mL) were added sequentially. The resulting solution was removed from the cooling bath and stirred at rt for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and poured into H_2O (30 mL). The resulting layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:3) to

afford 615 mg (82%) of **519** as a clear oil (*dr* = 96:4 by ^{1}H-NMR). The minor diastereomer was separated by column chromatography on SiO_2 using gradient elution with EtOAc/hexanes (0:1 → 1:3 → 2:3). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (comp, 2 H), 7.27-7.23 (m, 1 H), 7.21-7.18 (comp, 2 H), 5.89-5.80 (m, 1 H), 5.13-5.09 (m, 1 H), 5.05-5.02 (m, 1 H), 4.72-4.67 (m, 1 H), 4.25-4.19 (comp, 2 H), 4.17-4.09 (comp, 2 H), 3.28 (dd, *J* = 13.5, 3.4 Hz, 1 H), 2.75-2.69 (m, 1 H), 2.68-2.55 (comp, 3 H), 2.44-2.38 (m, 1 H), 1.63-1.50 (comp, 2 H), 1.18 (d, *J* = 7.0 Hz, 3 H), 0.12 (s, 9 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.8, 153.7, 135.3, 135.2, 129.4, 129.0, 127.4, 117.3, 110.9, 85.2, 70.4, 66.0, 55.6, 47.3, 40.5, 38.0, 32.1, 23.8, 21.4, 0.1; IR (neat) 3524, 2963, 2165, 1782, 1698, 1386, 1249, 1208, 1102, 842, 760, 701 cm^{-1}; MS (CI +) m/z 428.2254 [$C_{24}H_{34}NO_4Si$ (M + 1) requires 428.2257], 428 (base), 412, 356, 250.

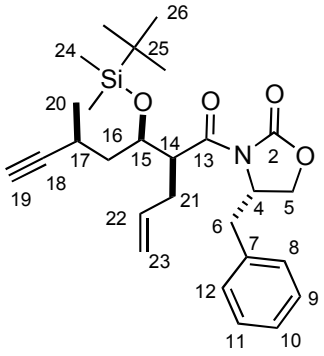
NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (comp, 2 H, C9-H, C11-H), 7.27-7.23 (m, 1 H, C10-H), 7.21-7.18 (comp, 2 H, C8-H, C12-H), 5.89-5.80 (m, 1 H, C22-H), 5.13-5.09 (m, 1 H, C23-H), 5.05-5.02 (m, 1 H, C23-H), 4.72-4.67 (m, 1 H, C4-H), 4.25-4.19 (comp, 2 H, C14-H, C15-H), 4.17-4.09 (comp, 2 H, C6-H), 3.28 (dd, *J* = 13.5, 3.4 Hz, 1 H, C5-H), 2.75-2.69 (m, 1 H, C17-H), 2.68-2.55 (comp, 3 H, C5-H, C21-H, C15-OH), 2.44-2.38 (m, 1 H, C21-H), 1.63-1.50 (comp, 2 H, C16-H), 1.18 (d, *J* = 7.0 Hz, 3 H, C20-H), 0.12 (s, 9 H, C24-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.8 (C13), 153.7 (C2), 135.3 (C7), 135.2 (C22), 129.4 (C8, C12), 129.0 (C9, C11), 127.4 (C10), 117.3 (C23), 110.9 (C19), 85.2 (C18), 70.4 (C15), 66.0 (C6), 55.6 (C4), 47.3 (C14), 40.5 (C16), 38.0 (C5), 32.1 (C21), 23.8 (C17), 21.4 (C20), 0.1 (C24).



3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanoxyl)-(5*S*)-methyl-7-trimethyl-silanylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (520). Freshly distilled TBDMSOTf (0.72 mL, 3.1 mmol) was added to a solution of **519** (463 mg, 1.08 mmol) and 2,6-lutidine (1.2 mL, 10 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC. The resulting pale-yellow solution was stirred at 0 ^oC for 2 h. The reaction was quenched by adding phosphate buffer (pH = 7) (10 mL) and then poured into H_2O (50 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with EtOAc/hexanes (2:3) to afford 536 mg (92%) of **520** as a pale-yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (comp, 2 H), 7.26-7.22 (m, 1 H), 7.22-7.19 (comp, 2 H), 5.90-5.81 (m, 1 H), 5.14-5.09 (m, 1 H), 5.04-5.01 (m, 1 H), 4.64-4.59 (m, 1 H), 4.25-4.21 (m, 1 H), 4.17-4.14 (m, 1 H), 4.12-4.03 (m, 1 H), 3.28 (dd, *J* = 13.3, 3.1 Hz, 1 H), 2.67 (dd, *J* = 13.3, 10.0 Hz, 1 H), 2.58-2.48 (comp, 2 H), 2.34-2.26 (m, 1 H), 1.81-1.75 (m, 1 H), 1.68-1.63 (m, 1 H), 1.18 (d, *J* = 6.9 Hz, 3 H), 0.84 (s, 9 H), 0. 13 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.0, 153.1, 135.5, 135.3, 129.5, 128.9, 127.3, 117.1, 111.4, 85.5, 71.9, 65.7, 56.0, 48.1, 41.5, 37.7, 33.1, 25.7, 24.0, 21.6, 18.0, 0.2, -4.4, -4.7; IR (neat) 2955, 2167, 1784, 1696, 1384, 1248, 1207, 1095, 837, 778 cm^{-1};

MS (CI +) m/z 542.3120 [$C_{30}H_{48}NO_4Si_2$ (M + 1) requires 542.3122], 542 (base), 526, 484, 410.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (comp, 2 H, C9-H, C11-H), 7.26-7.22 (m, 1 H, C10-H), 7.22-7.19 (comp, 2 H, C8-H, C12-H), 5.90-5.81 (m, 1 H, C22-H), 5.14-5.09 (m, 1 H, C23-H), 5.04-5.01 (m, 1 H, C23-H), 4.64-4.59 (m, 1 H, C4-H), 4.25-4.21 (m, 1 H, C14-H), 4.17-4.14 (m, 1 H, C15-H), 4.12-4.03 (m, 1 H, C6-H), 3.28 (dd, *J* = 13.3, 3.1 Hz, 1 H, C5-H), 2.67 (dd, *J* = 13.3, 10.0 Hz, 1 H, C5-H), 2.58-2.48 (comp, 2 H, C17-H, C21-H), 2.34-2.26 (m, 1 H, C21-H), 1.81-1.75 (m, 1 H, C16-H), 1.68-1.63 (m, 1 H,C16-H), 1.18 (d, *J* = 6.9 Hz, 3 H, C20-H), 0.84 (s, 9 H, C26-H), 0.13 (s, 9 H, C27-H), 0.09 (s, 3 H, C24-H), 0.05 (s, 3 H, C24-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.0 (C13), 153.1 (C2), 135.5 (C7), 135.3 (C22), 129.5 (C8, C12), 128.9 (C9, C11), 127.3 (C10), 117.1 (C23), 111.4 (C19), 85.5 (C18), 71.9 (C15), 65.7 (C6), 56.0 (C4), 48.1 (C14), 41.5 (C16), 37.7 (C5), 33.1 (C21), 25.7 (C26), 24.0 (C17), 21.6 (C20), 18.0 (C25), 0.2 (C27), -4.4 (C24), -4.7 (C24).

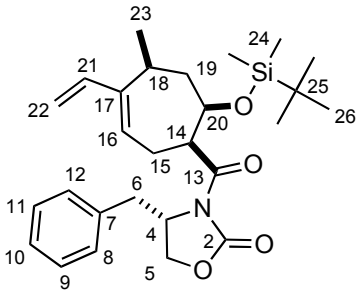


3-[(2*S*)-Allyl-(3*R*)-(*tert*-butyldimethylsilanoxyl)-(5*S*)-methylhept-6-ynoyl]-(4*S*)-benzyloxazolidin-2-one (521). Solid $AgNO_3$ (3.3 g, 19 mmol) was added in one portion to a solution of **520** (695 mg, 1.28 mmol) in THF/EtOH/H_2O/2,6-lutidine (1:1:1:0.1) (65 mL) at rt. The resulting dark-brown slurry was stirred at rt for 26 h,

whereupon a 1 N aqueous solution of KH_2PO_4 (20 mL) was added, and the mixture was stirred for an additional 0.5 h. The bright yellow slurry was then filtered though Celite, rinsing with Et_2O (300 mL). The filtrate was washed with brine (200 mL), and then H_2O (100 mL). The resulting layers were separated, and the aqueous phase was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to deliver a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 493 mg (82%) of **521** as a pale-yellow oil. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (comp, 2 H), 7.26-7.23 (m, 1 H), 7.22-7.19 (comp, 2 H), 5.89-5.80 (m, 1 H), 5.12-5.08 (m, 1 H), 5.04-5.00 (m, 1 H), 4.65-4.60 (m, 1 H), 4.28-4.24 (m, 1 H), 4.15-4.04 (comp, 3 H), 3.28 (dd, *J* = 13.4, 3.2 Hz, 1 H), 2.64 (dd, *J* = 13.5, 10.2 Hz, 1 H), 2.55-2.47 (comp, 2 H), 2.39-2.33 (m, 1 H), 2.05 (d, *J* = 2.2 Hz, 1 H), 1.78-1.67 (comp, 2 H), 1.21 (d, *J* = 7.0 Hz, 3 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.0, 153.1, 135.5, 135.2, 129.5, 128.9, 127.3, 117.1, 88.6, 71.9, 69.3, 65.7, 56.0, 48.0, 41.7, 37.8, 33,4, 25.8, 22.8, 21.8, 18.0, -4.4, -4.6; IR (neat) 3307, 2931, 1784, 1696, 1384, 1249, 1208, 1096, 837, 779 cm^{-1}; MS (CI +) m/z 470.2720 [$C_{27}H_{40}NO_4Si$ (M + 1) requires 470.2727], 470 (base), 454, 412, 338.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.32-7.28 (comp, 2 H, C9-H, C11-H), 7.26-7.23 (m, 1 H, C10-H), 7.22-7.19 (comp, 2 H, C8-H, C12-H), 5.89-5.80 (m, 1 H, C22-H), 5.12-5.08 (m, 1 H, C23-H), 5.04-5.00 (m, 1 H, C23-H), 4.65-4.60 (m, 1 H, C4-H), 4.28-4.24 (m, 1 H, C14-H), 4.15-4.04 (comp, 3 H, C15-H, C6-H), 3.28 (dd, *J* = 13.4, 3.2 Hz, 1 H, C5-H), 2.64 (dd, *J* = 13.5, 10.2 Hz, 1 H, C5-H), 2.55-2.47 (comp, 2 H, C17-H, C21-H), 2.39-2.33 (m, 1 H, C21-H), 2.05 (d, *J* = 2.2 Hz, 1 H, C19-H), 1.78-1.67

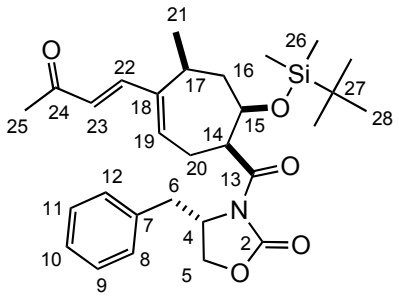
(comp, 2 H, C16-H), 1.21 (d, J = 7.0 Hz, 3 H, C20-H), 0.83 (s, 9 H, C26-H), 0.10 (s, 3 H, C24-H), 0.06 (s, 3 H, C24-H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 174.0 (C13), 153.1 (C2), 135.5 (C7), 135.2 (C22), 129.5 (C8, C12), 128.9 (C9, C11), 127.3 (C10), 117.1 (C23), 88.6 (C18), 71.9 (C15), 69.3 (C19), 65.7 (C6), 56.0 (C4), 48.0 (C14), 41.7 (C16), 37.8 (C5), 33.4 (C21), 25.8 (C26), 22.8 (C17), 21.8 (C20), 18.0 (C25), -4.4 (C24), -4.6 (C24).



4(*S*)-Benzyl-(3*S*)-[7(*R*)-(*tert*-butyldimethylsilanyloxy)-5(*S*)-methyl-4-vinylcyclohept-3-enecarbonyl]oxazolidin-2-one (529). Hoveyda-Grubbs second-generation catalyst (**90**) (6 mg, 9 μmol) was added in one portion to a mixture of **521** (21 mg, 45 μmol) and freshly distilled **502** in CH_2Cl_2 (9 mL) saturated with ethylene. The solution was stirred at rt under an atmosphere of ethylene for 22 h, whereupon DMSO (50 μL) was added, and stirring was continued for an additional 18 h. The reaction mixture was concentrated under reduced pressure to afford a crude brown oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:2) to afford 12 mg (57%) of **529** as a pale-yellow oil along with 9 mg (41%) of recovered **521**. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (comp, 2 H), 7.27-7.25 (m, 1 H), 7.21-7.19 (comp, 2 H), 6.21 (dd, J = 17.4, 10.9 Hz, 1 H), 5.74-5.71 (m, 1 H), 5.09 (d, J = 17.4 Hz, 1 H), 4.91 (d, J = 10.9 Hz, 1 H), 4.61-4.56 (m, 1 H), 4.24-4.21 (m, 1 H), 4.19-4.16 (m, 1H), 4.14-4.07 (comp, 2 H), 3.27 (dd, J = 13.3, 3.2 Hz, 1 H), 3.03-2.96 (m, 1 H), 2.83-2.76 (m, 1 H), 2.72 (dd, J = 13.3, 9.8 Hz, 1 H), 2.25-2.14 (comp, 2 H), 1.78 (ddd, J = 14.7, 6.1, 2.0 Hz,

1 H), 1.21 (d, J = 7.4 Hz, 3 H), 0.84 (s, 9 H), 0.05 (s, 3 H), -0.07 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.9, 153.3, 145.5, 140.2, 135.5, 129.5, 128.9, 128.4, 127.3, 110.4, 71.9, 65.8, 55.8, 45.8, 38.3, 37.9, 31.2, 25.8, 24.0, 20.5, 17.9, -4.4, -5.5; IR (neat) 2929, 1784, 1698, 1388, 1350, 1242, 1210, 1099, 1072, 835, 776 cm^{-1}; MS (CI +) m/z 470.2728 [$C_{27}H_{40}NO_4Si$ (M + 1) requires 470.2727], 470 (base), 338.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (comp, 2 H, C9-H, C11-H), 7.27-7.25 (m, 1 H, C10-H), 7.21-7.19 (comp, 2 H, C8-H, C12-H), 6.21 (dd, J = 17.4, 10.9 Hz, 1 H, C21-H), 5.74-5.71 (m, 1 H, C16-H), 5.09 (d, J = 17.4 Hz, 1 H, C22-H), 4.91 (d, J = 10.9 Hz, 1 H, C22-H), 4.61-4.56 (m, 1 H, C4-H), 4.24-4.21 (m, 1 H, C20-H), 4.19-4.16 (m, 1 H, C14-H), 4.14-4.07 (comp, 2 H, C6-H), 3.27 (dd, J = 13.3, 3.2 Hz, 1 H, C5-H), 3.03-2.96 (m, 1 H, C15-H), 2.83-2.76 (m, 1 H, C18-H), 2.72 (dd, J = 13.3, 9.8 Hz, 1 H, C5-H), 2.25-2.14 (comp, 2 H, C19-H, C15-H, 1.78 (ddd, J = 14.7, 6.1, 2.0 Hz, 1 H, C19-H), 1.21 (d, J = 7.4 Hz, 3 H, C23-H), 0.84 (s, 9 H, C26-H), 0.05 (s, 3 H, C24-H), -0.07 (s, 3 H, C24-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 173.9 (C13), 153.3 (C2), 145.5 (C7), 140.2 (C21), 135.5 (C17), 129.5 (C8, C12), 128.9 (C9, C11), 128.4 (C16), 127.3 (C10), 110.4 (C22), 71.9 (C20), 65.8 (C6), 55.8 (C4), 45.8 (C14), 38.3 (C19), 37.9 (C5), 31.2 (C18), 25.8 (C26), 24.0 (C15), 20.5 (C25), 17.9 (C23), -4.4 (C24), -5.5 (C24).

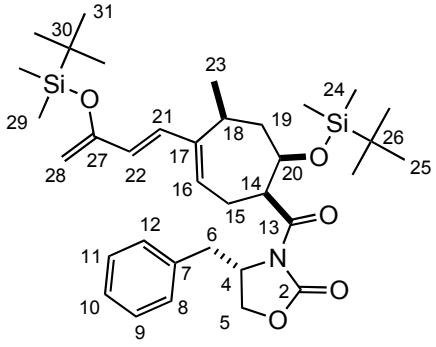


4(*S*)-Benzyl-(3*S*)-[7(*R*)-(*tert*-butyldimethylsilanyloxy)-5(*S*)-methyl-4-(3-oxobut-1-enyl)cyclohept-3-enecarbonyl]oxazolidin-2-one (530). Hoveyda-Grubbs

second-generation catalyst (**90**) (97 mg, 0.16 mmol) was added in one portion to a mixture of **521** (364 mg, 0.775 mmol) and freshly distilled MVK (320 μL, 3.88 mmol) in CH_2Cl_2 (155 mL). The resulting solution was stirred under Ar at 42 ^oC for 20 h, whereupon the mixture was cooled to rt and DMSO (0.6 mL) was added. Stirring was continued for an additional 18 h, and then the mixture was concentrated under reduced pressure. The crude brown oil thus obtained was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:1) to afford a green viscous oil that solidified upon standing and was recrystallized from warm hexanes to deliver 245 mg (62%) of **530** as a white crystalline solid (Mp = 24-46 ^oC). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (comp, 2 H), 7.28-7.24 (m, 1 H), 7.20-7.18 (comp, 2 H), 7.02 (d, *J* = 16.1 Hz, 1 H), 6.20 (m, 1 H), 6.08 (d, *J* = 16.1 Hz, 1 H), 4.61-4.56 (m, 1 H), 4.27-4.25 (m, 1 H), 4.16-4.07 (comp, 3 H), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1 H), 3.13-3.06 (m, 1 H), 2.82-2.75 (m, 1 H), 2.73 (d, *J* = 13.3, 9.7 Hz, 1 H), 2.32-2.27 (comp, 4 H), 2.23-2.17 (m, 1 H), 1.80 (ddd, *J* = 14.7, 5.6, 1.8 Hz, 1 H), 1.23 (d, *J* = 7.2 Hz, 3 H), 0.85 (s, 9 H), 0.05 (s, 3 H), -0.08 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.9, 173.3, 153.3, 147.6, 144.7, 138.8, 135.3, 129.4, 129.0, 127.4, 124.8, 71.7, 65.9, 55.8, 45.7, 38.0, 37.8, 31.8, 27.3, 25.8, 24.4, 20.4, 17.8, -4.3, -5.6; IR (neat) 2928, 2856, 1778, 1702, 1667, 1590, 1386, 1354, 1256, 1195, 985, 837, 774 cm^{-1}; MS (CI +) m/z 512.2833 [$C_{29}H_{42}NO_5Si$ (M + 1) requires 512.2832], 512 (base), 494, 454, 380, 362, 205, 163.

NMR Assignments. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (comp, 2 H, C9-H, C11-H), 7.28-7.24 (m, 1 H, C10-H), 7.20-7.18 (comp, 2 H, C8-H, C12-H), 7.02 (d, *J* = 16.1 Hz, 1 H, C22-H), 6.20 (m, 1 H, C19-H), 6.08 (d, *J* = 16.1 Hz, 1 H, C23-H), 4.61-4.56 (m, 1 H, C4-H), 4.27-4.25 (m, 1 H, C15-H), 4.16-4.07 (comp, 3 H, C6-H, C14-H), 3.27 (dd, *J*

= 13.4, 3.3 Hz, 1 H, C5-H), 3.13-3.06 (m, 1 H, C20-H), 2.82-2.75 (m, 1 H, C17-H), 2.73 (d, *J* = 13.3, 9.7 Hz, 1 H, C5-H), 2.32-2.27 (comp, 4 H, C20-H, C25-H), 2.23-2.17 (m, 1 H, C16-H), 1.80 (ddd, *J* = 14.7, 5.6, 1.8 Hz, 1 H, C16-H), 1.23 (d, *J* = 7.2 Hz, 3 H, C21-H), 0.85 (s, 9 H, C28-H), 0.05 (s, 3 H, C26-H), -0.08 (s, 3 H, C26-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 198.9 (C24), 173.3 (C13), 153.3 (C2), 147.6 (C22), 144.7 (C18), 138.8 (C19), 135.3 (C7), 129.4 (C8, C12), 129.0 (C9, C11), 127.4 (C10), 124.8 (C23), 71.7 (C15), 65.9 (C6), 55.8 (C4), 45.7 (C14), 38.0 (C16), 37.8 (C5), 31.8 (C17), 27.3 (C25), 25.8 (C28), 24.4 (C20), 20.4 (C21), 17.8 (C27), -4.3 (C26), -5.6 (C26).



4(*S*)-Benzyl-(3*S*)-[7(*R*)-(*tert*-butyldimethylsilanyloxy)-4-[3-(*tert*-butyldimethylsilanyloxy)-buta-1,3-dienyl]-5(*S*)-methylcyclohept-3-enecarbonyl]-oxazolidin-2-one (536). A solution of 2.45 M *n*-BuLi in hexanes (45 μL, 0.11 mmol) was added to a solution of diisopropylamine (17 μL, 0.12 mmol) in THF (50 μL) at −78 °C. The mixture was stirred for 10 min at −78 °C, at −5 °C for 15 min, and then added via syringe to a solution of **530** (51 mg, 97 μmol) in THF (0.27 mL) and HMPA (70 μL). The resulting dark-yellow mixture was stirred for 45 min, and then a −10 °C solution of TBDMSCl (18 mg, 0.12 mmol) in THF (0.4 mL) was added via cannula. The resulting yellow solution was stirred at −78 °C for 5 min, and then transferred to a 5 °C bath (ice/H_2O). The reaction mixture was allowed to warm to ambient temperature over a

period of 2 h, whereupon the mixture was poured into H_2O (10 mL) and hexanes (5 mL). The resulting layers were separated, and the aqueous phase was extracted with hexanes (3 x 15 mL). The combined organic extracts were rinsed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a crude yellow oil that was purified by flash chromatography (SiO_2) eluting with Et_2O/pentane (1:3) to afford 34 mg (55%) of **536** as a white foam. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37-7.31 (comp, 2 H), 7.30-7.25 (m, 1 H), 7.24-7.19 (comp, 2 H), 6.44 (d, *J* = 15.4 Hz, 1 H), 5.98 (d, *J* = 15.7 Hz, 1 H), 5.86-5.82 (m, 1 H), 4.64-4.58 (m, 1 H), 4.32 (d, *J* = 1.4 Hz, 2 H), 4.27-4.24 (m, 1 H), 4.17-4.10 (comp, 3 H), 3.22 (dd, *J* = 13.3, 3.1 Hz, 1 H), 3.06-2.97 (m, 1 H), 2.86-2.76 (comp, 2 H), 2.27-2.17 (comp, 2 H), 1.78 (app dq, *J* = 14.4, 5.5, 1.7 Hz, 1 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 0.99 (s, 9 H), 0.87 (s, 9 H), 0.20 (s, 6 H), 0.08 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR δ 173.9, 156.0, 153.6, 154.3, 136.0, 133.5, 129.9, 129.2, 127.5, 123.6, 95.6, 72.3, 66.3, 55.9, 46.3, 38.7, 38.0, 36.8, 32.4, 26.0, 24.5, 18.6, 18.1, -4.3, -4.5, -4.6, -5.5; IR (neat) 3501, 3078, 2945, 1699, 1639, 1409, 1379, 1337, 1180, 1107, 1029, 908, 769 cm^{-1}; MS (CI) *m/z* 264.1957 [$C_{16}H_{26}NO_2$ (M + 1) requires 264.1964], 264 (base).

NMR Assignments. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37-7.31 (comp, 2 H, C8-H, C11-H), 7.30-7.25 (m, 1 H, C10-H), 7.24-7.19 (comp, 2 H, C9-H, C12-H), 6.44 (d, *J* = 15.4 Hz, 1 H, C21-H), 5.98 (d, *J* = 15.7 Hz, 1 H, C22-H), 5.86-5.82 (m, 1 H, C16-H), 4.64-4.58 (m, 1 H, C4-H), 4.32 (d, *J* = 1.4 Hz, 2 H, C28-H), 4.27-4.24 (m, 1 H), 4.17-4.10 (comp, 3 H), 3.22 (dd, *J* = 13.3, 3.1 Hz, 1 H), 3.06-2.97 (m, 1 H), 2.86-2.76 (comp, 2 H), 2.27-2.17 (comp, 2 H), 1.78 (app dq, *J* = 14.4, 5.5, 1.7 Hz, 1 H), 1.24 (d, *J* = 7.2 Hz, 3 H, C23-H), 0.99 (s, 9 H, C31-H), 0.87 (s, 9 H, C25-H), 0.20 (s, 6 H, C29-H), 0.08 (s, 3 H,

C24-H), -0.05 (s, 3 H, C24-H); ^{13}C NMR δ 173.9 (C13), 156.0 (C27), 153.6 (C2), 154.3 (C17), 136.0 (C7), 133.5 (C21), 129.9 (C9, C11), 129.2 (C8, C10, C12), 127.5 (C16), 123.6 (C22), 95.6 (C28), 72.3 (C20), 66.3 (C5), 55.9 (C14), 46.3 (C4), 38.7 (C6), 38.0 (C19), 36.8 (C18), 32.4 (C25, C31), 26.0 (C15), 24.5 (C23), 18.6 (C26), 18.1 (C30), -4.3 (C24), -4.5 (C24), -4.6 (C29), -5.5 (C29).

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