Title

Synthesis of the Tricyclic Core of Guanacastepene A, Decarboxylative Rearrangement of Allenylic N-Tosyl Carbamates and Phosphine-catalyzed Intramolecular γ-Umpolung Addition of α-Aminoalkylallenic Esters, and the Enantioselective Total Synthesis of (...

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Synthesis of the Tricyclic Core of Guanacastepene A, Decarboxylative Rearrangement of Allenylic *N*-Tosyl Carbamates and Phosphine-catalyzed Intramolecular γ-Umpolung Addition of α-Aminoalkylallenic Esters, and the Enantioselective Total Synthesis of (+)-Ibophyllidine

Dissertation submitted in partial fulfillment of the requirements

for the degree of Doctor of Philosophy in Chemistry

by

Ian Paul Andrews

2012

ABSTRACT OF THE DISSERTATION

Synthesis of the Tricyclic Core of Guanacastepene A,

Decarboxylative Rearrangement of Allenylic *N*-Tosyl Carbamates and Phosphine-catalyzed Intramolecular γ-Umpolung Addition of α-Aminoalkylallenic Esters, and the Enantioselective Total Synthesis of (+)-Ibophyllidine

by

Ian Paul Andrews

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2012

Professor Ohyun Kwon, Chair

Chapter 1

The synthesis of the tricyclic core of the diterpene guanacastepene A is described. Based on previous studies in the laboratory of professor Ohyun Kwon, the densely functionalized six-membered ring of the natural product was constructed utilizing an intermolecular Diels–Alder cycloaddition between maleic anhydride and a highly substituted alkoxydiene. The requisite diene was synthesized via a Stille cross coupling reaction for which an efficient synthesis of the necessary vinyl stannane was developed. An alternative synthesis of the diene based on copper mediated coupling of vinyl boronates with alcohols was also devised, which allowed for the preparation of gram quantities with minimal purification. The five-membered ring of

guanacastepene A was appended through coupling with a highly functionalized zinc cuprate. While previous studies in the Kwon laboratory showed that a conjugate addition/Mukaiyama aldol strategy to install the C11 methyl group and forge the seven-membered ring was efficient in forming the two desired carbon–carbon bonds, poor diastereoselectivity of the initial conjugate addition was observed. The research described here uses the Nozaki–Hiyama–Kishi reaction to close the central seven-membered ring without prior installation of the C11 methyl group.

Chapter 2

The synthesis of 3-carbethoxy-2-substituted-3-pyrrolines via the phosphine-catalyzed intramolecular γ-umpolung addition of *N*-tosyl α-aminoalkylallenic esters is described. The current transformation provides a compliment to the known syntheses of similarly substituted pyrrolines via the phosphine-catalyzed [3 + 2] annulation between imines and allenoates. The flexibility in substitution at the 2-position, including alkyl groups, offers benefits over many of the previously reported syntheses of similarly substituted pyrrolines. The *N*-tosyl α-aminoalkylallenic esters were prepared via a novel decarboxylative rearrangement of allenylic carbamates.

Chapter 3

The enantioselective total synthesis of the monoterpene indole alkaloid (+)-ibophyllidine is described. The employed strategy was based on a key asymmetric phosphine-catalyzed [3 + 2] annulations between a γ-ethyl allenoate and the *N*-tosyl imine derived from indole-3-aldehyde using Kwon's L-4-hydroxyproline-derived chiral phosphine catalyst. This key transformation

constructed the stereochemically dense D-ring with exceptional levels of diastereo- and enantioselectivity. A subsequent diastereoselective hydrogenation of the pyrroline double bond led to the fully functionalized, all *syn* pyrrolidine ring of the natural product. An intramolecular alkylation at the C3 position of indole formed the C-ring while an intramolecular aza Baylis–Hillman reaction was utilized to forge the E-ring leading to the pentacyclic skeleton of (+)-ibophyllidine.

The dissertation of Ian Paul Andrews is approved.

Patrick Harran

Jing Huang

Ohyun Kwon, Committee Chair

University of California, Los Angeles

2012

This dissertation is dedicated to my parents Paul and Sharon. I am forever indebted to them for their unwavering encouragement and support.

I would like to thank my advisor, Professor Ohyun Kwon, for her guidance and tremendous support over the course of my graduate career. Her encouragement for me to continuously improve has facilitated personal and professional growth to a level that has surpassed the goals I set when entering the graduate program. Through various stages of failures and successes, her attitude toward perpetually looking forward ultimately resulted in accomplishments that, without this outlook, may not have been achieved. Her support outside of the laboratory as well, when faculty support was needed for positions after graduation or for funding opportunities, has been remarkable, and for all of this I would like to express my sincere gratitude.

I would like to thank Professor Patrick Harran, for his willingness to provide advice and support on numerous occasions, as well as the other members of my committee; Professor Paula Diaconescu, and Professor Jing Huang. I would like to thank Professor Neil Garg for reading my first year research report and taking the time to give me useful feedback. I would like to thank Professor Michael Jung for his support and for myriad interesting and useful conversations over many competitive racquetball games played out on the courts of the John Wooden center.

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Acknowledgements

Chapter 1 is based partially on the work represented in "A concise synthesis of the functionalized [5–7–6] tricyclic skeleton of guanacastepene A" Du, X.; Chu, H, V.; Kwon, O. *Tetrahedron Lett.*, **2004**, *45*, 8843; and "Highly efficient palladium-catalyzed hydrostannation of ethyl ethynyl ether" Andrews, I. P.; Kwon, O. *Tetrahedron Lett.* **2008**, *49*, 7097. Chapter 2 is based on the work represented in "Phosphine-catalyzed intramolecular γ-umpolung addition of α-aminoalkylallenic esters: facile synthesis of 3-carbethoxy-2-alkyl-3-pyrrolines" Andrews, I. P.; Blank, B. R.; Kwon, O. *Chem. Commun.* **2012**, *48*, 5373. Chapter 3 is based on the work summarized in "Enantioselective total synthesis of (+)-ibophyllidine via an asymmetric phosphine-catalyzed [3 + 2] annulation" Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510. Financial support was provided by NIH R01GM071779 and P41GM081282, NSF equipment grant CHE-1048804, and the National Center for Research Sources S10RR025631.

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Presentations

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Oral Presentation: Andrews, I. P.; Kwon, O. "Application of the Phosphine-Catalyzed [3+2] Annulation: Total Synthesis of Ibophyllidine." 243rd ACS National Meeting, San Diego, CA, March 25th–29th, 2012.

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Oral Presentation: Andrews, I. P. "Catalytic Asymmetric Diels–Alder Reactions". Second Year Colloquium *University of California*, Los Angeles. February 4, 2008.

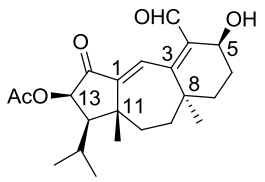
Chapter 1

Synthesis of the Tricyclic Core of Guanacastepene A

Section 1.1 Introduction

Guanacastepene A (**1**, Figure 1) was first isolated in 1999 from the extract of an endophytic fungus found on the bark of the *Daphnopsis Americana* tree, native to the guanacaste conservation area in Costa Rica.[1] The structure of guanacastepene A was assigned based on a combination of mass spectrometry, ^{1}H NMR, ^{13}C NMR, two-dimensional NMR, and X-ray diffraction analyses. Fast atom bombardment mass spectrometry (FABMS) indicated a molecular formula of $C_{22}H_{30}O_5$. Interestingly, the ^{13}C NMR spectrum of the isolated material showed only 13 distinct signals. Room temperature two dimensional NMR experiments indicated the presence of a small number of functional groups with limited connectivity. Low temperature ^{1}H and ^{13}C NMR experiments were carried out at –50 °C and suggested the presence of a dynamic equilibrium between two conformational isomers. It is believed that interconversion of the two conformers is responsible for the masking of some of its NMR signals. The missing signals of carbons 3, 5, 7, 8, 9, 10, 12, 16, and 17 all reside around the central seven membered ring and could be a result of the flexibility of the bottom region (C9 through C10) of the cycloheptene ring. It was found using the MM2 force field that there were two conformers around the C9–C10 bond differing by about 0.14 kcal/mol, with a 15 kcal/mol barrier for conversion. The existence of both conformers and their ability to interconvert at room temperature on the NMR time scale could account for the broad and missing NMR signals. Due to the complexities associated with guanacastepene's NMR spectra, the structure of the molecule was ultimately assigned via single crystal X-ray diffraction techniques.

The molecule consists of a 5-7-6 fused tricyclic skeleton that is host to an array of diverse functional groups about the perimeter. The relatively non-polar southern hemisphere contains the molecule's two quaternary carbon stereocenters, both of which contain an angular



guanacastepene A
(**1**)

Figure 1 Structure of guanacastepene A

methyl group in a *trans*-relationship to one another at C11 and C8. Also present in this portion of the molecule is the isopropyl-bearing, C12 stereocenter. The northern portion of the molecule consists of the C13 stereogenic acetate, C14 ketone, C15 α,β-unsaturated aldehyde, and the C5 secondary hydroxyl group. Further isolation studies have lead to the discovery of a whole family of guanacastepenes B–O (**2**–**15** Figure 2).[2] While in all cases the 5-7-6 tricyclic core is conserved among the guanacastepenes, functional group arrangement surrounding the skeleton is highly variable and many in the family include additional heterocyclic rings.

Section 1.2 Biological Activity

Studies aimed at identifying novel antibiotics were carried out on guanacastepene A. Agar diffusion assays on pure samples of guanacastepene A revealed its potent antibiotic activity.[1] It was discovered that the molecule exhibited antimicrobial properties against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF), two very problematic drug resistant bacteria.[3] Treatment with 100 μg of guanacastepene produced an 11 mm zone of growth inhibition on bacterial lawns against MRSA. The same

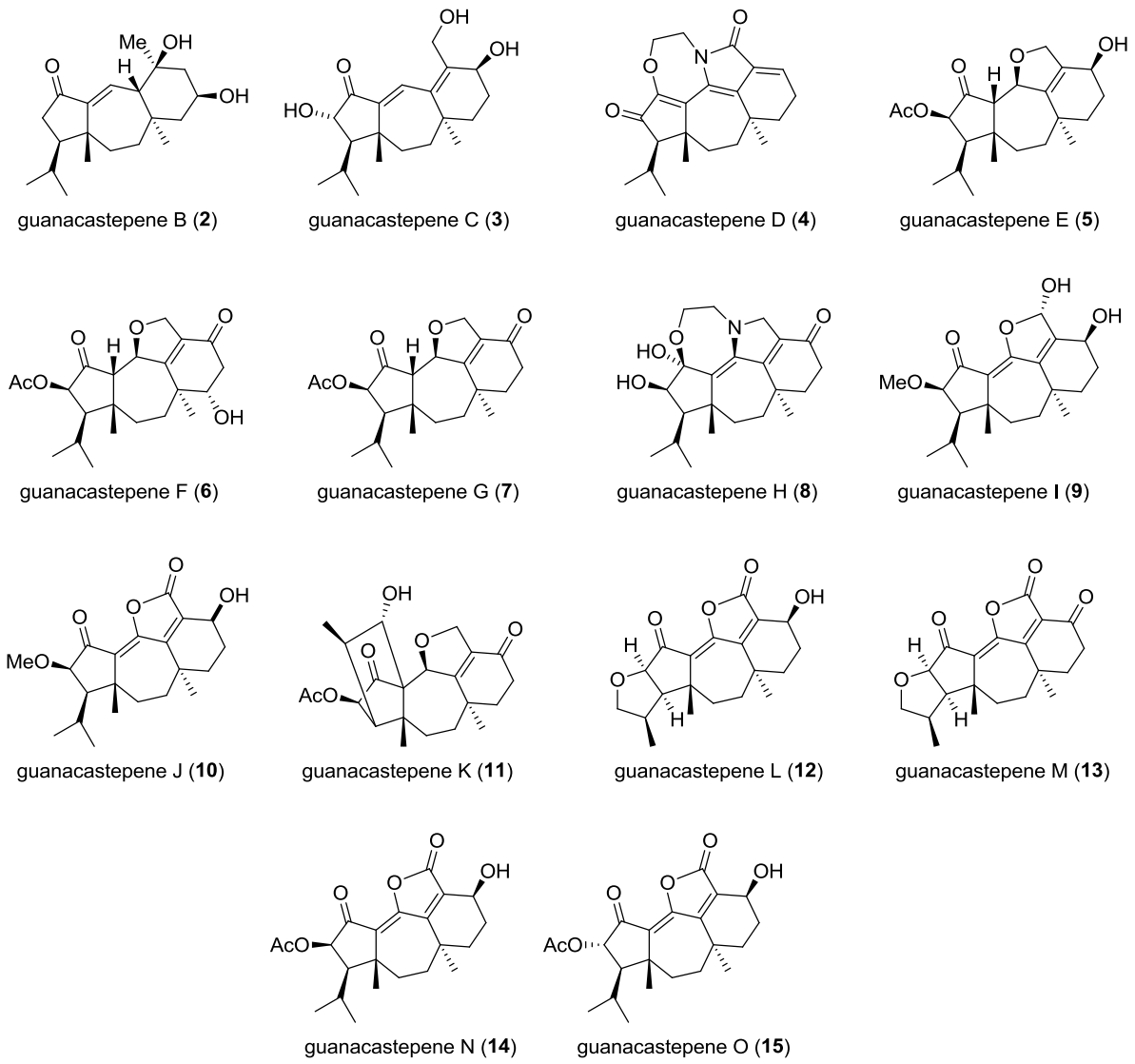
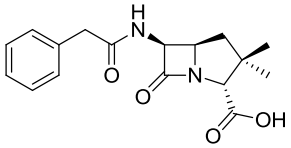


Figure 2 Guanacastepene family of natural products

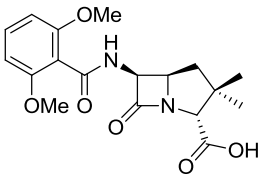
experiment using vancomycin produced a 17 mm area of growth inhibition. Against VREF, guanacastepene produced a 9 mm growth inhibition zone while vancomycin was ineffective.[1]

Section 1.3 Significance of Guanacastepene A's Biological Activity

In the early 1940's, penicillin G (**16**) emerged as a wildly effective antibiotic against nearly all strains of *Staphylococcus aureus* throughout the world (Figure 3). However, by 1944 it had been observed that certain strains of *S. aureus* were unaffected by penicillin G treatment. The mode of antibiotic resistance was ascribed to the ability of these strains to deactivate penicillin by way of a *B*-lactamase enzyme.[3] Today, it is estimated that over 95% of *S. aureus*



penicillin G (**16**)



methicillin (**17**)

Figure 3 Structure of penicillin G and methicillin

strains exhibit some resistance to various antibiotics including penicillin and ampicillin.[3] A temporary solution to this issue arose with the emergence of methicillin (**17**), developed in 1959 as a semi-synthetic penicillin (Figure 3). Methicillin was found to be an effective antibiotic for the treatment of infections attributed to *B*-lactamase producing bacteria such as *S. aureus*. However, methicillin-resistant *S. aureus* eventually emerged, with the first observed case in the United States reported in the early 1980's. This posed a substantial health risk due to the bacteria's resistance against all *B*-lactam as well as myriad other antibiotics.[3] This has led to an increase in vancomycin (**18**) use as one of the few effective treatments against an MRSA infection (Figure 4).[3,4] Increased and improper use of vancomycin, however, has helped facilitate the emergence of vancomycin-resistant strains of other bacterial species including

Enterococcus faecalis which will be discussed later in this text.[3] The threat of MRSA is not due to a greater clinical virulence than that of its methicillin susceptible counterpart, but rather to a higher risk of infection for those who are hosting the resistant bacterial strain. This, along with MRSA's strong antimicrobial resistance, has rendered the bacterium a prevalent nosocomial pathogen in many long-term health care centers and thus a major health care problem.[4]

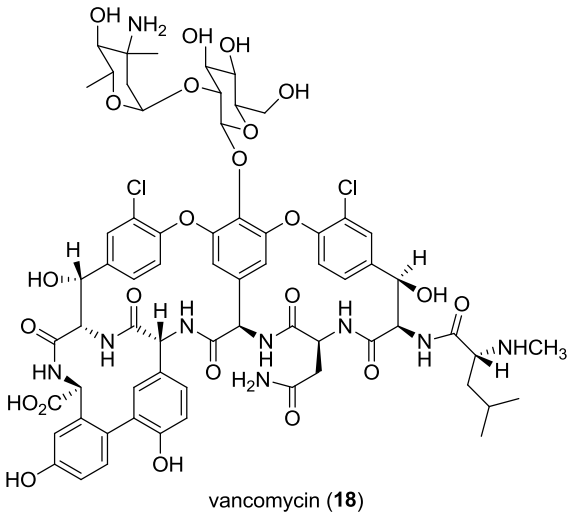


Figure 4 Stucture of vancomycin

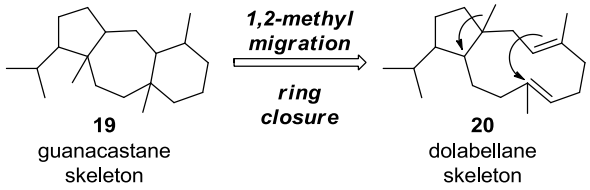
Another source of serious nosocomial infections come from the vancomycin-resistant *Enterococcae* (VRE), including vancomycin-resistant *Enterococcus faecalis*. The first observed cases of infection from highly resistant *Enterococcus* strains were observed in 1986 and the frequency of potentially life threatening infections from VRE has been steadily rising since that time.[5] Factors leading to vancomycin resistance include prior use of vancomycin in a patient, and failure to enforce proper use of antibiotics in hospitals, often relying on a homogeneous use of a single antibiotic or class of antibiotics.[5] The consequences of vancomycin-resistant strains are many; increased morbidity, increased mortality rates, and inflated hospital costs for infected

patients are some of the critical problems associated with the emergence of vancomycin-resistant strains of *Enterococci*. Patients suffering from infection of a resistant bacterium suffer higher incidence of recurrent infection and experience a higher occurrence of risky invasive procedures when compared to patients infected by strains that are more susceptible to standard treatments.[5] The antimicrobial treatment options against VRE are very scarce, hence any possible new treatment option is observed with great interest. Bacterial resistance to antimicrobials represents a possible epidemic problem in the future and there has been a movement in the U.S. for research and development of new antimicrobial agents, like guanacastepene A, that have promising antimicrobial activity against these highly resistant strains of bacteria.[5]

Further studies on guanacastepene A concluded that its mechanism of action involves damage to the bacterial cell membrane.[6] This phenomenon was not limited to bacterial cells, as guanacastepene A was found to rupture the membrane of human red blood cells as well. Unfortunately, the potential for guanacastepene A to be used directly as a therapeutic is severely diminished due to this hemolytic activity. Nevertheless, this unique molecule has garnered significant interest from the synthetic chemistry community based on its novel structure and the potential as a starting point for development of less toxic antimicrobial agents.

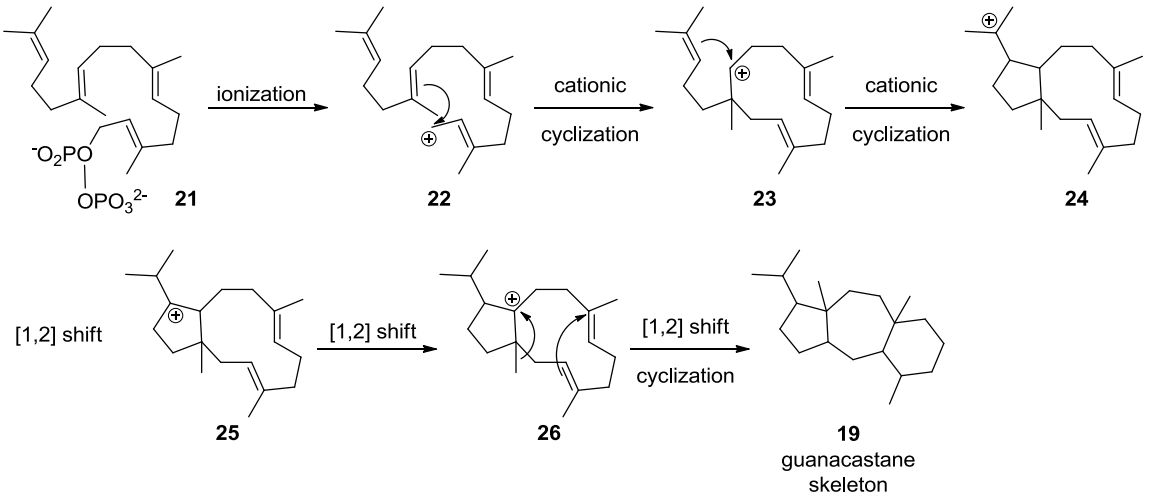
Section 1.4 Proposed Biosynthesis of Guanacastepene A

The guanacastane architecture **19** is proposed to arise through a 1,2-methyl group migration and ring closure from the closely related dolabellane skeleton **20** (Scheme 1).[1] The



Scheme 1 Proposed synthesis of the guanacastepene architecture from the dolabellane skeleton

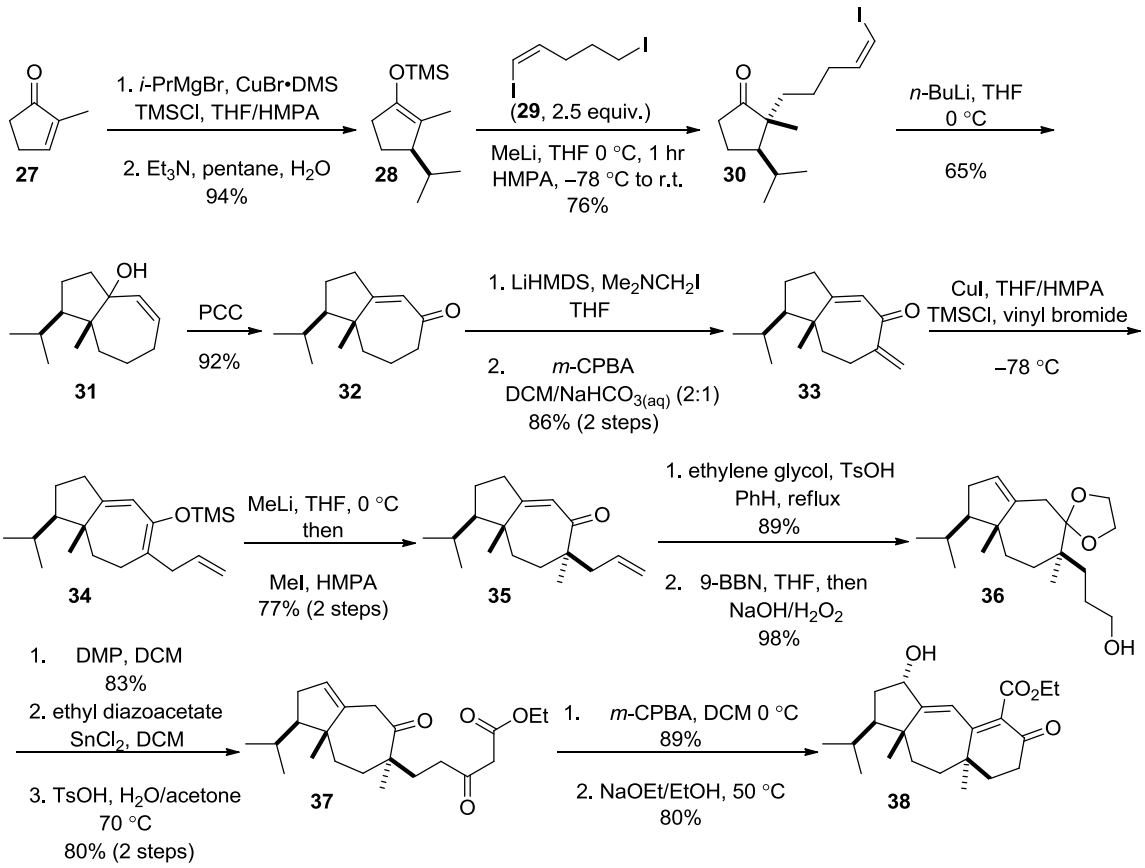
well precedented dolabellane skeleton has been proposed to arise from geranylgeranyl pyrophosphate (**21**) (Scheme 2). Ionization through loss of the pyrophosphate group leads to allyl cation **22** that undergoes cationic cyclization at the terminal carbon to give cation **23** capable of undergoing a second cyclization to provide cation **24**. A [1,2] hydride shift leading to cation **25** followed by a second [1,2] hydride shift yields cation **26**. A [1,2] methyl migration as previously mentioned, followed by cyclization of the diene unit provides the skeletal structure of the guanacastepenes **19**.[7,8]



Scheme 2 Proposed biosynthesis of the guanacastane skeleton

Section 1.5 Syntheses of Guanacastepene A

The first and only non-formal total synthesis of guanacastepene A was reported by Danishefsky in 2002.[9] The synthesis of the tricyclic core is outlined in Scheme 1. Conjugate addition of the copper reagent derived from isopropyl magnesium bromide to cyclopentenone **27** followed by trapping of the enolate with trimethylsilyl chloride furnished silyl enol ether **28** in 94% yield. Silyl ether cleavage with methyllithium and trapping of the resultant enolate with iodide **29** generates cycopentane **30** in 76% yield, bearing what will become the C11 all carbon quaternary center. The stereochemical outcome of the reaction is dictated by preferential attack of the electrophile from the face opposite to that of the bulky isopropyl substituent. Metallation of the vinyl iodide of **30** via lithium halogen exchange, followed by intramolecular nucleophilic addition onto the pendant ketone forged the seven membered ring, providing alcohol **31** in 65% yield. Oxidative rearrangement of the tertiary allylic alcohol with PCC generates the unsaturated ketone **32** in 92% yield. Eschenmoser methylenation provides exocyclic olefin **33** in 86% yield. Conjugate addition of the copper reagent derived from vinyl bromide to the *exo*-methylene of cyclic ketone **33** and trapping of the enolate with TMS chloride gives silyl enol ether **34**, alkylation of which with methyl iodide provides ketone **35** in 77% yield over two steps. This alkylation process serves to generate the second all carbon quaternary center at what will become C8 of the natural product. The stereochemical outcome of this sequence was found to be dependant of the order of introduction of groups (i.e. allyl and methyl groups). It was

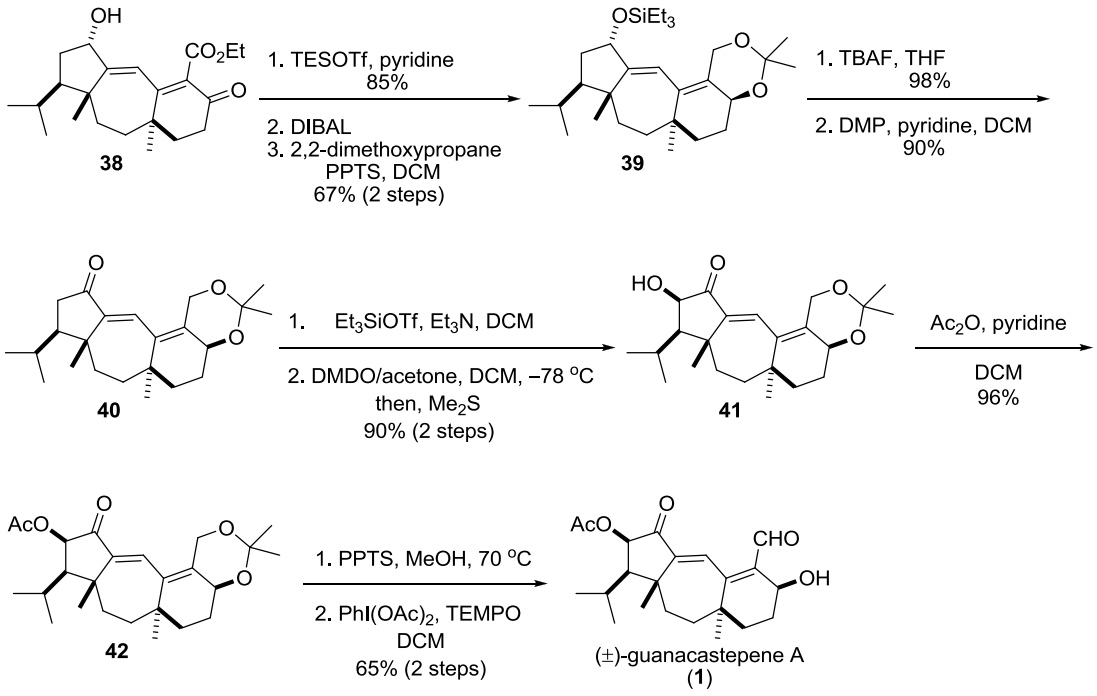


Scheme 3 Danishefsky's route to the tricyclic core of guanacastepene A

determined that alkylation of silyl enol ethers like that of **34** will do so with approach of the incoming electrophile from the opposite face of the C11 angular methyl substituent. Protection of the ketone as the dioxolane accompanied by double bond isomerization of the internal olefin, followed by hydroboration/oxidation of the terminal olefin, provided alcohol **36** in 89 and 98% yields, respectively. Dess–Martin periodinane (DMP) oxidation of the primary alcohol procceded in 83% yield (aldehyde not shown). The Roskamp homologation with ethyldiazoacetate followed by cleavage of the dioxolane provided β-ketoester **37** in 80% yield over two steps. Epoxidation of the olefin with *m*-CPBA (intermediate not shown) followed by treatment with sodium ethoxide in ethanol at 50 °C facilitated intramolecular Knoevenagel

condensation to construct the six- membered ring and eliminative epoxide opening to provided tricycle **38** in 89 and 80% yields, respectively.

Completion of the total synthesis is outlined in Scheme 4. Protection of the secondary alcohol as the triethylsilyl ether (85% yield) followed by DIBAL reduction of the ester and

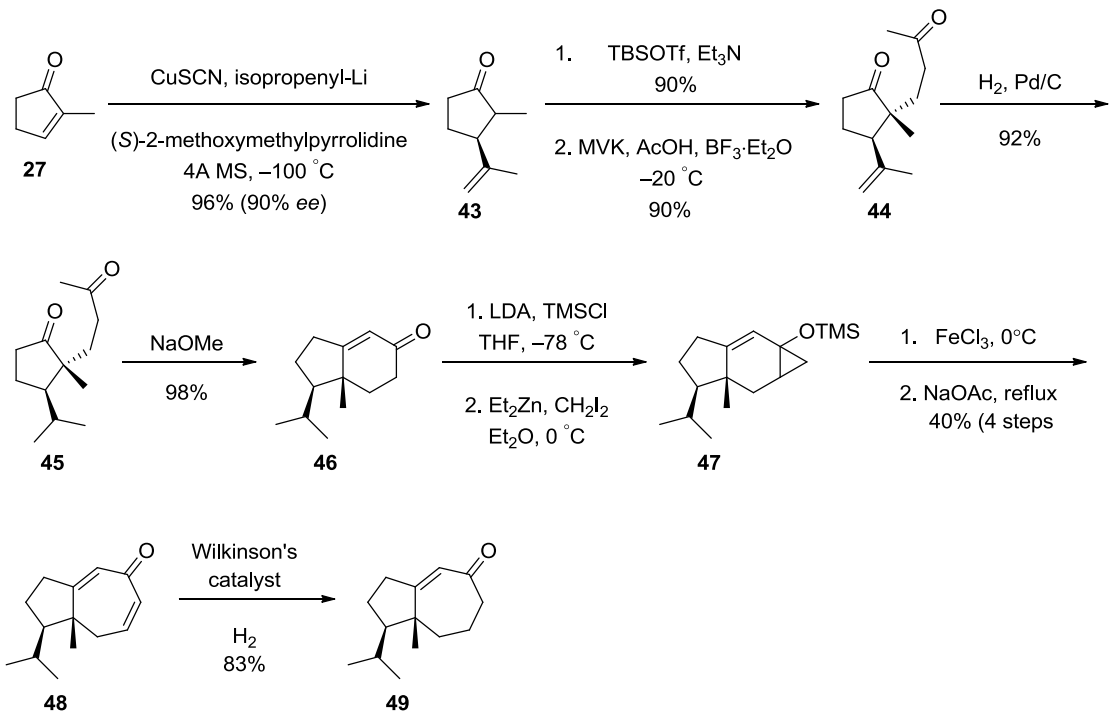


Scheme 4 Completion of Danishefsky's guanacastepene A synthesis

ketone functional groups of **38** and protection of the resultant diol with 2,2-dimethoxypropane, provided protected tricycle **39** (67% yield over two steps). Deprotection of the silyl ether and oxidation to ketone **40** proceeded in 98 and 90% yields, respectively. A diastereoselective Rubottom oxidation provided access to α-hydroxy ketone **41** in 90% isolated yield. [10] Acetylation of the resultant alcohol with acetic anhydride provided the *O*-acetate found in the

natural product (96% yield). Cleavage of the cyclic acetal followed by oxidation of the allylic alcohol provided (±)-guanacastepene A (**1**) in 65% from **42**.

Danishefsky later reported the synthesis of an optically active sample of intermediate **32** (see Scheme 3), referred to as **49** in Scheme 5, representing an asymmetric formal synthesis of guanacastepene A utilizing his strategy (Scheme 5).[11] Starting again from cyclopentenone **27**, an



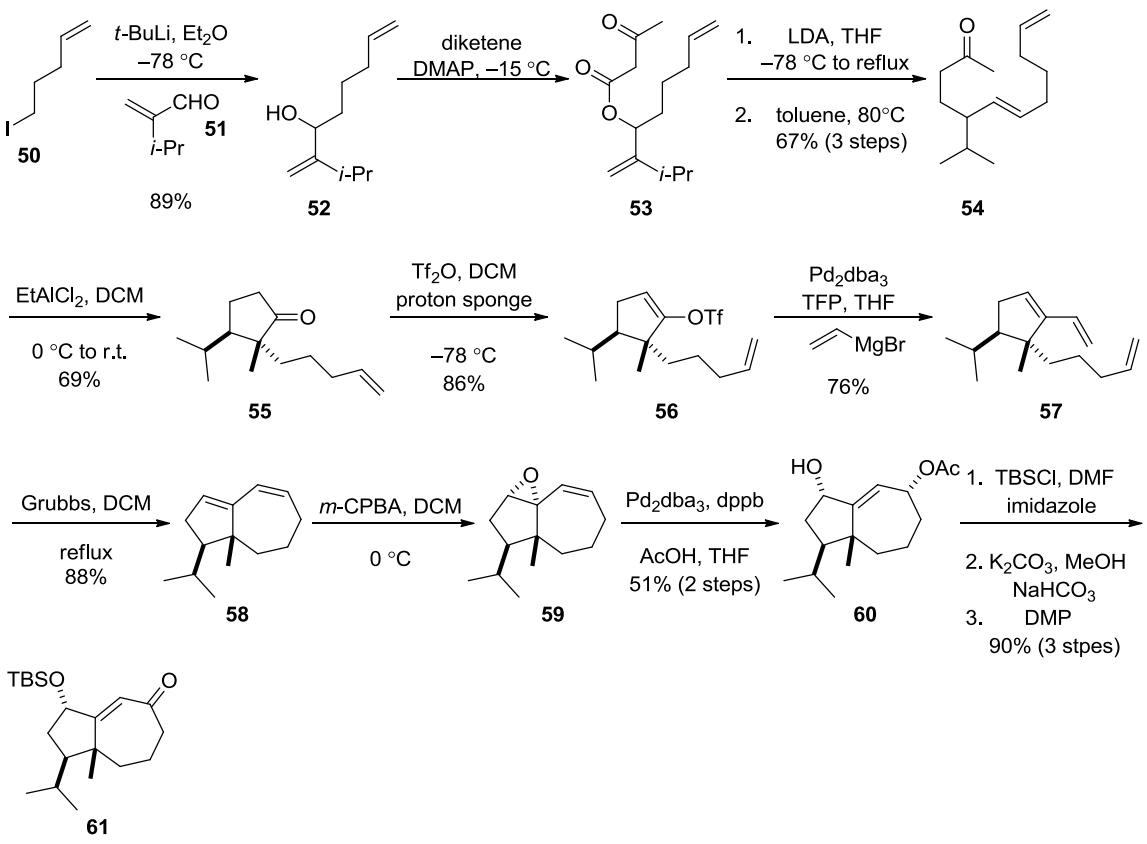
Scheme 5 Danishefsky's asymmetric approach to guanacastepene A

asymmetric conjugate addition of the cuprate, derived from isopropenyllithium, in the presence of (*S*)-2-methoxymethylpyrrolidine generated cyclopentanone **43** in 96% yield and 90% *ee*. Conjugate addition of the silyl enol ether of **43**, formed in 90% yield by treatment with TBSOTf and triethylamine, to methyl vinlyl ketone (MVK) furnished diketone **44** in 90% yield.

Hydrogenation of the terminal olefin to give **45** followed by intramolecular aldol/dehydration proceeded in 92 and 98% yields, respectively to provide cyclic enone **46**. Cyclopropanation of the silyl enol ether derived from **46** gave silyl ether **47**. Treatment with iron(III) chloride provided the ring expanded 7-membered β-chloroketone (not shown), which underwent elimination of the chloride with sodium acetate to provide cyclic dienone **48** in 40% yield over four steps. Hydrogenation of the less hindered double bond with Wilkinson's catalyst gave 83% of intermediate **49**, completing the asymmetric formal synthesis.

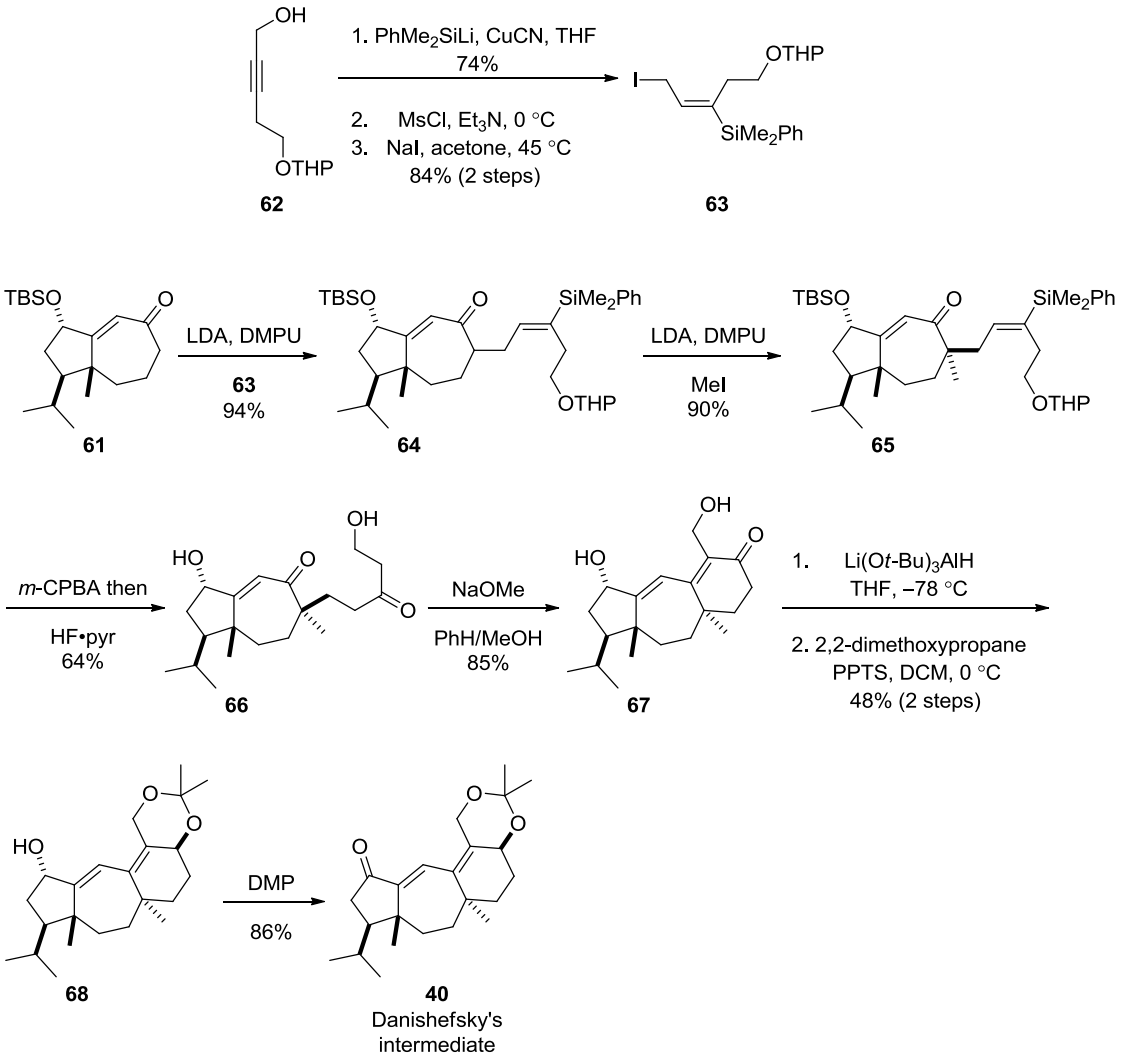
In 2003 Barry Snider reported a formal synthesis of guanacastepene based on Danishefsky's tricyclic intermediate **40**.[12] Snider's synthesis of the hydroazulene core is outlined in Scheme 6. Addition of the alkyllithium reagent derived from lithium-halogen exchange on iodide **50** to aldehyde **51** provided alcohol **52** in 89% yield. Acylation of the resultant alcohol with diketene provided β-ketoester **53**. The Carroll–Claisen rearrangement then provided ketone **54** in 67% yield from **52**. Treatment of **54** with ethylaluminum dichloride promoted an intramolecular Prins reaction followed by a [1,2] methyl shift to provide the highly substituted cyclopentanone **55** in 69% yield.[13] Enol triflate formation (**56**, 86% yield) followed by Kumada coupling with vinyl magnesium bromide gave alkene **57** in 76% yield. Ring closing metathesis occurred smoothly providing diene **58** (88% yield), which was chemoselectively epoxidized with *m*-CPBA yielding epoxide **59**. 1,4-addition to the epoxide with acetic acid gave way to alcohol **60** in 51% yield from diene **58**. Protection of the alcohol as the TBS ether, acetate deprotection and DMP oxidation provided cyclic enone **61** in 90% yield over 3 steps.

Conversion of the in tact hydroazulene **61** into Danishefsky's intermediate **40** is outlined in Scheme 7. Propargyl alcohol **62** was converted to iodide **63** in three steps involving silyl-



Scheme 6 Snider's synthesis of the hydroazulene core

cupration of the alkyne with a dimethylphenylsilyl copper cyanide reagent in 74% yield followed by mesylation of the alcohol and displacement of the mesylate with iodide, which proceeded in 84% yield over two steps. Alkylation of the lithium enolate derived from hydroazulene **60** with iodide **63** yielded 94% of the alkylation product **64**. A second enolate alkylation with methyl iodide provided the fully substituted enone **65** in 90% yield. Oxidation of the vinyl silane accompanied by cleavage of both the TBS ether and THP ether gave ketone **66** in 64% yield. An intramoleular aldol condensation with sodium methoxide provided tricycle **67** in 85% yield. Diastereoselective reduction of the ketone in **67** with lithium (tri-*tert*-butoxy)aluminum hydride and protection of the resulatant 1,3-bis allylic alcohol via condensation with

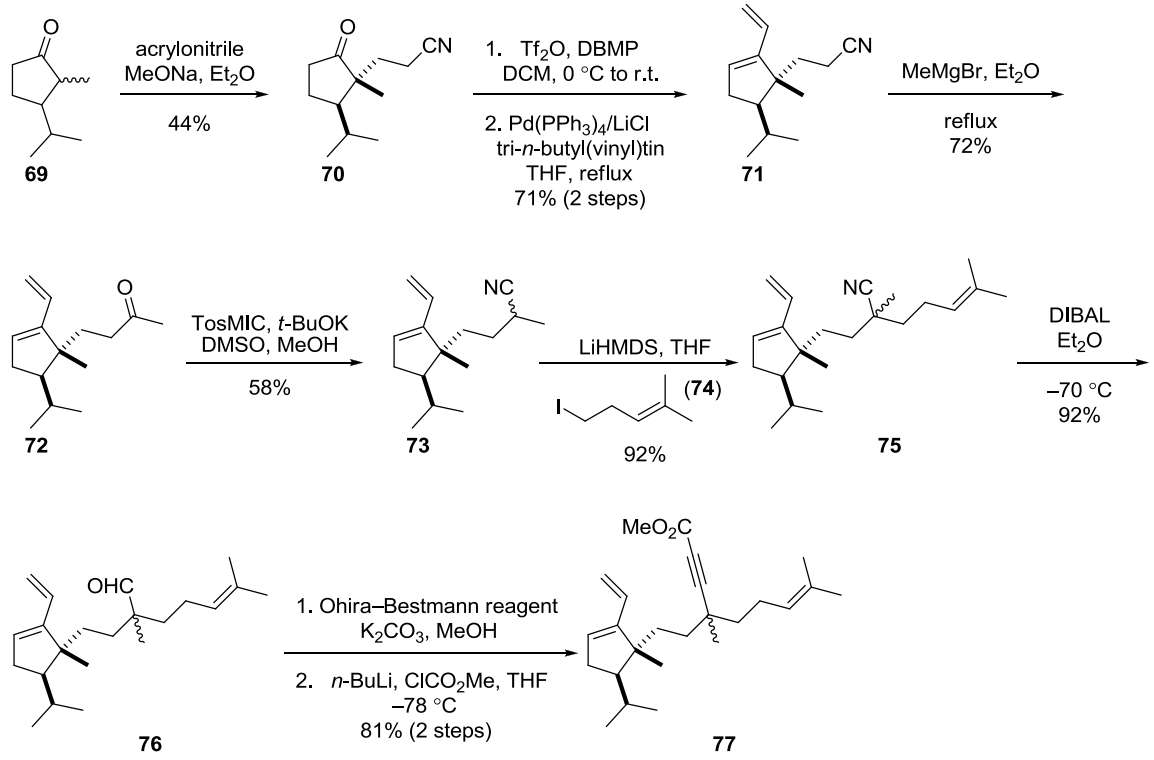


Scheme 7 Completion of Snider's formal synthesis of guanacastepene A

2,2-dimethoxypropane provided acetal **68** in 48% over two steps. Oxidation of the secondary alcohol with DMP resulted in the formation of the Danishefsky intermediate **40**, completing a formal synthesis of guanacastepene A.

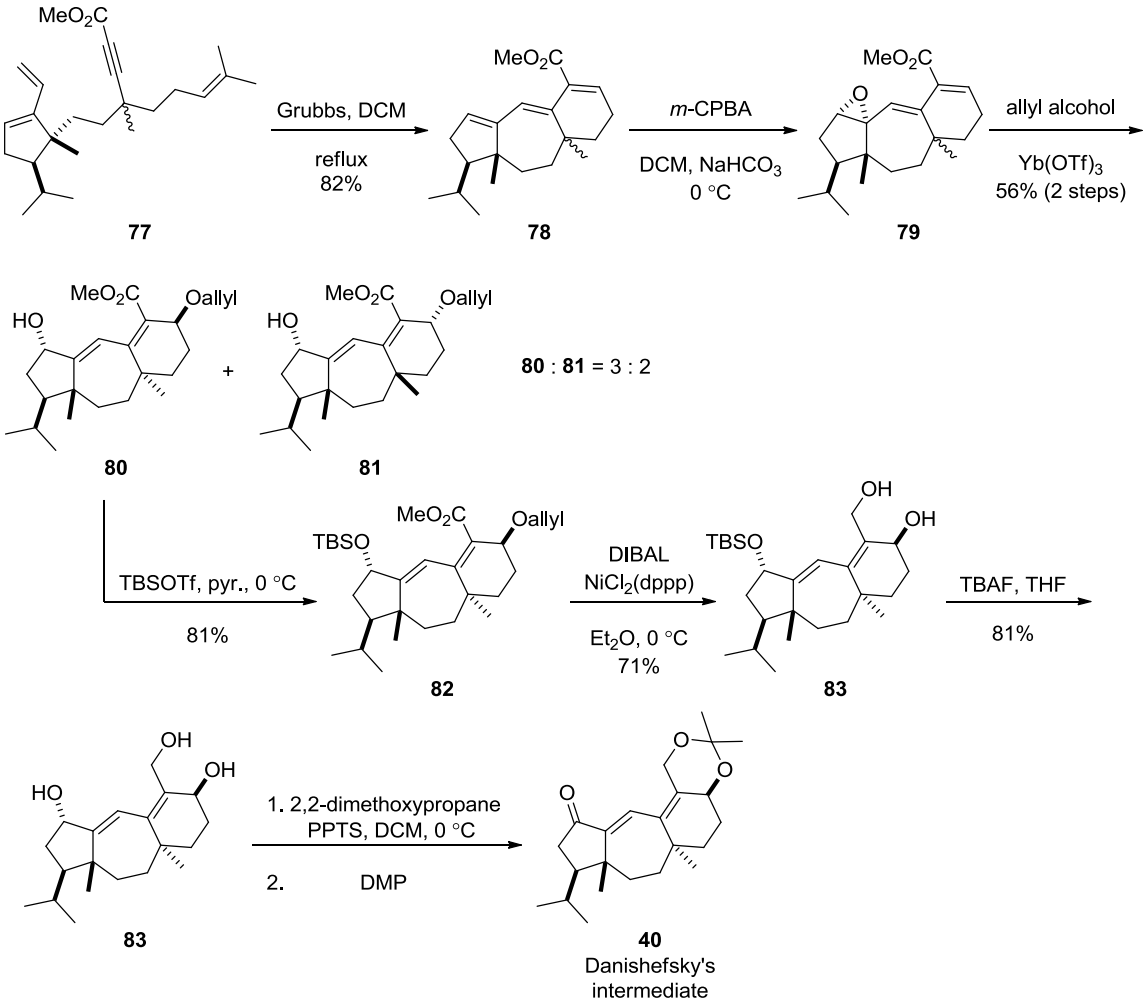
In 2004, Hanna published a tandem ring-closing-metathesis (RCM) strategy toward the 5–7–6 fused tricyclic core of the guanacastepenes that culminated in the formal synthesis of guanacastepene A.[14] This strategy, like Snider's discussed above, intercepts Danishefsky's late

stage intermediate **40**. The synthesis of the key tandem RCM substrate is outlined in Scheme 8. Starting from substituted cyclopentanone **69**, diastereoselective enolate addition to acrylonitrile proceeded in 44% yield to give **70**. Vinyl triflate formation and cross coupling with tributylvinyl tin led to diene **71** in 71% yield over two steps. Addition of methylmagnesium bromide to the nitrile functional group of **71** resulted in the formation of keton **72** in 72% yield.



Scheme 8 Synthesis of Hanna's key tandem ring-closing-metathesis substrate **77**

Subsequent treatment with toluenesulfonylmethyl isocyanide (TosMIC) and potassium *tert*-butoxide in DMSO/MeOH provided the homologated nitrile **73** in 58% yield. Alkylation α to the nitrile with iodide **74** followed by DIBAL reduction of nitrile **75** provided aldehyde **76** in 92% yield for both steps, respectively. Homologation to the alkyne using the Ohira–Bestmann



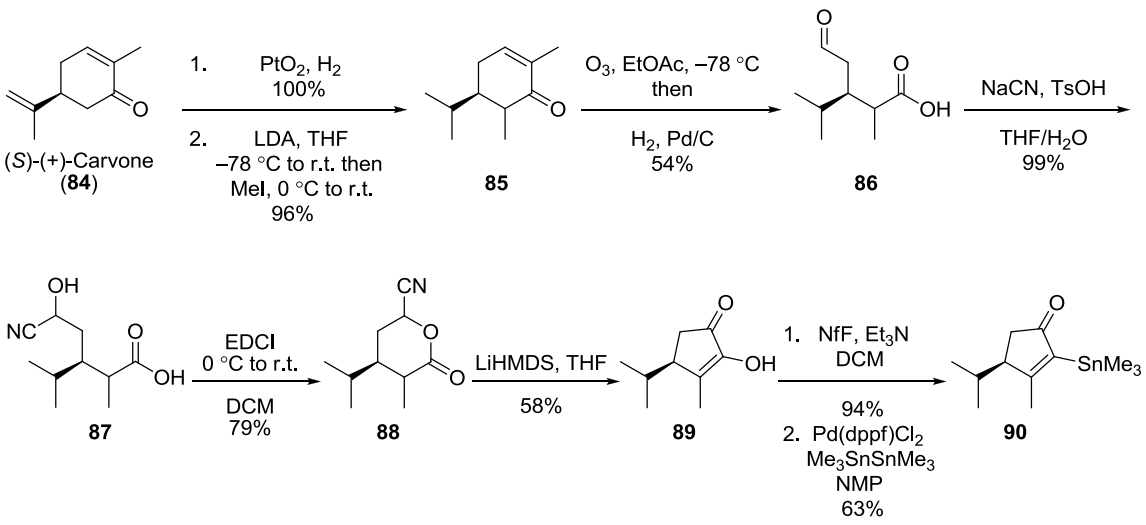
Scheme 9. Tandem RCM reaction and completion of the formal synthesis

reagent followed lithium acetylide addition to methyl chloroformate provided tandem RCM precursor **77** in 81% yield.

Conversion of intermediate **77** into the Danishefsky intermediate **40** is illustrated in Scheme 9. Treatment of **77** with the Grubbs catalyst in refluxing dichloromethane resulted in the formation of tricycle **78** in 82% yield as a 1:1 mixture of C8 epimers. Epoxidation of the cyclopentene double bond of **78** followed by nucleophilic conjugate addition of allyl alcohol to

open the epoxide provided the necessary C14 and C15 oxygenation, respectively, providing a 3:2 mixture of the diastereomeric tricycles **80** and **81** in 56% combined yield over two steps. Protection of the secondary alcohol in tricycle **80**, with the desired stereochemical arrangement about the tricycle, as the TBS ether **82** procceded in 81% yield. Subsequent reduction of the ester functional group and concomitant allyl ether cleavage using DIBAL and Dichloro[1,3-bis(diphenylphosphino)propane]nickel of the ester functional group to provide diol **83** in 71% yield. Cleavage of the silyl ether with tetra-*n*-butylammonium fluoride provided triol **84** in 81% yield which could be converted to the known Danishefsky intermediate **40** in two additional transformations involving 1,3-diol protection and subsequent alcohol oxidation (yields not provided).

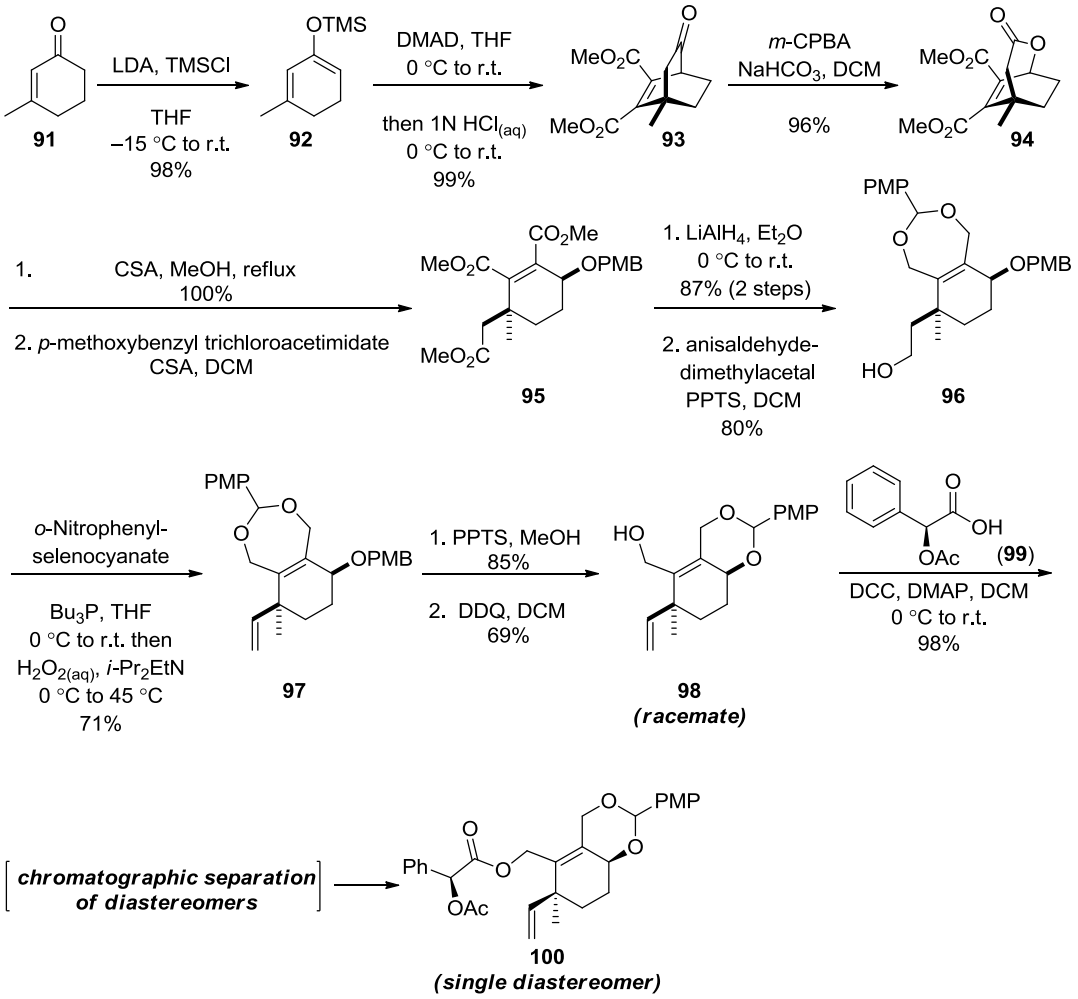
The group of Erik Sorensen published an article in 2006 describing an asymmetric formal synthesis of guanacastepene A.[15] Starting from readily available (*S*)-(+)-Carvone (**84**) as a chiral starting material, the functionalized five membered ring **89** was prepared as a single enantiomer (Scheme 10). Reduction of the terminal olefin of carvone followed by enolate alkylation proceeded in 100 and 96% yields, respectively to provide cyclohexenone **85**. Reductive ozololysis yielded acyclic intermediate **86** in 54% yield. Formation of cyanohydrin **87** (99% yield) followed by lactonization with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) provided compound **88** in 79% yield. Subsequent treatment with lithium hexamethyldisilazide (LiHMDS) led to the formation of cyclopentane dione **89** (shown as the enol tautomer) in 58% yield. Transformation to vinyl stannane **90** was accomplished by conversion to the nonaflate followed by coupling with hexamethylditin in 94 and 63% yields respectively. Synthesis of optically active six-membered ring portion of the molecule was achieved by classical resolution (Scheme 11). Cyclohexenone **91** was converted to the dienol ether **92** in 98% yield, which



Scheme 10 Synthesis of the guanacastepene 5-membered ring starting from carvone

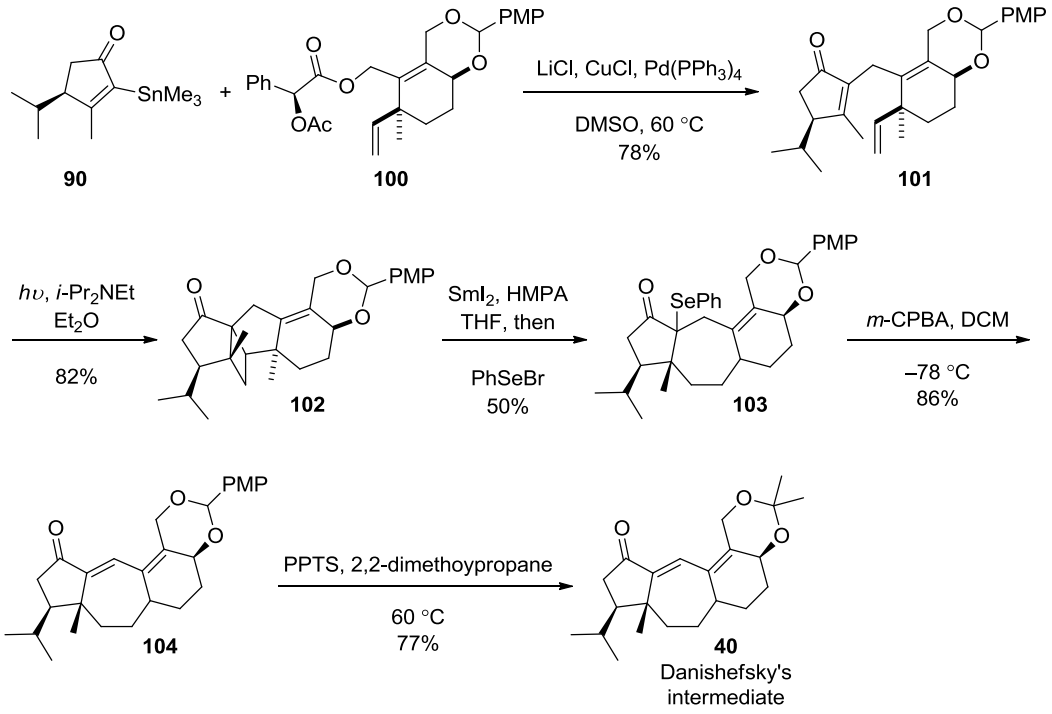
underwent smooth Diels–Alder cyclization with dimethylacetylene dicarboxylate (DMAD) in 99% to yield cycloadduct **93**. Baeyer–Villiger oidation with *m*-CPBA resulted in formation of lactone **94** in 96% yield. Lactone opening (100 % yield) and protection of the resulatant alcohol as the PMB ether provided cyclohexene **95**. LAH reduction of the triester (87% yield over two steps) followed by cyclic acetal formation, in 80% yield, provided alcohol **96**. Alcohol selenation and selenide oxidation resulted in elimination to provide olefin **97** in 74% yield. Methanolysis of the acetal and reaction with DDQ provided racemic alcohol **98** in 85 and 69% yields, respectively. Then necessary resolution was carried out by ester formation with (*S*)-(+)-mandelic acid (**99**) in 98% yield. The two stereoisomers were chromatographically separated to provide functionalized cyclohexene **100** as a single diastereomer.

The union of intermediates **90** and **100** and the conversion of the coupling adduct into Danishefsky's intermediate **40** is outlined in Scheme 12. Coupling of the two key substrates by way of a π-allyl Stille coupling proceeded in 78% yield to provide the tethered bicycle **101**.



Scheme 11 Sorensen's synthesis of guanacastepene A's six membered ring portion as a single enantiomer by classical resolution methods

Construction of the central seven-membered ring with concomitant forging of the second all carbon quaternary center was achieved using a photochemical [2 + 2] cycloaddition between the pendant olefin and the tetrasubstituted cyclopentene double bond to provide tetracycle **102** in 82% yield. Reductive fragmentation of the cyclobutane ring with samarium diiodide followed by trapping of the resultant samarium enolate with phenylselenium bromide resulted in tricycle **103** in 50% yield. Oxidation with *m*-CPBA and facile elimination of the resultant selenoxide



Scheme 12 Completion of Sorensen's guanacastepene A formal synthesis

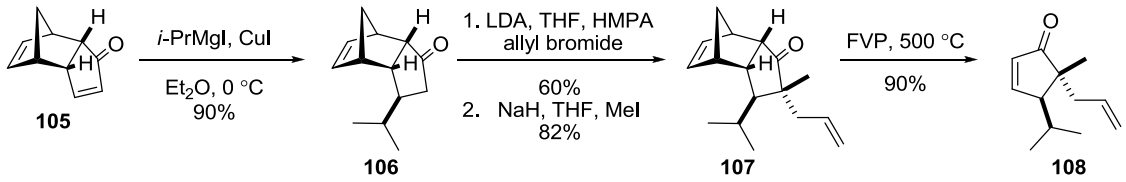
yielded 77% of enone **104** which was converted to Danishefsky's intermediate **40** by acetal exchange with 2,2-dimethoxypropane.

Section 1.6 Successful Strategies Employed in the Syntheses of Other Guanacastepenes

In 2005 Mehta reported the total synthesis of guanacastepene C based on the well established propensity of readily available *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene-5-one (**105**) to react on the *exo* face (Scheme 13).[16,17] This Diels–Alder adduct between cyclopentadiene and cyclopentadienone was used to control the stereochemical outcome during functionalization of the 5-membered ring. Conjugate addition of isopropyl Grignard gave addition product **106** in 90% yield. Sequential enolate alkylation with allyl bromide then methyl iodide furnished highly substituted bicycle **107** in 60 and 82% yields respectively. Flash vacuum pyrolysis at 500

degrees celcius facilitated a retro Diels–Alder reaction liberating cyclopentadiene and cyclopentenone **108** in 90% yield.

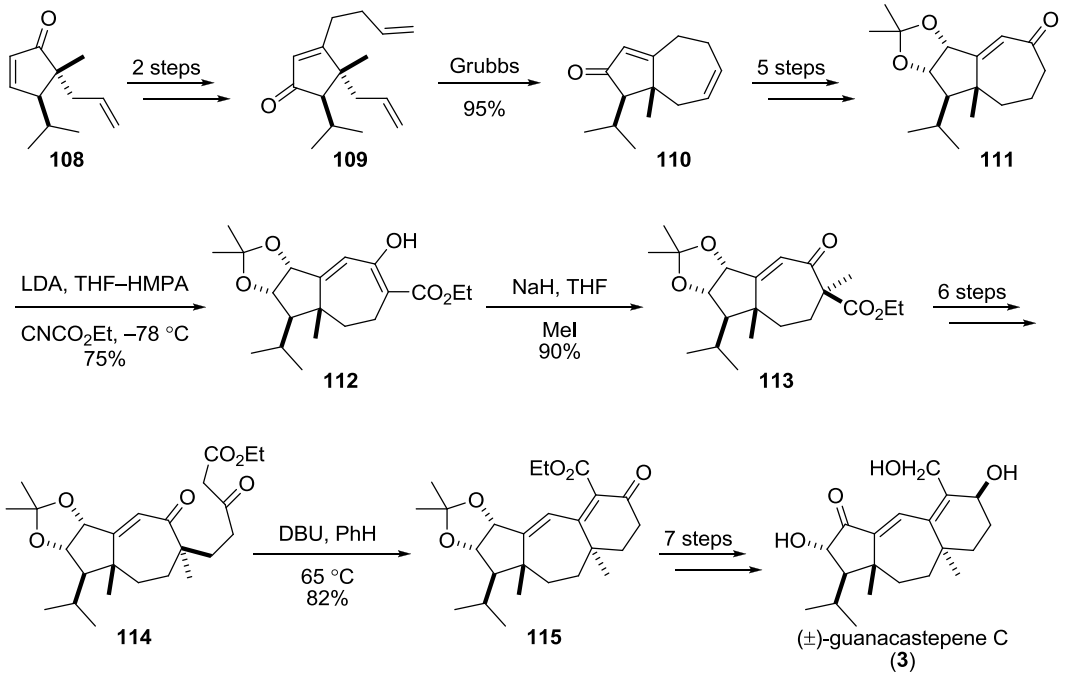
The route used to convert cyclopentene **108** to guanacastepene C is summarized in Scheme 14. Two step conversion to triene **109** set the stage for formation of the hydroazulene



Scheme 13 Mehta's use of cyclopentadiene as an auxiliary to control the stereochemistry during 5-membered ring functionalization

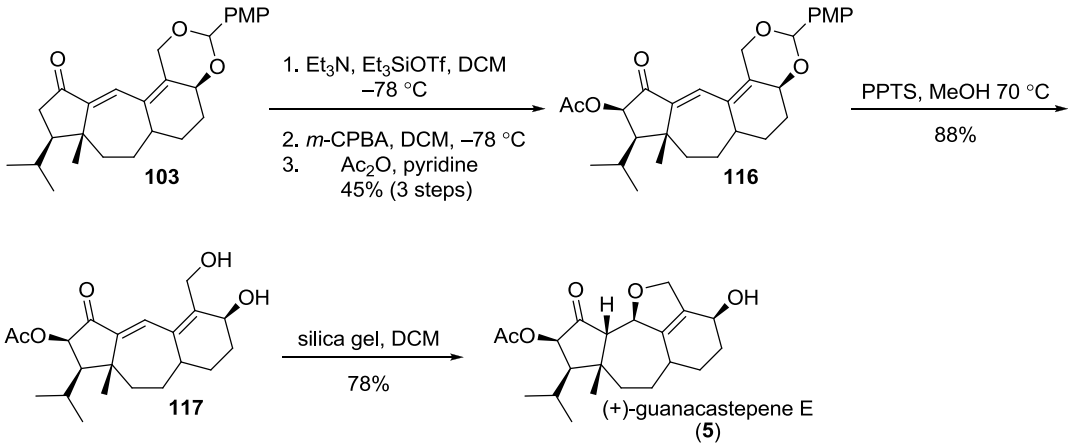
core **110** in 95% via ring-closing-metathesis with Grubbs' catalyst. Conversion to the cyclic enone **111** in 5 steps allowed for the stereoselective installation of the second all carbon quaternary center. Enolate trapping with ethyl cyanoformate, forming β-ketoester **112** in 75% yield (shown in the enol form), followed by alkylation with methyl iodide furnished functionalized hydroazulene **113** in 90% yield. Conversion to β-ketoester **114** in six steps allowed for an intramolecular Knoevenagel condensation to forge the six membered ring of tricycle **115** in 82% yield. This intermediate was carried forward in a seven step sequence to provide guanacastepene C (**3**).

During the course of Sorensen's previously described studies on the formal synthesis of guanacastepene A, the first route to guanacastepene E (**5**) was developed (Scheme 15).[15b] Starting from tricycle **113**, used in Sorensen's formal synthesis of guanacastepene A, the Rubottom oxidation and acetylation of the resultant alcochol provided the fully functionalized five- membered ring containing tricycle **116** in 45% overall yield. Cleavage of the cyclic acetal



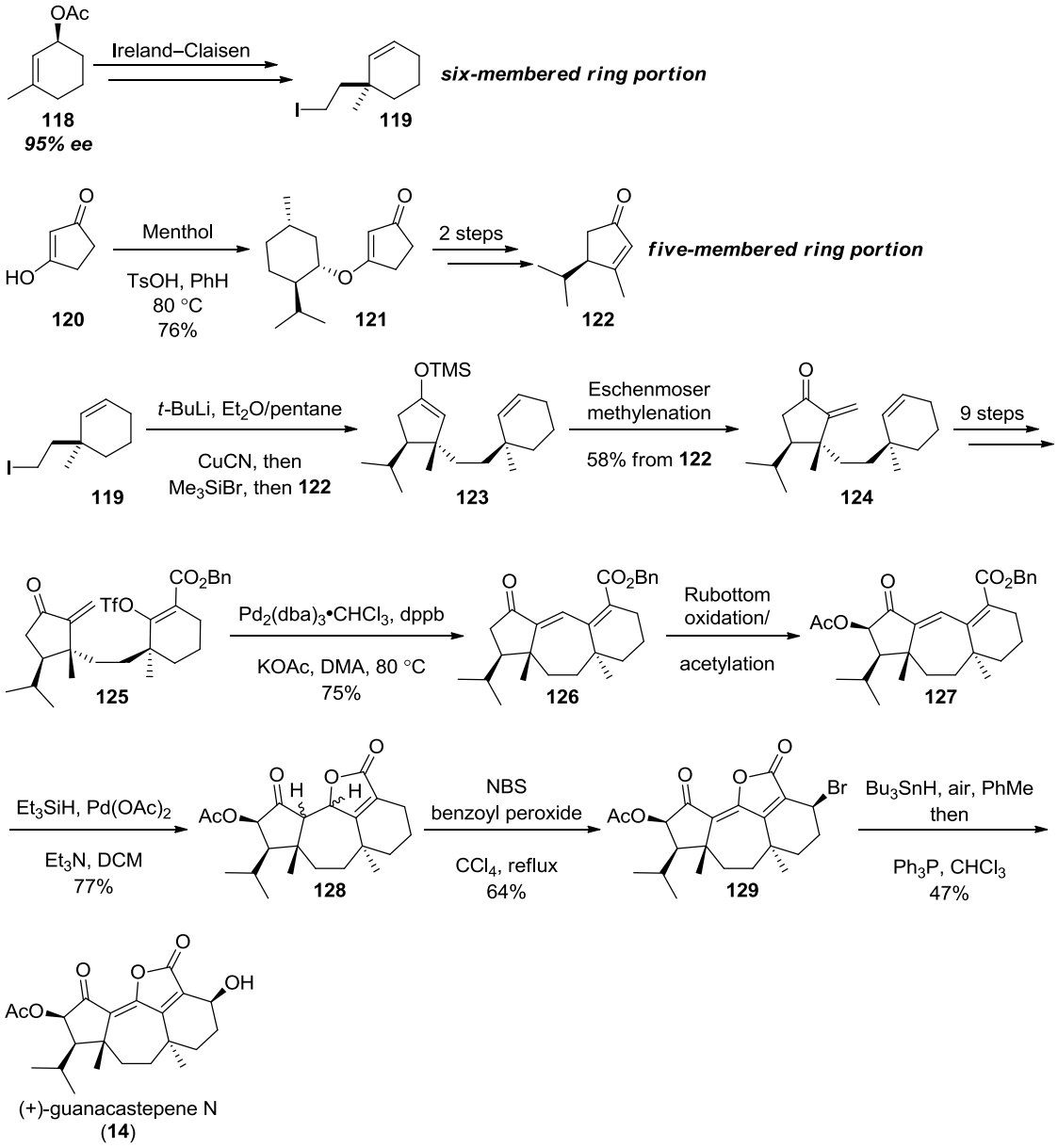
Scheme 14 Completion of Mehta's synthesis of (±)-guanacastepene C

proceeded in 88% to provide diol **117** which underwent intramolecular oxy-Michael addition to yield (+)-guanacastepene E in 78% yield.



Scheme 15 Sorensen's synthesis of (+)-guanacastepene E

In 2006 the group of Larry Overman reported an asymmetric route to (+)-guanacastepene N (**14**) involving the use of a rarely observed 7-*endo* Heck cyclization to form the central ring of the tricyclic core (Scheme 16).[18] The synthesis of the enantioenriched six-membered ring portion of the molecule began with an enzymatic resolution of racemic 3-methylcyclohex-2-enyl

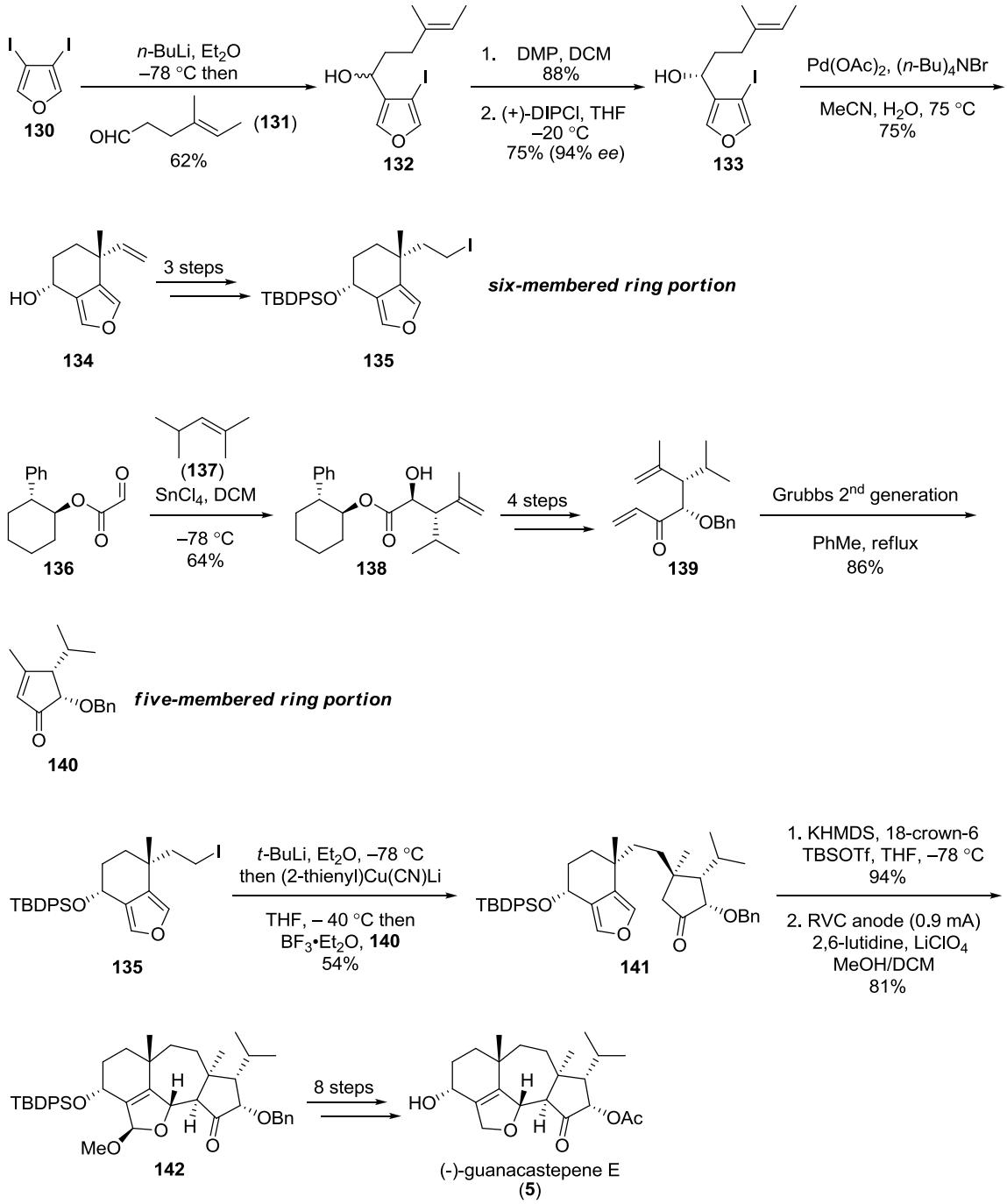


Scheme 16 Overman's asymmetric synthesis of (+)-guanacastepene N

acetate **118** which provided enantioenriched material in 95% *ee*. This material was converted to iodide **119** in four steps, the most critical step being an Ireland–Claisen rearrangement that forged the C8 quaternary center. The five-membered ring portion **122** was prepared using a Stork–Danheiser alkylation of the menthol enol ether of 1,3-cyclopentane dione (**121**), derived directly from 1,3-cyclopentanedione **120** and menthol, followed by addition of methyllithium.[19] These two key fragment were unified by conjugate addition of the organocuprate reagent derived from **119** to the enone unit of cyclopentene **122** and trapping of the enolate as the TMS enol ether **123** which was then subjected to an Eschenmoser methylenation to provide exocyclic enone **124** in 58% yield from **122**. Nine additional steps converted **124** into the Heck cyclization precursor **125**. Intramolecular 7-*endo* Heck cyclization proceeded at 80 °C in the presence of palladium dibenzylideneacetone chloroform adduct to provide tricycle **126** in 75% yield. The three step protocol for α-acetoxylation devised by Danishefsky utilizing a stereoselective Rubottom oxidation yielded the fully functionalized five-membered ring containing tricycle **127**. Treatment with triethylsilane and palladium acetate served to cleave the benzyl ester and facilitate acyloxy-Michael addition leading to tetracycle **128** as a mixture of all four possible diastereomers. Allylic bromination with NBS and benzoyl peroxide brominated C5 while reinstalling the necessary C1-C2 double bond (**129**, 64% yield). The authors suggest this may arise through allylic bromination at C2 followed by elimination. Air oxidation of the allylic radical derived from **129** and reduction of the allylic peroxide with triphenylphosphine provided (+)-guanacastepene N (**14**) in 47% yield.

Also in 2006, the Trauner group reported the asymmetric total synthesis of the unnatural enantiomer of guanacastepene E (**5**) utilizing an electrochemical oxidation reaction to form the central seven-membered ring (Scheme 17).[20] The asymmetric synthesis of the six-membered

ring portion **135** commenced with addition of monolithiated furan **130** to aldehyde **131**, yielding 62% of the secondary alcohol **132**. Oxidation with DMP (88% yield) followd by asymmetric

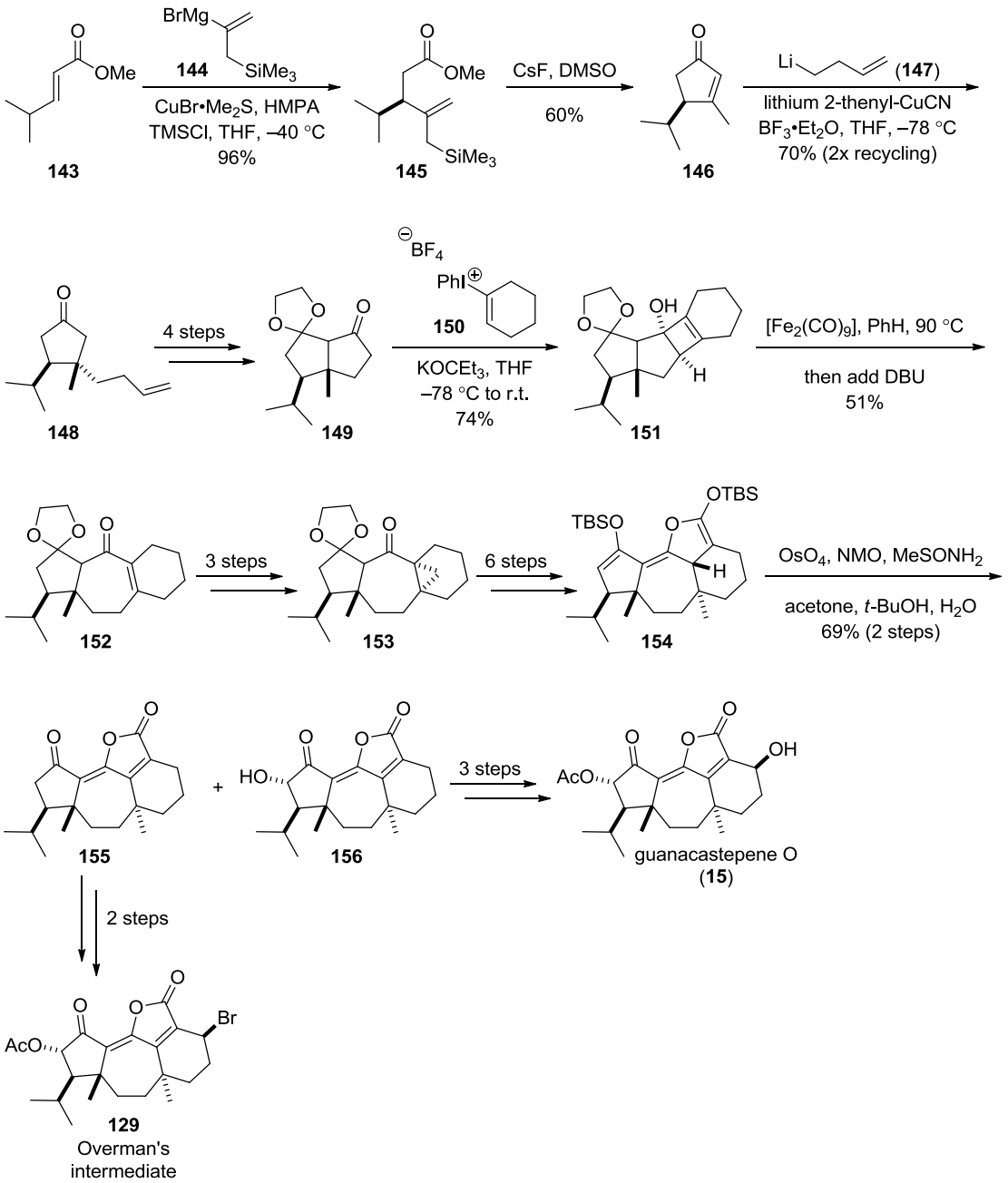


Scheme 17 Trauner's synthesis of (–)-guanacastepene E

ketone reduction using (+)-*β*-chlorodiisopinocampheylborane provided chiral secondary alcohol **133** in 75% yield in 95% *ee*. An intramolecular Heck reaction forged the six-membered ring of **134** in 75% yield while forming one of the all carbon quaternary centers. Intermediate **134** was converted to iodide **135** in three additional steps to provide the six-membered ring portion of the molecule. The five-membered ring portion was derived from known chiral glyoxalate **136**. A carbonyl ene reaction between **136** and alkene **137** provided alcohol **138** in 64% yield, which was converted to diene **139** in four additional steps. Ring-closing-metathesis promoted by Grubb's second generation ruthenium catalyst in refluxing toluene facilitated formation of the necessary five-membered ring **140** in 86% yield. Conjugate addition of the organocopper reagent derived from **135** to the enone unit of **140** brought the two pieces together and constructed the second all carbon quaternary center **141** in 54% yield. Silyl enol ether formation (94% yield) followed by electrochemical oxidation of this functional group followed by addition of the furan moiety and trapping with methanol forged the seven-membered ring via C1–C2 bond formation **142** in 81% yield. The fully functionalized tetracycle **137** formed in this process was converted to (–)-guanacastepene E (**5**), the unnatural enantiomer, in eight additional steps.

More recently, in 2011, Erick Carreira reported the formal synthesis of guanacastepene N (**14**) and the total synthesis of guanacastepene O (**15**) (Scheme 18).[21] Copper catalyzed conjugate addition of Grignard reagent **144** to enoate **143** provided ester **145** in 96% yield. Intramolecular allylation accompanied by a subsequent olefin isomerization was instigated upon treatment with cesium fluoride to generate cyclopentenone **146** in 60% yield. The first all carbon quaternary center was installed using a Lipshutz higher order cyanocuprate derived from organolithium reagent **147** to provide cyclopentanone **148** in 70% yield after two rounds of recycling unreacted starting material.[22] An additional four transformations provided the 5,5-

fused bicycle **149**. The enolate of **149** underwent addition to cyclohexyne, derived *in-situ* from iodonium salt **150** to provide cyclobutanol **151** in 74% yield. Iron-mediated ring opening of the

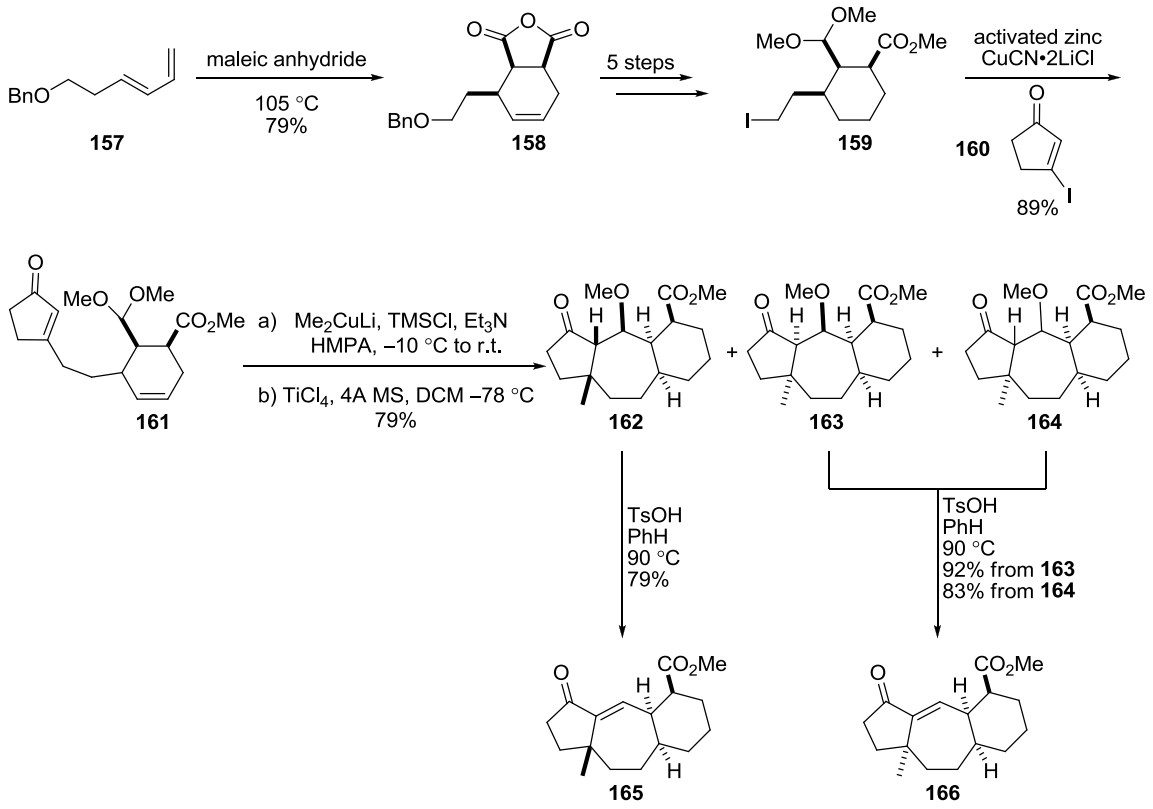


Scheme 18 Carreira's formal synthesis of guanacastepene N and total synthesis of guanacastepene O

cyclobutane ring afforded tricycle **152** in 51% yield. Installation of the second all carbon quaternary center was achieved in an additional three steps involving ketone reduction, cyclopropanation, and reoxidation back to the ketone to provide cyclopropane **153** which in six more steps was transformed tetracycle **154**. Oxidation of this intermediate led to the formation of compounds **155** and **156** in 69% overall yield. The less highly oxidized product **155** was converted to Overman's known intermediate **129** utilized in the synthesis of guanacastepene N over two additional steps. The hydroxylated counterpart **156** was carried forward in three operations to guanacastepene O (**15**).

Section 1.7 Kwon's Previous Studies On Guanacastepene A Total Synthesis

The laboratory of Ohyun Kwon published a report on the synthesis of a guanacastepene model system that utilized an intermolecular Diels–Alder reaction to construct the six-membered ring portion of the molecule, an intermolecular conjugate addition to couple the five and six-membered rings, and an intramolecular Mukaiyama aldol reaction to form the central seven membered ring (Scheme 19).[23] Diene **157**, lacking the C8 methyl substituent and C5 oxygenation underwent a thermal Diels–Alder reaction with maleic anhydride to provide the *endo* cycloadduct **158** in 79% yield. A five step sequence providing iodide **159** set the stage for organocuprate coupling with β-iodocyclpentenone (**160**) to give tethered bicycle **161** in 89% yield. 1,4-Addition of the methyl Gilman regent and trapping of the enolate as the silyl enol ether allowed for seven membered ring formation to proceed via a subsequent Mukaiyama aldol reaction mediated by titanium(IV) chloride. This two-step sequence provided stereoisomeric tricycles **162**, **163**, and **164** in 79% combined yield, all of which underwent elimination upon heating in the presence of toluenesulfonic acid to give the two diastereomeric tricycles **165** and

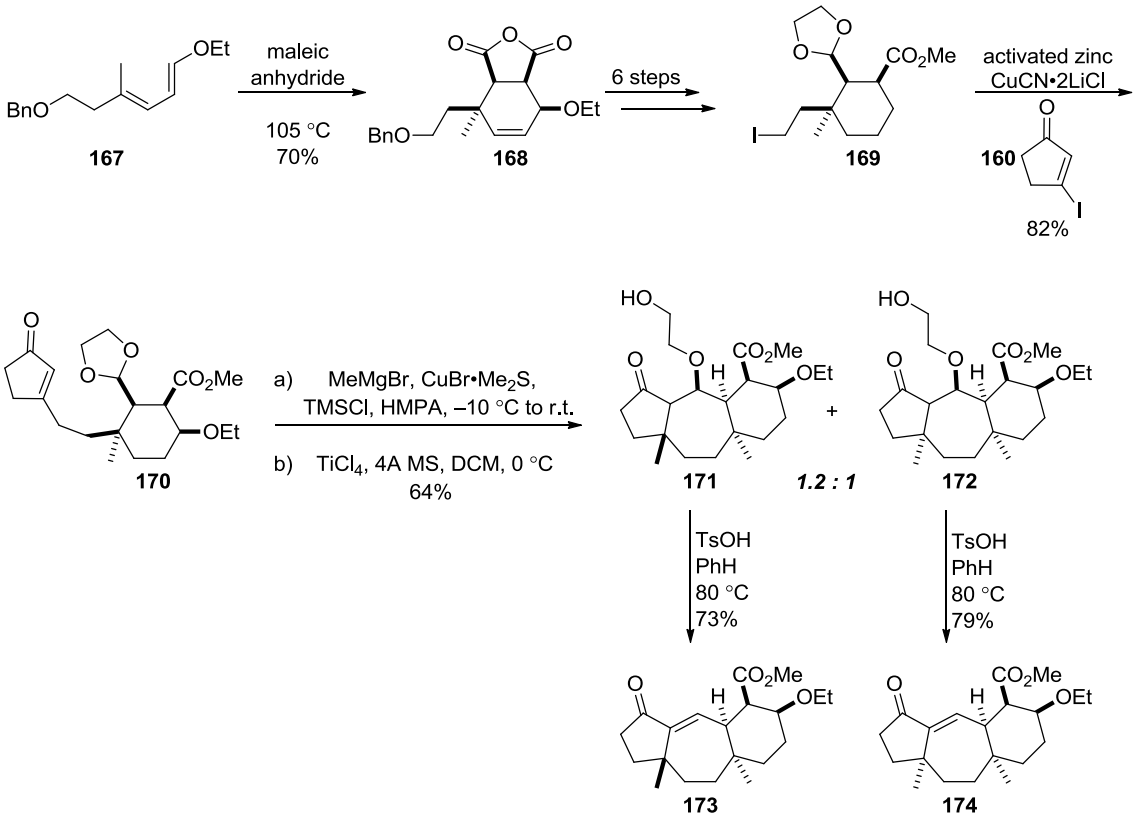


Scheme 19 Kwon's model system exploring the use of key Diels–Alder and Mukaiyama aldol reactions

166 in 79, 92, and 83% yields, respectively.

Implementation of this strategy utilizing a fully functionalized six-membered ring was disclosed shortly thereafter (Scheme 20).[24] Diels–Alder reaction between the highly substituted diene **167** and maleic anhydride proceeded with exclusive *endo* selectivity providing the cycloadduct **168** in 70% yield. Conversion to iodide **169** was accomplished in six additional steps, at which point organocuprate coupling with β-iodocyclopentenone (**160**) was achieved to provide tethered bicycle **170** in 82% yield. Application of the conjugate addition/Mukaiyama aldol strategy studied in the model system provided tricycles **171** and **172** in 64% yield as a 1.2:1 mixture of diastereomers. Elimination of the hydroxyethoxy groups of these intermediates gave

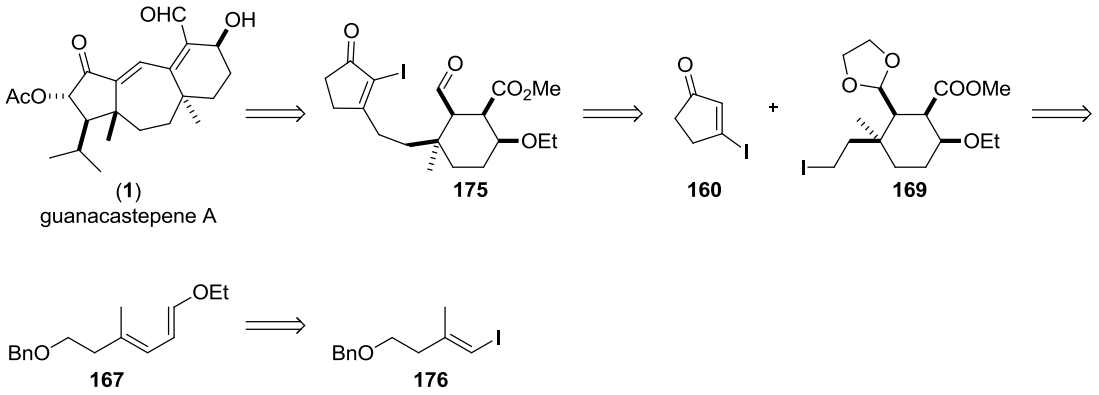
tricycles **173** and **174** in 73 and 79% yields, respectively. While this strategy was found to be effective for formation of the functionalized tricyclic core of guanacastepene A in a remarkably concise manner, the lack of stereoselectivity during the course of methyl group conjugate addition was undesirable. It was anticipated that formation of the seven-membered ring prior to



Scheme 20 Kwon's fully functionalized system

installation of the C11 methyl group would provide a more rigid platform to which methyl addition could occur more stereoselectively. With this in mind, a modified synthetic strategy was planned that would allow for seven-membered ring formation without prior installation of the C11 methyl group. This strategy is represented retrosynthetically in Scheme 21. The guanacastepene A (**1**) tricyclic architecture was to be completed by way of an intramolecular

addition of an organometallic derived from the iodide of intermediated **175** to the pendant aldehyde. This intermediate could be accessed following the same route established in the conjugate addition/Mukaiyama aldol approach involving organocuprate coupling of iodides **160** and **169**, the latter of which being accessible via Diels–Alder cyclization between highly functionalized diene **167**, prepared from vinyl iodide **176**, and maleic anhydride.



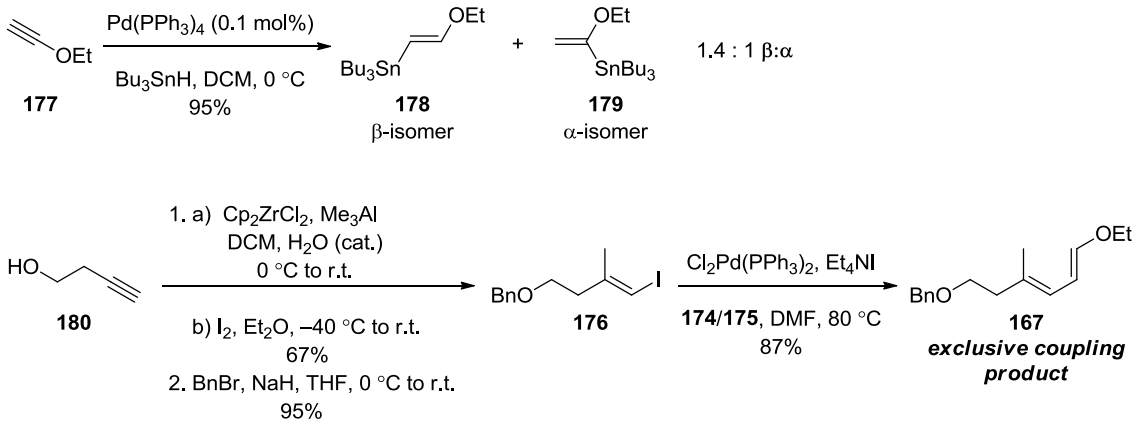
Scheme 21. Slightly modified retrosynthetic analysis based of the use of intermediates **160** and **169**

Section 1.8 Work On the Intramolecular Organometallic Addition Strategy

The synthetic studies commenced with the preparation of diene **167** for which two routes were developed. The first, more concise route, is outlined in Scheme 22. Commercially available ethoxyacetylene **177** was efficiently hydrostannylated under the optimized conditions utilizing 0.1 mol% (tetrakis)triphenylphosphine palladium(0) and tributyltin hydride to provide 95% isolated yield as an approxamitely 1.5:1 mixture of vinyl stannanes **178** and **179**.[25] The two stannanes could be utilized without separation as only the desired stannane **178** uderwent the desired Stille coupling (*vide-infra*). The iodide coupling partner **176** was prepared in two steps from 3-butyn-1-ol (**180**) involving a Negishi carboalumination of the alkyne, and subsequent

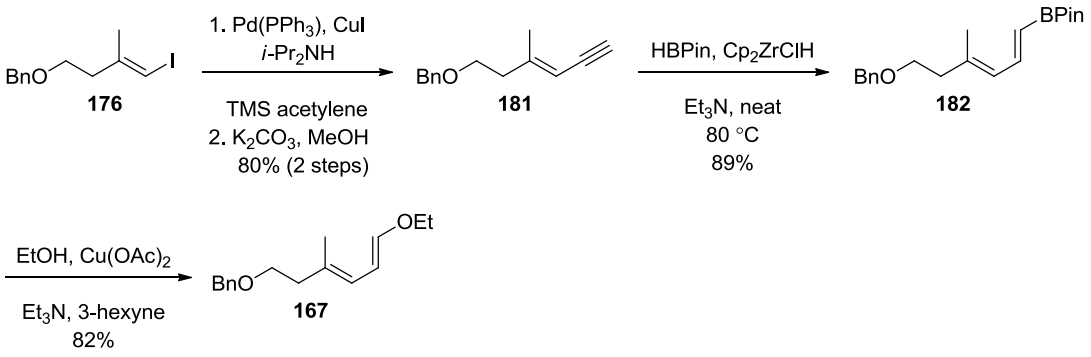
trapping of the vinyl aluminum species with iodine, followed by protection of the primary alcohol as the benzyl ether.[26] The performance of the carboalumination, especially on a larger scale, proved difficult in terms of reproducibility and the cleanliness of the isolated material. Known modifications to the original procedure were studied, including those reported by Wipf and Lipshutz.[27,28] It was observed that Wipf's modification involving the addition of a catalytic amount of water provided the most consistent results, with good yields even on a large scale. Under the optimized conditions, the carboalumination and benzylation proceeded in 67 and 95% yields, respectively. Stille coupling between stannane **178** and iodide **176** could be carried out directly with the isolated mixture of both stannane regioisomers, resulting in cross coupling exclusively with the less hindered β-isomer **178**.[29] While this route was highly step economical resulting in a concise synthesis of diene **167**, a few attributes rendered it cumbersome to carry out on scales necessary to support the rest of the synthetic effort. Ethoxyacetylene (**177**) is an expensive starting material of which over 40% is discarded as the undesirable α-hydrostannylation isomer **179**. Upon completion of the coupling reaction a large excess of the α-isomer remains in the crude reaction mixture. With diene **167** unstable towards typical silica gel chromatography it becomes difficult to isolate material of high purity.

In order to circumvent the issues associated with the unproductive use of ethoxyacetylene in the formation of the undesired stannane regioisomer **179** and the difficulty with separating diene **167** from the large quantities of unreacted vinyl stannane, an alternate route was investigated (Scheme 23). Sonagashira coupling of the previously described iodide **176** with TMS acetylene and subsequent cleavage of the silyl group provided enyne **181** in 80% yield over two steps. Schwartz's reagent facilitated hydroboration with pinacolborane, forming the vinylboronic ester **182** in 89% yield, followed by copper-promoted coupling with ethanol yielded



Scheme 22 Stille coupling route to the required alkoxydiene

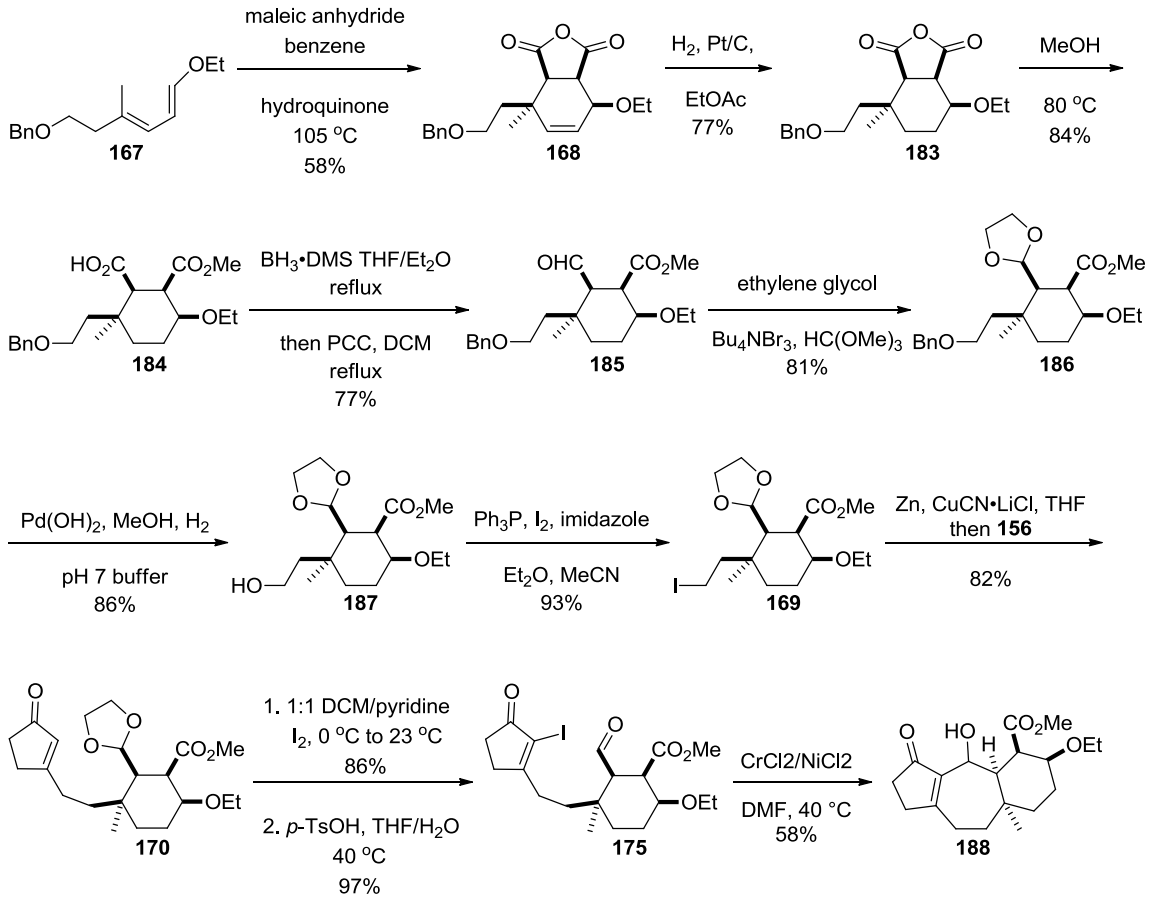
82% of the requisite diene **167**.[30] The crude reaction mixture was purified via aqueous workup which after a quick passage through a column of basic alumina provided high purity samples of alkoxydiene. This procedure could be carried out on multigram scale while maintaining high purity of the isolated diene.



Scheme 23 Alternate route to the necessary alkoxydiene

With multigram quantities of the requisite diene in hand its' Diels–Alder reaction with maleic anhydride was carried out (Scheme 24). Addition of recrystallized maleic anhydride to a

degassed solution of diene **167** in benzene and heating to 105 °C in a pressure tube with a small amount of hydroquinone, as a radical inhibitor, afforded *endo* cycloadduct **168** in 58% yield. Reduction of the double bond with platinum on carbon afforded cyclohexane **183** in 77% yield. Regioselective methanolysis of the anhydride moiety provided carboylic acid **184** in 84% yield,



Scheme 24 Synthesis of the tricyclic core of guanacastepene A

the carboxylic acid of which was chemoselectively reduced to aldehyde **185** in 77% yield.[31] Protection of the aldehyde as the dioxolane **186** followed by hydrogenolytic debenzylation gave alcohol **187** in 81 and 86% yields, respectively. Conversion of the alcohol to the iodide set the

stage for zinc cuprate formation from iodide **169** and coupling with iodide **160** to provide tethered bicycle **170** in 93 and 82% yields, respectively.[32] Conversion to the precursor necessary for seven-membered ring formation, aldehyde **175**, was carried out by α-iodination of the cyclopentenone ring and dioxolane cleavage which proceeded in 86 and 97% yields, respectively. Attempts at addition of the lithiated enone derived from lithium halogen exchange with the iodide of **175** to the aldehyde were not successful. It was discovered that the Nozaki–Hiyama–Kishi coupling protocol using chromium(II) chloride doped with 1% nickel(II) chloride could be used to form the desired tricycle in 58% yield. Although the Nozaki–Hiyama–Kishi coupling protocol was found to be effective, a significant amount of undesired deiodination was found to occur. Extensive optimization studies were carried out in order to identify conditions that would suppress this side reaction. Solvent variation, addition of additives for the ligation of the chromium metal center, catalytic methods, and the addition of various drying agents all failed to provide any improvement in the isolated yield of the tricycle. Under the optimized conditions the desired product was obtained in 58% yield.

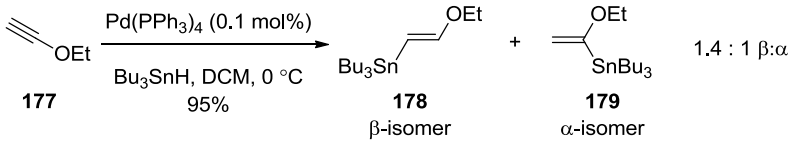
Section 1.9 Conclusions

The tricyclic core of the diterpene antibiotic guanacastepene A has been synthesized. The route utilized an intermolecular Diels–Alder reaction between a highly functionalized alkoxydiene that can be prepared convergently via Stille cross coupling or in a more linear synthesis involving copper-mediated coupling of vinyl boronic esters and alcohols. The five-membered ring portion was appended by preparing a highly functionalized zinc cuprate and coupling it with β-iodocyclopentenone. The central seven membered ring was formed via an intramolecular Nozaki–Hiyama–Kishi coupling reaction.

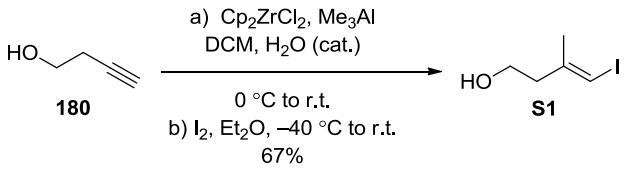
Section 1.10 Materials and Methods

Unless otherwise stated, all reactions were performed in flame-dried glassware fitted with a rubber septum, under an Ar atmosphere, and stirred with a Teflon-coated stirrer bar. All reaction solvents were distilled immediately prior to use [dichloromethane (DCM), acetonitrile (MeCN), benzene (PhH), and toluene (PhMe) were distilled from CaH_2; tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl; methanol (MeOH) was distilled from magnesium methoxide] and transferred with an oven-dried needle and a disposable syringe using standard Schlenk techniques. Thin layer chromatography (TLC) was performed using SiliCycle silica gel 60 F-254–precoated glass-backed plates (thickness: 0.25 mm) and visualized under UV light and through anisaldehyde or permanganate staining. Flash column chromatography was performed using SiliCycle Silica-P silica gel (particle size: 40–63 μm). ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance-500, ARX-400, and ARX-500 MHz spectrometers, with ^{13}C operating frequencies of 125, 100, and 125 MHz respectively. Chemical shifts are reported in ppm (δ) with respect to the residual solvent ($CHCl_3$; δ = 7.26 ppm for ^{1}H; δ = 77 ppm for ^{13}C). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and number of protons. The following abbreviations are used for ^{1}H NMR multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; td = triplet of doublets; tdd = triplet of doublet of doublets; m = multiplet; br = broad; app = apparent. Data for ^{13}C NMR spectra are reported with respect to chemical shift (ppm). IR spectra were recorded using a Perkin–Elmer paragon 1600 FT-IR.

Section 1.11 Experimental Pocedures

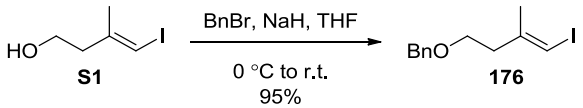


Vinyl Stannanes 178 and 179. Vinyl stannanes **178** and **179** were prepared according to the literature procedure.[25] A flame dried round bottom flask equipped with a stir bar was charged with tetrakis(triphenylphosphine)-palladium(0) (125 mg, 0.1 mmol, 0.001 equiv) and purged with argon. Freshly distilled dichloromethane (384 mL) was added via syringe resulting in a homogeneous yellow solution. A freshly distilled solution of ethoxyacetylene (**177**) (7.56 g of ethoxyacetylene, 108 mmol) in hexanes was added and the mixture was cooled to 0 °C. Tributyltin hydride (28.6 mL, 108 mmol) was added dropwise over five minutes. After 20 minutes the solvent was evaporated *in-vacuo*. To the resulting dark oil was added chilled pentanes until no further precipitate was formed. The brown precipitate was removed through gravity filtration and the solvent was removed *in-vacuo*. The crude residue was further purified through high vacuum distillation (110–115 °C at 0.25 mmHg) to yield an approximately 1.4:1 mixture of stannanes **178** and **179** in a comined yield of 95%. The spectral data of products were consistent with that reported in the literature.[33]



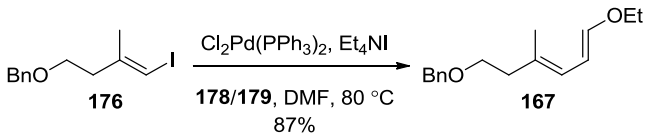
Vinyl Iodide S1. Zirconocene dichloride (15.16 g, 51.5 mmol, 0.22 equiv) was weighed into a flame dried round bottom flask equipped with a stir bar in the glove box. The flask was

transferred out of the glove box and placed under a positive pressure of argon. Freshly distilled dichloromethane (892 mL) was introduced to the flask and the zirconocene dichloride was dissolved. The solution was cooled to –13 °C (ice/salt bath) and trimethylaluminum (52.7 g, 366 mmol, 1.6 equiv) was added slowly via syringe. After ten minutes at –13 °C, water (6.6 mL, 366 mmol, 1.6 equiv) was added very slowly to the reaction which was then allowed to stir for an additional ten minutes at –13 °C. 3-butyn-1-ol (**180**) (16.5 g, 235 mmol, 1 equiv) in freshly distilled dichloromethane (180 mL) was cooled to 0 °C and treated with trimethylaluminum (5.14 g, 35.6 mmol, 0.15 equiv). The pretreated solution of **180** was slowly added to the reaction flask. The reaction flask was warmed to room temperature and allowed to stir for 2.5 hours. The reaction was cooled back down to –13 °C and iodine (71.4 g, 281 mmol, 1.2 equiv) in freshly distilled diethyl ether (540 mL) was added dropwise to the mixture. The reaction was allowed to warm to room temperature and stir for an additional 2.5 hours. The reaction was cooled to 0 °C and quenched by the careful addition of water. The biphasic mixture was washed with an aqueous solution of $Na_2S_2O_3$ then the separated organic phase was washed with brine, dried over sodium sulfate, filtered, concentrated *in-vacuo* and purified by flash column chromatography (20% Et_2O/hexanes) to yield the alcohol **S1** (33 g, 67%) the spectral data of which was consistant with that reported in the literature.[34]

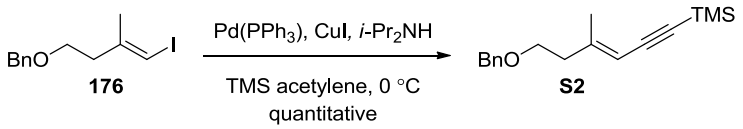


Benzyl Ether 176. Sodium Hydride (60% by weight dispersion in mineral oil, 1.25g, 52.4mmol) was washed three times with hexanes. The sodium hydride was suspended in THF (77mL). Alcohol **S1** (7.4g, 34.9mmol) was added and the reaction was cooled to 0 ^{o}C. Benzyl

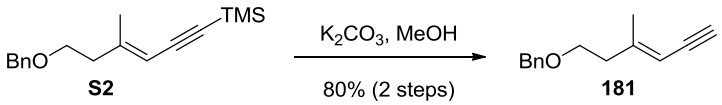
bromide (6.56g, 38.4mmol) was added. Reaction was allowed to warm to room temperature and stir for 12 hours. The reaction was quenched with deionized water. The reaction was extracted three times with ethyl acetate. The organic layers were combined and washed once with water followed by one wash with brine. The organic layers were dried with sodium sulfate. The solution was filtered and the solvents were removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography using a 5% ethyl acetate/hexanes gradient starting from hexanes. Yielded 10.07g of yellow oil (95%). Spectral data was consistent with that reported in the literature.[35]



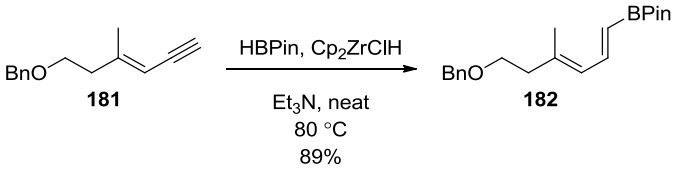
Diene 167. Tetraethylammonium chloride (6 g, 36.3 mmol) and trans-dichloro-bis-triphenylphosphine palladium(II) (1.25 g, 1.8 mmol) were weighed out in the glove box then dissolved in anhydrous DMF (121 mL). Vinyl iodide **176** (10.97 g, 36.3 mmol) was added followed by vinyl stannane **178** (19.74 g, 54.5 mmol). The reaction was heated to 80^{o}C for two hours. The reaction was cooled to room temperature and 70mL of 30% aqueous KF was added. The reaction was stirred for 30 min. The reaction was filtered over celite and rinsed with ethyl acetate. The product was extracted three times with ethyl acetate. The combined organic layers were combined and washed thoroughly with water then brine. The organic layer was dried over sodium sulfate, filtered, and the solvents were removed under reduced pressure. The crude reaction mixture was purified by high vacuum distillation (oil bath heated to 165 $^{\circ}$C). Yielded 7.84 g of yellow oil (87%). Spectral data was consistent with that reported in the literature.[24]



TMS Protected Enyne S2. A flame dried round bottom flask equipped with a stirbar was charged with copper(I) iodide (397 mg, 2.1 mmol, 0.1 equiv), capped with a septum and transferred out of the glove box. Tetrakis(triphenylphosphine)palladium(0) (728 mg, 0.6 mmol, 0.03 equiv) was added and the solid mixture was put under a positive pressure of argon. Diisopropylamine (45 mL) was added and the mixture was cooled to 0 °C. Iodide **176** (6.3 g, 21 mmol, 1 equiv) was dissolved in diisopropylamine (20 mL) and added to the reaction followed by TMS acetylene (3.8 mL, 27.1mmol, 1.3 equiv). The milky green heterogeneous mixture turned to a brown heterogeneous mixture within 10–20 minutes. Once the starting material had been consumed (as determined by TLC) the reaction was quenched with a saturated aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated *in-vacuo*. The crude material was purified by flash column chromatography (5% EtOAc/hexanes) to provide the coupling product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.38–5.36 (m, 1H), 3.55 (t, J = 6.8 Hz, 2H), 2.40 (t, J = 6.8 Hz, 2H), 1.93 (d, J = 1.1 Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 138.3, 128.4, 127.7, 127.6, 106.5, 103.2, 97.1, 73.0, 68.4, 38.7, 19.8, 0.1; IR (film) 3301, 2959, 2900, 2859, 2133, 1252, 1104 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{17}H_{24}OSiNa$, 295.1494, found 295.06.

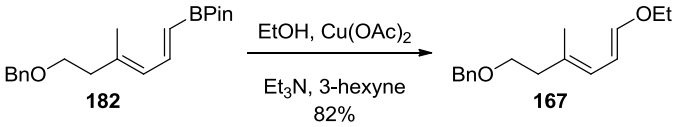


Enyne 181. TMS-protected enyne **S2** (assumed 5.7 g, 20.9 mmol, 1 equiv) was dissolved in freshly distilled methanol (80 mL). Potassium carbonate (3.2 g, 22.9 mmol, 1.1 equiv) was added and the reaction was stirred for approximately two hours at room temperature at which point the starting material was consumed (as determined by TLC). The reaction was quenched with an aqueous solution of ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude residue was purified by flash column chromatography (2.5% EtOAc/hexanes) to yield a light yellow oil (3.4 g, 80% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4H), 7.33–7.28 (m, 1H), 5.38–5.35 (m, 1H), 4.53 (s, 2H), 3.59 (t, J = 6.7 Hz, 2H), 3.06 (d, J = 2.3 Hz, 1H), 2.43 (d, J = 6.7 Hz, 2H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 138.3, 128.6, 127.8, 127.7, 105.5, 81.7, 80.1, 73.0, 68.3, 38.6, 19.6; IR (film) 3296, 3085, 3064, 3031, 2937, 2912, 2857, 2094, 1449, 1361, 1099 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) [M + H]$^{+}$ calcd $C_{14}H_{16}OH$, 201.1279, found 201.10.



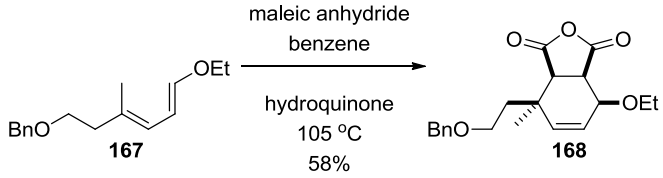
Vinyl Boronic Ester 182. To a flask under a positive pressure of argon, containing enyne **181** (9.8 g, 49 mmol, 1 equiv), was added freshly distilled triethylamine (676 μL, 4.9 mmol, 0.1 equiv). Pinacolborane (7.7 mL, 53 mmol, 1.1 equiv) was added followed by an aliquot of Schwartz's reagent (1.3 g, 5 mmol, 0.1 equiv) which was introduced as a solid in a single portion. The reaction vessel was covered with aluminum foil to protect from light and heated to

60 °C. After approximately 1.5 hours the starting material had been consumed (as determined by TLC) and the reaction was quenched with pH 7 buffer solution (careful, gas evolution may occur) and the aqueous phase was extracted with ethyl acetate until a TLC of the organic phase indicated that no further material was being extracted. The combined organics were washed with water then brine, dried over sodium sulfate, filtered, and concentrated *in-vacuo*. A quick silica gel column eluting initially with 10% EtOAc/hexanes followed by 15% EtOAc/hexanes yielded a faintly yellow oil (14.2 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.27 (m, 6H), 6.04 (d, J = 11.1 Hz, 1H), 5.50 (d, J = 17.7 Hz, 1H), 4.56 (s, 2H), 3.62 (t, J = 6.9 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 1.91 (br d, J = 0.9 Hz, 3H), 1.32 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 140.7, 138.4, 128.8, 128.4, 128.4, 127.7, 127.6, 83.1, 73.0, 68.7, 40.0, 24.8, 17.5; IR (film) 3087, 3067, 3031, 2978, 2932, 2859, 1637, 1600, 1453, 1360, 1339, 1315, 1140, 1103 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{29}BO_3H$, 329.2288, found 329.21.

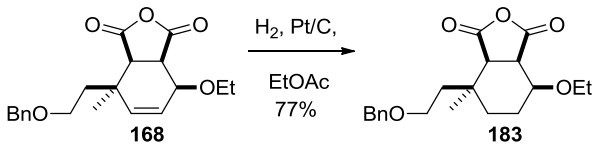


Diene 167. Vinyl boronic ester **182** (5g, 15 mmol, 1 equiv) was dissolved in ethanol (98 mL). Freshly distilled triethylamine (8.5 mL, 60 mmol, 4 equiv) was added followed by 3-hexyne (7.6 mL, 60 mmol, 4 equiv) and copper(II) acetate (5.5 g, 30 mmol, 2 equiv). The reaction was capped with a teflon stopper and stirred at room temperature overnight. The reaction was poured into an aqueous solution of sodium bicarbonate and extracted with ethyl acetate until TLC analysis of the organic phase showed that no more material was being extracted. The combined organic phases were washed twice with an aqueous solution of sodium bicarbonate, once with water, and once with brine. The organic solution was dried over sodium sulfate, filtered, and

concentrated *in-vacuo*. The crude material was further purified by flash column chromatography using basic alumina as the solid phase (3% EtOAc/hexanes) to yield a colorless oil (3.1 g, 82%) the spectral data of which was consistent with that reported in the literature.[24]

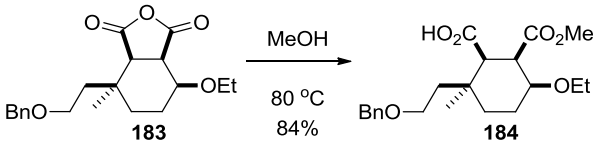


Diels–Alder Adduct 168. Hydroquinone (55 mg, 0.5 mmol) was weighed into a pressure tube. Maleic anhydride (5.85 g, 59.8 mmol) that had been recrystallized from benzene was added to the pressure tube. Anhydrous benzene (50 mL) was used to dissolve diene **167** (4.91 g, 19.93 mmol). The diene solution was added to the pressure tube and the reaction mixture was degassed by three cycles of freeze-pump-thaw. The reaction was purged with argon for 30 minutes and then the pressure tube was sealed. The reaction was heated to 105 °C for 3 days. The solvents were removed under reduced pressure and the reaction was purified by flash chromatography using a 15% ethyl acetate/hexanes gradient starting from hexanes. Yielded 3.97 g of yellow oil (58%). Spetral data was consistent with that reported in the literature.[24]

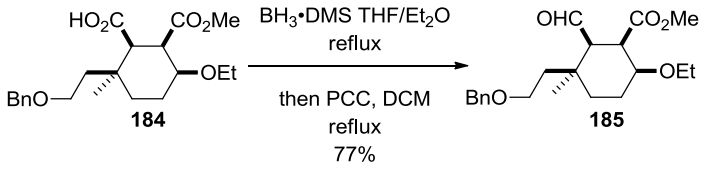


Cyclohexane 183. 10% platinum on carbon (113 mg, 0.0848 mmol) was weighed out in the glove box. Diels-Alder adduct **168** (292 mg, 0.848 mmol) was dissolved in anhydrous ethyl acetate (11.75 mL) and added to the flask containing the Pt catalyst. The reaction was put under

vacuum for 1 minute and purged with hydrogen. The reaction flask was evacuated and purged two more times. The reaction was stirred for 30 minutes and monitored by NMR. Reaction was finished after 30 minutes and stopped after 1 hour. The reaction was filtered over celite and the solvents were removed under reduced pressure. The crude oil was purified by flash chromatography using 2:1 hexanes/ethyl acetate to yield 227 mg of clear oil (77%). The spectral data was consistent with that reported in the literature.[24]

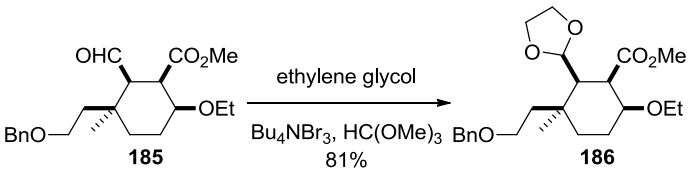


Carboxylic Acid 184. Diels-Alder adduct **183** (227 mg, 0.656 mmol) was azeotroped three times with benzene and put under high vacuum. 4.6 mL of anhydrous methanol was added and the mixture was transferred to a pressure tube. The reaction was purged with argon for twenty minutes and the tube was sealed. The reaction was heated to 80 °C for 24 hours. The solvent was removed under reduced pressure and the crude yellow oil was purified by flash chromatography using 20% ethyl acetate/hexanes yielding 200 mg (0.55 mmol) of clear oil (84%). The sprectal data was consistent with that reported in the literature.[24]



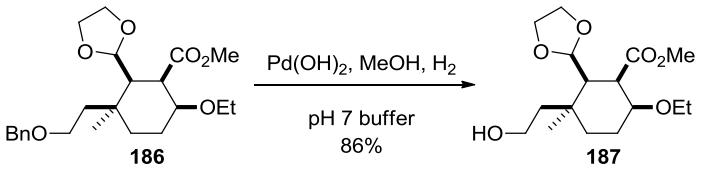
Aldehyde 185. Carboxylic acid **184** (2.3 g, 6 mmol, 1 equiv) was dissolved in freshly distilled THF (6 mL) and subsequently diluted with freshly distilled diethyl ether (30 mL). The round bottom flask was capped with a Claisen adapter and reflux condenser and put under a positive

pressure of argon. Borane dimethylsulfide complex (3 mL of a 2M solution in THF, 6 mmol, 1 mmol) was added through the Claisen adapter dropwise during which time a rapid evolution of gas took place. The reaction was heated to reflux for two hours then allowed to cool to room temperature. The mixture was concentrated *in-vacuo* (the rotary evaporator was replenished with argon) and the crude boroxine was placed under high-vac for 30 minutes. The crude material was redissolved in freshly distilled dichloromethane (10 mL) and added via syringe to a round bottom flask equipped with a Claisen adapter and reflux condenser containing PCC (2.6 g, 12 mmol, 2 equiv) in freshly distilled dichloromethane (25 mL). The reaction was refluxed for one hour at which point a second aliquot of PCC (650 mg, 3 mmol, 0.5 equiv) was added. The reaction was refluxed for an additional 30 minutes. The reaction was cooled to room temperature and filtered through a pad of celite. The crude material was concentrated *in-vacuo* and purified by flash column chromatography (20% EtOAc/hexanes) to yield a colorless oil (1.7 g, 77%) the spectral data of which was consistant with that reported in the literature.[24]

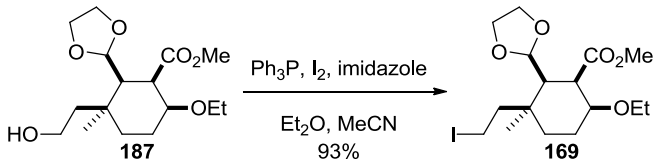


Dioxolane 186. To a round bottom flask equipped with a stir bar and charged with aldehyde **185** (202 mg, 0.74 mmol, 1 equiv) was added ethylene glycol (172 µL, 3.1 mmol, 4.1 equiv) followed by trimethyl orthoformate (122 µL, 1.1 mmol, 1.5 equiv). Tetrabutylammonium tribromide (2.7 mg, 0.006 mmol, 0.008 equiv) was weighed out in the glove box and added to the reaction flask as a solid in a single portion. The mixture was stirred for 2 hours then quenched

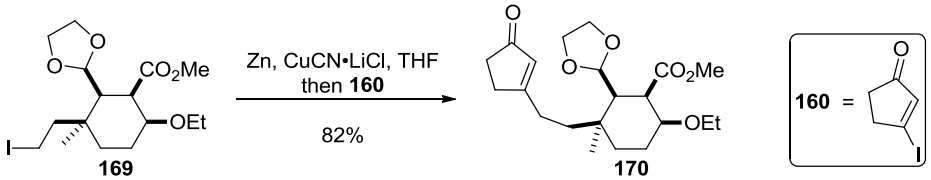
with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude material was purified by flash column chromatography (20% EtOAc/hexanes) to provide a colorless oil (181 mg, 81%) the spectral data of which was consistant with that reported in the literature.[24]



Alcohol 187. A round bottom flask equipped with a stir bar was charged with palladium hydroxide 20 wt% on carbon (6.61g, 9.4 mmol, 0.6 equiv). Freshly distilled methanol (177 mL) was added followed by pH 7 buffer (64 mL). Benzyl ether **186** (6.4 g, 15.7 mmol, 1 equiv) was dissolved in freshly distilled methanol (14 mL) and was added to the heterogeneous reaction mixture. The reaction was put under an atmosphere of hydrogen using a balloon and stirred for four days. The crude reaction mixture was filtered over celite and the filtered solution was poured into brine. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude residue was recrystallized from diethyl ether to yield a white solid (4.3 g, 86%) the spectral data of which was consistent with that reported in the literature.[24]

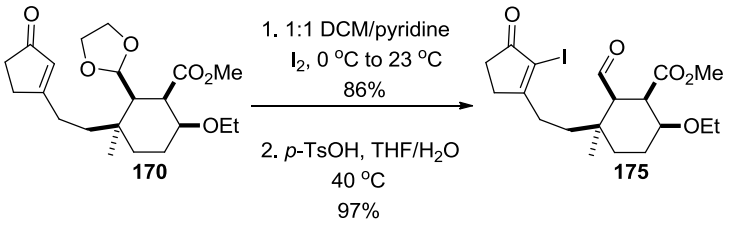


Iodide 169. A flame dried round bottom flask equipped with a stir bar was charged with triphenylphosphine (855 mg, 3.3 mmol, 1.2 equiv) and imidazole (222 mg, 3.3 mmol, 1.2 equiv). The solid mixture was dissolved in freshly distilled acetonitrile (4 mL) and diethyl ether (12 mL) and cooled to 0 °C. Iodine (827 mg, 3.3 mmol, 1.2 equiv) was added and the reaction was allowed to warm to reoom temperature and stir for 30 minutes. During this time a yellow precipitate formed. The reaction was cooled back down to 0 °C and alcohol **187** (860 mg, 2.7 mmol, 1 equiv) was dissolved in freshly distilled dichloromethane (5 mL) was added. The reaction was allowed to warm to room temperature and stirred for 1.5 hours. Pentanes was added and the resulting precipitate was removed by decanting the supernatant. The solids were rinsed with 1:1 Et_2O/pentanes and the supernatant was decanted. The crude residue was concentrated *in-vacuo* and purified by flash column chromatography (5–10% EtOAc/hexanes) to give a colorless oil (1.1 g, 93%) the spectral data of which was consistent with that reported in the literature.[24]



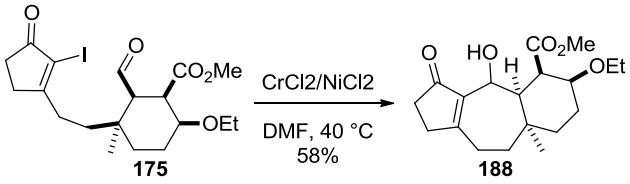
Enone 170. A flame dried round bottom flask equipped with a stir bar was charged with zinc metal (919 mg, 14.1 mmol, 1.7 mmol, 1.7 equiv). The zinc was suspended in freshly distilled THF (5 mL) and 1,2-dibromoethane (47 μL) was added. The reaction was heated to reflux for

three minutes and allowed to cool back down to room temperature. This was repeated two more times. Freshly distilled chlorotrimethylsilane (55 μL) was added and the reaction was stirred for an additional 20 minutes. The reaction was heated to 30 °C and iodide **169** (5.76 g, 13.5 mmol, 1.7 equiv) in freshly distilled THF (10 mL) was added. The reaction was heated at 40 °C for 4 hours. The reaction was cooled to –10 °C and a solution of copper cyanide (1.07 g, 11.9 mmol, 1.5 equiv) and lithium chloride (1 g, 23.6 mmol, 2.9 equiv) in freshly distilled THF (10 mL) was added. The reaction was stirred at 0 °C for 15 minutes. The reaction was cooled to –40 °C and enone **160** (1.7 g, 8.1 mmol, 1 equiv) in freshly distilled THF (9 mL) was added dropwise to the reaction mixture.[36] The reaction was stirred at 0 °C for 1.5 hours then at room temperature for 2 hours. The reaction was quenched with an aqueous solution of ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were washed with aqueous $Na_2S_2O_3$, water, 1M KOH, then brine. The combined organics were dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude material was purified by flash column chromatography to yield a colorless oil (2.38 g, 87% based on enone **160**) the structural data of which was consistent with that reported in the literature.[24]



Cyclization Precursor 175. Enone **170** (300 mg, 0.89 mmol, 1 equiv) was dissolve in 1:1 DCM/pyridine (3.4 mL) and coolded to 0 °C. Iodine (954 mg, 3.8 mmol, 4.3 equiv) dissolved in 1:1 DCM/pyridine (3.4 mL) was added dropwise to the cooled solution. The reaction was

allowed to warm to room temperature and stir overnight. The crude mixture was concentrated *in-vacuo* and redissolved in ethyl acetate. The solution was washed consecutively with aqueous solutions of $Na_2S_2O_3$, copper(II) sulfate then brine. The organic phase was dried over sodium sulfate and concentrated *in-vacuo*. The crude material was purified by flash column chromatography (30% EtOAc/hexanes) to give a the α-iodinated enone (not shown) as an oil (390 mg, 86%). This material (207 mg, 0.41 mmol, 1 equiv) was dissolved in THF (6.2 mL) and water (2.1 mL). *p*-toluenesulfonic acid (84 mg, 0.49 mmol, 1.2 equiv) was added and the reaction was heated to reflux until the starting material had been consumed (as determined by TLC). The reaction was cooled to room temperature and an aqueous solution of sodium bicarbonate was added. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in-vacuo*. The crude material was purified by flash column chromatography (10–40% EtOAc/hexanes) to provide a yellow oil (184 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (d, J = 5.0 Hz, 1H), 4.16–4.13 (m, 1H), 3.70 (s, 3H), 3.65–3.56 (m, 1H), 3.42–3.33 (m, 1H), 2.91 (dd, J = 4.9, 3.0 Hz, 1H), 2.84–2.69 (m, 2H), 2.67–2.59 (m, 2H), 2.58–2.53 (m, 3H), 2.06–1.98 (m, 1H)1.79–1.56 (m, 4H), 1.38–1.29 (m, 1H), 1.11 (t, J = 6.9 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 203.8, 183.6, 172.5, 102.3, 73.7, 64.7, 54.7, 52.0, 45.7, 38.7, 35.6, 33.0, 32.5, 29.5, 29.3, 24.2, 22.9, 15.5; IR (film) 2974, 2928, 2875, 2765, 1735, 1706, 1600, 1437, 1205, 1087, 911, 724 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{19}H_{27}IO_5H$, 463.0981, found 463.05.



Tricycle 188. Cyclization precursor **175** (25 mg, 0.07 mmol, 1 equiv) was weighed out into a flame dried pressure tube equipped with a stir bar. Chromium(II) chloride (100 mg, 0.8 mmol, 11 equiv) and nickel(II) chloride (1 mg, 0.008 mmol, 0.1 equiv, 1% by mass compared to $CrCl_2$) that had been dried overnight under vacuum at 180 °C were weighed out into a flame dried round bottom flask and suspended in degassed (3 cycles of freeze-pump-thaw) DMF. The heterogeneous suspension was cannulated into the pressure tube and the mixture was purged with argon for an additional 10 minutes. The pressure tube was sealed and heated to 40 °C for approximately 12 hours. The reaction was quenched with an aqueous solution of ammonium chloride and chloroform. The layers were separated and the aqueous phase was extracted four times with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude residue was purified by flash column chromatography (100% hexanes until purple band was eluted, then 30–40% EtOAc/hexanes) to provide a white solid (10.6 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (d, J = 1.8 Hz, 1H), 4.58 (s, 1H), 4.09 (s, 1H), 3.72–3.61 (m, 5H), 2.74 (dd, J = 5.7, 1.8 Hz, 1H), 2.66–2.30 (m, 7H), 2.11–2.00 (m, 2H), 1.90 (br d, J = 14.6 Hz, 1H), 1.52–1.42 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H), 1.14–1.07 (m, 1H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 179.9, 172.8, 143.3, 72.3, 65.5, 63.1, 51.7, 47.2, 45.9, 39.0, 36.6, 34.7, 32.0, 31.1, 28.4, 25.3, 24.6, 15.3; IR (solid) 3369, 2952, 2921, 2899, 2868, 1735, 1694, 1649, 1453, 1200, 1079, 1010, 638 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{19}H_{28}O_5Na$, 359.1834, found 359.09.

Section 1.12 References

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Chapter 2

Decarboxylative Rearrangement of Allenylic *N*-Tosyl Carbamates and Phosphine-catalyzed Intramolecular γ-Umpolung Addition of α-Aminoalkylallenic Esters

2.1 Introduction

Nitrogen containing heterocycles have been established as prominent structural features among a large number of natural products and pharmaceutically active compounds (Figure 1).[1] A vast number of terpenoid indole alkaloids display structures with an indole nucleus in conjunction with additional heterocyclic amines (see aspidospermidine (**1**) and yohimbine (**3**)). Martinellic acid (**2**) contains a tetrahydroquinoline motif and a pyrrolidine nucleus. A number of top selling pharmaceuticals including Lipitor (**4**), Plavix (**5**), and Argatroban (**6**), all contain one or more nitrogen containing heterocycles (Figure 1). Amongst this class of heterocycle, 3-pyrrolines (**7**, Figure 2) are particularly versatility because they can be transformed into the more

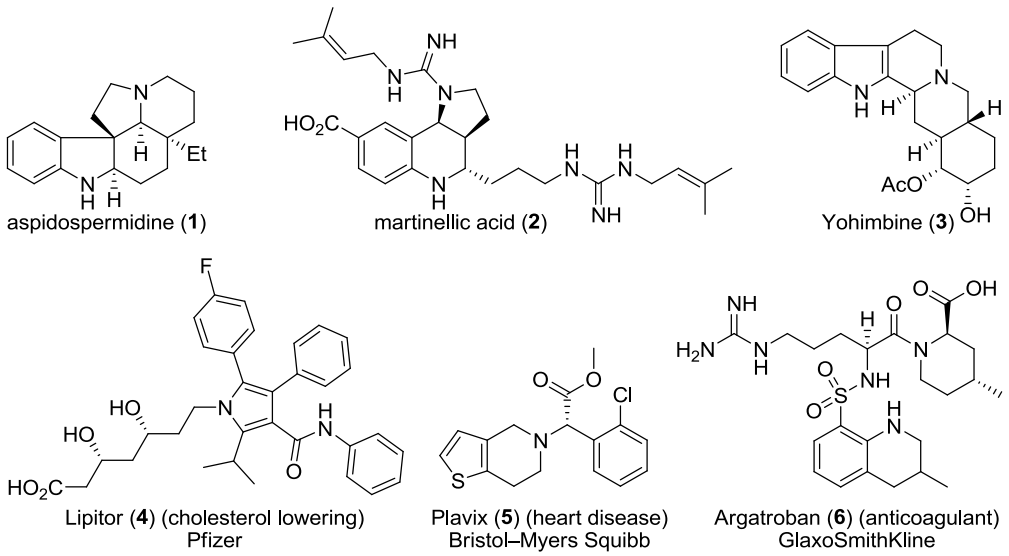


Figure 1 Important natural products and drug molecules containing nitrogen heterocycles

highly oxidized pyrrole **8** and pyrrolinone **9**, or reduced to the fully saturated pyrrolidine **10** (Figure 2). This five-membered nitrogen-containing heterocyclic scaffold will be the focus of this discussion.

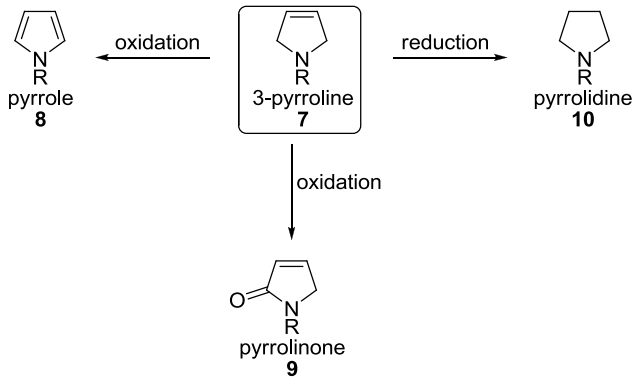
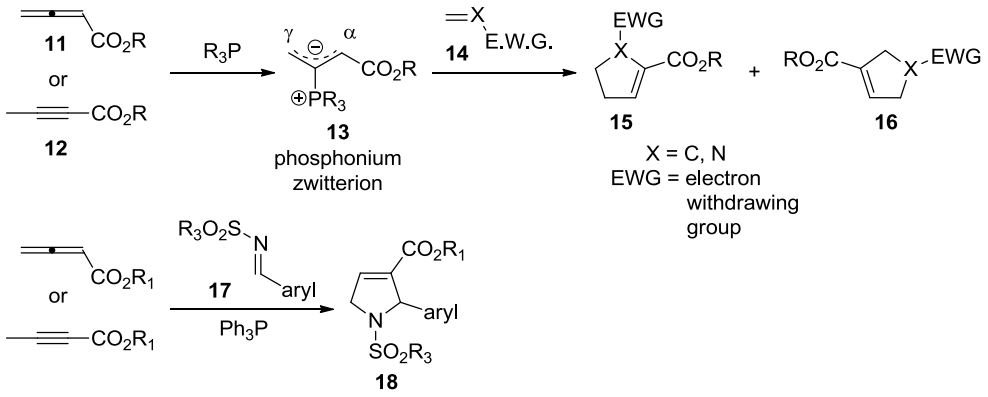


Figure 2 Versatility of the 3-pyrroline scaffold toward the synthesis of other heterocycles

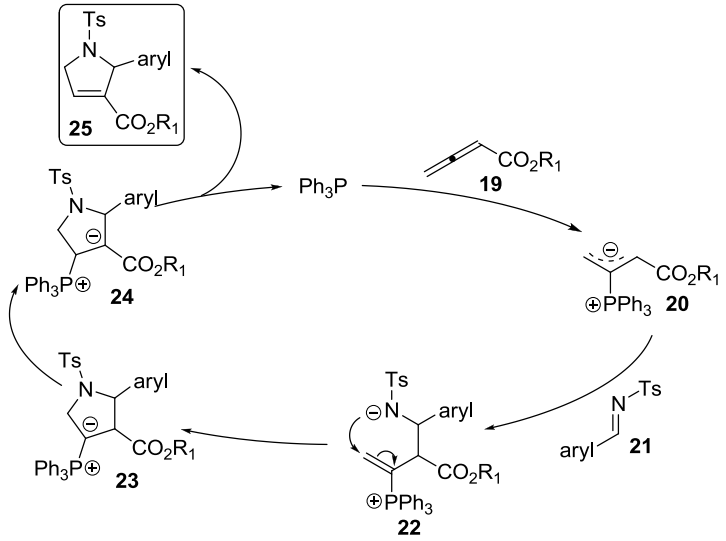
One particularly useful method for the preparation of functionalized 3-pyrrolines relies on the seminal work of Xiyan Lu in the area of nucleophilic phosphine catalysis.[2] Lu discovered that the resonance delocalized phsosphonium zwitterion **13**, generated from the addition of nucleophilic tertiary phosphines to allenoates **11**, and butynoates **12**, can be intercepted by various electron deficient pi systems **14**, yielding [3 + 2] adducts as a mixture of two regioisomeric products **15** and **16**, arising from competition between addition of the phosphonium zwitterions to the pi system at either the γ or α positions, respectively (Scheme 1). When employing *N*-sulfonyl aldimines **17** as the dipolarophile, 2-substituted-pyrroline-3-carboxylates **18** are formed in good yields. Unlike with activated olefin dipolarophiles, the [3 + 2] annulation with imines proceeds to generate 3-pyrrolines as a single regioisomer via α-addition of the *in-situ* generated phosphonium dienolate to the imine. One drawback to this efficient process is the limited scope of imine reaction partners. The annulations were successful only with *N*-sulfonyl imines derived from non-enolizable aldehydes.

The proposed mechanism for Lu's [3 + 2] annulation is outlined in Scheme 2. Addition of



Scheme 1 Generation of phosphonium zwitterions and their reactions with dipolarophiles

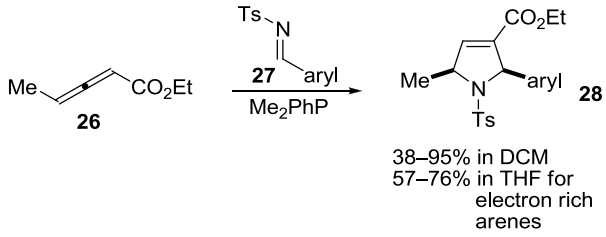
triphenylphosphine to allenoate **19** forms phosphonium dienolate **20**. α-Addition of the phosphonium dienolate to the imine **21** generates sulfonamide anion **22**. The sulfonamide anion undergoes 5-*endo* cyclization to yield phosphorus ylide **23**. Proton transfer to give zwitterion **24**, followed by elimination of the catalyst, provides the desired 3-pyrroline **25** and reintroduces triphenylphosphine into the catalytic cycle.[3]



Scheme 2 Proposed mechanism for Lu's phosphine-catalyzed [3 + 2] annulation with imines

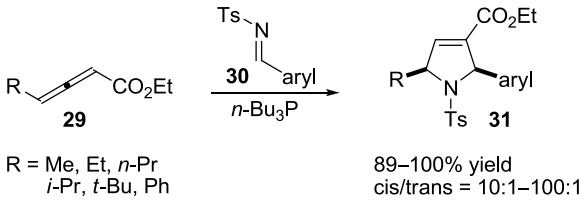
Section 2.2 Modifications of Lu's Original Allene–Imine [3 + 2]

Since Lu's original reports on the phosphine catalyzed [3 + 2] annulation, there has been a considerable breadth of research dedicated to developing novel annulation processes involving phosphine activation of electron deficient pi systems to generate nitrogen containing 5-membered heterocycles. In 2005, Shi reported the use of γ-methyl allenoate (**26**, Scheme 3) as a competent reaction partner in a similar annulation with electron deficient imines **27**.[4] This synthesis of 1,2,3,5-tetrasubstituted pyrrolines **28** was catalyzed by dimethylphenylphosphine and the use of the *N*-tosyl imines derived from benzaldehyde provided the desired heterocycle in 95% yield. The yields, when employing substituted aryl imines, were generally low and the optimized conditions for alternatively substituted substrates were not general, requiring a substitution of the solvent from DCM to THF in order to accommodate electron donating groups on the imine aryl ring. Perhaps the most notable distinction from Lu's original phosphine-catalyzed [3 + 2] is the additional substituent on the allenoate, which results in the generation of a second stereocenter. The reaction was found to be highly diastereoselective with the 2,5-*syn*-adduct predominating or being formed exclusively in all cases. Similarly to Lu's case however, the use of enolizable alkyl imines was not tolerated.



Scheme 3 Shi's phosphine-catalyzed [3 + 2] annulation with γ-methyl allenoate

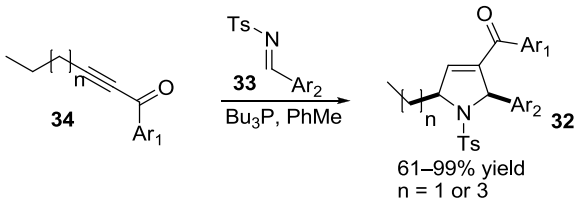
Shortly before Shi's aforementioned report, Kwon independently disclosed the results of a study that more comprehensively expanded the scope of Lu's original [3 + 2] annulation by employing various γ-substituted allenoates (**29**, Scheme 4) and the more nucleophilic tri-*n*-butylphosphine in place of triphenylphosphine. The result was a synthesis 3-carbethoxy-2,5-disubstituted-3-pyrrolines **31**, which, in analogy to Shi's report, exhibited high *syn*-selectivity.[5] In this case however, the allenoate γ-substituent was varied to include not only methyl, but ethyl, *n*-propyl, *i*-propyl, *t*-butyl, and phenyl, which all engaged in high yielding annulations. The conditions reported here (20 mol% tri-*n*-butylphosphine in benzene) proved very general, providing exceptional yields of pyrrolines with a wide array of *N*-sulfonyl aldimines **30**. This methodological extension shares a number of features with Lu's original pyrroline synthesis including the need for particularly activated *N*-sulfonyl imines derived from non-enolizable aldehydes. The authors also show that 4-nitrobenzenesulfonyl, and SES groups are effective alternatives to the tosyl group for imine activation. The requisite non-enolizable imines are limited largely to those derived from aryl aldehydes.



Scheme 4 Kwon's phosphine-catalyzed [3 + 2] annulation with various γ-substituted allenoates

In 2008 Xue reported the synthesis of 1,2,3,5-tetrasubstituted pyrrolines **32** utilizing the phosphine-catalyzed [3 + 2] annulation between *N*-tosyl imines **33** and substituted acetylenic

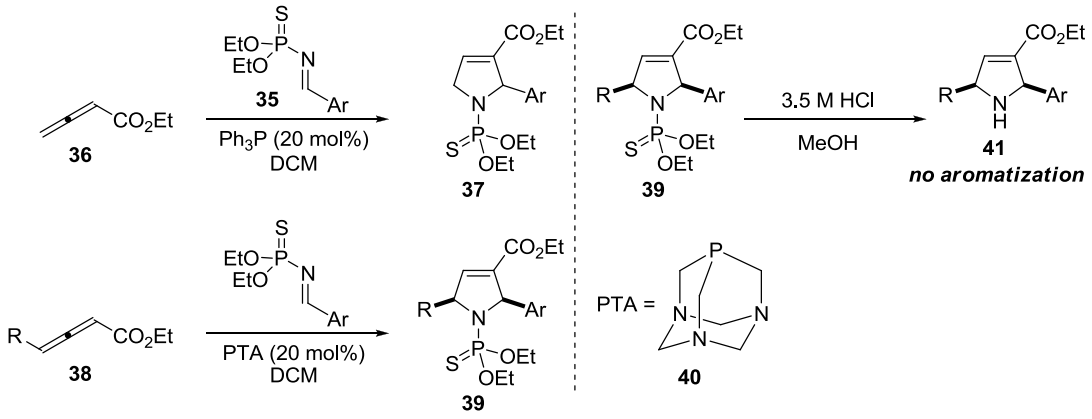
ketones **34** (Scheme 5).[6] This provides a departure from the aforementioned phosphine-catalyzed pyrroline syntheses by providing direct access to ketone substituents at the 3 position instead of carboxylates. While the reaction provides the desired pyrrolines in moderate to excellent yields, the substrate scope reported was somewhat limited. Aromatic aldimines with *N*-sulfonyl groups were required as enolizable imines were again not competent reaction partners. The acetylenic ketone must be substituted with an aromatic group and was only reported to provide 5-ethyl or 5-*n*-butyl substituted pyrrolines, although no comment was made as to whether other alkynone β-substituents were screened.



Scheme 5 Xue's phosphine-catalyzed [3 + 2] annulation with acetylenic ketones

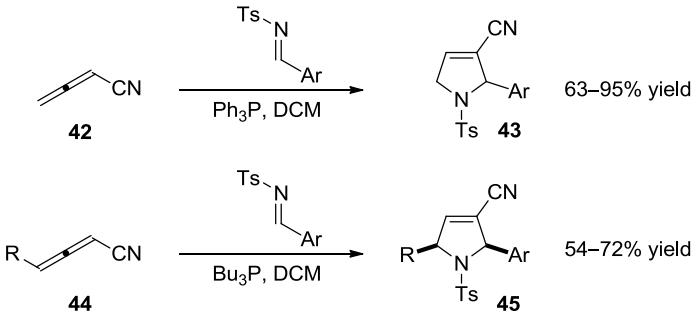
In a 2008 report by He, it was disclosed that activation of imine reacting partners with *N*-thiophosphoryl groups provided competent substrates for Lu-type phosphine-catalyzed [3 + 2] annulations (**35**, Scheme 6).[7] Utilization of unsubstituted allenoates **36** proceeded in the presence of triphenylphosphine whereas additional γ-substitution **38** required the more nucleophilic 1,3,5-triaza-7-phospaadamantane (PTA) **40** in order to facilitate the annulations. While most reaction features such as *syn*-diastereoselectivity and the necessity for aryl imines were similar to previously disclosed Lu-type annulations, the use of the *N*-thiophosphoryl group offers orthogonal reactivity for amine deprotection compared to previously employed sulfonyl groups. While the typically utilized *N*-tosyl, nosyl, or even SES groups are removed with

contrasting methods from one another, each requires basic conditions. This can be problematic as the deprotected pyrrolines often oxidize to the aromatic pyrroles under these circumstances. The thiophosphoryl groups were shown to be easily removed using methanolic hydrochloric acidic without aromatization (**41**), potentially due to the formation of an ammonium salt upon deprotection that is less susceptible toward oxidation.



Scheme 6 He's use of *N*-thiophsophoryl imines in phosphine-catalyzed [3 + 2] annulations

Further substrate scope expansion was reported in 2011 by Kinderman who employed allenyl nitriles in place of the commonly utilized allenoates in Lu-type [3 + 2] annulations (Scheme 7).[8] 3-Pyrroline formation proceeded in the presence of triphenylphosphine when utilizing 1-cyano-2,3-butadiene (**42**) and various *N*-tosyl aryl imines to give the corresponding 1,2,3-trisubstituted pyrrolines **43** in moderate to excellent yields. Switching to the more nucleophilic tri-*n*-butylphosphine allowed for the use of γ-substituted allenyl nitriles **44**, forming the 1,2,3,5-tetrasubstituted pyrrolines **45** in moderate to good yields. In these cases the reaction proceeded to give the *syn*-diastereomer with high selectivity. *N*-Benzenesulfonyl and SES groups were also found to be competent activating groups on the imine. Aldimines derived from

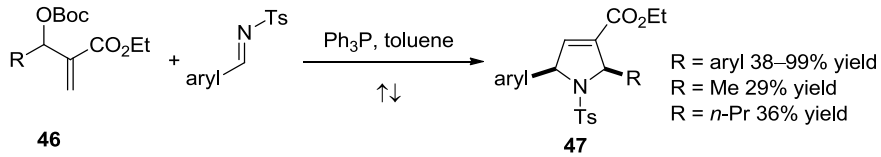


Scheme 7 Kinderman's use of allenyl nitriles in phosphine-catalyzed [3 + 2] annulations

aromatic aldehydes were the only disclosed competent coupling partners.

All of the aforementioned Lu [3 + 2] annulations and variations thereof rely on the formation of the phosphonium zwitterionic intermediate by addition of a nucleophilic phosphine to an electron deficient allene or alkyne. Recently there have been reports on the reactions of phosphorous ylides generated from modified Baylis–Hillman adducts, like that of **46** (Scheme 8), that are capable of undergoing similar annulation processes. In 2008 Lu reported the use of *N*-sulfonyl imines in trapping of the *in-situ* generated zwitterions leading to the formation of 3-pyrrolines **47** in moderate to excellent yields (Scheme 8).[9]

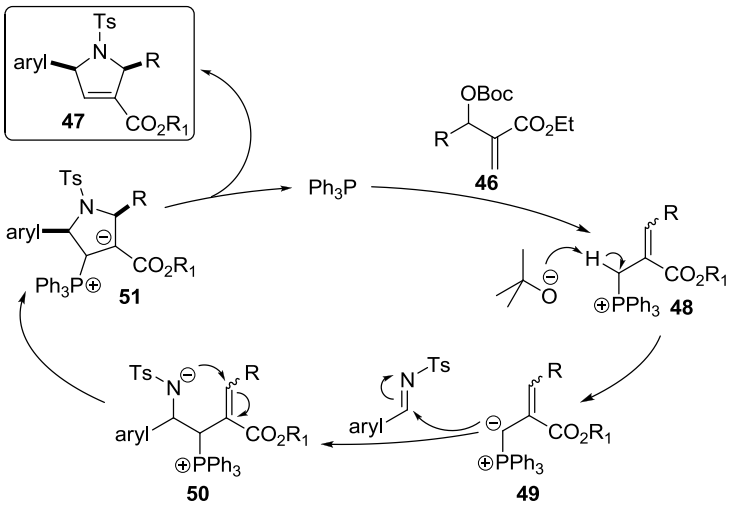
This variation stands apart from the previously discussed [3 + 2] annulations in the way the zwitterion is generated. The proposed mechanism is shown in Scheme 9. The reaction is initiated upon addition of the nucleophilic phosphine to the modified Baylis–Hillman adduct **46** and elimination of the allylic Boc group (Boc = *tert*-butyloxycarbonyl) to yield the allyl



Scheme 8 Lu's phosphine-catalyzed [3 + 2] annulation using modified MBH adducts

phosphonium ion **48**. The eliminated Boc group decomposes into carbon dioxide and *tert*-butoxide. The *in*-situ generated *tert*-butoxide then deprotonates α to the phosphonium in **48** generating phosphorus ylide **49**. The phosphorus ylide adds to the imine generating sulfonamide anion **50**. Sulfonamide **50** undergoes intramolecular Michael addition to generate the cyclic zwitterion **51**. Elimination of the catalyst liberates the pyrroline product **47** and reintroduces triphenylphosphine into the catalytic cycle. While the 3-pyrrolines generated in this reaction bare a strong resemblance to those formed in the phosphine-catalyzed [3 + 2] annulations between allenoates or alkynoates and imines, it is noteworthy that in this reaction the imine aryl group ends up in the 5-position of the 3-pyrroline instead of the 2-position that is observed in the phosphine-catalyzed allene–imine [3 + 2] annulation. Despite the alternative mode of reactivity exploited in the reactions with modified MBH adducts, the prerequisite for the use of non-enolizable, typically aryl substituted, sulfonyl imines remained.

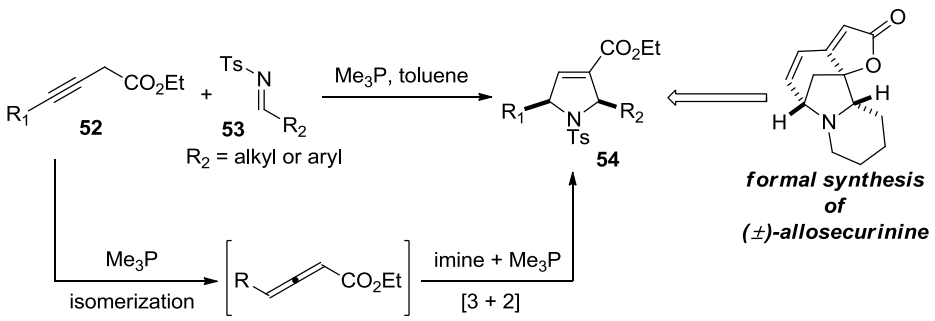
Despite such diversity in reaction partners that is available for carrying out phospine-



Scheme 9 Proposed mechanism for the [3 + 2] annulation using modified MBH adducts

catalyzed [3 + 2] annulations with imines, the annulations have been limited in substrate scope with respect to the imine substituent, with the use of non-enolizable imines being necessary in most cases. The nearly exclusive use of aryl imines in efficient phosphine-catalyzed [3 + 2] annulations is the product of these limitations. Overcoming this restriction would increase the potential for use of the phosphine-catalyzed 3-pyrroline syntheses toward applications requiring non-aryl groups at the 2-position of the heterocycle.[10] While the aforementioned annulation with MBH adducts derived from aliphatic aldehydes was reported to provide 2-alkyl pyrrolines, the only two examples provided the 2-methyl and 2-*n*-propyl substituted pyrrolines in only 29 and 36% yields, respectively (Scheme 8). Marinetti has reported the successful use of an isopropyl-substituted *N*-tosyl imine in phosphine-catalyzed annulations with conjugated dienes in modest yields, but a system amenable to the incorporation of a broad scope of alkyl imines in phosphine-catalyzed [3 + 2] annulations remained elusive for many years.[11]

The highly successful use of various alkyl-substituted *N*-sulfonyl imines was reported only recently when used in conjunction with a trimethylphosphine-catalyzed isomerization of 3-alkynoates (Scheme 10).[12] The utility of the 2-alkyl substituted pyrroline synthesis was immediately demonstrated in the formal synthesis of the *Securinega* alkaloid (±)-allosecurinine. This isomerization/[3 + 2] protocol was highly variable in terms of substrate scope. The variable 3-alkynoate **52** substituent was amenable to electronically different aryl groups, primary alkyl groups, hydrogen, and esters. With aryl substituted alkynoates as substrates, aromatic *N*-methanesulfonyl imines were also tolerated. Most remarkably, the use of various alkyl substituted imines **53** (R_2 = alkyl) were very well tolerated in the annulations. Primary, secondary and even secondary cycloalkyl groups all proceeded to give the pyrroline products **54** in good yields and with high *syn* selectivity in most cases.

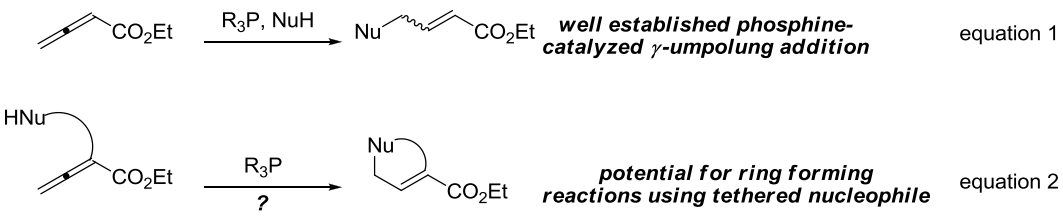


Scheme 10 Loh's phosphine-catalyzed isomerization/[3 + 2] annulation

There have also been asymmetric versions of the phosphine-catalyzed [3 + 2] annulation with aryl, and more recently, alkyl imines. For a discussion of these reports see section 3.5.

Section 2.3 Hypothesized Reaction

Based on the mild, metal free conditions typically employed in nucleophilic phosphine catalysis, we chose to pursue the development of an alternative phosphine-catalyzed 3-pyrroline synthesis that would circumvent the problems commonly associated with limited imine scope. Based on the well established precedent for the γ-functionalization of allenoates by way of phosphine-catalyzed umpolung addition of various nucleophiles (Scheme 11, equation 1), it was hypothesized that this strategy could be implemented to achieve this goal. By tethering a



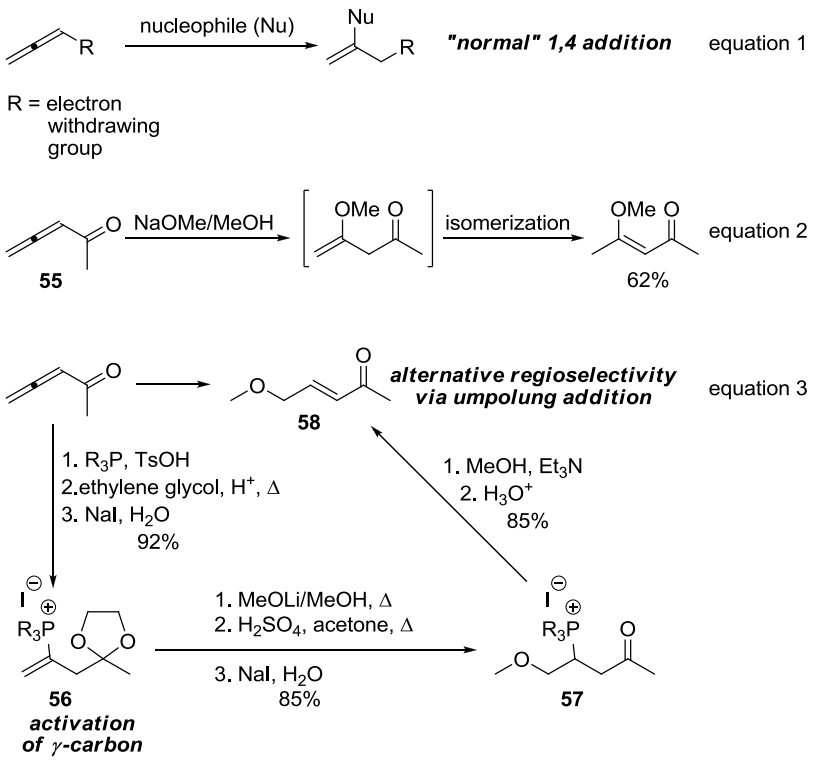
Scheme 11 Well established γ-fuctionalization of allenoates and the possible application toward heterocycle synthesis.

nucleophile to the allenoate, the potential for ring forming reactions could be realized (Scheme 11, equation 2).

Section 2.4 Early Examples of Phosphine-catalyzed γ-umpolung Addition and Intramolecular Examples of Such Reactivity

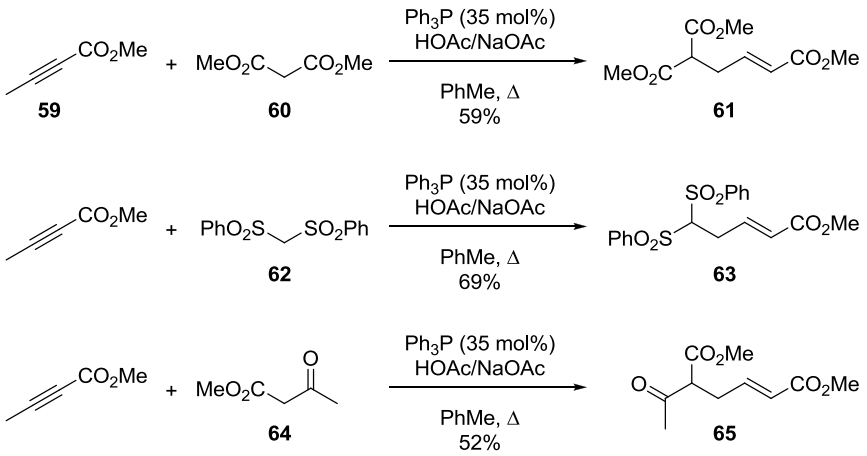
The first reported use of a trivalent phosphine for inducing electrophilic character at the γ-carbon of electron deficient allenes was disclosed by Cristau in 1982. Electron deficient allenes typically undergo addition at the β-carbon when reacted with nucleophiles (Scheme 12, equation 1). In this study, Cristau demonstrated that the typical regioselectivity of methoxide addition to methyl allenyl ketone (**55**, Scheme 12, equation 2) could be encouraged to occur at the γ-carbon by preactivation with a tertiary phosphine (Scheme 12, equation 3).[13] In order to obtain the product of regioisomeric γ-addition, it was shown that addition of a triarylphosphine to methyl allenyl ketone (**55**) followed by dioxolane formation and counterion exchange resulted in the isolation of vinylphosphonium iodide **56** in 92% overall yield. Lithium methoxide adds to the now activated γ-carbon of **56**, which after ketal cleavage and counterion exchange generates phosphonium salt **57** in 85% yield. Elimination of the phosphine led to the unsaturated ketone **58** in 85% yield (E/Z = 95:5). Although this process represents the earliest example of phosphine activation of electron deficient allenes leading to γ-addition of nucleophiles, the multistep process involved and stoichiometric use of a phosphine that is not incorporated into the final product render the method impractical. More recent work however, has shown that catalytic amounts of phosphines can be used to promote the γ-umpolung addition of various pronucleophiles in a single operation.

In 1994 Barry Trost published the first account of a phosphine-catalyzed γ-umpolung addition alkynoates (Scheme 13). [14] This seminal report showed that in the

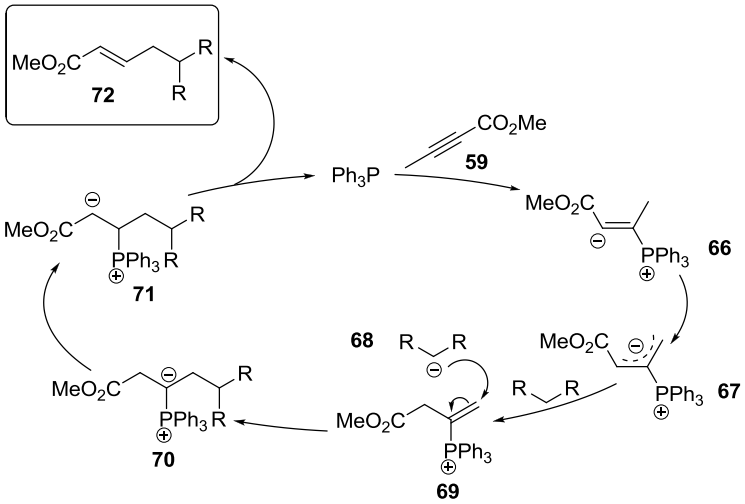


Scheme 12 First example of allene γ-activation with via addition of a nucleophilic phosphine

presence of a catalytic amount of triphenylphosphine, with acetic acid and sodium acetate as additives, various activated methylene compounds would undergo nucleophilic addition to the γ-carbon of electron deficient alkyne **59** (Scheme 13). A number of different carbon-based pronucleophiles were employed successfully including malonates **60**, bissulfones **62**, and acetoacetates **64**, to provide the products **61**, **63**, and **65,** respectively. A plausible mechanism for this reaction is shown at the bottom of Scheme 13. Conjugate addition of the triphenylphosphine catalyst to methyl butynoate (**59**) yields vinyl phosphonium zwitterion **66** which isomerizes into vinylphosphonium zwitterion **67** through proton transfer. Deprotonation of the pronucleophile and its nucleophilic addition at the γ-carbon of the concomitantly formed vinyl phosphonium ion **69** provides ylide **70**. Proton transfer, providing zwitterions **71**, followed



proposed mechanism

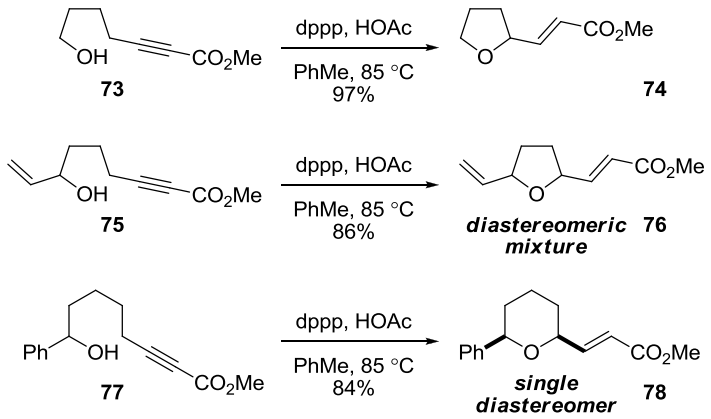


Scheme 13 Trost's phosphine-catalyzed γ-umpolung addition to butynoates

by elimination of triphenylphosphine, provides the γ-umpolung addition product, α,β-usaturated ester **72**.

Trost's initial publication was quickly followed up by a report in which more elaborately functionalized acetylenic esters bearing a tethered alcohol **73**, **75**, and **77** could undergo intramolecular γ-umpolung addition to yield various 5- and 6-membered oxygen containing heterocycles **74**, **76**, and **78** (Scheme 14).[15] Mechanistically analogous to the intermolecular γ-

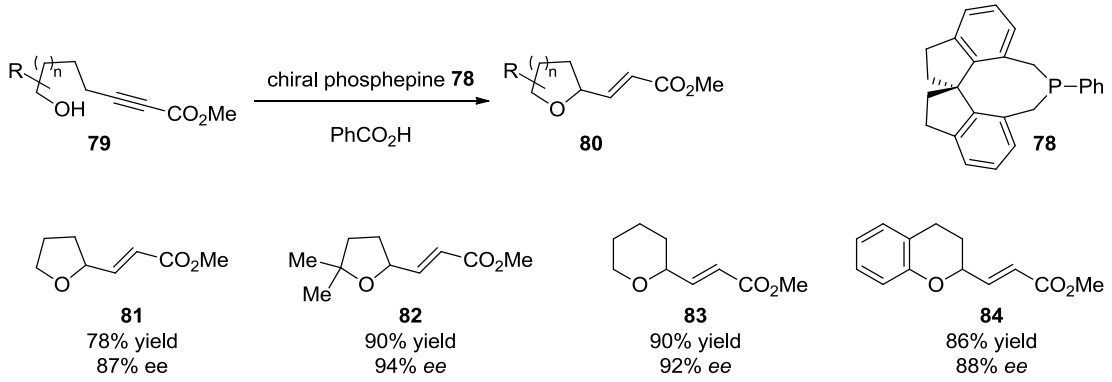
umpolung addition shown in Scheme 13, 5- and 6-exo trig cyclizations took place efficiently to provide access to variably substituted tetrahydrofurans and tetrahydropyrans While 2,5-disubstituted tetrahydrofurans were generated as a diastereomeric mixture, the corresponding 2,6-disubstituted tetrahydropyrans were formed as a single 2,6-*syn* diastereomer.



Scheme 14 Intramolecular phosphine-catalyzed γ-umpolung addition of oxygen nucleophiles

Fu later reported a highly enantioselective version of Trost's intramolecular γ-umpolung addition to generate oxygen containing heterocycles when utilizing chiral phosphepine **78** as catalyst (**79** → **80**, Scheme 15).[16] A number of variously substituted tetrahydrofurans and tetrahydropyrans (**81**–**83**) were synthesized in good yields with high *ee*'s. The use of ortho-substituted phenols provided access to benzodihydropyrans **84**.

Lu reported similar reactivity when utilizing allenoates in place of butynoates **85** (Scheme 16).[17] A number of different carbon-based nucleophiles, including malonates **86**, diketones **88**, and acetoacetates **90** participated in the transformation to provide the products

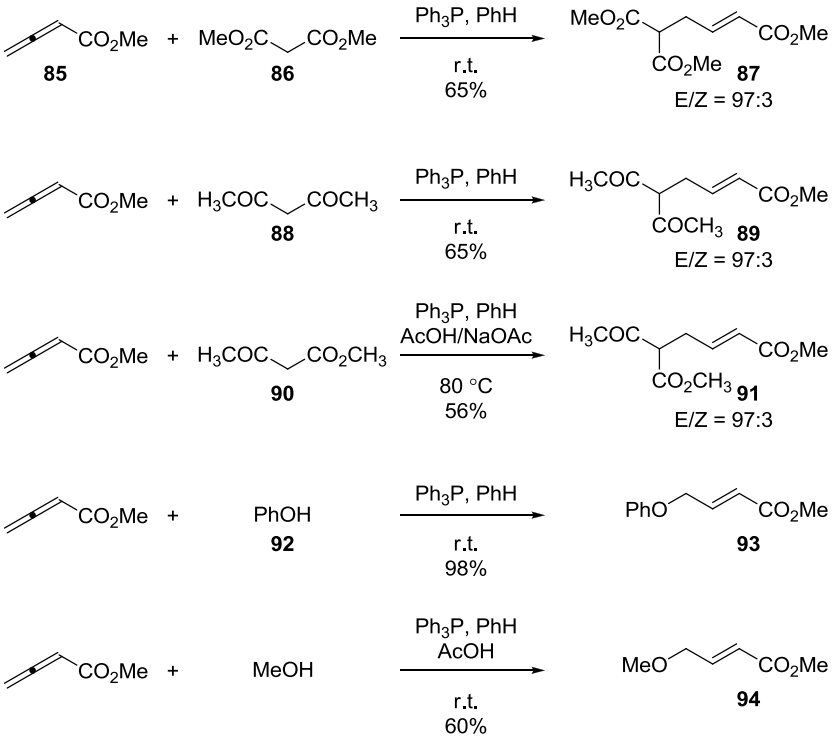


Scheme 15 Fu's asymmetric version of Trost's intramolecular phosphine-catalyzed γ-umpolung addition of oxygen nucleophiles

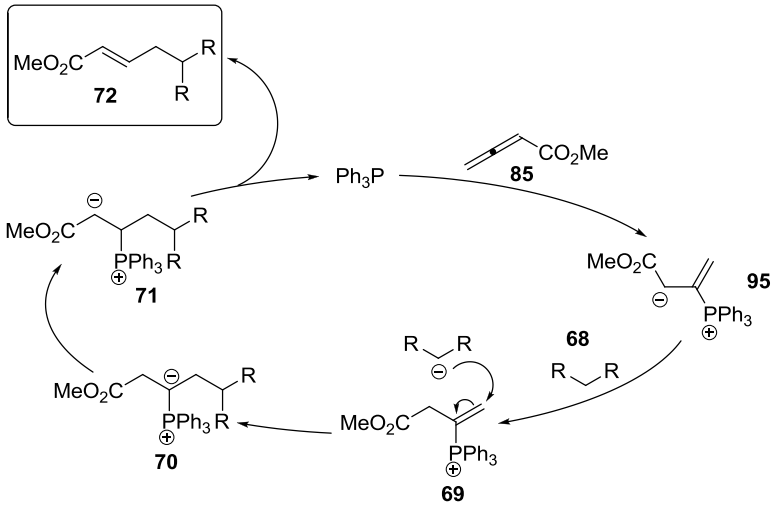
of γ-umpolung addition **87**, **89**,and **91** respectively. Phenol **92** was also well tolerated while benzyl alcohol (not shown) was less effective. It was shown however, that the less acidic alcohols such as benzyl alcohol and methanol could be used effectively when utilizing acetic acid as an additive to provide the desired addition product **94**. The proposed mechanism is shown at the bottom of Scheme 16. Conjugate addition of triphenylphosphine to allenoate **85** yields the phosphonium dienolate **95** at which point the mechanism proceeds the same as that proposed for the γ-umpolung addition to butynoates discussed in Scheme 13.

Section 2.5 Reaction Design

It was hypothesized that the well established phosphine-catalyzed γ-umpolung addition of electron deficient allenes described above could be applied to the synthesis of pyrrolines. Shown in Scheme 17 is the rational design plan to execute this process. The established γ-umpolung addition produces γ-substituted α,β-unsaturated esters **96**, a structural feature that can be found in pyrroline-3-carboxylates **97**. Based on this retrosynthetic disconnection it was rationalized that

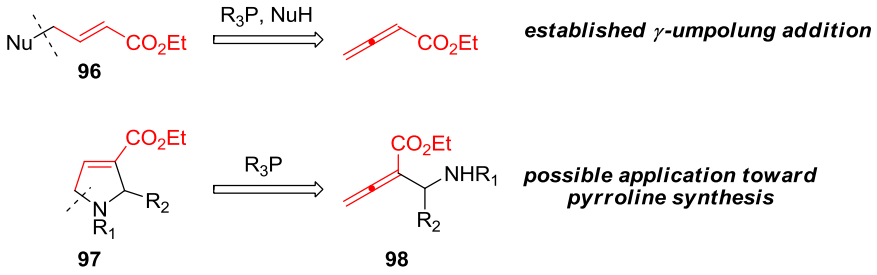


proposed mechanism



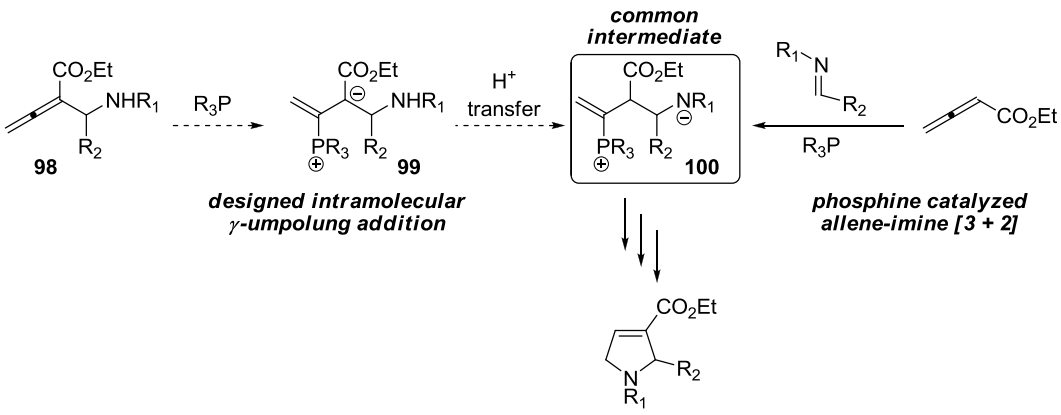
Scheme 16 Phosphine-catalyzed γ-umpolung addition to allenoates

α-aminoalkylallenic esters **98** could undergo a phosphine-catalyzed cycloisomerization process to provide the desired 3-pyrrolines. Although there was no literature precedent for



Scheme 17 Design plan for the phosphine-catalyzed synthesis of 3-pyrrolines via intramolecular γ-umpolung addition

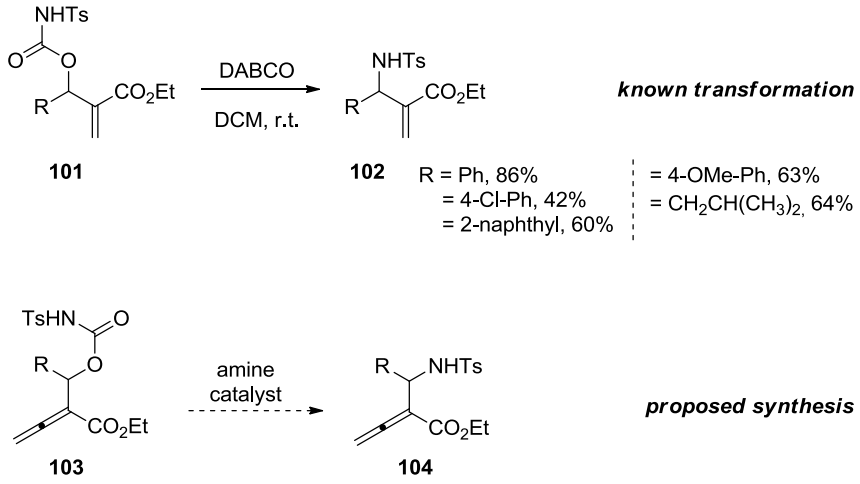
intramolecular phosphine-catalyzed γ-umpolung addition using nitrogen based pronucleophiles, nor any examples of phosphine catalyzed umpolung additions that take place in a 5-*endo* fashion, this type of cyclization is proposed as one of the mechanistic steps in Lu-type [3 + 2] annulations (*vide supra*). It was believed that upon addition of a nucleophilic phosphine catalyst to an α-aminoalkylallenic ester **98**, a phosphonium dienolate **99** would be formed that could undergo proton transfer, yielding the amide anion **100**, an intermediate that is analogous to that proposed in phosphine catalyzed allene-imine [3 + 2] annulations (Scheme 18). The potential benefit of the designed cycloisomerization is that the use of imines could be avoided and a wide variety of substitution at the 2-position could be achieved.



Scheme 18 Mechanistic rationale for the use of α-aminoalkylallenic esters as substrates for phosphine catalyzed pyrroline synthesis

Section 2.6 Results and Discussion

In order to explore the proposed reaction, a synthesis of the requisite α-aminoalkylallenic esters **98** was necessary. As targets, the *N*-tosylated α-aminoalkylallenic esters were chosen. In order to synthesize these substrates we drew inspiration from the reported rearrangement of allylic *N*-tosyl carbamates **101**, derived from Baylis-Hillman adducts, to *N*-tosyl allylic amines **102** (Scheme 19).[18] It was hoped that a similar transformation performed with *N*-tosyl allenylic carbamates **103** would provide the desired *N*-tosyl α-aminoalkylallenic esters **104**.

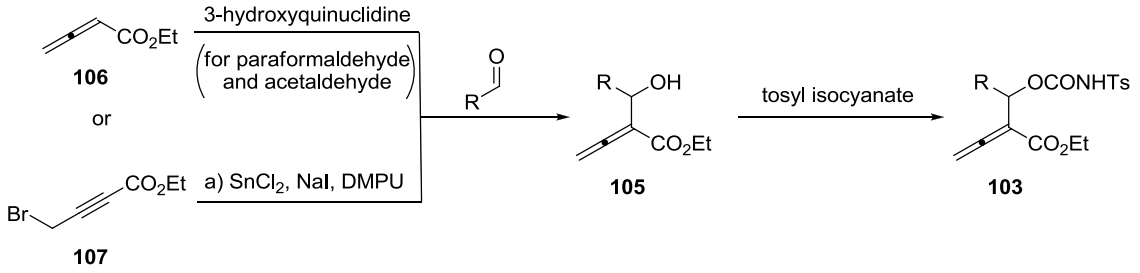


Scheme 19 Decarboxylative rearrangement of allylic *N*-tosylcarbamates and the potential analogous reaction with allenylic *N*-tosylcarbamates

The requisite allenic carbamates **103a–h** were synthesized by treatment of various allenic alcohols with tosyl isocyanate (Scheme 20). The allenic alcohols utilized, **105a–h**, were synthesized through the Baylis–Hillman reaction with ethyl 2,3-butadienoate **106** in the case of R = H and R = Me. Higher order allenic alcohols were prepared via the Barbier-type reaction of propargyl bromide **107** and the corresponding aldehydes.[19] A summary of the yields obtained for the synthesis of these substrates is shown in Table 1. The alcohols **105a** and **105b** were

prepared by the aforementioned Baylis–Hillman method in 66 and 73% yields, respectively (entries 1 and 2). Higher order analogues **105c–h** were prepared in 50–80% yield utilizing the Barbier reaction (entries 3–8). The allenic carbamates **103a–h** were synthesized directly from these alcohols by treatment with tosyl isocyanate in 74–93% yield (entries 1–8).

With the allenylic carbamates in hand we were prepared to test the proposed synthesis of the requisite α-aminoalkylallenic esters **104**. Our investigation began with the slow addition of an acetonitrile solution of the allenoate **103a** (R = H) to 1 equivalent of DABCO (in acetonitrile) over the course of 12 hours. Gratifyingly, the desired α-aminomethyl allenic ester



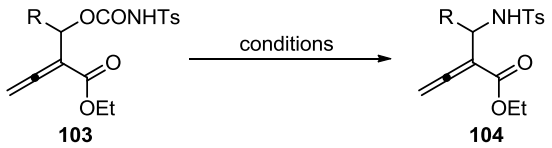
entry	R	alcohol product (yield)	carbamate product (yield)
1	H	**105a** (66 %)	**103a** (82 %)
2	methyl	**105b** (73 %)	**103b** (87 %)
3	ethyl	**105c** (50 %)	**103c** (82 %)
4	*i*-propyl	**105d** (56 %)	**103d** (93 %)
5	*n*-pentyl	**105e** (57 %)	**103e** (84 %)
6	cyclopropyl	**105f** (65 %)	**103f** (78 %)
7	cyclopentyl	**105g** (62 %)	**103g** (83 %)
8	cyclohexyl	**105h** (80 %)	**103h** (74 %)

Scheme 20/Table 1 Synthesis of allenylic carbamates **103a–h**

104a was obtained in 37% isolated yield (Table 2, entry 1). The reaction proceeded in a number of different reaction media, with CH_2Cl_2 and benzene (entries 2 and 3, respectively) resulting in the highest yield of 42%. Performing the reaction in THF yielded none of the desired product

(entry 5). We also tested the allenylic carbamate **103c** (R = ethyl) as a substrate for the rearrangement. After slow addition of a benzene solution of the ethyl-substituted allenoate to 1 equivalent of DABCO, we isolated the desired product **104c** in 54% yield (entry 8). Decreasing the catalyst loading had a negative effect on the reaction, lowering the yield to 35% (entry 9); simply adding the catalyst quickly to a solution of the starting material decreased the yield further, to 18% (entry 10). We speculate that slow addition of the allenoate to a stoichiometric amount of the catalyst ensured that a very low concentration of unreacted allenoate was present in the reaction mixture, resulting in suppression of undesired reaction pathways. 3-Quinuclidinol also effected the reaction, albeit with diminished efficiency (36% yield, entry 11); in contrast, DMAP, DBU, pyridine, and imidazole all failed to yield any of the desired product (entries 12–15). In an interesting observation, we isolated the allenoate **104a** in the highest yield (56%) when using dimethyl sulfide as the catalyst in MeCN (entry 7). Dimethyl sulfide failed to provide any of the desired rearrangement products when any substituent larger than a hydrogen atom was present. It is possible that with the decreased steric demands for this substrate, direct displacement may have been in operation, rather than our proposed S_N2' displacement.

Under the optimized conditions, a number of α-aminoalkylallenic esters could be generated using this rearrangement procedure (Table 3). The highest yield of 65% was realized when a methyl substituent was present (entry 2). Longer alkyl chains reduced the yield to 56% when R = ethyl (entry 3) and 27% when R = *n*-pentyl (entry 4). Branched alkyl groups were well tolerated with an isopropyl substituent resulting in 52% yield (entry 5). Cycloalkyl groups were also incorporated, cyclopropyl, cyclopentyl, and cyclohexyl substituted allenic carbamates led to the desired α-aminoalkylallenic esters in 45%, 45%, and 51% yields, respectively (entries 6–8). Interestingly, with hydrogen as the substituent the highest yield, 56% of the rearranged



103 104

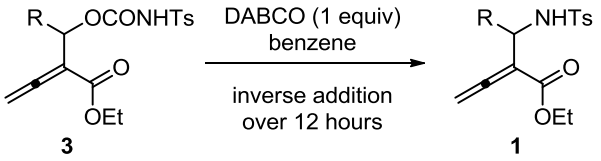
entry	R (allenoate)	catalyst (equiv)	solvent	addition method[a]	product	yield[b]
1	H (**103a**)	DABCO (1)	MeCN	A	**104a**	37 %
2	H (**103a**)	DABCO (1)	DCM	A	**104a**	42 %
3	H (**103a**)	DABCO (1)	PhH	A	**104a**	42 %
4	H (**103a**)	DABCO (1)	MeOH	A	**104a**	23 %
5	H (**103a**)	DABCO (1)	THF	A	**104a**	0 %
6	H (**103a**)	DABCO (1)	DMF	A	**104a**	35 %
7	H (**103a**)	Dimethyl sulfide (1)	MeCN	A	**104a**	56 %
8	Et (**103c**)	DABCO (1)	PhH	A	**104c**	54 %
9	Et (**103c**)	DABCO (0.2)	PhH	A	**104c**	35 %
10	Et (**103c**)	DABCO (0.2)	PhH	B	**104c**	18 %
11	Et (**103c**)	3-quinuclidinol (1)	PhH	A	**104c**	36 %
12	Et (**103c**)	DMAP (1)	PhH	A	**104c**	0 %
13	Et (**103c**)	DBU	PhH	A	**104c**	0 %
14	Et (**103c**)	Pyridine	PhH	A	**104c**	0 %
15	Et (**103c**)	imidazole	PhH	A	**104c**	0 %

[a]A: Slow addition of a solution of the allenoate to a solution of the catalyst; B: addition of the catalyst quickly to a solution of the allenoate. [b]Isolated yield after SiO_2 column chromatography.

Table 2 Optimization of the decarboxylative rearrangement of *N*-tosylallenylic carbamates

product was obtained when dimethylsulfide was employed as the catalyst as previously mentioned (entry 1). Utilization of aryl substituted allenic carbamates failed to provide any of the desired product (entry 9).

A plausible mechanism for this transformation is shown in Scheme 21. The reaction is believed to proceed in analogy to the similar rearrangement of allylic carbamates. Conjugate addition of the amine catalyst providing ammonium dienolate **108** and subsequent elimination of the carbamate yields ammonium diene **109**. The eliminated carbamate decomposes into carbon dioxide and *p*-toluenesulfonamide anion **110**. The sulfonamide anion adds in a Michael fashion to the α,β-unsaturated ester of phosphonium diene **109** to provide phosphonium dienolate **111**.

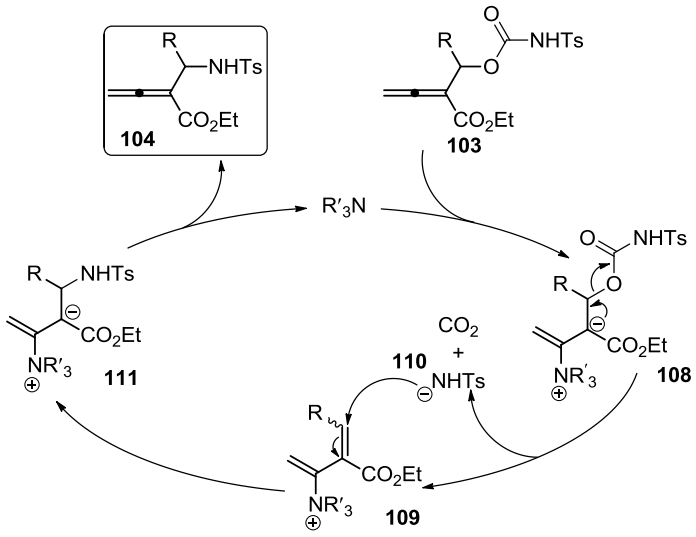


entry	R	product	yield[a]
1	H	**104a**	56 %[b]
2	methyl	**104b**	65 %
3	ethyl	**104c**	56 %
4	*n*-pentyl	**104d**	27 %
5	*i*-propyl	**104e**	52 %
6	cyclopropyl	**104f**	45 %
7	cyclopentyl	**104g**	45 %
8	cyclohexyl	**104h**	51 %
9	phenyl	**104i**	0 %

[a]Isolated yield after column chromatography. [b]Dimethyl sulfide was used as the catalyst with MeCN as the solvent.

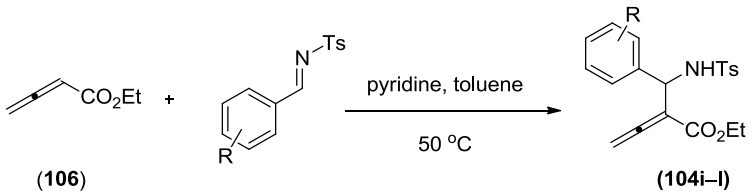
Table 3 Decarboxylative rearrangement of various *N*-tosylallenylic carbamates

Elimination of the catalyst yields the desired α-aminoalkylallenic ester **104**.



Scheme 21 Plausible mechanism for the decarboxylative rearrangement of *N*-tosylallenylic carbamates

In order to access aryl substituted substrates, an aza-Baylis–Hillman reaction between ethyl 2,3-butadienoate (**106**) and *N*-tosyl imines was employed and the summarized results are shown in Table 4. The phenyl substituted α-aminoalkylallenic ester **104i** was produced in 56% yield while the 4-chlorophenyl substituent affected the yield only slightly (54% of **104j**, entry 2). Utilizing the 4-methoxyphenyl and 4-cyanophenyl substituted imines provided the desired products **104k** and **104l** in more modest 33 % and 25 % yields, respectively (entries 3 and 4).



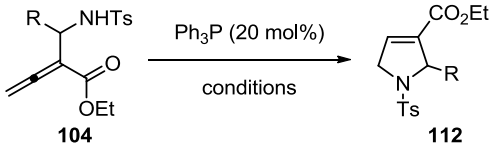
(**106**) (**104i–l**)

entry	R	product	yield[a]
1	phenyl	**104i**	56 %[b]
2	4-chlorophenyl	**104j**	54 %
3	4-methoxyphenyl	**104k**	33 %
4	4-cyanophenyl	**104l**	25 %

Table 4 Aza-Baylis–Hillman reaction between ethyl 2,3-butadienoate and *N*-tosyl imines

With access to a number of the desired *N*-tosyl α-aminoalkylallenic esters, their reactivity under the influence of nucleophilic phosphines was explored (Table 5). Based on the effective use of aryl substituents in other phosphine-catalyzed pyrroline syntheses, we chose this as our starting point. Addition of 20 mol% triphenylphosphine to a solution of **104i** in dichloromethane resulted in the formation of the desired pyrroline **112i** in 62% yield (entry 1). A brief solvent screen identified aromatic solvents as optimal, with benzene providing the highest yield of 93% (entries 2–5). Employing the more nucleophilic tri-*n*-butylphosphine as catalyst led to a marked reduction in the time necessary to consume the starting material (1 hour compared to 18 hours),

but with an unacceptable reduction in yield (29% compared to 93%, entry 6). While this initial result was gratifying, it was still unclear as to whether the developed method would be amenable to the synthesis of 2-alkyl-substituted pyrrolines. In order to probe this question we subjected the ethyl-substituted α-aminoalkylallenic ester **104c** to 20 mol% triphenylphosphine in benzene. It was delightful to discover that the desired pyrroline **112c** was formed in 92% yield after 52 hours at room temperature (entry 7). The necessity for prolonged reaction times was exacerbated upon implementing substrates with branched alkyl substituents. α-aminoalkylallenic ester **104g**,



104 **112**

entry	R	solvent	additives	time	product	yield[a]
1	Ph	CH_2Cl_2	none	40 h	**112i**	62 %
2	Ph	PhMe	none	40 h	**112i**	89 %
3	Ph	THF	none	40 h	**112i**	0 %[b]
4	Ph	MeCN	none	40 h	**112i**	0 %
5	Ph	PhH	none	18 h	**112i**	93 %
6[c]	Ph	PhH	none	1 h	**112i**	29 %
7	Et	PhH	none	52 h	**112c**	92 %
8	Cyp	PhH	none	10 days	**112g**	44 %
9	Et	PhH	AcOH/NaOAc	32 h	**112c**	97 %
10	Cyp	PhH	AcOH/NaOAc	4 days	**112g**	85 %

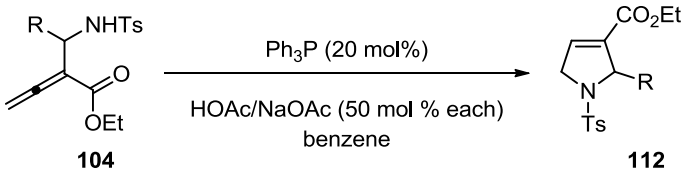
[a]Isolated yield after silica gel chromatography. [b]Recovered starting material. [c]Bu_3P was used

Table 5 Optimization of the intramolecular γ-umpolung addition of α-aminoalkylallenic esters

with R = cyclopentyl, required 10 days at 40 °C to reach completion and provided only 44% of the desired pyrroline **112g** (entry 8). In order to reduce reaction times and to improve the yields of some of the more challenging substrates, a screening of additives was undertaken. It was

found that addition of 50 mol% of both acetic acid and sodium acetate generally reduced reaction times while improving yields. Using these conditions, the ethyl substituted α-aminoalkylallenic ester **104c** cyclized in 97% yield in only 32 hours. The most dramatic improvement being the isolation of pyrroline **104g** in 85% yield in less than half the time as compared to the reaction without additives (entry 10, 4 days compared to 10 days).

Under these optimized conditions a number of α-aminoalkylallenic esters were cyclized to the corresponding 3-pyrrolines (Table 6). In general, the yields for the phosphine-catalyzed cycloisomerizations were excellent. α-Aminoalkylallenic esters **104a** (R = H) and **104j** (R = 4-chlorophenyl) cyclized in the highest yields (87 % and 88 % yields, respectively) without the addition of acetic acid and sodium acetate as additives (entries 1 and 10), while all other



104 **112**

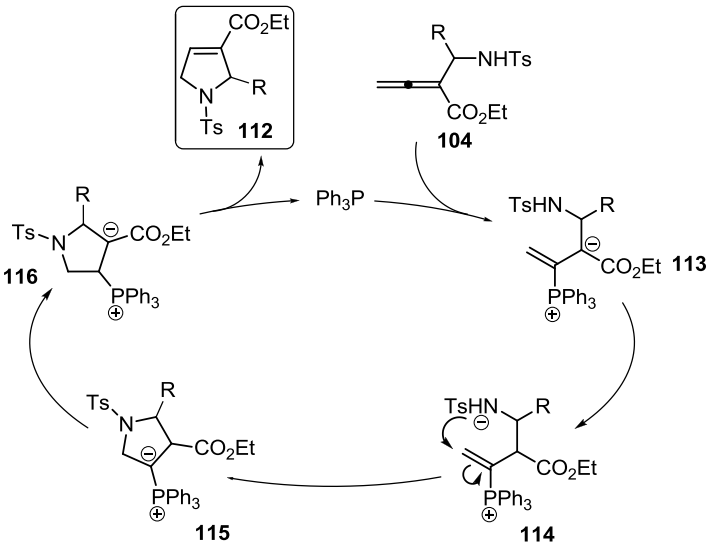
entry	R	time (h)	product	yield (%)
1	H	18	**112a**	87[a]
2	Me	19	**112b**	99
3	Et	32	**112c**	97
4	*n*-Pent	48	**112d**	69
5	*i*-Pr	77	**112e**	97
6	cyclopropyl	72	**112f**	95
7	cyclopentyl	96	**112g**	85
8	cyclohexyl	96	**112h**	93[b]
9	phenyl	12	**112i**	99
10	4-chlorophenyl	4.5	**112j**	88[a]
11	4-methoxyphenyl	22	**112k**	99
12	4-cyanophenyl	2	**112l**	85

[a]Yield in the absence of any additives. [b]Based on recovered starting material (69% isolated yield).

Table 6 Phosphine-catalyzed intramolecular γ-umpolung addition of various α-aminoalkylallenic esters

substrates cyclized with the highest efficiency in the presence of the additional Brønsted acid/base additives. Substrates with primary alkyl substituents cyclized efficiently with only a slight decrease in yield when changing from methyl to ethyl (99% to 97% yield, entries 2 and 3). Increasing the chain length further with an *n*-pentyl substituent resulted in a further decrease in yield (69% yield, entry 4). Secondary alkyl groups including cycloalkyl substituents were well tolerated as well (85–97 % yield, entries 5–8). Aromatic substituents led to facile transformations to the corresponding 2-aryl-3-pyrrolines. With R = phenyl, the desired cyclization proceeded in 99% isolated yield (entry 9). The electron deficient 4-cyanophenyl group resulted in a slightly lower yield of 85% of the 3-pyrroline **112l** (entry 12). The electron rich 4-methoxyphenyl substituted allenoate **104k** cyclized in 99% yield (entry 11).

A plausible mechanism for the intramolecular phosphine catalyzed γ-umpolung addition of α-aminoalkylallenic esters is shown in Scheme 22. Conjugate addition of the triphenylphosphine catalyst to α-aminoalkylallenic ester **104** generates phosphonium dienolate



Scheme 22 Plausible mechanism for the phosphine-catalyzed intramolecular γ-umpolung addition of α-aminoalkylallenic esters

113. A proton transfer event leads to phosphonium sulfonamide **114**, an intermediate analogous to that proposed in the mechanism for Lu's phosphine catalyzed [3 + 2] annulation between allenes and imines (see section 2.1, Scheme 2). 5-*endo* cyclization yields the resonance stabilized phosphorus ylide **115**. A second proton transfer event leads to zwitterion **116** which when followed by elimination of the phosphine catalyst provides the desired pyrroline **112** and reintroduces triphenylphosphine into the catalytic cycle.

Section 2.7 Conclusions

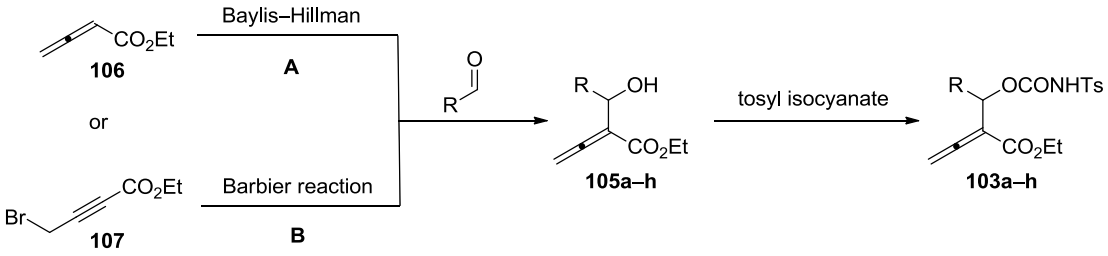
The studies described here resulted in the development of a high yielding and flexible synthesis of 2-substituted 3-pyrrolines, including 2-alkyl substituted 3-pyrrolines, by way of an intramolecular phosphine-catalyzed γ-umpolung addition of α-aminoalkylallenic esters.[20] This work represents the first example of an intramolecular phosphine-catalyzed γ-umpolung addition of a nitrogen based nucleophile and the first example of an intramolecular phosphine-catalyzed γ-umpolung addition to occur via a 5-*endo* cyclization. This method takes advantage of the mild, metal free conditions often encountered in reactions catalyzed by tertiary phosphines. Utilizing triphenylphosphine as a catalyst renders the transformation particularly operationally simple as this phosphine requires no special handling and is almost indefinitely stable on the bench top. The method circumvents the typical drawback of many phosphine-catalyzed pyrroline syntheses by allowing the incorporation of alkyl groups onto the heterocyclic structure. The necessary α-aminoalkylallenic esters can be prepared in moderate yields employing the aza-Baylis–Hillman reaction between *N*-tosyl imines and ethyl 2,3-butadienoate in the case of aryl of substituted substrates or a novel decarboxylative rearrangement of allenic carbamates in the case of alkyl substituted α-aminoalkylallenoates.

Section 2.8 Materials and Methods

Unless otherwise stated, all reactions were performed in flame-dried glassware fitted with rubber septa, under an Ar atmosphere, and agitated with a Teflon-coated stirrer bar. All reaction solvents were distilled immediately prior to use [dichloromethane (CH_2Cl_2), acetonitrile (MeCN), benzene (PhH), and toluene (PhMe) from CaH_2; tetrahydrofuran (THF) from Na/benzophenone ketyl; methanol (MeOH) from magnesium methoxide] and transferred with an oven-dried needle and a disposable syringe using standard Schlenk techniques. Thin layer chromatography (TLC) was performed using SiliCycle silica gel 60 F-254–precoated glass-backed plates (thickness: 0.25 mm) and visualized under UV light and through permanganate staining. Flash column chromatography was performed through SiliCycle Silica-P silica gel (particle size: 40–63 μm). ^1H and ^{13}C NMR spectra were recorder using Bruker Avance-300, Avance-500, ARX-400, and ARX-500 MHz spectrometers (^{13}C operating frequencies of 75, 125, 100, and 125 MHz, respectively). Chemical shifts (δ) are reported with respect to the solvent (^1H: δ = 7.26 ppm for $CHCl_3$; ^{13}C: δ = 77 ppm for $CDCl_3$). ^1H NMR spectroscopic data are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and number of protons. The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; pent = pentet; sext = sextet; sept = septet; oct = octet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; d sept = doublet of septets; ddd = doublet of doublets of doublets; m = multiplet; br = broad; app = apparent. ^{13}C NMR spectroscopic data are reported with respect to chemical shift (ppm). MALDI mass spectra were recorded using an AB/PerSpective DE-STR instrument. Samples for MALDI mass spectrometric analysis were dissolved in 2,5-dihydroxybenzoic acid as the matrix.

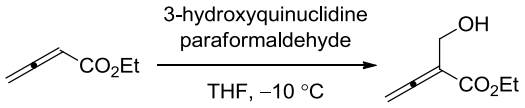
Section 2.9 Experimental Procedures

General strategy for the synthesis of allenylic carbamates



The allenylic carbamates **103a–h** were synthesized using the general strategy displayed above. The carbamates were synthesized by reacting the corresponding allenylic alcohols (**105a–h**) with tosyl isocyanate. The allenylic alcohols were synthesized by one of two methods: (i) a Baylis–Hillman reaction between ethyl 2,3-butadienoate (**106**) and the requisite aldehyde or (ii) a Barbier reaction between propargyl bromide (**107**) and the requisite aldehyde.[21]

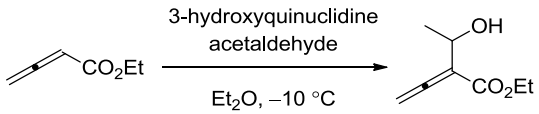
Synthesis of allenylic alcohols (105a–h)



3-Ethoxycarbonyl-1,2-butadiene-4-ol (105a)

Paraformaldehyde (2.8 g, 89.2 mmol, 5 equiv) was dried under vacuum for 45 min in a flame-dried round-bottom flask heated at 55 °C in an oil bath. After cooling to room temperature, dry THF (10 mL) was added and the solution was cooled to –10 °C (ice water/salt bath). 3-Hydroxyquinuclidine (91 mg, 0.72 mmol, 0.2 equiv) was introduced as a solution in THF (5 mL). A solution of ethyl-2,3-butadienoate (400 mg, 3.57 mmol, 1 equiv) in dry THF (5 mL) was then added dropwise to the chilled reaction mixture. The reaction temperature was maintained at

–10 °C for 1 h and then the flask was removed from the ice bath and warmed to room temperature with stirring for an additional 2.5 h. The reaction was quenched through the addition of saturated aqueous ammonium chloride. The layers were separated and the organic phase extracted with EtOAc. The combined organic extracts were washed sequentially with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified through flash column chromatography (15% EtOAc/hexane). The product was isolated in 66% yield as a thick oil. Spectral data was in accordance with that reported in the literature.[22]

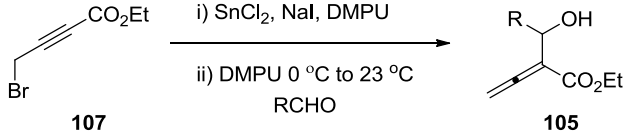


3-Ethoxycarbonyl-4-methyl-1,2-butadiene-4-ol (105b)

A flame-dried round-bottom flask equipped with a magnetic stirrer bar was charged with 3-hydroxyquinuclidine (114 mg, 0.9 mmol, 0.2 equiv) and placed under an Ar atmosphere. Diethyl ether (3 mL) was added and then the solution was cooled to –10 °C (ice water/salt bath). Ethyl-2,3-butadienoate (500 mg, 4.46 mmol, 1 equiv) and acetaldehyde (500 μL, 8.92 mmol, 2 equiv) were added sequentially. The reaction temperature was maintained at –15 °C for 1 h, at which point the reaction was complete (determined by TLC). The reaction was quenched through the addition of saturated aqueous ammonium chloride. The layers were separated and the aqueous phase extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified through flash column chromatography (10% EtOAc/hexane). The product was isolated in 73% yield as a thick oil. IR (film) ν_{max} = 3433, 2982, 2935, 2907, 1966, 1708, 1266, 1059 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (d, J = 2.2 Hz, 2H), 4.62–4.51 (m, 1H),

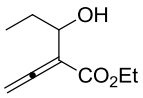
4.17 (d, J = 7.1 Hz, 1H), 4.12 (d, J = 7.1 Hz, 1H), 3.30 (d, J = 4.0 Hz, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 167.1, 104.3, 80.8, 64.7, 61.1, 21.0, 14.1. LRMS MALDI-MS: calculated for $C_8H_{12}O_3$ $[M + Na]^+$, m/z 179.07; found: 179.04.

General procedure for the formation of α-hydroxyalkyl allenoic esters 105c–h[19]

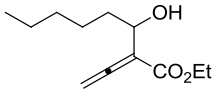


107 **105**

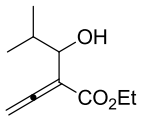
A flame-dried round-bottom flask equipped with a magnetic stirrer bar was placed under an Ar atmosphere and charged with propargyl bromide **107** (500 mg, 2.61 mmol, 1.25 equiv) and DMPU (4 mL). $SnCl_2$ (594 mg, 3.13 mmol, 1.5 equiv) and NaI (469 mg, 3.13 mmol, 1.5 equiv) were added sequentially as solids in single portions. The flask was covered with foil to protect the contents from light and then the mixture was stirred for 6 h. The flask was then cooled to 0 °C and a solution of the requisite aldehyde (2.1 mmol, 1 equiv) in DMPU (0.5 mL) was added over 15 min. The mixture was warmed to room temperature and stirred for 12 h; it was then cooled to 0 °C and diluted with diethyl ether. The reaction was quenched through the addition of saturated aqueous ammonium chloride. The aqueous phase was extracted four times with diethyl ether. The combined organic phases were combined, washed with brine, dried (Na_2SO_4), and filtered. The resulting solution was concentrated under reduced pressure and then the residue was purified through flash column chromatography (10–20% EtOAc/hexane).



3-Ethoxycarbonyl-4-ethyl-1,2-butadiene-4-ol (105c). Isolated in 50% yield. IR (film) ν_{max} = 3435, 2978, 2937, 1964, 1708, 1262, 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (d, J = 1.8 Hz, 2H), 4.31 (br s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.04 (br s, 1H), 1.65 (p, J = 7.2 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 167.1, 102.9, 80.5, 70.7, 61.2, 28.3, 14.2, 10.2. MALDI-MS: calculated for $C_9H_{14}O_3$ $[M + Na]^+$, m/z 193.1; found: 198.1.

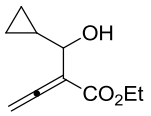


3-Ethoxycarbonyl-4-*n*-pentyl-1,2-butadiene-4-ol (105d). Isolated in 56% yield. IR (film) ν_{max} = 3445, 2933, 2860, 1965, 1712, 1259, 1069 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (d, J = 1.9 Hz, 2H), 4.37 (t, J = 6.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.04 (br s, 1H), 1.65–1.57 (m, 2H), 1.49–1.39 (m, 1H), 1.33–1.20 (m, 8H), 0.85 (t, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 167.1, 103.2, 80.5, 69.2, 61.2, 35.3, 31.6, 25.4, 22.6, 14.1, 14.0. MALDI-MS: calculated for $C_{13}H_{22}O_3$ $[M + Na]^+$, m/z 235.3; found: 235.1.

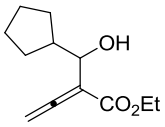


3-Ethoxycarbonyl-4-isopropyl-1,2-butadiene-4-ol (105e). Isolated in 57% yield. IR (film) ν_{max} = 3478, 2963, 2874, 1964, 1709, 1254, 1022 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (d, J

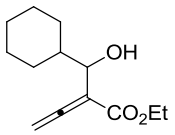
= 1.6 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.02 (t, J = 7.0 Hz, 1H), 2.93 (d, J = 7.4 Hz), 1.90 (app oct, J = 6.8 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 166.9, 102.1, 80.1, 75.3, 61.1, 33.0, 19.5, 17.9, 14.1. MALDI-MS: calculated for $C_{10}H_{16}O_3$ $[M + Na]^+$, m/z 207.10; found: 207.10.



3-Ethoxycarbonyl-4-cyclopropyl-1,2-butadiene-4-ol (105f). Isolated in 65% yield. IR (film) ν_{max} = 3465, 2986, 1963, 1710, 1256, 1208 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (d, J = 1.9 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.73 (d, 7.9 Hz, 1H), 3.12 (d, J = 3.4 Hz, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.18–1.10 (m, 1H), 0.63–0.56 (m, 1H), 0.52–0.40 (m, 2H), 0.27–0.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 167.0, 102.9, 80.2, 73.7, 15.8, 14.0, 3.5, 2.6. MALDI-MS: calculated for $C_{10}H_{14}O_3$ $[M + Na]^+$, m/z 205.08; found: 205.08.

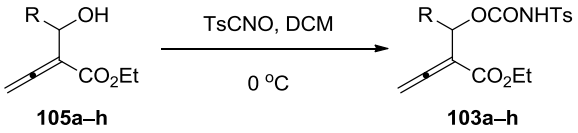


3-Ethoxycarbonyl-4-cyclopentyl-1,2-butadiene-4-ol (105g). Isolated in 62% yield. IR (film) ν_{max} = 3479, 2955, 2869, 1964, 1704, 1255, 1071, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.19 (br s, 1H), 2.17 (sext, J = 8.1 Hz, 1H), 1.88–1.76 (m, 1H), 1.67–1.41 (m, 7H), 1.25 (t, J = 4.8 Hz, 3H), 1.18–1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 167.1, 102.6, 80.0, 74.1, 61.1, 44.2, 29.44, 29.11, 25.6, 25.5, 14.0. MALDI-MS: calculated for $C_{12}H_{18}O_3$ $[M + Na]^+$, m/z 233.12; found: 233.12.

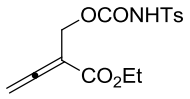


3-Ethoxycarbonyl-4-cyclohexyl-1,2-butadiene-4-ol (105h). Isolated in 80% yield. IR (film) ν_{max} = 3478, 2982, 2927, 2852, 1964, 1710, 1255, 1067 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (d, J = 1.0 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 2.96 (br s, 1H), 1.97 (d, J = 12.8 Hz, 1H), 1.76–1.54 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.22–1.09 (m, 3H), 1.02–0.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 166.9, 101.5, 79.8, 74.7, 61.0, 42.5, 29.7, 28.4, 26.3, 25.9, 25.7, 14.0. MALDI-MS: calculated for $C_{13}H_{20}O_3$ $[M + Na]^+$, m/z 247.13; found: 247.12.

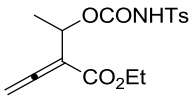
Synthesis of allenylic carbamates (103a–h)



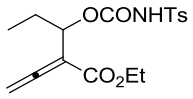
A flame-dried round-bottom flask equipped with a magnetic stirrer bar was charged with the requisite α-hydroxyalkylallenoate (**105**) (1.29 mmol, 1 equiv) and placed under an Ar atmosphere. Dry CH_2Cl_2 (10 mL) was added and the resulting solution cooled to 0 °C. Tosyl isocyanate (217 μL, 1.4 mmol, 1.1 equiv) was added in a single portion. The mixture was stirred without replacing the ice bath until all of the starting material had been consumed (TLC). The solution was concentrated under reduced pressure and then the crude residue was purified through flash chromatography (15% EtOAc/hexane).



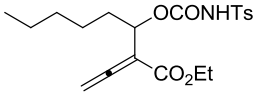
Ethyl-2-(tosylcarbamoyloxymethyl)-2,3-butadienoate (103a). Isolated in 82% yield as a white crystalline solid; m.p. 111–114 °C. This compound could also be recrystallized from EtOAc/hexanes. IR (film) ν_{max} = 3224, 2985, 1966, 1752, 1711, 1448, 1160 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.18 (t, J = 2.1 Hz, 2H), 4.76 (t, J = 2.1 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.42 (s, 1H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 165.1, 150.2, 145.0, 135.5, 129.6, 128.5, 96.3, 81.0, 62.9, 61.5, 21.7, 14.1. MALDI-MS: calculated for $C_{15}H_{17}NO_6S$ $[M + Na]^+$: m/z 362.07; found: 362.06.



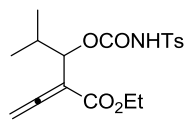
3-Ethoxycarbonyl)-(4-tosylcarbamoyloxy)-4-methyl-1,2-butadiene (103b). Isolated in 87% yield as a thick oil. IR (film) ν_{max} = 3232, 2988, 1967, 1750, 1717, 1450, 1357, 1286, 1224, 1162 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 5.53–5.48 (m, 1H), 5.20 (dd, J = 14.7, 2.1 Hz, 1H), 5.15 (dd, J = 14.6, 2.1 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.11 (t, J = 7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 164.7, 149.8, 144.7, 135.6, 129.3, 128.2, 101.8, 82.2, 69.4, 61.2, 60.4, 21.4, 18.9, 14.0, 13.8. MALDI-MS: calculated for $C_{16}H_{19}NO_6S$ $[M + Na]^+$: m/z 376.08; found: 376.04.



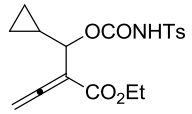
3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-ethyl-1,2-butadiene (103c). Isolated in 82% yield as a thick oil. IR (film) ν_{max} = 3231, 2981, 2938, 1970, 1750, 1717, 1447, 1162 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 5.38–5.35 (m, 1H), 5.20, (dd, J = 14.6, 1.9 Hz, 1H), 5.15 (dd, J = 14.6, 2.0 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.79–1.63 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 164.7, 149.7, 144.8, 135.6, 129.4, 128.3, 100.6, 81.7, 74.2, 61.2, 26.3, 21.5, 13.9, 9.3. MALDI-MS: calculated for $C_{17}H_{21}NO_6S$ [M + Na]$^+$: m/z 390.41; found: 390.21.



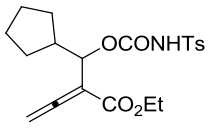
3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-*n*-pentyl-1,2-butadiene (103d). Isolated in 93% yield as a thick oil. IR (film) ν_{max} = 3236, 2950, 2921, 2862, 1748, 1713, 1450, 1164, 1082 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 2H) 7.29 (d, J = 8.2 Hz, 2H), 5.43–5.40 (m, 1H), 5.20 (dd, J = 14.5, 1.8 Hz, 1H), 5.14 (dd, J = 14.5, 1.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.71–1.58 (m, 2H), 1.22–1.15 (m, 9H), 0.83–0.79 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 164.7, 149.8, 144.7, 135.6, 129.4, 128.2, 100.9, 81.8, 73.1, 61.1, 33.1, 31.1, 24.6, 22.2, 21.5, 13.9, 13.8. MALDI-MS: calculated for $C_{20}H_{27}NO_6S$ [M + Na]$^+$: m/z 432.49; found: 432.32.



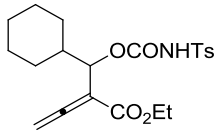
3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-isopropyl-1,2-butadiene (103e). Isolated in 84% yield as a thick oil. IR (film) ν_{max} = 3230, 2970, 2926, 2874, 1970, 1750, 1714, 1447, 1258, 1162, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.23–5.21 (m, 1H), 5.15 (dd, J = 14.5, 1.6 Hz, 1H), 5.08 (dd, J = 14.5, 1.9 Hz, 1H), 4.13 (dq, J = 7.1, 1.0 Hz, 2H), 2.42 (s, 3H), 2.05 (app oct, J = 6.7 Hz, 1H), 1.21 (t, J = 7.2 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 164.8, 149.8, 144.8, 135.6, 129.4, 128.2, 100.1, 81.4, 77.6, 61.2, 31.2, 21.5, 18.6, 17.1, 13.9. MALDI-MS: calculated for $C_{18}H_{23}NO_6S$ $[M + Na]^+$: m/z 404.11; found: 404.18.



3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-cyclopropyl-1,2-butadiene (103f). Isolated in 78% yield as a thick oil. IR (film) ν_{max} = 3230, 2985, 1964, 1715, 1448, 1353, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.27 (dd, J = 14.6, 1.4 Hz, 1H), 5.23 (dd, J = 14.6, 1.3 Hz, 1H), 4.88 (d, J = 9.0 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28–1.21 (m, 1H), 1.15 (t, J = 7.1 Hz, 3H), 0.52–0.40 (m, 3H), 0.32–0.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 164.7, 150.0, 144.6, 135.7, 129.3, 128.2, 100.9, 81.6, 77.2, 61.2, 60.4, 21.5, 14.0, 13.9, 3.9, 2.9. MALDI-MS: calculated for $C_{18}H_{21}NO_6S$ $[M + Na]^+$: m/z 402.10; found: 402.11.

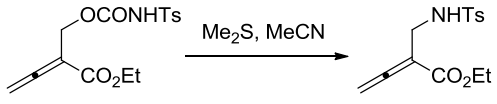


3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-cyclopentyl-1,2-butadiene (103g). Isolated in 83% yield as a thick oil. IR (film) ν_{max} = 3229, 2958, 2868, 1964, 1750, 1701, 1447, 1162. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 5.32 (d, J = 8.1 Hz, 1H), 5.19 (d, 14.6 Hz, 1H), 5.13 (d, J = 14.5, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 2.25 (app sext, J = 8.0 Hz, 1H), 1.61–1.34 (m, 6H), 1.26–1.20 (m, 2H), 1.74 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 164.9, 150.0, 144.6, 135.7, 129.3, 128.2, 100.8, 81.5, 76.4, 61.1, 42.8, 28.6, 28.3, 25.2, 25.2, 21.5, 13.9. MALDI-MS: calculated for $C_{20}H_{25}NO_6S$ [M + Na]$^+$: m/z 430.13; found: 429.95.



3-Ethoxycarbonyl-(4-tosylcarbamoyloxy)-4-cyclohexyl-1,2-butadiene (103h). Isolated in 74% yield as a thick oil. IR (film) ν_{max} = 3231, 2929, 2854, 1718, 1448, 1161, 1091 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 5.24–5.22 (m, 1H), 5.20 (dd, J = 14.6, 1.4 Hz, 1H), 5.14 (dd, J = 14.5, 1.6 Hz, 1H), 4.15 (q, J = 7.4 Hz, 2H), 2.44 (s, 3H), 1.73–1.59 (m, 4H), 1.54 (d, J = 12.7 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.20–0.84 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 164.9, 150.0, 144.7, 135.7, 129.4, 128.2, 99.8, 81.4, 77.1, 61.1, 40.6, 28.8, 27.5, 25.9, 25.4, 21.5, 13.9. MALDI-MS: calculated for $C_{21}H_{27}NO_6S$ [M + Na]$^+$: m/z 444.15; found: 444.16.

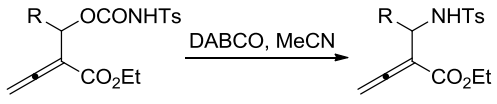
Synthesis of 3-ethoxycarbonyl-4-tosylamino-1,2-butadiene (1a)



103a **104a**

A flame-dried round-bottom flask equipped with a magnetic stirrer bar was placed under an Ar atmosphere and then dry MeCN (2 mL) was added followed by dimethyl sulfide (10.9 μL, 0.147 mmol, 1 equiv). A solution of the allenylic carbamate **103a** (50 mg, 0.147 mmol, 1 equiv) in dry MeCN (2 mL) was added via syringe pump over the course of 6 h; the mixture was then stirred for an additional 12 h at room temperature. The solution was concentrated under reduced pressure and the residue purified through flash column chromatography (10–20% EtOAc/hexane). The product was isolated in 56% yield as a yellow solid. IR (film) ν_{max} = 3289, 2985, 1970, 1700, 1330, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.22 (t, J = 6.4 Hz, 1H), 5.10 (t, J = 1.9 Hz, 2H), (4.11 (q, J = 7.1 Hz, 2H), 3.85–3.77 (m, 2H), 2.40 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 166.0, 143.3, 137.4, 129.5, 127.0, 96.5, 80.5, 77.2, 77.0, 76.7, 61.3, 42.2, 21.4, 14.0. MALDI-MS: calculated for $C_{14}H_{17}NO_4S$ $[M + Na]^+$: m/z 318.08; found: 318.04.

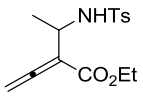
Synthesis of β′-alkyl-α-aminoalkylallenic esters (104b–h)



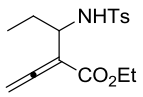
103 **104**

A flame-dried round-bottom flak equipped with a magnetic stirrer bar was charged with DABCO (63.5 mg, 0.566 mmol, 1 equiv), which was dissolved in dry benzene (8 mL) under an Ar atmosphere. The requisite allenylic carbamate **103** (0.566 mmol, 1 equiv) was dissolved in dry

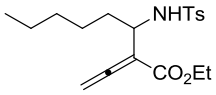
benzene (8 mL) and added via syringe pump over the course of 12 h. The solution was concentrated under reduced pressure and the crude residue purified through flash column chromatography (5–20% EtOAc/hexane).



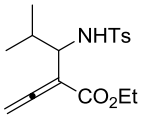
3-Ethoxycarbonyl-4-tosylamino-4-ethyl-1,2-butadiene (104b). Isolated in 65% yield as a thick oil. IR (film) ν_{max} = 3287, 2985, 2938, 1966, 1701, 1328, 1264, 1163 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 5.29 (d, J = 9.8 Hz, 1H), 5.07 (d, J = 14.2 Hz, 1H), 5.03 (d, J = 14.3 Hz, 1H), 4.26–4.20 (m, 1H), 4.10 (dq, J = 7.1, 1.0 Hz, 2H), 2.41 (s, 3H), 1.35 (d, J = 6.9 Hz, 3H), 1.97 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 165.3, 143.0, 137.9, 129.3, 127.1, 101.4, 80.6, 61.0, 49.6, 21.9, 21.3, 13.9. MALDI-MS: calculated for $C_{15}H_{19}NO_4S$ $[M + Na]^+$: m/z 332.09; found: 332.12.



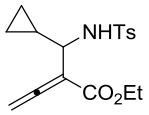
3-Ethoxycarbonyl-4-tosylamino-4-ethyl-1,2-butadiene (104c). Isolated in 54% yield as a thick oil. IR (film) ν_{max} = 3287, 2973, 2983, 1964, 1700, 1252, 1163 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 5.39 (d, J = 10.3 Hz, 1H), 5.01 (dd, J = 14.3, 0.9 Hz, 1H), 4.94 (dd, J = 14.3, 0.7 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 4.00–3.91 (m, 1H), 2.39 (s, 3H), 1.72–1.62 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 165.5, 143.1, 138.2, 129.4, 127.2, 99.7, 80.1, 61.1, 55.7, 28.7, 21.5, 14.1, 10.6. MALDI-MS: calculated for $C_{16}H_{21}NO_4S$ $[M + Na]^+$: m/z 346.11; found: 346.36.



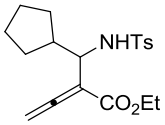
3-Ethoxycarbonyl-4-tosylamino-4-*n*-pentyl-1,2-butadiene (104d). Isolated in 27% yield as a thick oil. IR (film) ν_{max} = 3289, 2931, 2860, 1965, 1706, 1330, 1163 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 5.30 (d, J = 10.1 Hz, 1H), 5.03 (dd, J = 14.3, 0.8 Hz, 1H), 4.97 (dd, 14.2, 0.7 Hz, 1H), 4.16–3.99 (m, 1H), 4.07 (q, J = 7.4 Hz, 2H), 2.41 (s, 3H), 1.69–1.60 (m, 2H), 1.31–1.17 (m, 9H), 0.84 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 165.4, 142.9, 138.1, 129.2, 127.2, 99.9, 79.9, 60.9, 54.1, 35.3, 30.9, 25.4, 22.3, 21.3, 13.9, 13.8. MALDI-MS: calculated for $C_{19}H_{27}NO_4S$ $[M + Na]^+$: m/z 388.16; found: 387.99.



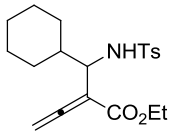
3-Ethoxycarbonyl-4-tosylamino-4-isopropyl-1,2-butadiene (104e). Isolated in 52% yield as a thick oil. IR (film) ν_{max} = 3282, 2967, 1976, 1695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.37 (d, J = 10.7 Hz, 1H), 4.96 (d, J = 14.3 Hz, 1H), 4.89 (d, J = 14.2 Hz, 1H), 3.75 (dd, J = 10.6, 7.9 Hz, 1H), 2.38 (s, 3H), 1.90 (app oct, J = 6.9 Hz, 1H), 1.16 (t, J = 7.1 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 165.7, 143.1, 138.1, 129.3, 127.2, 99.3, 80.1, 61.1, 59.7, 32.6, 21.5, 19.7, 18.7, 14.1. MALDI-MS: calculated for $C_{17}H_{23}NO_4S$ $[M + Na]^+$: m/z 360.12; found: 360.15.



3-Ethoxycarbonyl-4-tosylamino-4-cyclopropyl-1,2-butadiene (104f). Isolated in 45% yield as a white solid. IR (film) ν_{max} = 3287, 3067, 2989, 1967, 1702, 1425, 1327, 1254, 1156 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 5.50 (d, J = 9.4 Hz, 1H), 5.05 (d, J = 14.2 Hz, 1H), 4.99 (d, J = 14.2 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.41(t, J = 9.1 Hz, 1H), 2.41 (s, 3H), 1.25–1.18 (m, 4H), 0.54–0.44 (m, 2H), 0.34–0.29 (m, 1H), 0.27–0.23 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 165.7, 143.0, 138.2, 129.2, 127.1, 99.1, 79.9, 61.1, 58.7, 21.4, 16.6, 14.0, 4.6, 3.9. MALDI-MS: calculated for $C_{17}H_{21}NO_4S$ $[M + Na]^+$: m/z 358.11; found: 358.07.

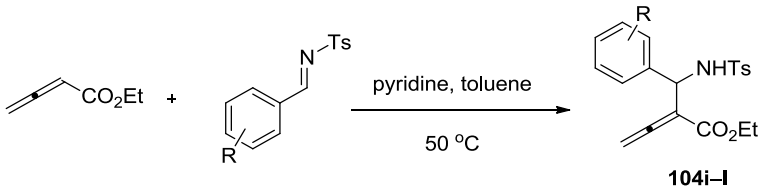


3-Ethoxycarbonyl-4-tosylamino-4-cyclopentyl-1,2-butadiene (104f). Isolated in 45% yield as a thick oil. IR (film) ν_{max} = 3293, 2954, 1700, 1162 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 10.5 Hz, 1H), 4.98 (d, J = 14.0 Hz, 1H), 4.89 (d, J = 14.2 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.78 (t, J = 10.1 Hz, 1H), 2.40 (s, 3H), 2.20 (sext, J = 8.3 Hz, 1H), 1.84–1.77 (m, 1H), 1.62–1.46 (m, 5H), 1.40–1.32 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.15–1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 165.6, 142.9, 138.1, 129.2, 127.1, 99.3, 79.4, 60.9, 58.8, 44.3, 29.9, 29.8, 25.1, 25.0, 21.4, 14.0. MALDI-MS: calculated for $C_{19}H_{25}NO_4S$ $[M + Na]^+$: m/z 386.14; found: 386.24.



3-Ethoxycarbonyl-4-tosylamino-4-cyclohexyl-1,2-butadiene (104g). Isolated in 51% yield as a thick oil. IR (film) ν_{max} = 3290, 2928, 2853, 1965, 1699, 1704, 1163 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 5.37 (d, J = 10.7 Hz, 1H), 4.95 (d, J = 14.2 Hz, 1H), 4.87 (d, J = 14.2 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 3.78 (t, J = 8.6 Hz, 1H), 2.40 (s, 3H), 1.98 (d, J = 13.7 Hz, 1H), 1.64–1.55 (m, 5H), 1.17 (t, J = 7.2 Hz, 3H), 1.15–1.12 (m, 3H), 0.93–0.90 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 165.6, 142.8, 138.1, 129.2, 127.1, 98.5, 79.5, 60.9, 59.1, 41.5, 29.9, 29.2, 26.0, 25.7, 25.6, 21.3, 13.9. MALDI-MS: calculated for $C_{20}H_{27}NO_4S$ $[M + Na]^+$: m/z 400.16; found: 400.16.

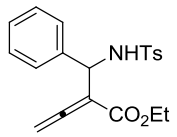
Synthesis of *β′*-aryl-*α*-aminoalkylallenic esters (104i–l)[23a]



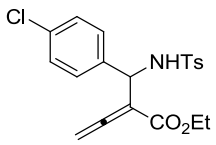
104i–l

A flame-dried round-bottom flask equipped with a magnetic stirrer bar was charged with the requisite imine (1.78 mmol, 1 equiv), which was dissolved in dry toluene (8 mL) under an Ar atmosphere. Ethyl-2,3-butadienoate (300 mg, 2.68 mmol, 1.5 equiv) was added, followed by pyridine (28.7 µL, 0.356 mmol, 0.2 equiv). The mixture was heated at 50 °C for 12 h, at which point a second portion of pyridine was added (28.7 µL, 0.356 mmol, 0.2 equiv). The mixture was then stirred at 50 °C for an additional 12 h. The solution was concentrated under reduced

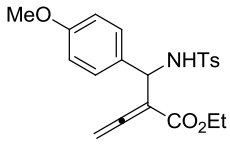
pressure and the crude residue purified through flash column chromatography (20% EtOAc/hexane).



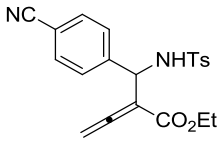
3-Ethoxycarbonyl-4-tosylamino-4-phenyl-1,2-butadiene (104i). Isolated in 56% yield as a yellow solid. All spectral data were in accordance with those in the literature.[21b]



3-Ethoxycarbonyl-4-tosylamino-4-*p*-chlorophenyl-1,2-butadiene (104j). Isolated in 54% yield as a yellow solid. All spectral data were in accordance with those in the literature.[21b]

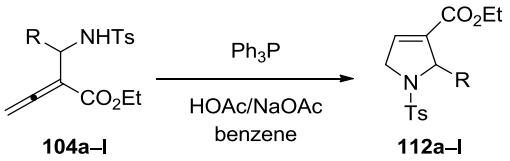


3-Ethoxycarbonyl-4-tosylamino-4-*p*-methoxyphenyl-1,2-butadiene (104k). Isolated in 33% yield as a yellow solid. All spectral data were in accordance with those in the literature.[21b]



3-Ethoxycarbonyl-4-tosylamino-4-*p*-cyanophenyl-1,2-butadiene (104l). Isolated in 25% yield as a thick oil. IR (film) ν_{max} = 3274, 2985, 2220, 1700, 1339, 1163 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 6.03 (d, J = 9.7 Hz, 1H), 5.32, (d, J = 9.7 Hz, 1H), 5.22 (d, J = 14.7 Hz, 1H), 5.12 (d, J = 14.8 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 164.9, 144.5, 143.6, 132.1, 129.5, 127.3, 127.0, 118.4, 11.4, 99.8, 81.7, 61.5, 56.2, 21.4, 13.9. MALDI-MS: calculated for $C_{21}H_{20}N_2O_4S$ $[M + Na]^+$: m/z 419.10; found: 419.06.

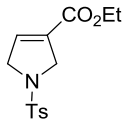
Procedure for intramolecular γ-umpolung addition, formation of pyrrolines (112a–l)



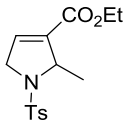
104a–l **112a–l**

A flame-dried round-bottom flask equipped with a magnetic stirrer bar was charged with the requisite allenoate **104** (0.123 mmol, 1 equiv), Ph_3P (6.46 mg, 0.025 mmol, 0.2 equiv), and NaOAc (5.04 mg, 0.062 mmol, 0.5 equiv), which were placed under an Ar atmosphere. Dry benzene (4.1 mL) was added to this mixture, followed by AcOH (3.52 µL, 0.62 mmol, 0.5 equiv). The mixture was stirred at room temperature and monitored (TLC) for consumption of the starting allenoate **104**. Upon completion of the reaction, the solution was concentrated under

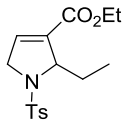
reduced pressure and the crude residue purified through flash column chromatography (10–20% EtOAc/hexane).



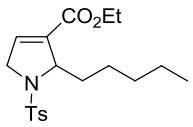
3-Carbethoxy-3-pyrroline (112a). Isolated in 62% yield. Following the same procedure as outlined above, but without the addition of NaOAc and AcOH, the product was isolated in 87% yield. All spectral data were in accordance with those reported in the literature.[24]



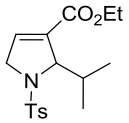
3-Carbethoxy-2-methyl-3-pyrroline (112b). Isolated in 99% yield as a thick oil. IR (film) ν_{max} = 2985, 2926, 2862, 1717, 1347, 1267, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 6.53 (s, 1H), 4.78–4.67 (m, 1H), 4.41–4.26 (m, 1H), 4.26–4.12 (m, 3H), 2.41 (s, 3H), 1.53 (t, J = 6.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 143.5, 136.5, 135.1, 134.6, 129.7, 127.3, 62.0, 60.7, 54.4, 22.1, 21.4, 14.0. MALDI-MS: calculated for $C_{15}H_{19}NO_4S$ $[M + Na]^+$: m/z 332.09; found: 332.16.



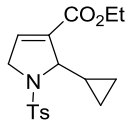
3-Carbethoxy-2-ethyl-3-pyrroline (112c). Isolated in 97% yield as a thick oil. IR (film) ν_{max} = 2972, 1718, 1347, 1249, 1164, 1083, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.59–6.57 (m, 1H), 4.81–4.79 (m, 1H), 4.24–4.22 (m, 2H), 4.19–4.13 (m, 2H), 2.41 (s, 3H), 2.08–2.00 (m, 1H), 1.94–1.87 (m, 1H), 1.25 (t, J = 7.1, 3H), 0.83 (t, J = 7.4, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 143, 136.2, 134.6, 134.3, 129.7, 127.2, 66.6, 60.7, 55.3, 26.6, 21.4, 14.0, 7.4. MALDI-MS: calculated for $C_{16}H_{21}NO_4S$ [M + Na]$^+$: m/z 346.11; found: 346.13.



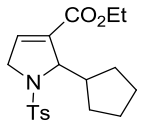
3-Carbethoxy-2-*n*-pentyl-3-pyrroline (112d). Isolated in 69% yield as a thick oil. IR (film) ν_{max} = 2929, 2860, 1717, 1349, 1262, 1164, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.54 (br d, J = 1.6 Hz, 1H), 4.80 (app s, 1H), 4.27–4.21 (m, 2H), 4.20–4.11 (m, 2H), 2.41 (s, 3H), 1.98–1.90 (m, 1H), 1.88–1.80 (m, 1H), 1.38–1.11 (m, 6H), 1.25 (t, J = 11.3 Hz, 3H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 143.5, 135.9, 134.9, 134.7, 129.7, 127.2, 66.0, 60.7, 55.1, 33.6, 31.6, 23.0, 22.4, 21.4, 14.0, 13.9. MALDI-MS: calculated for $C_{19}H_{27}NO_4S$ [M + Na]$^+$: m/z 388.18; found: 388.15.



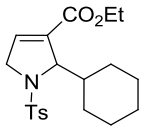
3-Carbethoxy-2-isopropyl-3-pyrroline (112e). Isolated in 97% yield as a thick oil. IR (film) ν_{max} = 3084, 2966, 2933, 2874, 1717, 1463, 1348, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.49 (pent, J = 1.3 Hz, 1H), 4.75 (dt, J = 3.1, 1.0 Hz, 1H), 4.22 (dd, J = 18.3, 2.5 Hz, 1H), 4.14 (dq, J = 7.1, 1.4 Hz, 2H), 4.09 (ddd, J = 18.4, 4.4, 1.7 Hz, 1H) 2.39 (s, 3H), 2.2 (d sept, J = 6.9, 2.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 143.5, 136.5, 135.3, 134.4, 129.6, 127.4, 71.3, 60.6, 55.9, 32.9, 21.4, 19.3, 16.7, 13.9. MALDI-MS: calculated for $C_{17}H_{23}NO_4S$ $[M + Na]^+$: m/z 360.12; found: 360.12.



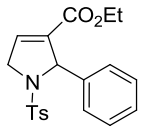
3-Carbethoxy-2-cyclopropyl-3-pyrroline (112f). Isolated in 95% yield as a thick oil. IR (film) ν_{max} = 3078, 2979, 2916, 2852, 1717, 1346, 1261, 1163 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3, 2H), 6.51 (s, 1H), 4.54 (t, J = 5.2 Hz), 4.28–4.12 (m, 4H), 2.40 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.12–1.01 (m, 1H), 0.81–0.71 (m, 1H), 0.60–0.37 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 143.5, 136.5, 135.5, 135.0, 129.6, 127.3, 28.3, 60.7, 54.9, 21.4, 16.0, 14.009, 3.4, 2.4. GC-MS: calculated for $C_{17}H_{21}NO_4S$ $[M]^+$: m/z 335.12; found: 335.1.



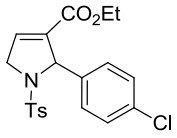
3-Carbethoxy-2-cyclopentyl-3-pyrroline (112g). Isolated in 85% yield as a thick oil. IR (film) ν_{max} = 2955, 2870, 1717, 1345, 1257, 1163, 1091. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 6.43 (app. s, 1H), 4.92, (t, J = 4.1 Hz, 1H), 4.21 (dd, J = 18.4, 2.6 Hz, 1H), 4.18–4.09 (m, 3H), 2.39 (s, 3H), 2.31–2.24 (m, 1H), 1.74–1.66 (m, 3H), 1.63–1.45 (m, 4H), 1.33–1.26 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 143.5, 136.4, 135.9, 134.4, 129.6, 127.4, 68.5, 60.6, 55.7, 45.0, 28.5, 27.4, 25.0, 24.4, 21.4, 14.0. MALDI-MS: calculated for $C_{19}H_{25}NO_4S$ $[M + Na]^+$: m/z 386.14; found: 386.17.



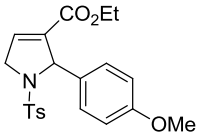
3-Carbethoxy-2-cyclohexyl-3-pyrroline (112h). Isolated in 69% yield (93% based on recovered starting material) as a thick oil. IR (film) ν_{max} = 2985, 2928, 2854, 1717, 1345, 1164 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 4.70 (app s, 1H), 4.20 (dd, J = 18.4, 2.7 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.06 (dd, J = 2.0, 2.74 Hz, 1H), 2.37 (s, 3H), 1.81–1.68 (m, 4H), 1.65–1.56 (m, 2H), 1.40 (dq, J = 12.5, 3.0 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.18–1.02 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 143.5, 136.4, 135.1, 134.4, 129.5, 127.4, 71.0, 60.6, 55.8, 42.8, 30.0, 27.1, 26.3, 26.3, 26.11, 21.4, 14.0. MALDI-MS: calculated for $C_{20}H_{27}NO_4S$ $[M + Na]^+$: m/z 400.16; found: 400.16.



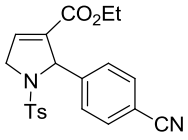
3-Carbethoxy-2-phenyl-3-pyrroline (112i). Isolated in 93% yield. All spectral data were in accordance with those reported in the literature.[22]



3-Carbethoxy-2-*p*-chlorophenyl-3-pyrroline (112j). Isolated in 88% yield (procedure was performed as described above, but without the addition of AcOH and NaOAc). All spectral data were in accordance with those reported in the literature.[25]



3-Carbethoxy-2-*p*-methoxyphenyl-3-pyrroline (112k). Isolated in 99% yield. All spectral data were in accordance with those reported in the literature.[23]



3-Carbethoxy-2-*p*-cyanophenyl-3-pyrroline (112l). Isolated in 85% yield. IR (film) ν_{max} = 3068, 2983, 2229, 1722, 1347, 1163, 1093 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J*

= 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.79 (J = 8.2 Hz, 2H), 6.79 (app d, J = 1.8 Hz, 1H), 5.68 (app s, 1H), 4.49–4.40 (m, 2H), 4.06–3.95 (m, 2H), 2.38 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 145.1, 143.9, 136.4, 134.9, 134.8, 132.0, 129.7, 128.5, 127.0, 118.5, 111.6, 28.4, 61.0, 55.2, 21.4, 13.8. MALDI-MS: calculated for $C_{21}H_{20}N_2O_4S$ $[M + Na]^+$: m/z 419.10; found: 419.08.

Section 2.10 References

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[1] Nitrogen containing heterocycles are present in six of the top ten best selling pharmaceuticals of 2009 (as ranked by worldwide sales); Lipitor® (Pfizer), Zyprexa® (Lilly), Crestor® (AstraZeneca), Seroquel® (AstraZeneca), Nexium® (AstraZeneca), Plavix® (Bristol–Meyers Squibb). See: Mack, D. J.; Brichacek, M.; Plichta, A,; Njardarson, J. T. Top 200 Pharmaceutical Products by Worldwide Sales in 2009. http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster (accessed in February 2011).

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Chapter 3

Enantioselective Total Synthesis of (+)-Ibophyllidine

Section 3.1 Introduction

The isolation of (+)-ibophyllidine (**1**) from the leaves of *Tabernanthe iboga* and *Tabernanthe subsessilis* was first reported in 1976 (Figure 1).[1] The structure of this architecturally novel alkaloid was assigned based on mass spectrometry, ultraviolet spectroscopy, infrared spectroscopy, ^{1}H nuclear magnetic resonance and ^{13}C nuclear magnetic resonance analyses. In 1980, two separate reports described a total of five related family members isolated from *Tabernaemontana albiflora*: 20-*epi*-ibophyllidine (**2**), 18-hydroxy-20-*epi*-ibophyllidine (**3**), 19-hydroxy-ibophyllidine (**4**), 19-hydroxy-20-*epi*-ibophyllidine (**5**), and desethylibophyllidine (**6**).[2] These six natural products represent the entirety of the known ibophyllidine family of alkaloids, all of which posses an uncommon pyrrolizino[1,7-*cd*]carbazole ring system that varies with respect to the substitution and stereochemistry at C20 (ibophyllidine numbering, see Figure 1). The structure of the ibophyllidines (**7**) is closely related to those of the aspidosperma/kopsia (**8**) and strychnos (**9**) families of alkaloids, all of which originate from the

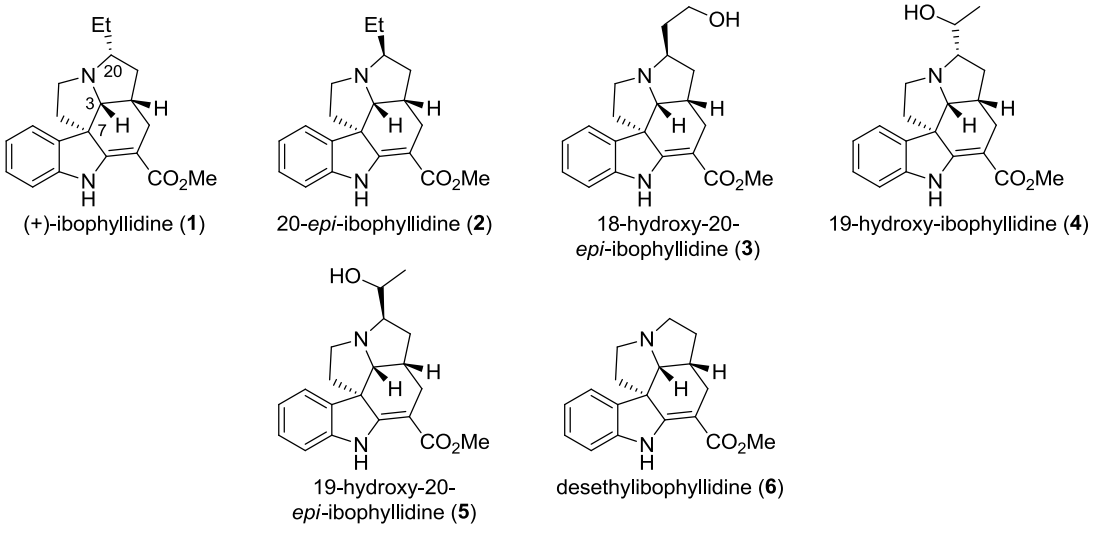


Figure 1 Ibophyllidine family of natural products

same biosynthetic precursors, tryptamine (**10**) and secologanin (**11**) (Figure 2).[3] As seen in Figure 2, these alkaloid families share the same A-B-C-E ring fused tetracycle, but vary with respect to the structure of the more highly variable D-ring. Of particular interest in the structural variation among these alkaloids is the fact that in most cases, all ten carbon atoms (nine in those lacking the ester functional group) from secologanin (not counting the glucose residue) are conserved. However, in the case of the ibophyllidine alkaloids only nine carbons from the terpene unit remain in the final product (seven in the case of desethylibophyllidine). The resultant natural products thus contain a unique 5-membered pyrrolidine D-ring in place of the more commonly encountered 6-membered piperidine ring of the aspidosperma, pseudoaspidospermidine, and some iboga alkaloids. This characteristic architectural difference is proposed to arise from a biogenetic excision of a single carbon atom from the pandoline alkaloids (*vide infra*). From a structural standpoint, the ibophyllidines are classified as "iboga"

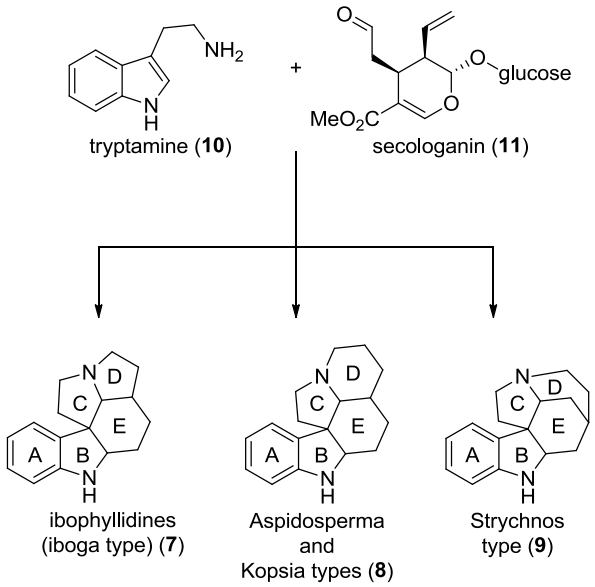


Figure 2 Common biosynthetic origins of the ibophyllidines, aspidosperma/kopsia, and strychnos alkaloids

type alkaloids. The classification of monoterpene indole alkaloids derived from these two biosynthetic precursors is based on the arrangement of the secologanine-derived carbon atoms in the natural product (Figure 3).[4] The corynanthe type alkaloids [e.g., ajmalicine (**12**)] maintain the same arrangement that is found in secologanin while the iboga [e.g., ibophyllidine (**1**)], and aspidosperma types [e.g., vincadifformine (**13**)] exhibit rearranged carbon connectivity.

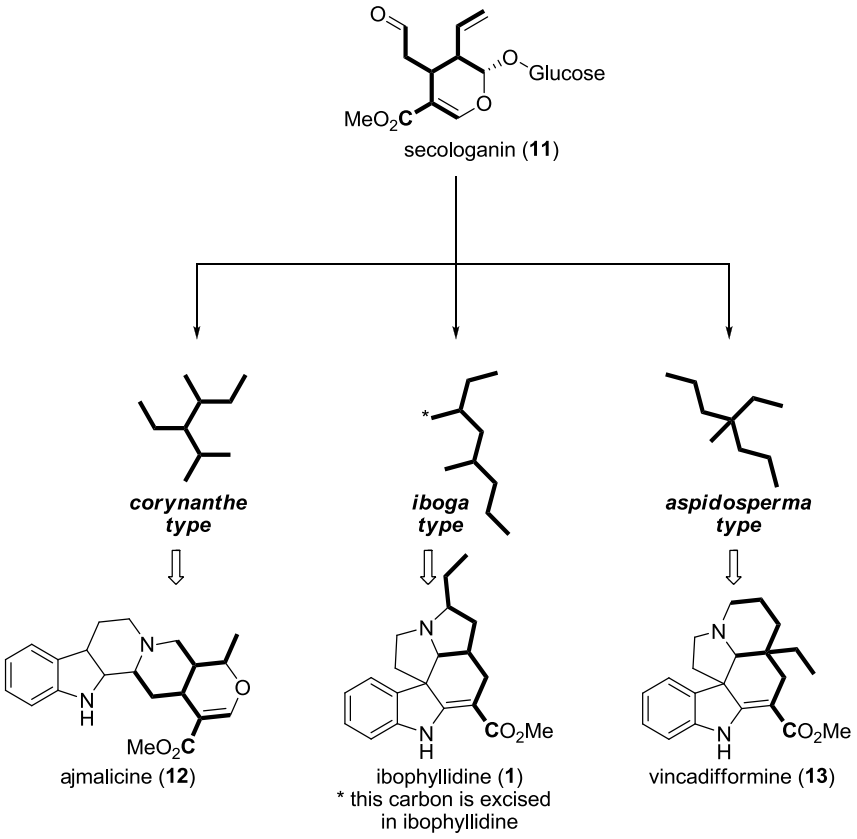
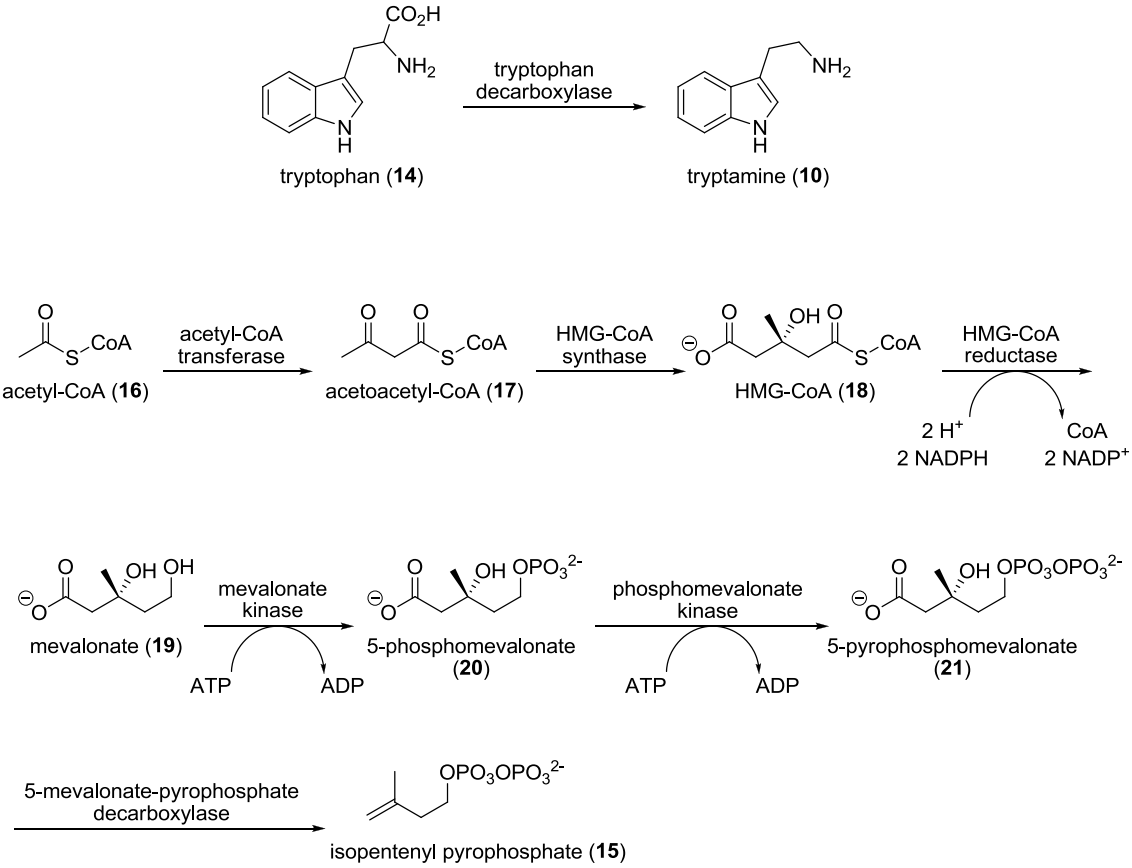


Figure 3 Arrangement of secologanin's carbon atoms in corynanthe, iboga, and aspidosperma type alkaloids

Section 3.2 Biosynthesis

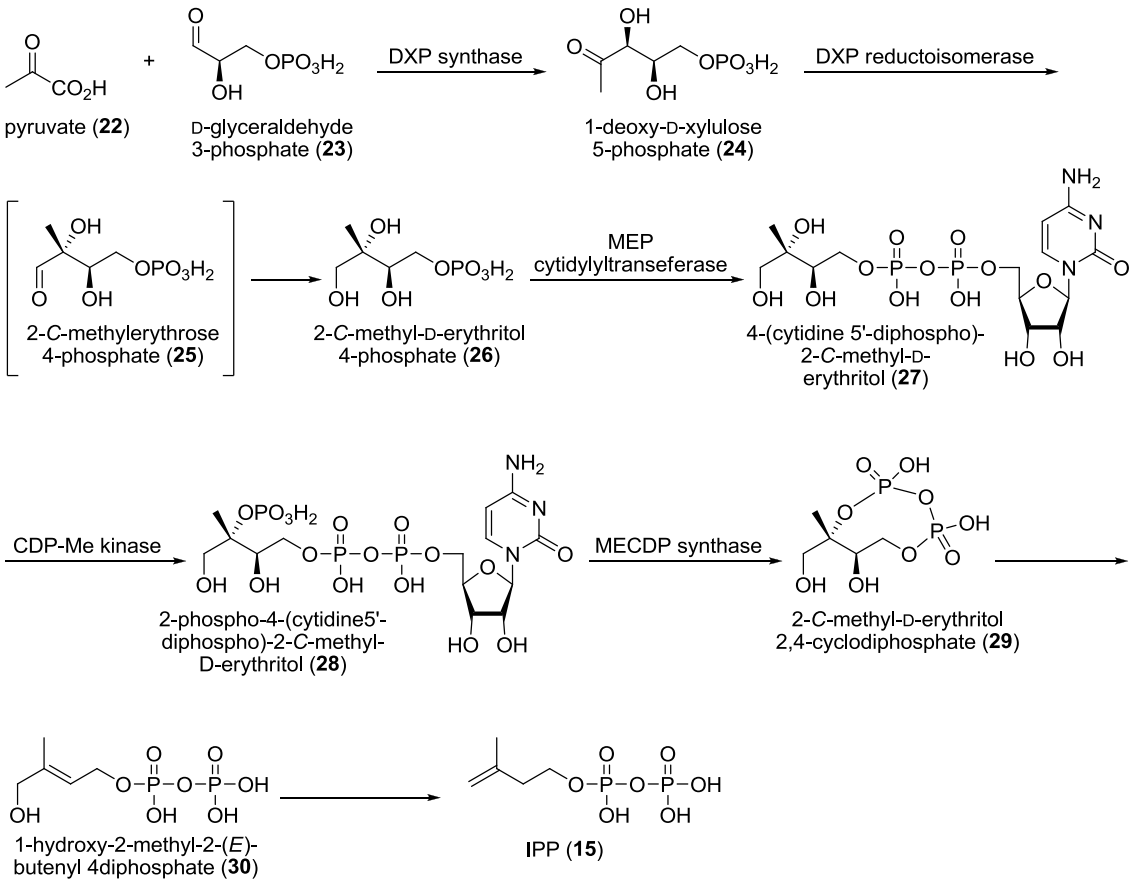
As previously mentioned, all natural products of the terpene indole alkaloid variety can be traced to a biosynthetic feedstock consisting of tryptamine (**10**) and secologanin (**11**). Tryptamine is synthesized within the plant of origin by the decarboxylation of the naturally occurring amino acid L-tryptophan (**14**) by tryptophan decarboxylase, a homogeneously isolated and fully characterized enzyme (Scheme 1).[5] Secologanin biosynthesis is a considerably more involved process uitilizing isopentenyl pyrophosphate (IPP, **15**), which can be biosynthetically generated in one of two ways.[6] The first possibility, outlined in Scheme 1, is as follows: Acetyl-CoA (**16**) first undergoes a self-condensation to yield acetoacetyl-CoA (**17**), mediated by acetyl-



Scheme 1 Biosynthesis of tryptamine and secologanin

CoA transferase. A third acetyl-CoA is then added and hydrolyzed in the presence of HMG-CoA synthase to yield 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, **18**). HMG-CoA is then reduced to mevalonate (**19**) by NADPH in the presence of HMG-CoA reductase. Mevalonate is converted to 5-phosphomevalonate (**20**) via mevalonate kinase, followed by conversion to 5-pyrophosphomevalonate (**21**) by phosphomevalonate kinase. IPP is then produced by decarboxylation of 5-pyrophosphomevalonate by mevalonate-5-pyrophosphate decarboxylase.

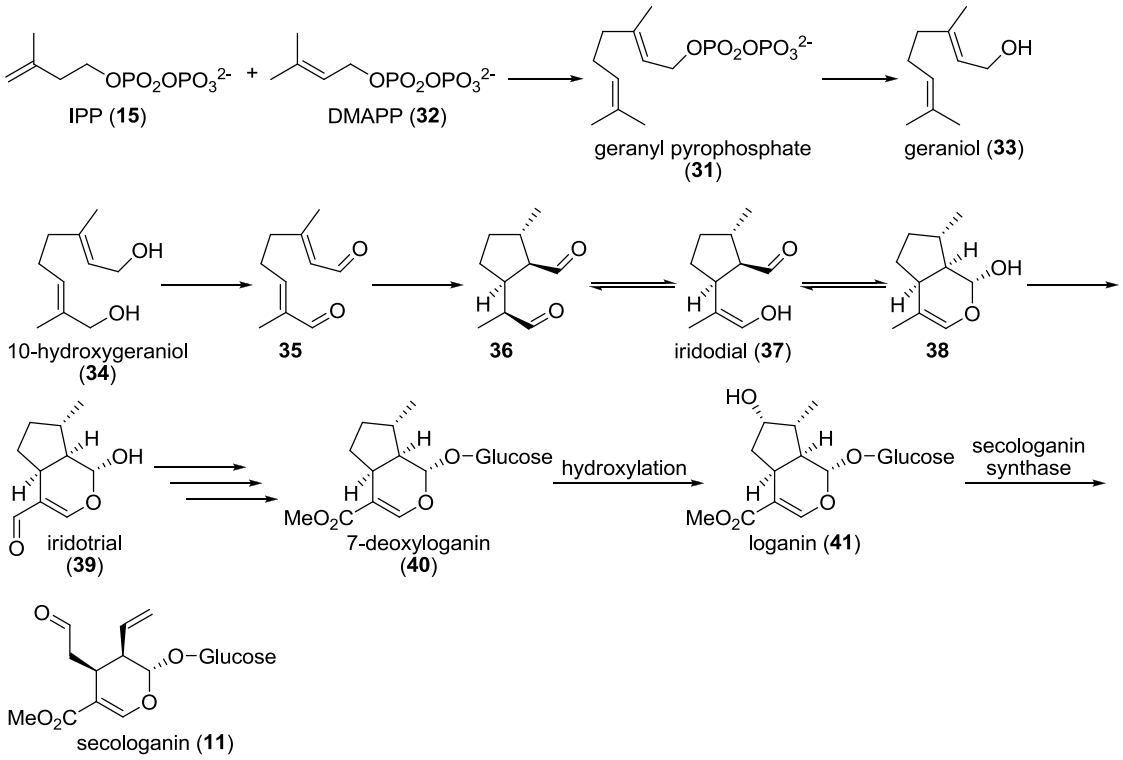
The aforementioned biosynthesis of IPP is the typically invoked process for terpene biosynthesis as well as the often invoked origin of IPP in monoterpene-indole alkaloid formation. However, more recent *in-vitro* feeding studies of cells from *catharanthus roseus* provide strong



Scheme 2 Non-mevalonate pathway for isopentenyl pyrophosphate biosynthesis

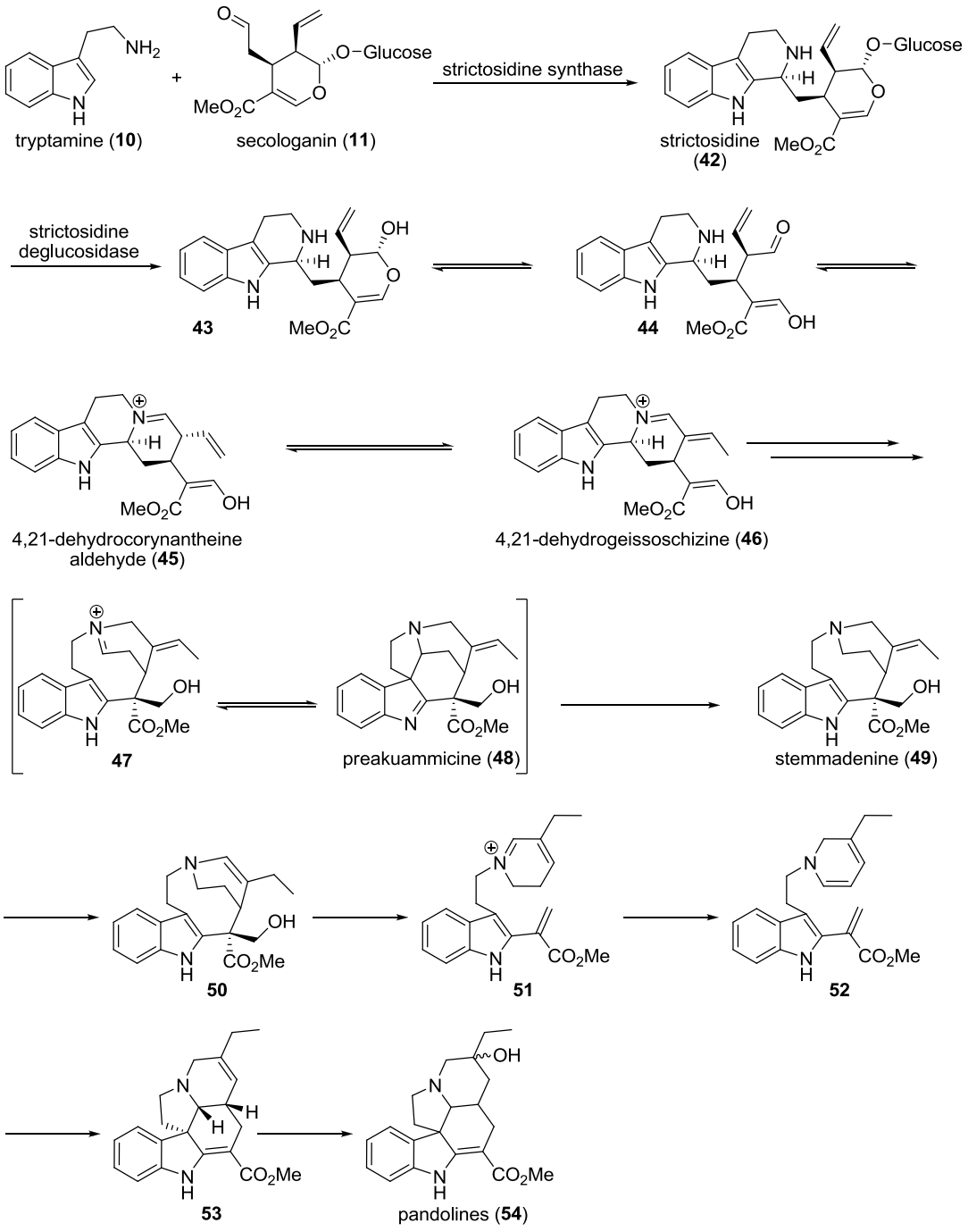
evidence in support of secologanin biosynthesis utilizing IPP generated from the trios phosphate/pyruvate pathway that does not utilize mevalonate.[7] In this alternative pathway the first step involves condensation of pyruvate (**22**) and D-glyceraldehyde-3-phosphate (**23**) to produce 1-deoxy-D-xylulose 5-phosphate (DXP, **24**) (Scheme 2). This molecule then undergoes a carbon skeleton rearrangement to give 2-*C*-methylerythrose 4-phosphate (**25**), followed by reduction, yielding 2-*C*-methyl-D-erythritol 4-phosphate (MEP, **26**), all mediated by the enzyme DXP reductoisomerase. MEP is converted to 4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol (CPD-ME, **27**) by cytidylyltransferase. The tertiarty carbinol of CPD-ME is converted to the corresponding phosphate by CDP-Me kinase to yield 2-phospho-4-(cytidine 5′-diphospho)-2-*C*-methyl-D-erythritol (**28**). MECDP synthase converts this to the cyclic diphosphate 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate (MECDP, **29**). This is then converted to 1-hydroxy-2-methyl-2-(*E*)-butenyl 4-diphosphate (**30**) which is then converted to isopentenyl pyrophosphate (IPP, **15**) that can be utilized for terpenoid synthesis.

Biosynthesis of all terpenoids begins with the production of geranyl pyrophosphate (**31**) from IPP (**15**) and its double bond isomer dimethylallyl pyrophosphate (DMAPP, **32**) (Scheme 3). Hydrolysis of geranyl pyrophosphate to geraniol (**33**) followed by hydroxylation by geraniol-10-hydroxylase yields 10-hydroxy-geraniol (**34**). Although not all of the enzymes have been characterized, the pathway to secologanin is believed to proceed by oxidation to dialdehyde **35** and cyclization to give cyclopentane **36** which is in equilibrium with its enol form, iridodial (**37**). Hemiacetal formation from iridodial to yield bicycle **38** followed by allylic oxidation yields iridotrial **39** which undergoes oxidation, glycosylation, and esterification to provide 7-deoxyloganin (**40**). Hydroxylation of 7-deoxyloganin yields loganin (**41**), which is converted to secologanin (**11**) via the known enzymatic transformation of secologanin synthase.



Scheme 3 Synthesis of secologanin from isopentenyl pyrophosphate

The first committed step toward terpene indole alkaloid synthesis involves the enzymatic Pictet–Spengler cyclization between tryptamine (**10**) and secologanin (**11**) (Scheme 4). The cyclization product, strictosidine (**42**) is then deglycosylated by strictosidine deglucosidase to yield **43**. This compound is in equilibrium with the open dialdehyde form (shown as the enol, **44**) which is also equilibrium with the intramolecular condensation product 4,21-dehydrocorynantheine (**45**). This intermediate undergoes allylic isomerization to provide 4,21-dehydrogeissoschizine (**46**). Although the evidence for 4,21-dehydrogeissoschizine's role as a metabolic precursor is not completely confirmed, nor is the exact mechanism fully understood, it is generally proposed that fragmentation of this intermediate yields the unstable secondary metabolite preakuammicine (**48**) via cyclization of iminium ion **47**. Reductive

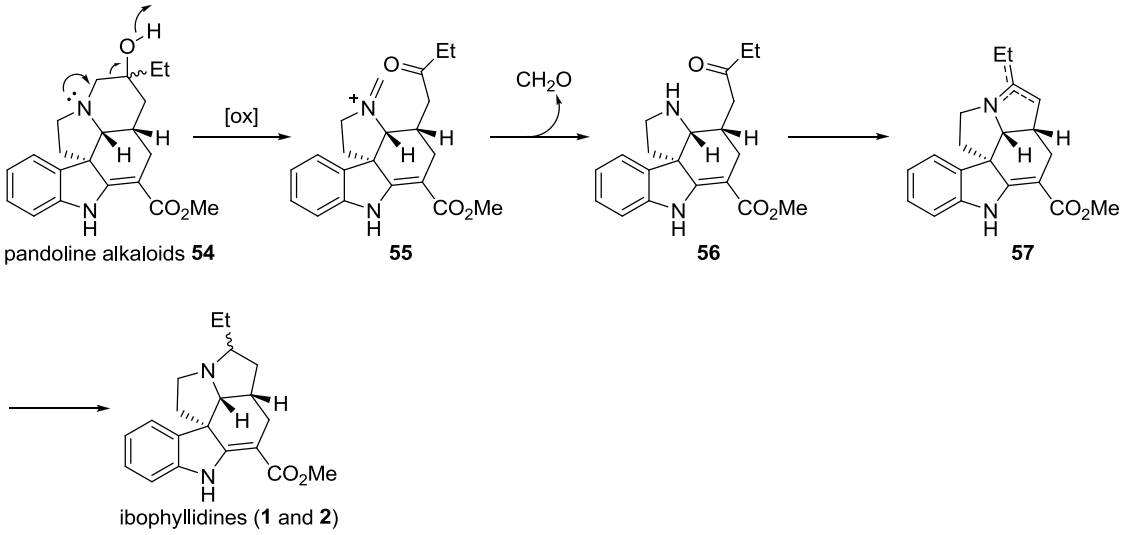


Scheme 4 Proposed biosynthesis of the pandoline alkaloids

cleavage of preakuammicine's pyrrolidine ring yields stemmadenine (**49**). Isomerization of the exocyclic olefin of stemmadenine into the piperidine ring provides cyclic enamine **50**, which

upon fragmentation results in iminium ion **51**. Proton transfer results in the formation of diene **52**. This intermediate undergoes an intramolecular Diels–Alder type cyclization to yield the pentacyclic skeleton of a number of pseudoaspidospermidine alkaloids (**53**). Oxidation of the olefin yields the pandoline alkaloids **54**.[3b] It is proposed that ibophyllidine and 20-*epi*-ibophyllidine are derived from the pandoline alkaloids via the biogenetic excision of a single carbon atom.

The proposed biosynthesis of the ibophyllidines from the pandoline alkaloids is shown in Scheme 5.[2b] Oxidative cleavage of either pandoline or 20-*epi*-pandoline **54** leads to keto-iminium ion **55**. Hydrolytic cleavage of the iminium ion liberates formaldehyde representing the necessary carbon loss. Intramolecular condensation of the pyrrolidine amine and the pendant ketone results in an equilibrium mixture of iminium and enamine **57**. Reduction of this mixture leads to ibophyllidine and 20-*epi*-ibophyllidine (**1** and **2**). Although the literature is remiss of evidence in support of the proposed oxidative cleavage, the condensation/reduction sequence has been successfully carried out in the laboratory during the course of a number of total synthesis

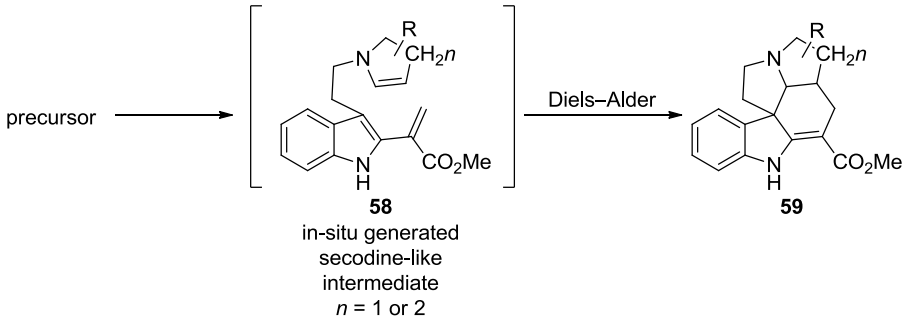


Scheme 5 Proposed biosynthesis of ibophyllidine alkaloids from the pandolines

efforts (*vide infra*).

Section 3.3 Previous Syntheses of Ibophyllidine Alkaloids

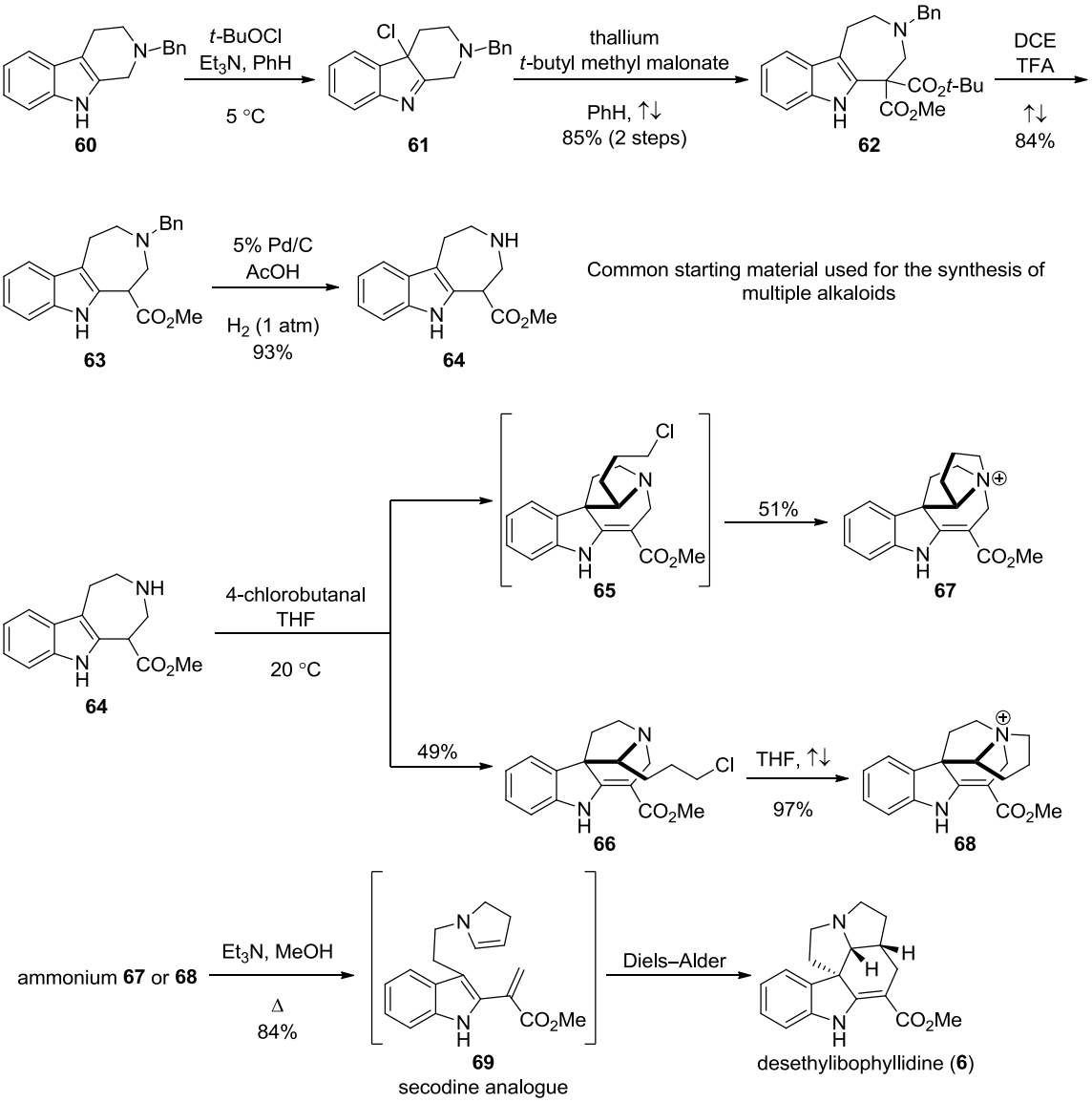
The first reported synthesis of an ibophyllidine alkaloid was reported by Martin Kuehne in 1981.[8] Kuehne's effort toward the ibophyllidines is based on a biomimetically inspired strategy that was developed in order to access a number of aspidosperma/pseudoaspidosperma alkaloids. These syntheses involve *in-situ* generation of secodine-like intermediates **58** that participate in Diels–Alder cyclizations to form the C and D-rings (**58** → **59**), similar to those proposed in the biosynthesis (*vide-supra*) (Scheme 6).



Scheme 6 Kuehne's biomimetically inspired approach to aspidosperma/pseudoaspidosperma alkaloids

Kuehne's first application of this strategy is outlined in Scheme 7. Oxidation of the *N*-benzyl protected tetrahydrocarbazole **60** with *tert*-butyl hypochlorite yields chloroindolenine **61**. Reaction with thallium *tert*-butyl methyl malonate provides the diester indolazepine **62** in 85% yield from the tetrahydrocarbazole **60**. Decarboxylation of the *tert*-butyl ester by treatment with trifluoroacetic acid in refluxing 1,2-dichloroethane generates the monoester indolazepine **63** in 84% yield. Hydrogenolytic cleavage of the benzyl group is accomplished using 5% palladium

on carbon in acetic acid under one atmosphere of hydrogen gas to provide indolazepine **64**, a common intermediate for a number of alkaloids synthesized by this general strategy. Condensation of indolazepine **64** with 4-chlorobutanal followed by nucleophilic attack of indole C3 onto the resultant iminium ion (not shown) generates a diastereomeric mixture of tetracyclic amines **65** and **66**, of which **65** undergoes spontaneous quaternization ultimately yielding

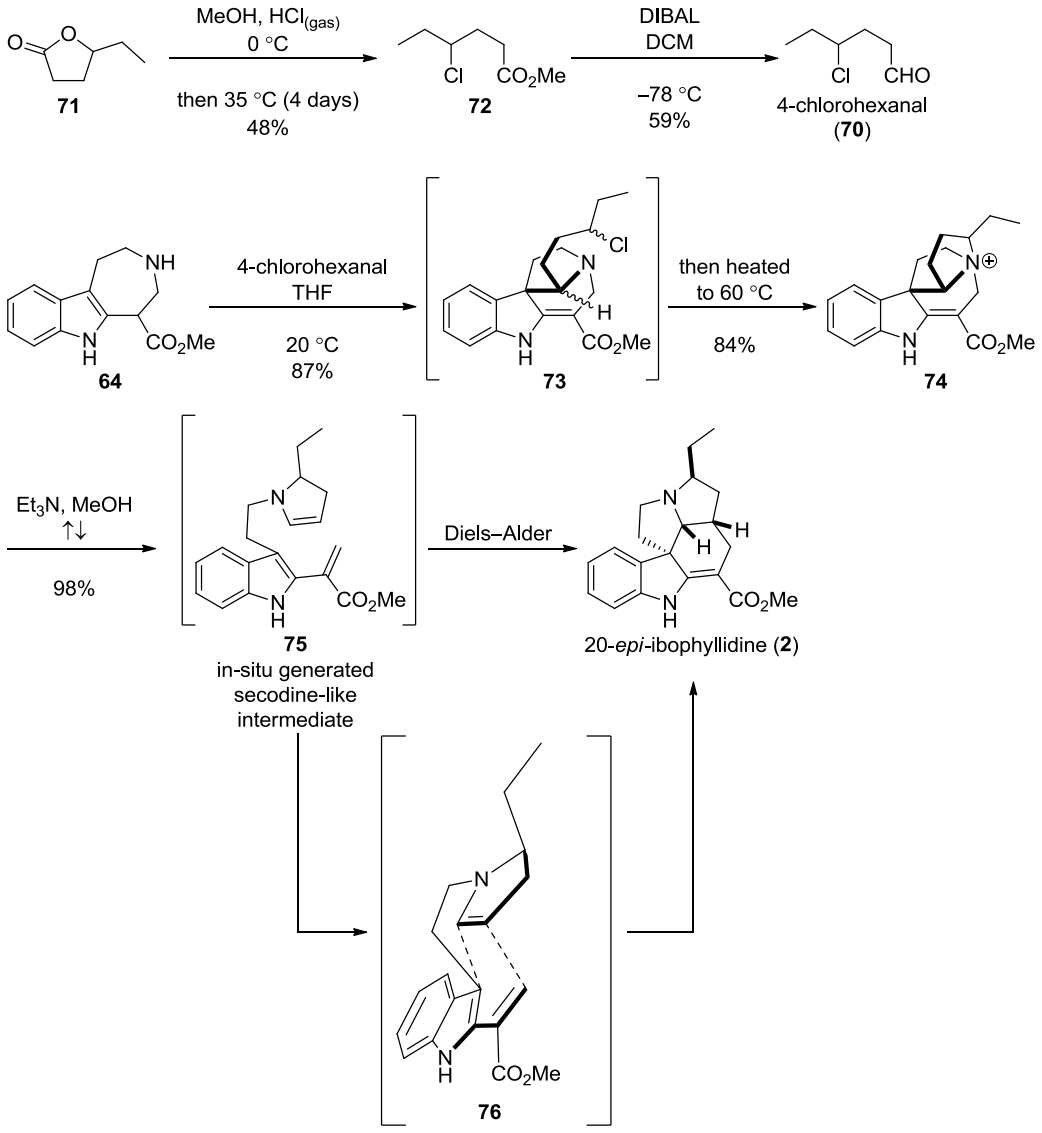


Scheme 7 Kuehne's synthesis of desethylibophyllidine

ammonium ion **67** in 51% yield and the amine **66** in 49% yield. The tertiary amine **66** could be converted to the corresponding pentacyclic ammonium ion **68** in 97% by refluxing in THF Heating either of the isomeric ammonium salts **67** or **68** in methanol with triethylamine facilitated fragmentation to the tricyclic secodine analogue **69**, which underwent a smooth Diels–Alder cyclization to yield desethylibophyllidine (**6**) in 84% yield.

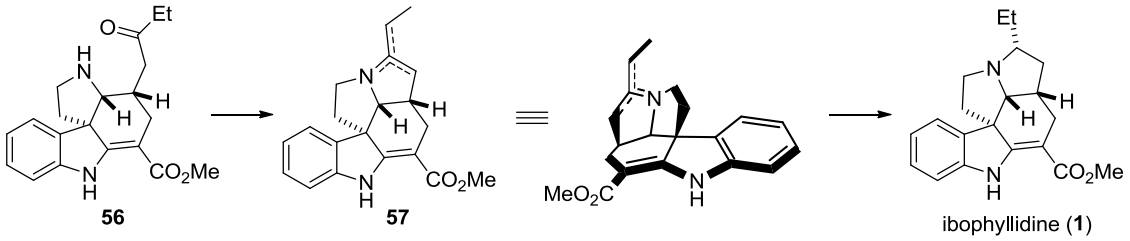
This strategy provides a remarkably concise and efficient synthesis of the ibophyllidine skeleton. The viability of this approach toward the C20 ethyl substituted ibophyllidines (ibophyllidine and 20-*epi*-ibophyllidine) was the focus of another investigation by Kuehne, wherein substitution of 4-chlorobutanal with 4-chlorohexanal (**70**) would provide the additional two carbon atoms of the C20 ethyl group of these alkaloids (Scheme 8).[9] The synthesis commenced with the preparation of 4-chlorohexanal from γ-ethylbutyrolactone (**71**). Treatment of a methanolic solution of γ-ethylbutyrolactone at 0 °C with gaseous hydrogen chloride followed by warming to 35 °C for four days yielded methyl 4-chlorohexanoate (**72**) in 48% yield. DIBAL reduction at –78 °C provided 4-chlorohexanal in 59% yield. Stirring a solution of indolazepine **64** and 4-chlorohexanal in THF at room temperature results in formation of a diastereomeric mixture of the bridged azepine **73** in 87% yield. However, simply heating the reaction mixture to 60 °C once the consumption of starting material was complete resulted in, after 96 hours, the isolation of quaternary salt **74**, the location of epimeric centers was not discussed. In accord with Kuehne's previous findings, refluxing a methanol solution of quaternary salt **74** in the presence of triethylamine yielded the ibophyllidine skeleton, in this case 20-*ep*-ibophyllidine (**2**) exclusively, in 98% yield. This transformation is again proposed to proceed via the secodine analogue **75** that is generated by fragmentation of the quaternary salt. The formation of 20-*epi*-ibophyllidine can be explained by a highly stereospecific, *exo* selective

Diels–Alder reaction wherein the diene approaches the dienophile from the face opposite that of the C20 ethyl substituent (see **76**). Although this strategy is well suited for the synthesis of



Scheme 8 Kuehne's synthesis of 20-*epi*-ibophyllidine

desethylibophyllidine and 20-*epi*-ibophyllidine, it is not amenable to the synthesis of ibophyllidine. In order to access the C20 epimeric natural product ibophyllidine, Kuehne devised a general strategy that until recently remained the only successful strategy to prepare this alkaloid, having been utilized in all four of the successful syntheses (Scheme 9).[9] This strategy intercepts the proposed biosynthetic amino ketone intermediate **56**. It was believed that this

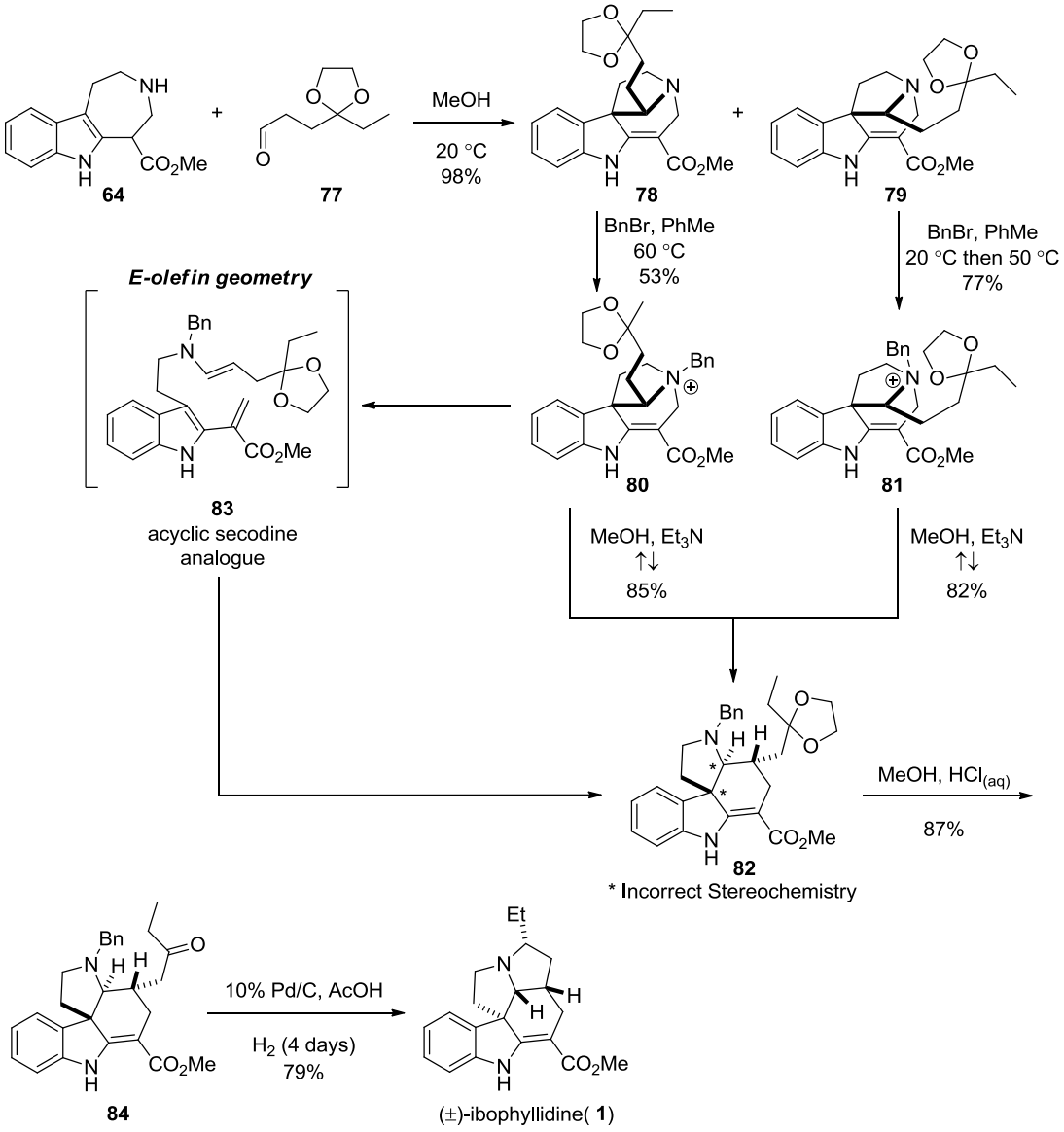


Scheme 9 General strategy for ibophyllidine synthesis

could undergo intramolecular condensation to yield another proposed biosynthetic intermediate, imine/enamine **57** that upon exposure to catalytic hydrogenation would deliver hydrogen from the more sterically accessible convex face to yield ibophyllidine (**1**). The key tetracyclic amino ketone **56** was envisioned to be prepared via a modification of the original Diels–Alder strategy implemented to prepare desethylibophyllidine and 20-*epi*-ibophyllidine.

The first implementation of this strategy, again by the Kuehne group, is outlined in Scheme 10. Condensation of indoleazepine **64** and the ethylene ketal of 4-oxohexanal **77** led to a diastereomeric mixture of bridged azepines **78** and **79** in 98% combined yield. The less reactive amine **78** was quaternized with benzyl bromide in toluene at 60 °C for 48 hours to yield ammonium **80** in 53%, isolated as the bromide salt. The more reactive amine **79** was treated with benzyl bromide in toluene at 20 °C for 15 hours followed by heating at 50 °C for an

additional 12 hours to give the corresponding bromide salt **81** in 77% yield. The quaternary salts were reacted under conditions identified in the desethylibophyllidine synthesis to yield the single tetracyclic amino ketal **82** in 85 and 82% yields, from **80** and **81**, respectively. As in the previous studies, the formation of **82** is proposed to proceed through, in this case an acyclic, secodine analogue **83** that readily undergoes an intramolecular Diels–Alder cyclization. The

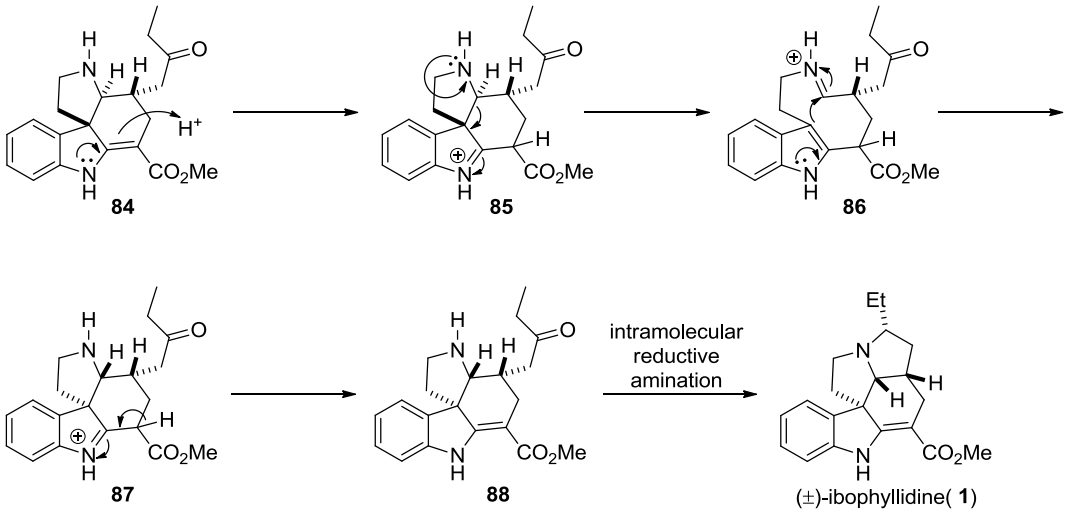


Scheme 10 Kuehne's synthesis of (±)-ibophyllidine

stereochemical outcome of this transformation is worth mention. In accord with similar systems applied toward the synthesis of structurally related *D*-secoaspidosperma alkaloids that utilize an analogous fragmentation/acyclic secodine analogue Diels–Alder sequence, it is presumed that the acyclic secodine analogue will form preferentially with the *E*-configuration of the dienophilic olefin resulting in the *trans*-stereochemistry observed in the tetracycle. The relative stereochemistry at C3 of the indole can be rationalized by the Diels–Alder reaction occurring analogously to that in the desethylibophyllidine synthesis, with the enamine nitrogen in the *exo* orientation during cyclization. Tetracycle **82** requires epimerization at C7 and C3 (ibophyllidine numbering, marked as *) in order to access the natural product. This is efficiently facilitated during the course of D-ring formation. Acetal hydrolysis and treatment of ketone **84** with 10% Pd/C in acetic acid for four days facilitates debenzylation, full epimerization of C7 and C3, and D-ring closure via reductive amination to yield 79% of ibophyllidine (**1**).

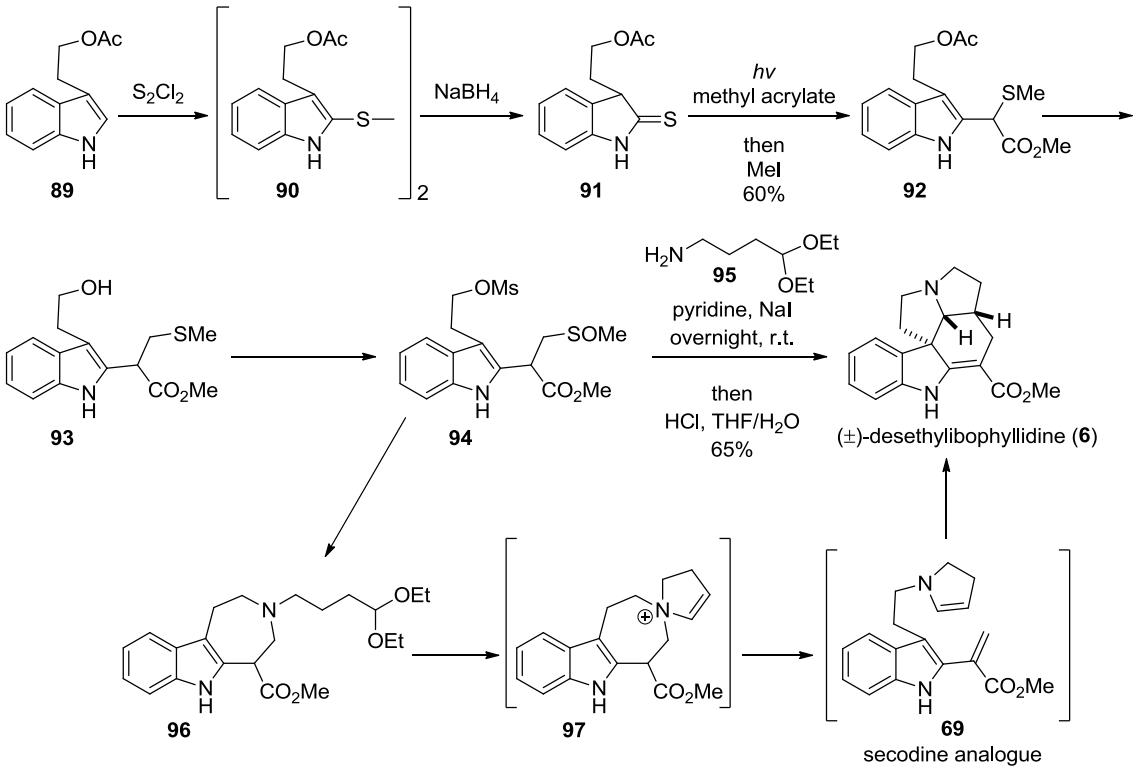
A plausible mechanism for the efficient epimerization observed during the course of the final transformation in Kuehne's original ibophyllidine synthesis is outline in Scheme 11. Protonation of the vinylogous urethane found in amino ketone **84** resulting in iminium ion **85** followed by fragmentation of the C/E ring juncture yields indole iminium **86**. Reestablishment of the C/E ring juncture via nucleophilic attack of the indole onto the iminium ion with the correct stereochemistry yielding **87**, followed by deprotonation, would provide **88** that is poised to undergo intramolecular reductive amination leading to ibophyllidine (**1**). It is possible that the proceeding condensation provides a thermodynamic sink by "trapping" the *syn*-stereoisomer with the *trans*-isomer being more reluctant to undergo cyclization.

A similar strategy toward the ibophyllidine alkaloids was published by Bhupesh Das in 1985.[10] The strategy employed by Das is similar to that disclosed by Kuehne in that an *in-situ*



Scheme 11 Plausible mechanism for the epimerization of C3 and C7

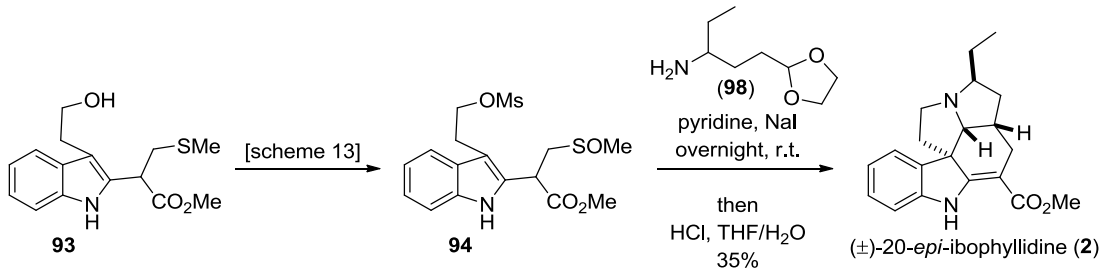
generated secodine analogue was envisioned as the precursor to the ibophyllidine framework (Scheme 12). Starting from the tryptophyl-*O*-acetate **89**, this compound was converted to the dimeric disulfide **90** by treatment with disulphur dichloride then converted to the indoline-2-thione **91** by reduction with sodium borohydride. Irradiation of **91** in the presence of methyl acrylate followed by alkylation provides substituted indole **92** in 60% yield, which is deacylated(conditions not reported) to provide the 2-substituted tryptophyl **93**. The alcohol was mesylated (conditions not reported) and the thioether was oxidized to the sulfoxide with *m*-chloroperbenzoic acid providing **94** (yield not reported). Reacting **94** with the diethyl acetal of 4-aminobutyraldehyde (**95**) in pyridine with catalytic sodium iodide provided azepine **96**. Due to the sensitivity of this intermediate, the crude azepine was quickly treated with hydrochloric acid. Acidic hydrolysis of the acetal followed by condensation of the liberated aldehyde with the amine yields cyclic ammonium ion **97** which readily undergoes fragmentation to the desired



Scheme 12 Das' synthesis of desethylibophyllidine

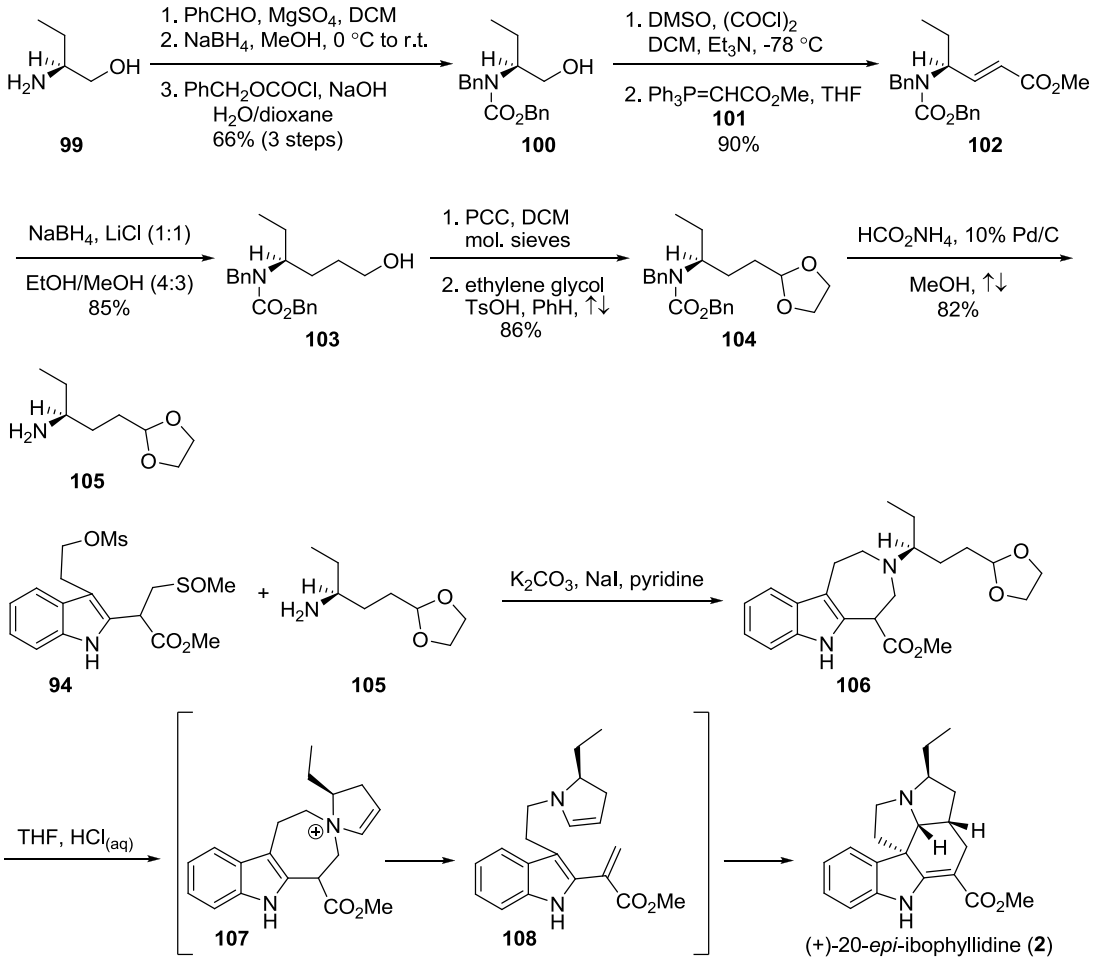
secodine analogue **69**, identical to that proposed in Kuehne's synthesis, that cyclized to generate desethylibophyllidine (**6**) in 65% yield.

This strategy was also utilized in the synthesis of the C20 ethyl substituted ibophyllidine skeleton (Scheme 13).[10b] Starting with the conversion of tryptophol **93** to the mesylate **94** in the same manner as discussed in Scheme 12, followed by reaction with amine **98**, led to the formation of the desired alkaloid framework. In analogy to Kuehne's results, 20-*epi*-ibophyllidine was formed. Although it was initially reported that the Diels–Alder reaction proceeded in 35% overall yield with approximately a 6:1 ratio of 20-*epi*-ibophyllidine to ibophyllidine, it was later reported that the observation of ibophyllidine in the reaction mixture was erroneous and 20-*epi*-ibophyllidine was in fact, formed exclusively.



Scheme 13 Das' synthesis of (±)-20-*epi*-ibophyllidine

Das was able to demonstrate the use of this method in the first synthesis of a non-racemic ibophyllidine alkaloid by taking advantage of the high levels of stereospecificity observed for the Diels–Alder reaction.[11] Preparation of optically active form of amine **98** (referred to as **105**) is outlined in Scheme 14. Commercially available (*S*)-(+)-2-amino-1-butanol (**99**) was successively protected with benzyl and benzyloxycarbonyl groups to provide alcohol **100** in 66% yield over three steps. Swern oxidation followed by Wittig olefination with the stabilized ylide **101** resulted in the formation of the *E* α,β-unsaturated ester **102** in 90 % overall yield. Complete reduction of **102** with sodium borohydride and lithium chloride yielded 85% of the saturated alcohol **103**. PCC oxidation followed by protection of the resultant aldehyde with ethylene glycol provided dioxolane **104** in 86% yield over two steps. Removal of both amine protecting groups using ammonium formate and palladium on carbon in refluxing methanol provided the desired chiral aminoacetal **105** in 82% yield. Reaction of this compound with mesylate **94** under the aforementioned conditions, provided indoleazepine **106**, which upon immediate treatment with HCl, generated ammonium ion **107** capable of fragmenting to the optically active secodine analogue **108**. *In-situ* Diels–Alder cyclization of **108** generates (+)-20-*epi*-ibophyllidine (**2**) in 35% yield from **94** and **105**. The authors note that the unnatural antipode of the natural product



Scheme 14 Das' enantiospecific synthesis of (+)-20-*epi*-ibophyllidine

was also easily accessed by utilizing the opposite enantiomer of the starting amino alcohol.

As part of a broader program involving the synthesis of numerous terpene indole alkaloids via a cyclization of *in-situ* generated secodine-like intermediates, it was deemed favorable to generate a common intermediate that could be elaborated to a number of different alkaloids. To this end, Kuehne reported the synthesis and utilization of what he dubbed "versatilines" (**109**), which were utilized as a common intermediate toward a number of alkaloids (Figure 4).[12] The synthesis of this useful intermediate and it's conversion to (±)-ibophyllidine is

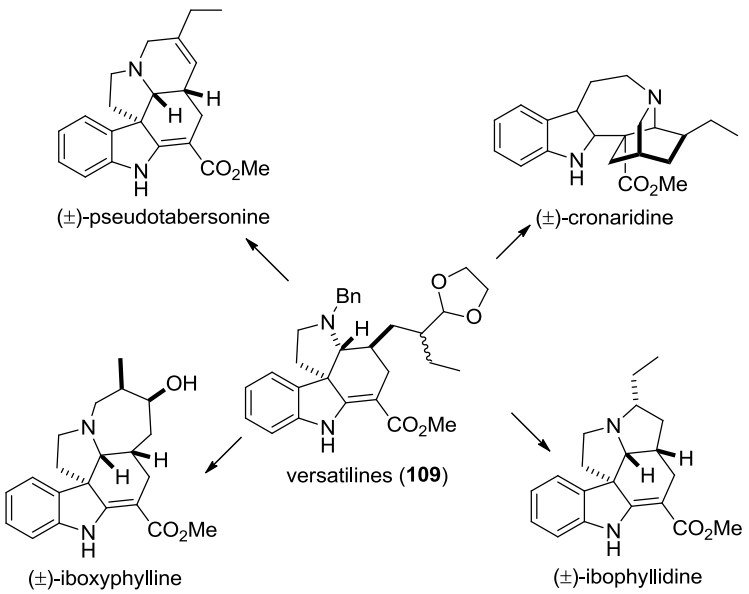
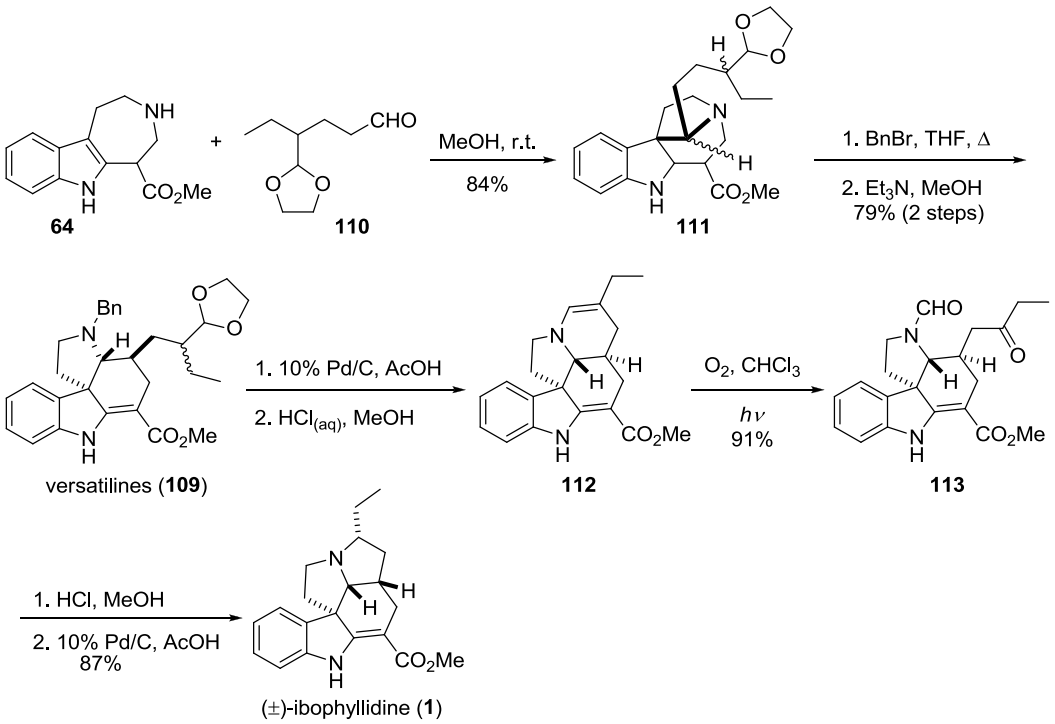


Figure 4 Kuehne's common intermediate useful for the synthesis of multiple alkaloids

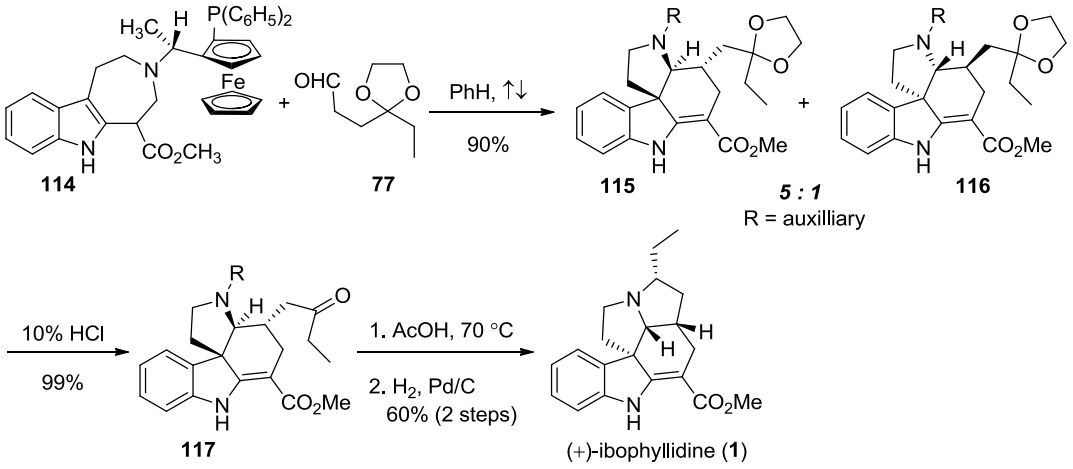
shown in Scheme 15. In analogy to Kuehne's aforementioned (±)-ibophyllidine synthesis, the indoleazepine **64** was condensed with aldehyde **110** to provide bridged azepine **111**. Conversion of the quaternary benzylated ammonium salt via fragmentation followed by Diels–Alder cyclization led to the desired diastereomeric versatilines (**109**) in 79% yield over two steps. Deprotection of the acetal and intramolecular condensation led to pentacycle **112** which was oxidatively cleaved to provide formamide **113** in 91% yield. Methanolysis of the formamide and concomitant epimerization/cyclization followed by hydrogenation furnished (±)-ibophyllidine (**1**) in 87% yield.

Kuehne later modified his original ibophyllidine synthesis to employ a chiral auxiliary in order to achieve the first non-racemic total synthesis of the alkaloid (Scheme 16).[13] The indoleazepine **114**, protected with a chiral ferrocynyl auxiliary, was refluxed in benzene with aldehyde **77**, facilitating condensation, fragmentation, and Diels–Alder cyclization. The key



Scheme 15 Kuehne's synthesis of (±)-ibophyllidine through a common intermediate

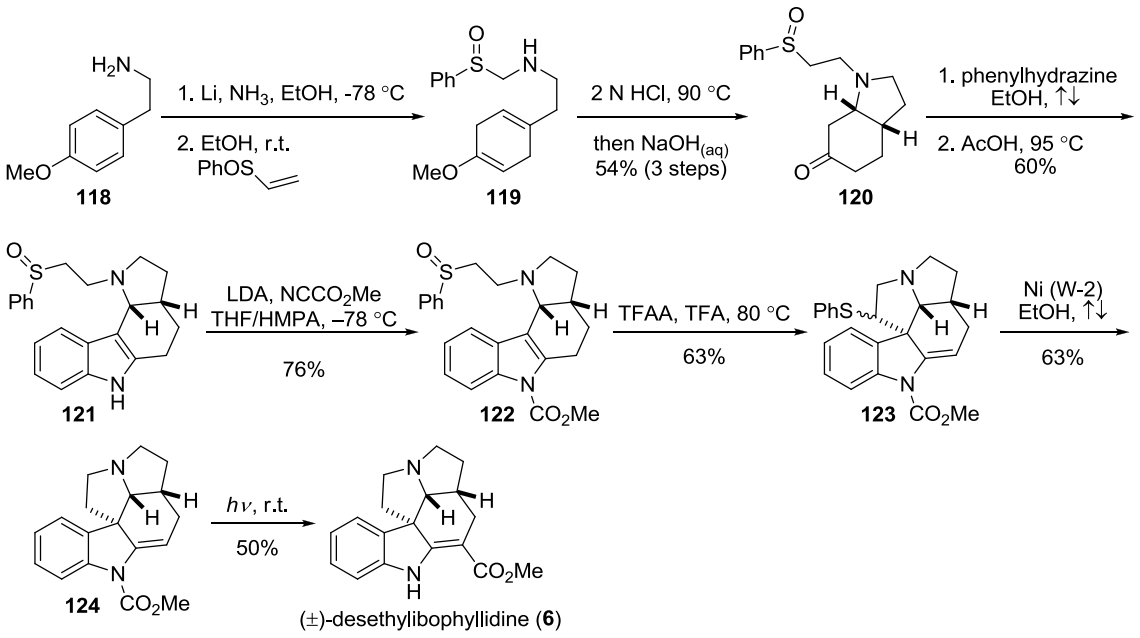
Diels–Alder cyclization event proceeded with 5:1 diastereoselectivity with respect to the auxiliary, providing tetracycles **115** and **116** in a combined yield of 90%. The dioxolane was



Scheme 16 Kuehne's enantiospecific total synthesis of (+)-ibophyllidine

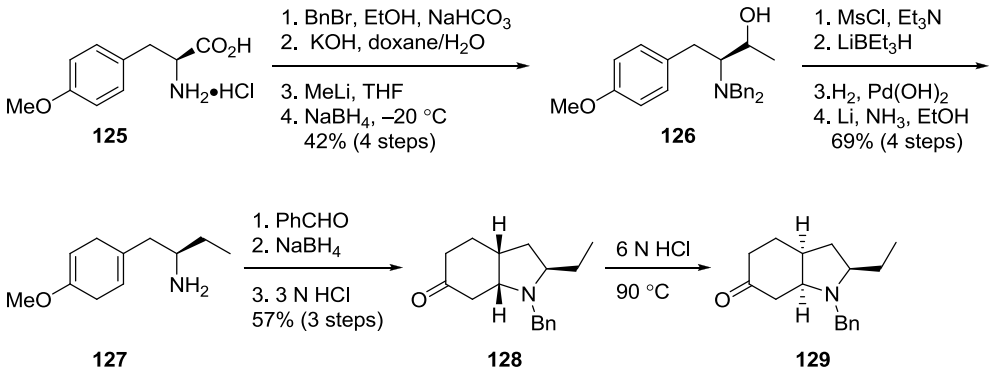
cleaved from the correct diastereomer **115** with 10% HCl to yield the *N*-protected amino ketone **117** in 99% yield. This intermediate was carried on to (+)-ibophyllidine (**1**) in 60% yield in analogy to Kuehne's earlier reports.

In a unique strategy reported by Bonjoch, a key Fischer indolization on an in-tact D/E-ring ketone was utilized to construct the A-B-D-E-ring tetracycle.[14] The C-ring was then closed using a Pummerer rearrangement, involving nucleophilic attack on the thionium ion intermediate. The successful implementation of this strategy toward the synthesis of desethylibophyllidine is outlined in Scheme 17. Birch reduction of 4-methoxyphenethylamine (**118**) followed by *N*-alkylation with phenyl vinyl sulfoxide provided access to dihydrobenzene derivitive **119**. Treatment of crude **119** with 2 N hydrochloric acid followed by basification provided *cis*- octahyroindolone **120** in 54% yield over three steps. Formation of the phenyl hydrozone followed by Fischer indolization promoted by acetic acid furnished indole **121** in 60% yield. The indole nitrogen was protected as the methoxycarbonyl derivative with lithium diisopropylamide and methyl cyanoformate in 76% yield providing indole **122**. Pummerer rearrangement with trifluoroacetic anhydride and trifluoroacetic acid followed by intramolecular capture of the resultant thionium ion at indole C3 yielded 63% of pentacycle **123** as an inconsequential mixture of diastereomers. Reductive desulfurization with Raney nickel to yield pentacycle **124** followed by irradiation proceeded to provide (±)-desethylibophyllidine (**6**) in 63 and 50% yields, respectively. This overall process was highly diastereoselective and studies were undertaken to apply this method, in an enantiospecific manner, to the C20 ethyl substituted ibophyllidines. To this end, optically pure ethyl substituted azabicyclic ketone **120** (referred to as **129**) was prepared as outlined in Scheme 18.[15] The hydrochloride salt of *O*-methyltryptamine (**125**) was converted to the *N*,*N*-dibenzylated amino alcohol **126** in 42% overall



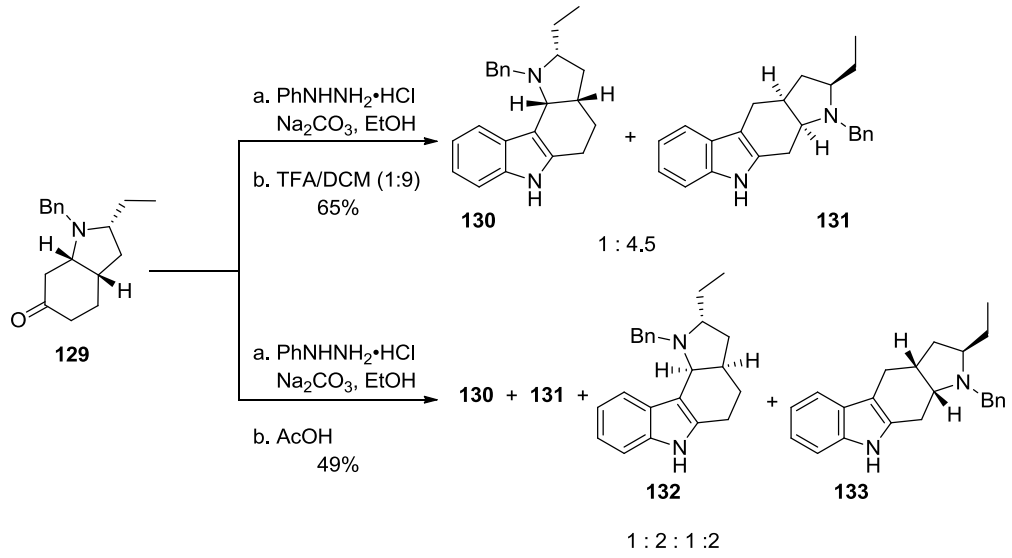
Scheme 17 Bonjoch's synthesis of (±)-desethylibophyllidine

yield. Mesylation, reduction, debenzylation, and Birch reduction provided the dihydrobenzene derivitive **127** in 69% over four steps. Benzylation and acid induced cyclization provided the desired bicyclic amino ketone in 57% yield as a mixture of diastereomers **128** and **129**.



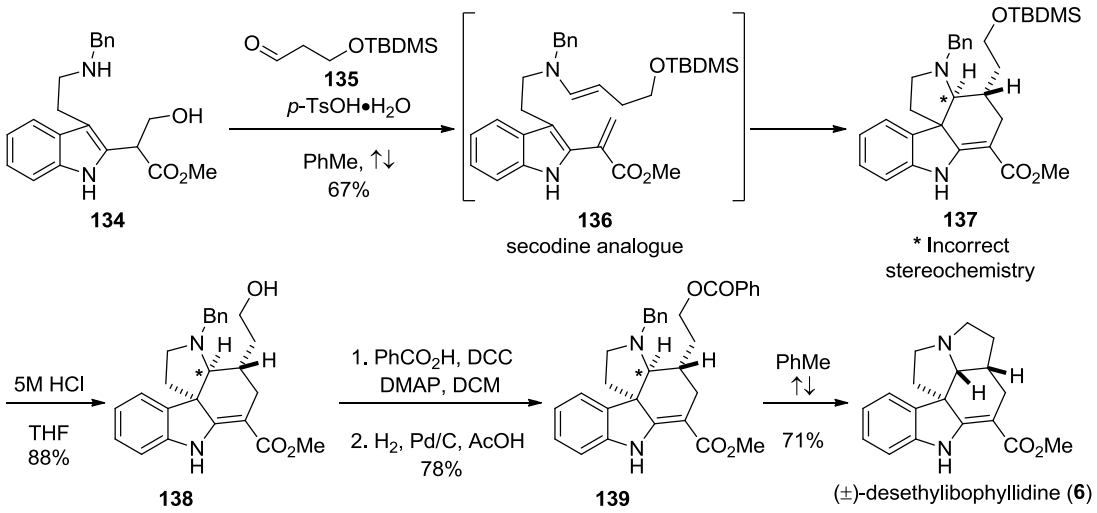
Scheme 18 Synthesis of optically pure bicyclic ketone **129**

Treatment of this mixture with 6 N HCl facilitated equilibration resulting in a 9:1 ratio in favor of **129**. Application of the Fischer indolization with bicyclic amino ketone **129** using trifluoroacetic acid in dichloromethane resulted in modest regioselectivity, forming the desired and undesired tetracycles **130** and **131** in a 1:4.5 ratio in 65% overall yield (Scheme 19). Employing acetic acid resulted in a mixture of **130**, **131**, **132**, and **133** in a 1:2:1:2 ratio (49% overall yield). Due to poor regioselectivities this method was not considered a desirable method for the synthesis of C20 substituted ibophyllidines and its use was not pursued further.



Scheme 19 Use of optically active bicyclic ketone **129** in the Fischer idolization strategy

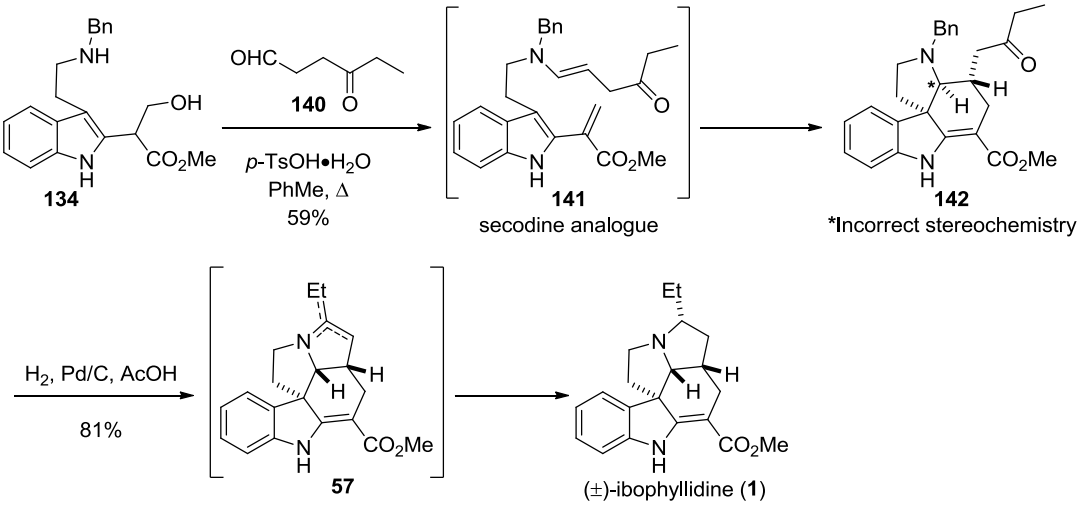
More recently, Kalaus reported a strategy that resulted in the successful synthesis of desethylibophyllidine, 20-*epi*-ibophyllidine, and ibophyllidine.[16,17] Substituted indole **134** was reacted with silyl protected hydroxypropanal **135** in the presence of *p*-toluenesulfonic acid to yield 67% of tetracycle **137** (Scheme 20). This transformation is proposed to proceed via Diels–Alder cyclization of an acyclic secodine analogue **136** similar to that reported by Kuehne.



Scheme 20 Kalaus' synthesis of (±)-desethylibophyllidine

Similar to the results obtained in Kuehne's synthesis of ibophyllidines, the C3 stereocenter is formed with the wrong relative configuration compared to that found in the natural product (the stereochemical outcome at C7 is not indicated by the authors). Deprotection of the TBDMS group and conversion of the primary alcohol in **138** to the phenyl carbonate provides the cyclization precursor **139**. Compound **39**, upon debenzylation, undergoes an acid catalyzed epimerization similar to that observed in Kuehne's studies, followed by intramolecular alkylation to yield (±)-desethylibophyllidine (**6**). This strategy was slightly modified to allow for incorporation of the C20 ethyl substituent found in ibophyllidine and 20-*epi*-ibophyllidine. The synthesis of (±)-ibophyllidine is outline in Scheme 21.

The synthesis began from the same substituted indole **134**. Condensation with keto aldehyde **140** and alcohol elimination leads to transient acyclic secodine analogue **141** which undergoes a Diels–Alder cyclization to provide tetracycle **142**. This intermediate, like in Kalaus' synthesis of desethylibophyllidine, requires inversion of

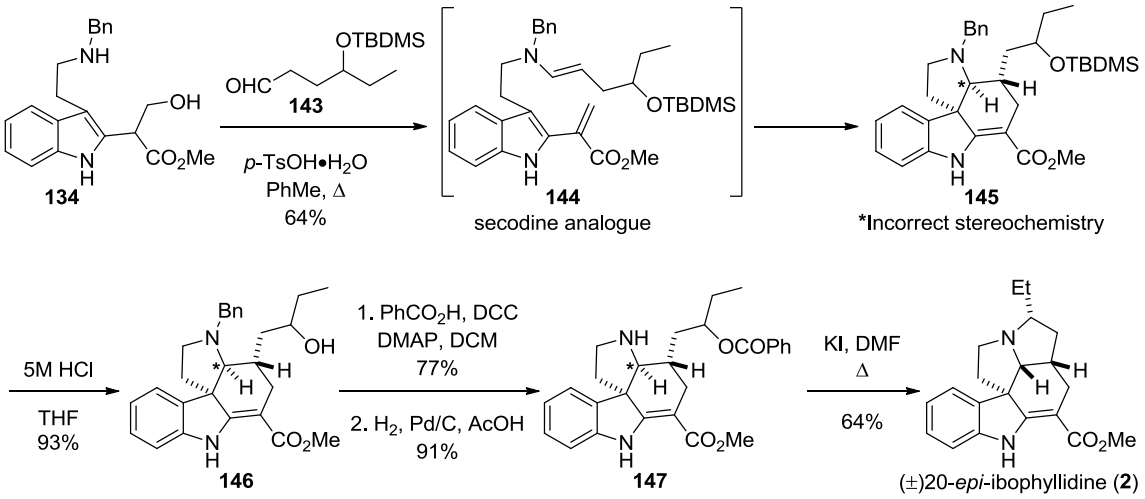


Scheme 21 Kalaus' synthesis of (±)-ibophyllidine

stereochemistry at C3 (indicated by *). The assigned stereochemistry at C7 suggests that the Diels–Alder cyclization proceeds with the enamine nitrogen in the *endo* orientation. The reason for the alternative *endo*/*exo* selectivity observed between this system and the system developed by Kuehne has not been investigated. Treatment of tetracycle **142** with palladium on carbon and hydrogen gas in acetic acid results in hydrogenolytic debenzylation and acid catalyzed epimerization (as previously described). After the necessary stereochemical inversion, the free amine condenses with the pendant ketone and the resultant imine/enamine **57**, which is reduced stereoselectively from the convex face of the cupped structure to furnish (±)-ibophyllidine (**1**) in 81% yield.

The utilization of the previously utilized condensation/reduction protocol to form the D-ring in Kalaus' synthesis was necessary in order to access the appropriate relative configuration at C20. Attempts to utilize an intramolecular alkylation strategy, similar to that utilized in his desethylibophyllidine synthesis led to formation of 20-*epi*-ibophyllidine (Scheme 22).

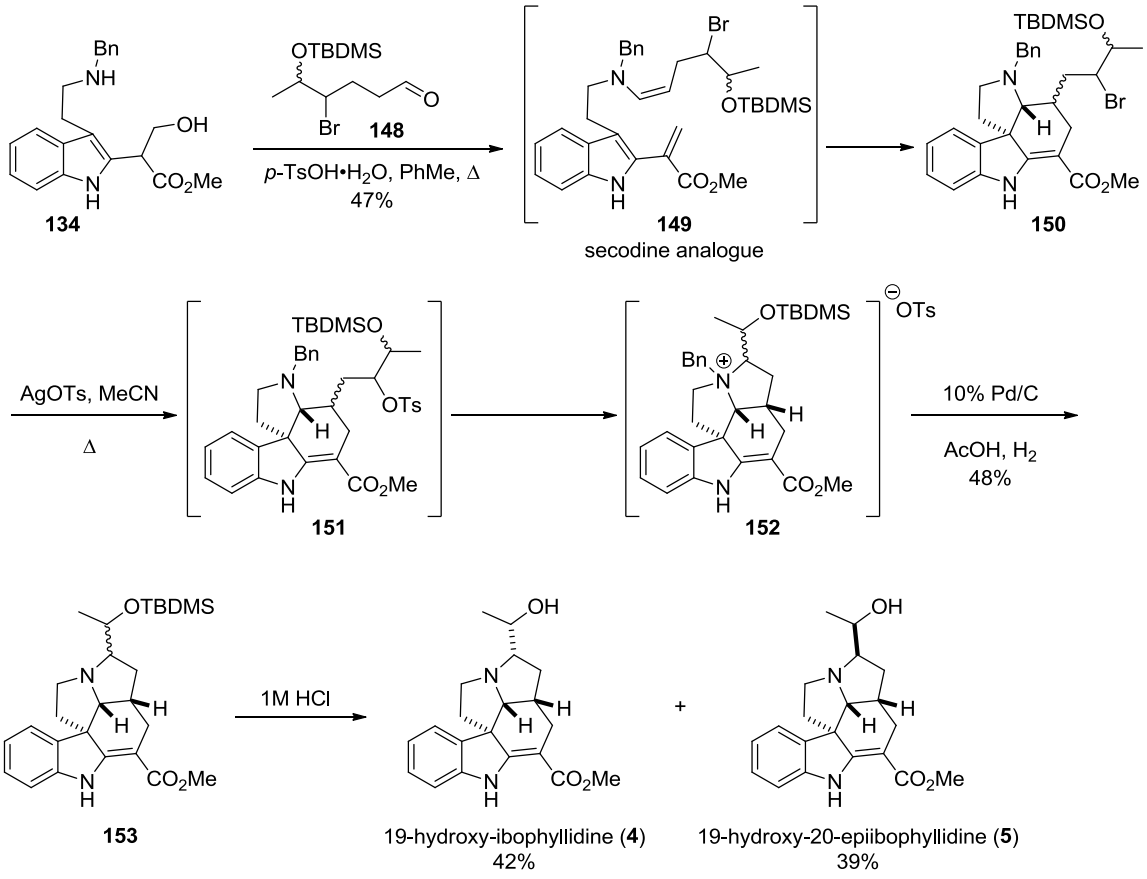
Condensation of *N*-benzyl tryptamine **134** with aldehyde **143** followed by elimination of water leads to the acyclic secodine analogue **144**. Diels–Alder cyclization of **144** provides tetracycle **145**, in 64% yield from **134**, again with the wrong relative configuration at C3. Cleavage of the silyl ether (93% yield), conversion of the secondary alcohol **138** to the phenyl carbonate (77% yield), and reductive cleavage of the *N*-benzyl group (91 % yield) yields tetracycle **147**. Intramolecular alkylation accompanied by full epimerization at C3 yields 20-*epi*-ibophyllidine (**2**) in 64% yield.



Scheme 22 Kalaus' synthesis of (±)-20-*epi*-ibophyllidine

In 2006, Kalaus reported the only synthesis to date of (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine (Scheme 23).[18] The *N*-benzyl tryptamine **134** was reacted at elevated temperature with aldehyde **148**, prepared in 4 steps from methyl-5-oxohexanoate, in the presence of *p*-toluenesulfonic acid, to provide tetracycle **150** as a mixture of diastereomers. This

reaction presumably takes place via acyclic secodine analogue **149** arising from enamine formation and elimination of the alcohol. Heating a solution of **150** in acetonitrile with silver *p*-toluenesulfonate resulted in exchange of the bromide for a tosylate (**151**) followed by *in-situ* intramolecular alkylation leading to the quaternary ammonium salt **152** as a diasteriomeric

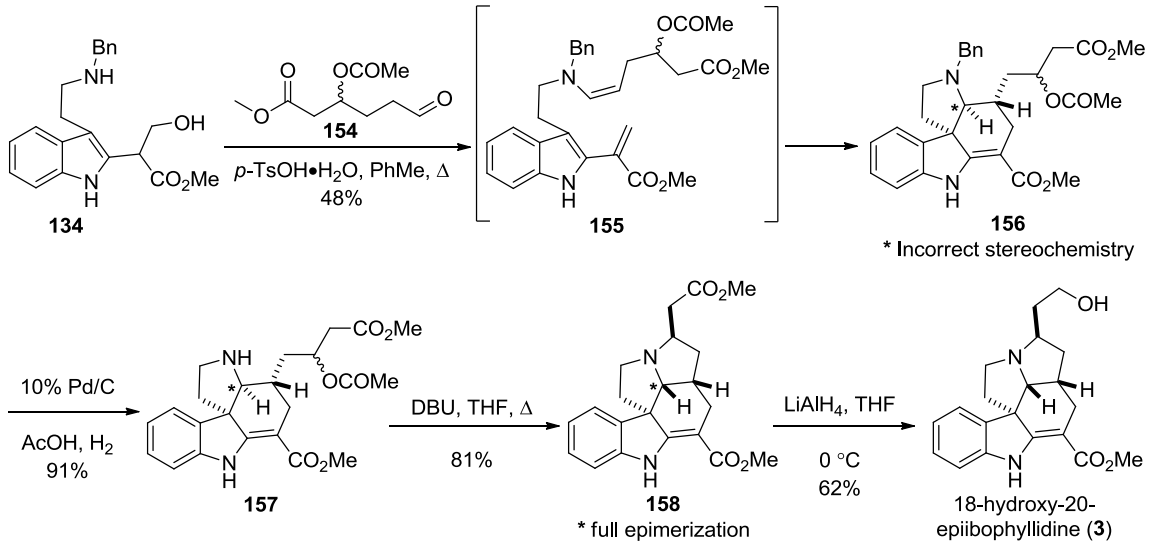


Scheme 23 Kalaus' synthesis of (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine

mixture. Ammonium salt **152** was immediately reductively debenzylated to provide tetracycle **153**. Compound **153** was treated with one molar aqueous hydrochloric acid to cleave the silyl ethers providing a mixture of (±)-19-hydroxy-ibophyllidine (**4**) and (±)-19-hydroxy-20-

epiibophyllidine (**5**). It is of importance to note that the stereochemistry at the C19 secondary carbinol is not indicated. The data supplied describes only two isomers suggesting that the target compounds, (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine, were each isolated as a single diastereomer at this position. To the best of our knowledge there is no discussion in the literature regarding the configuration at this position or whether or not the natural products are single isomers or C19 mixtures. It is also worth mentioning that while this approach does effectively generate the C20 epimer with the same relative stereochemistry as ibophyllidine without using Kuehne's enamine/iminium hydrogenation method, it does so as a near 1:1 diastereomeric mixture at this position. Although this is viewed beneficial in this case, as both natural products are generated, this arises as a consequence of poor diastereoselectivity.

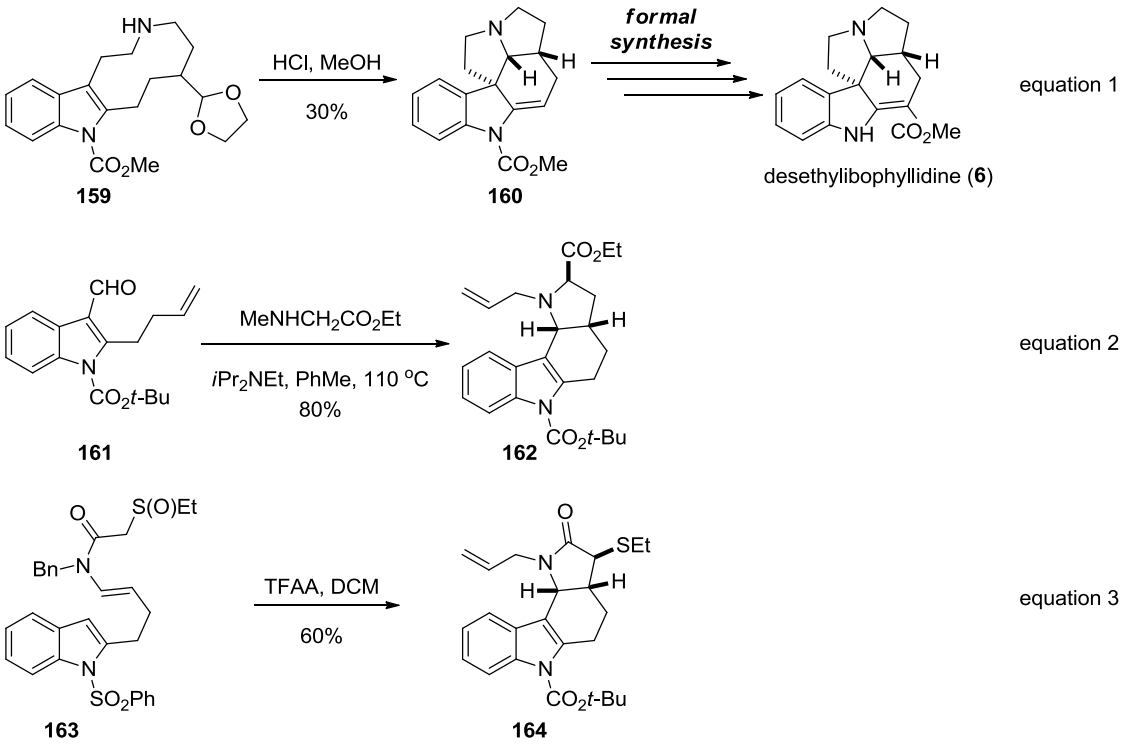
Shortly After, in 2007, Kalaus reported a similar approach to (±)-18-hydroxy-20-epiibophyllidine (Scheme 24).[19] The *N*-benzyl tryptamine **134** was reacted at elevated temperature with aldehyde **154**, prepared in 4 steps from 4(*tert*-butyl-dimethyl-silanoxy)butanal,



Scheme 24 Kalaus' synthesis of 18-hydroxy-20-*epi*-ibophyllidine

in the presence of *p*-toluenesulfonic acid to provide tetracycle **156** in 48% yield via the proposed acyclic secodine analogue **155**. Similar to other syntheses discussed above, this provided an intermediate with the wrong stereochemistry at C3 requiring full epimerization, which albeit is a fairly facile process, to access the natural product. Reductive debenzylation proceeded in 91% yield to provide the tetracyclic amine **157**. Intramolecular alkylation, facilitated by treatment with DBU in hot THF, provided pentacycle **158** in 81% yield along with full C3 epimerization. LAH reduction of the methyl ester provided 18-hydroxy-20-epiibophyllidine (**3**) in 62% yield. While this intramolecular alkylation strategy is reminiscent of the syntheses of the C19 hydroxylated ibophyllidines, the sequence outlined here provided a single diastereomer. This more highly selective process again favored the C20 configuration analogous to that found in 20-epiibophyllidine.

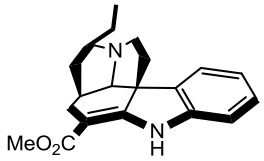
Although there are a number of other studies aimed at developing methods for the construction of the ibophyllidine framework, none of them have been shown to establish the all *syn*-pyrrolidine ring of ibophyllidine (Scheme 25). A double transannular annulation strategy was developed by Bonjoch and was utilized in a formal synthesis of desethylibophyllidine (**159** → **160**).[20] For this strategy to be amenable towards the synthesis of C20 ethyl substituted ibophyllidines, the annulation sequence would have to proceed stereospecifically with respect to the preinstalled C20 ethyl group. No studies on this type of modification are reported in the literature. A 1,3-dipolar cycloaddition strategy was developed and utilized to construct the A-B-D-E-ring tetracycle, the stereochemical outcome in this case provided access to the 20-*epi*-ibophyllidine stereochemical arrangement (**161** → **162**, equation 2, Scheme 25).[21] A Pummerer/Mannich cascade was reported by Padwa, but these studies did not



Scheme 25 Other strategies toward the ibophyllidine skeleton

look at any substrates that would provide substitution at C20 (**163** → **164**, equation 3, Scheme 25).[22]

Although the some of the strategies discussed provide rapid and efficient access to the ibophyllidine framework, it is clear that the stereochemical arrangement of the four stereocenters of ibophyllidine provides a challenging arena for development of reactions to prepare such structures. Also, there had been, prior to our studies, no successful synthesis of an ibophyllidine alkaloid that makes use of asymmetric catalysis as a tool to access optically pure targets. Of the known ibophyllidine alkaloids perhaps the most demanding from a synthetic standpoint is ibophyllidine. This can be attributed to the placement of the C20 ethyl group being placed on the sterically more demanding concave face of ibophyllidine's cupped structure (Figure 5).

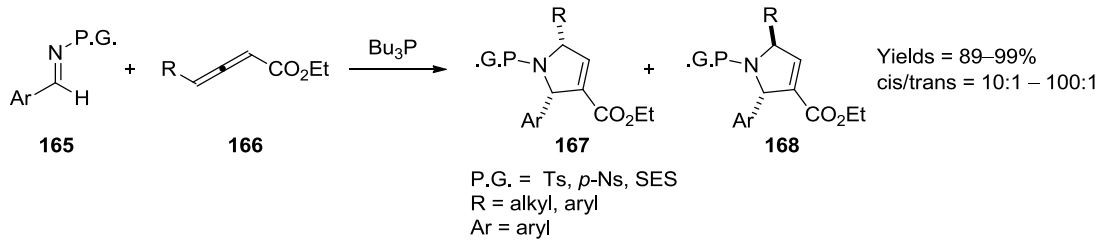


ibophyllidine (**1**)

Figure 5 3-D representation of ibophyllidine

Section 3.4 Kwon's Phosphine-catalyzed Allene–Imine [3 + 2] Annulation

Based on the development of a powerful method for formation of 1,2,3,5-tetrasubstituted pyrroline rings **167** and **168** via the phosphine-catalyzed [3 + 2] annulation between *N*-sulfonyl aryl aldimines **165** and γ-substituted 2,3-butadienoates **166**, we developed a synthetic strategy that would directly address the challenging stereochemical arrangement found in ibophyllidine. As shown in Scheme 26, the pyrroline synthesis is typically high yielding and highly diastereoselective, favoring the 2,5-*syn* diastereomer **167**.[23] It was believed that this process could be implemented in order to control the relative stereochemistry between the C20 ethyl group and the indole nucleus of ibophyllidine. We were particularly intrigued by the possibility of the absolute stereochemistry of this process being effectively controlled utilizing a chiral phosphine to promote the annulation. While effectively controlling the absolute stereochemistry

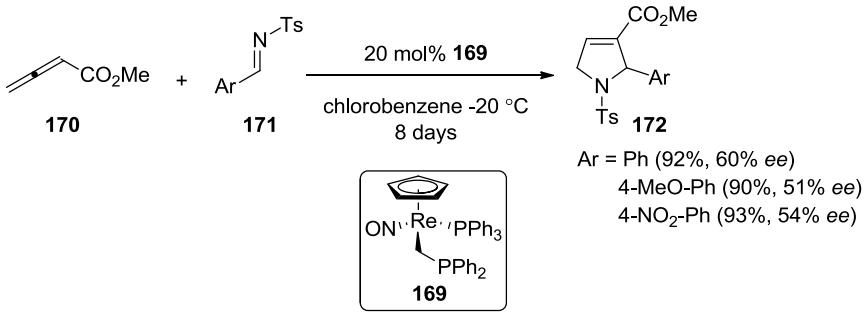


Scheme 26 Kwon's phosphine-catalyzed [3 + 2] between electron deficient allenes and activated imines

of phosphine-catalyzed [3 + 2] annulations between allenes and imines has remained somewhat of an elusive goal, there have been successful examples reported in the chemical literature.

Section 3.5 Asymmetric Phosphine-catalyzed Allene–Imine [3 + 2] Annulations

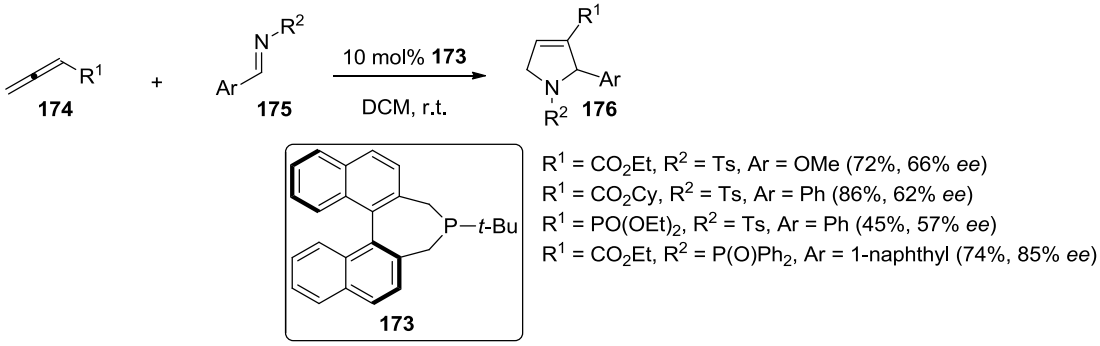
In 2006 Gladysz reported the use of a chiral rhenium based phosphine **169** as a catalyst in the allene–imine [3 + 2] annulation.[24] Methyl 2,3-butadienoate (**170**) was reacted with tosyl aldimines **171**, derived from aromatic aldehydes, in the presence of 20 mol% **169** in chlorobenzene at –20 °C. The reactions took up to eight days to reach completion, providing the desired pyrrolines **172** in high yields (Scheme 27). The *ee*'s were generally fairly modest. With the benzaldehyde derived imine, the pyrroline was formed in 60 % *ee*, while 4-methoxyphenyl and 4-nitrophenyl substituents resulted in pyrrolines in 51 and 54% *ee*, respectively.



Scheme 27 Asymmetric allene–imine [3 + 2] annulation catalyzed by chiral phosphine **169**

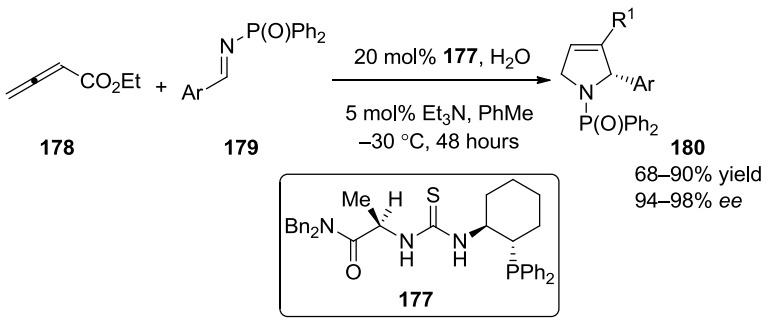
Also in 2006, Marinetti reported the screening of numerous known chiral phosphines in the allene–imine [3 + 2] annulation.[25] It was found that Gladiali's phosphepine **173** provided the best overall results (Scheme 28). Although the reaction with phosphepine **173** was tolerant of various electron withdrawing groups on the allene **174** and to different *N*-protecting groups on

the imine **175**, the substrates leading to useful *ee*'s were limited in scope. The *N*-diphenylphosphinoyl imine derived from naphthaldehyde was needed in order to produce a reasonable level of enantiomeric excess (74% yield, 85% *ee*) of the 2-substituted 3-pyrrolines **176**. Other substrates tended to give consistently low *ee*'s.



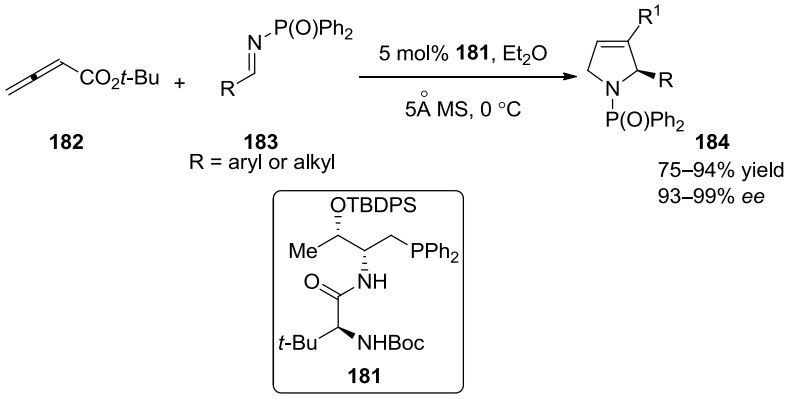
Scheme 28 Gladiali's chiral phosphepine **173** as a catalyst for the asymmetric phosphine-catalyzed allene–imine [3 + 2] annulation

While these early examples of asymmetric allene–imine [3 + 2] annulations proceeded with only moderate levels of asymmetric induction, the use of polyfunctional phosphine catalysts has recently provided more highly enantioselective versions of this reaction that can be applied to a broader substrate scope. In 2008, Jacobsen reported the use of a bifunctional chiral phosphinothiourea catalyst **177** to promote the [3 + 2] annulations between 2,3-butadienoates **178** and *N*-diphenylphosphinoyl imines **179** (Scheme 29).[26] The *N*-phosphinoyl-2-aryl-3-pyrrolines were formed in good to excellent yields and with exquisite levels of enantiocontrol. The reaction was amenable toward electron poor, electron rich, or electronically neutral aromatic substituents on the imine. Heteroaromatic substituents were well tolerated as well.



Scheme 29 Jacobsen's chiral phosphinothiourea as a catalyst in the phosphine-catalyzed allene–imine [3 + 2] annulation

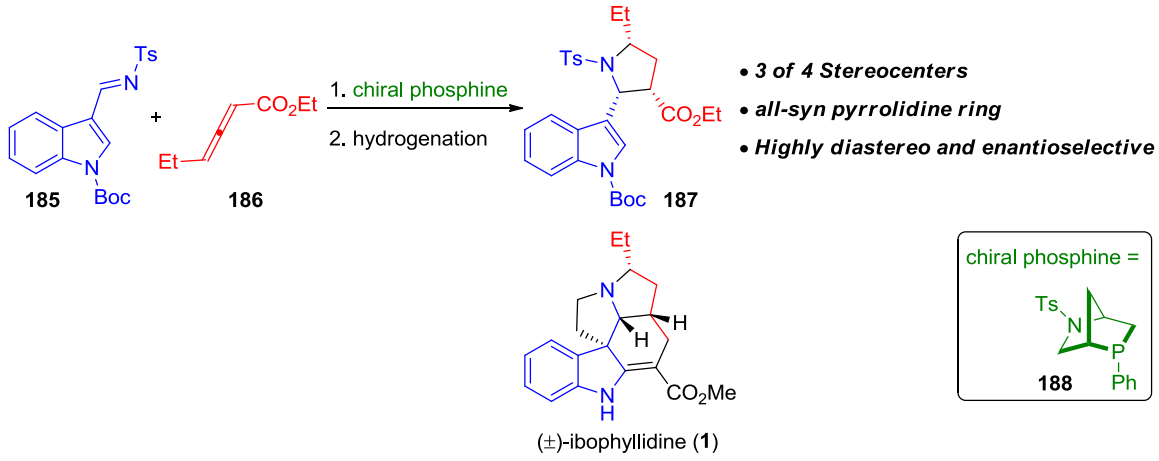
In 2011 Lu reported a similar transformation utilizing the amino acid based chiral phosphine **181** (Scheme 30).[27] Reacting *tert*-butyl 2,3-butadienoate (**182**) with various diphenylphosphinoyl imines **183**, a wide variety of *N*-phosphinoyl 2-substituted 3-pyrrolines **184** could be synthesized in good to excellent yields with remarkable levels of enantioselectivity. Similar to Jacobsen's system, electronically variable aryl substituents on the imine, including heteroaramatics, reacted well in the annulation. Particularly remarkable was the use of a variety of alkyl substituted *N*-phosphinoyl imines in the annulation that reacted with similar efficiency.



Scheme 30 Lu's peptide based chiral phosphine **181** as a catalyst in the asymmetric phosphine-catalyzed allene–imine [3 + 2] annulation

Section 3.6 Our Synthetic Strategy

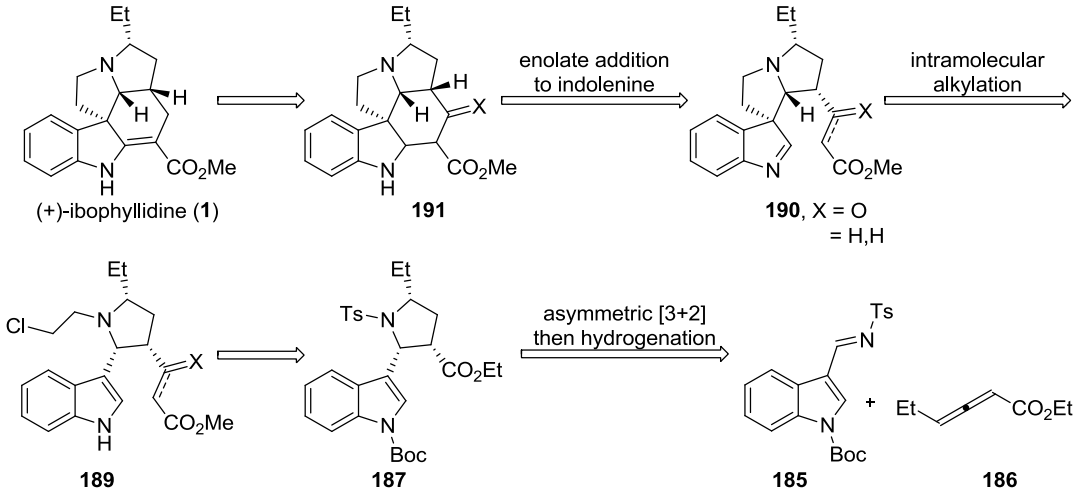
As shown in Scheme 31, application of an asymmetric version of Kwon's pyrroline synthesis toward ibophyllidine would require the phosphine catalyzed [3 + 2] annulation between the imine derived from *N*-Boc protected indole-3-carboxaldehyde **185** and 3-ethyl 2,3-butadienoate (**186**). It was envisioned that a subsequent diastereoselective hydrogenation of the pyrroline double bond would result in the all *syn*-pyrrolidine **187** harboring three out of the four stereocenters found in the natural product. Although the aforementioned examples of asymmetric [3 + 2] annulations of this type showed varying levels of success, the literature is remiss of any examples of asymmetric phosphine-catalyzed [3 + 2] annulations that employ γ-substituted allenoates. However, recently, and at this time unpublished, research in Kwon's laboratory has shown that the chiral phosphine **188**, derived from *trans*-L-4-hydroxyproline, promotes these types of annulations in high yields and high enantiomeric excess. It was anticipated that this phosphine would be effective in the proposed annulation.



Scheme 31 Application of the enantioselective phosphine-catalyzed [3 + 2]annulations toward (+)-ibophyllidine

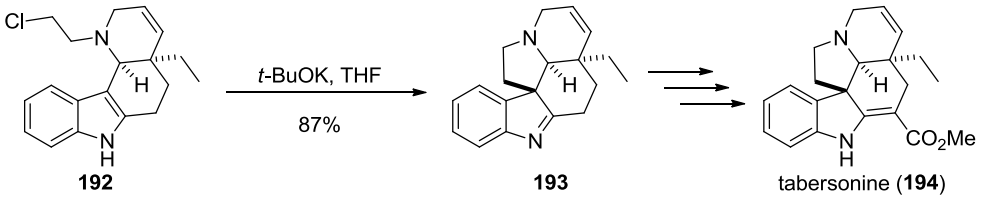
Section 3.7 Retrosynthetic Analysis

Based on the synthesis of pyrrolidine **187** as a key intermediate, the retrosynthetic analysis outlined in Scheme 32 was devised. The vinylogous urethane found in the natural product was planned to be installed late in the synthesis from a pentacyclic intermediate like that of **191**. E-ring formation was to occur through addition of an enolate (derived from the ester **190**, X = H + H, a more reactive β ketoester, or an unsaturated ester) to the spirocyclic indolenine of **190**. The tetracyclic spirocycle was envisioned to arise via intramolecular alkylation at indole C3 from indole **189**. This intermediate could be accessed from the key pyrrolidine **187** derived from an asymmetric [3 + 2] annulation between imine **185** and allene **186** followed by diastereoselective hydrogenation of the pyrroline double bond. The potential for the described synthetic plan was supported by literature examples that utilize intramolecular alkylations at C3 of indole to forge the C ring of similar alkaloids. One notable example of this was disclosed by Rawal during the total synthesis of the alkaloid tabersonine (**194**, Scheme 33).[28]



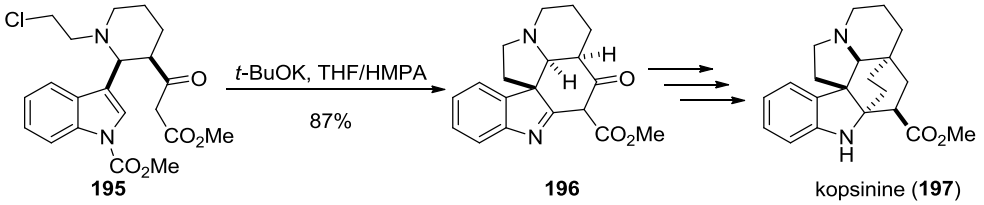
Scheme 32 Retrosynthetic analysis based on the phosphine-catalyzed [3 + 2] annulations

Tetracyclic chloroethylamine **192** underwent smooth alkylation at indole C3 upon treatment with potassium *tert*-butoxide in THF providing pentacyclic indolenine **193** in 87% yield, which was converted into the natural product.



Scheme 33 Rawal's synthesis of tabersonine

Even more encouraging was a report by Natsume describing a tandem indole C3 alkylation followed by an intramolecular nucleophilic addition to the newly formed indolenine (Scheme 34).[29] In this study, the highly substituted piperidine **195** was treated with potassium *tert*-butoxide in a mixture of THF and hexamethylphosphoramide (HMPA) which served to cleave the indole *N*-methylcarbamate, facilitating the intramolecular indole C3 alkylation. The enolate of the reactive β-ketoester was then able to add to the indolenine providing pentacycle **196** in 87% yield, forming two new rings in a single operation. This intermediate was taken on to complete a formal synthesis of kopsinine (**197**).

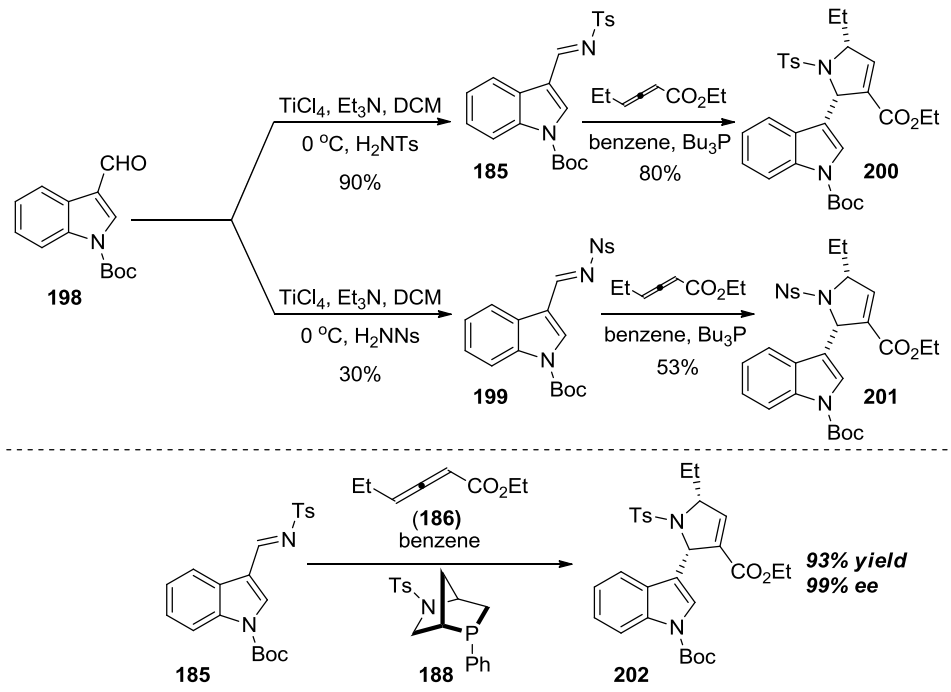


Scheme 34 Natsume's formal synthesis of kopsinine

Section 3.8 Exploration of the Key [3 + 2] Annulation

Although 3-ethyl 2,3-butadienoate (**186**) had been utilized previously in phosphine catalyzed [3 + 2] annulations with sulfonyl imines, it had not been determined whether or not imines derived from indole-3-aldehyde would serve as a viable substrate in the key transformation.[23] As shown in Scheme 35, indole **198**, prepared in two steps from indole, was condensed with *p*-toluenesulfonamide and *o*-nitrobenzenesulfonamide to give imines **185** and **199** in 90 and 30% yields, respectively (the nosyl imine formation was not optimized due to the low yield of the 3-pyrroline derived from it (*vide-infra*)). Under the conditions previously developed in our laboratory (20 mol% tri-*n*-butylphosphine in benzene), the *N*-tosyl pyrroline **200** was formed in 73% yield. The yield could be improved to 80% by using 50 mol% of the phosphine catalyst. Utilizing the *p*-nosyl imine resulted in only 53% yield of the desired pyrroline **201**. The ease of preparation of the *p*-tosyl imine, coupled with the efficiency of the annulations, led us to continue our synthetic studies with this substrate.

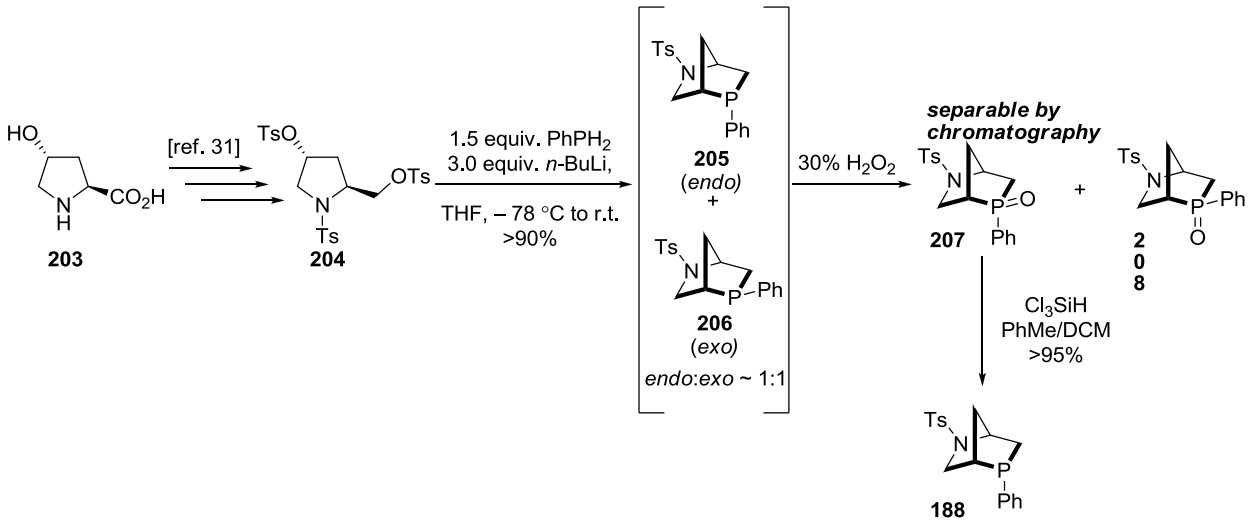
Having established that the *N*-tosyl imine derived from *N*-Boc indole-3-aldehyde (**185**) and γ-ethyl 2,3-butadienoate (**186**) were viable coupling partners in the key [3 + 2] annulation, the use of the newly developed chiral phosphine **188** was explored. Upon employing 30 mol% of the chiral phosphine in the annulation, the desired 3-pyrroline **202** was formed in a remarkable 99% yield and 99% *ee* (as determined by chiral SFC). Lowering the catalyst loading to 10 mol% had no negative effect on the *ee* while the yield dropped only slightly to 93%. In order for this transformation to be useful toward our total synthesis effort, optically active pyrroline **202** would need to be accessed in multigram quantities. We chose to move forward using this (condition employing 10 mol% of the chiral phosphine) to prepare multigram quantities of the optically



Scheme 35 Exploration of the key [3 + 2] annulation

active pyrroline. We were pleased to discover that the asymmetric [3 + 2] annulation performed remarkably well upon scale-up. When performing the reaction on nearly 30 grams of imine , the desired pyrroline was formed in 94% yield and 97% *ee*.

The synthesis of the utilized chiral phosphine is outlined in Scheme 36.[30] Trans L-hydroxyproline (**203**) is converted to the tritosylate **204** in three steps by known procedures involving selective *N*-tosylation, carboxylic acid reduction, and tosylation of the alcohols.[31] Diphenylphosphine (Danger!! Diphenylphosphine is pyrophoric and must be prepared and handled with care. Exposure to air must be strictly avoided.), prepared by lithium aluminum hydride reduction of dichlorophenylphosphine, is treated with *n*-butyllithium to generate the dianion of phenylphosphine. A solution of the tritosylate is added to the dilithiated



Scheme 36 Synthesis of the chiral phosphine catalyst

phenylphosphine and an efficient bis-alkylation takes place. This process is not diastereoselective and a near 1:1 mixture of the *endo* **205** and *exo* **206** bridged bicyclic phosphines is formed. Addition of 30% hydrogen peroxide to the reaction mixture results in quantitative conversion of these two phosphines to the corresponding oxides **207** and **208**. The diastereomeric oxides can be easily separated by silica gel chromatography. Reduction of the desired phosphine oxide with trichlorosilane provides chiral phosphine **188** as a single stereoisomer.

A plausible transition state, accounting for the high levels of enantioselectivity, has been generated by Dudding and coworkers based on DFT calculations. Based on this proposed model, a likely transition state for the specific asymmetric [3 + 2] utilized here is shown in Figure 6. Upon addition of chiral phosphine **188** to γ-ethyl allenoate **186**, a coulombic interaction between the negative charge on the oxygen atom of the phosphonium dienolate and the phosphonium ion holds the zwitterion portion in the orientation shown (coulombic interaction shown in red).

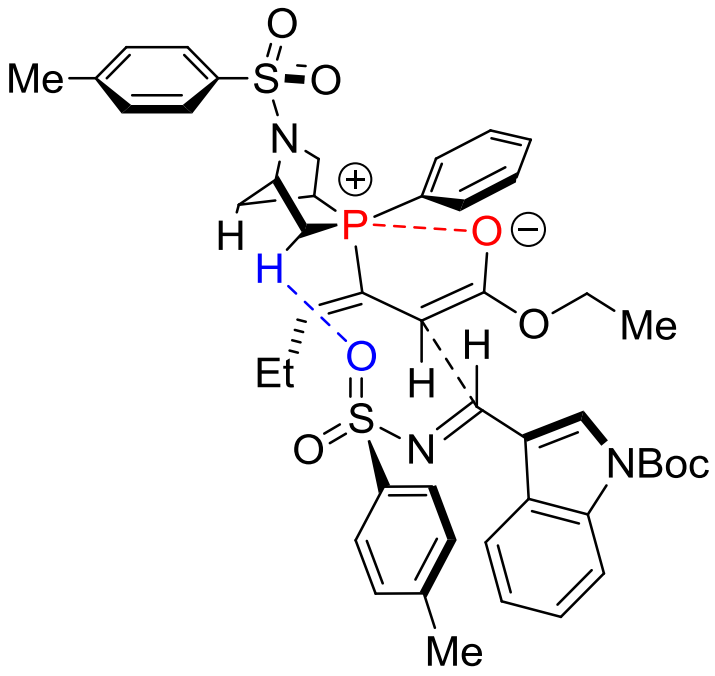
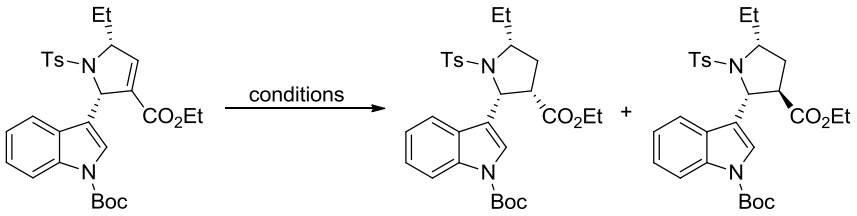


Figure 6 Proposed transition state for the [3 + 2] annulation between γ-ethylallenoate **186** and the *N*-tosyl imine derived from Boc-protected indole-3-aldehyde **185** catalyzed by chiral phosphine **188**

The facial selectivity of phosphonium dienolate addition to the imine is then dictated by a hydrogen bonding interaction between one of the sulfonyl oxygens of the tosyl group and one of the methylene hydrogens α to the phosphonium ion (hydrogen bonding interaction shown in blue). The hydrogen bonding interaction to the indicated hydrogen may be more favorable than other possible hydrogen bonds, with the hydrogen on the methine carbon that is at the alternative α-position to the phosphonium ion, based on less favorable steric interactions.

Section 3.9 Diastereoselective Hydrogenation of the Pyrroline Double Bond

In order to establish the third asymmetric center about ibophyllidine's D-ring, the hydrogenation of the double bond of pyrroline **202** was investigated.[32] Although there was no



202 **187** **209**

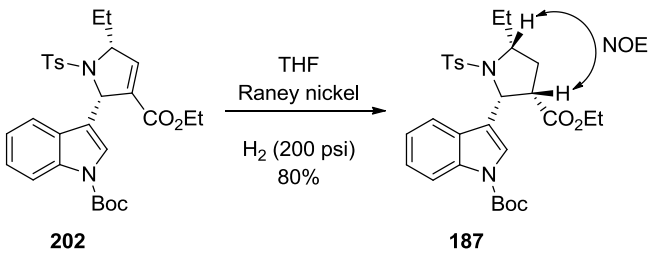
entry	catalyst	solvent	hydrogen source	**187**:**209**[a]
1	5% Pd/C	EtOH	H_2 balloon (50 °C)	1:37
2	5% Pd/C	MeOH	H_2 (balloon)	1:8
3	5% Pd/C	EtOAc	H_2 (balloon)	1:8
4	5% Pd/C	THF	H_2 (balloon)	1:5
5	5% Pd/C	PhH	H_2 (balloon)	1.8:1
6	5% Pd/C	PhH	H_2 (100 psi)	5:1
7	5% Pd/C	PhH	H_2 (200 psi)	5:1
8	5% Pd/C	PhH	H_2 (500 psi)	3.7:1
9	5% Pd/C	PhMe	H_2 (200 psi)	2.4:1
10	$(PPh_3)_2RhCl_2$	DCM	H_2 (balloon)	N/A[b,c]
11	$NiCl_2$	EtOH	$NaBH_4$ (2 equiv, 0 °C)	N/A[b]
12	$NiCl_2$	EtOH	$NaBH_4$ (10 equiv, 0 °C)	1:3 + **202**
13	N/A	EtOH	$NaBH_4$ (50 equiv, 3days)	N/A (see text)
14	Raney Ni	EtOH	H_2 (balloon)	8:1:0
15	Raney Ni	THF	none	N/A
16	Raney Ni	THF	H_2 (100 psi)	9:1
17	Raney Ni	THF	H_2 (200 psi)	16:1

[a] The reported diastereomeric ratio (dr) was obtained by the NMR spectrum of the crude product. [b] Mainly unreacted starting material was recovered. [c] This condition was also tried on the allylic alcohol resulting from the DIBAL-mediated reduction of **187**. Again, no reduction was observed in the NMR spectrum of the crude product.

Table 1 Hydrogenation of pyrroline **202**

literature precedent for the diastereoselective reduction of a 2,5-substituted pyrroline-3-carboxylate, it was anticipated that hydrogenation would occur from the opposite face of the C2and C5 (pyrroline numbering, not ibophyllidine numbering) substituents. This simplified model was not effective in prediction the selectivity of the ensuing reduction as the diastereoselectivity was observed to be heavily dependent on the conditions employed. A summary of the results obtained for the hydrogenation of the pyrroline **202** is provided in Table 1. The investigation commenced with the hydrogenation of **202** using 5% palladium on carbon in EtOH under a balloon of H_2 at 50 °C. Although the double bond was reduced, the hydrogenation proceeded to yield little of the desired compound **187**, favoring instead the undesired diastereomer **209** (entry 1). Employing milder conditions by operating at room temperature provided more of the desired diastereoisomer **187**, but still favored **209** with a diastereomeric ratio of 1:8 (entry 2). Switching the reaction medium to EtOAc provided no relative change in diastereoselectivity (entry 3), whereas upon performing the reaction in THF led to a small improvement, but still favored the undesired isomer **209** in a 1:5 ratio (entry 4). Utilizing benzene as the solvent had a remarkable effect on the dr, the ratio of products changed in favor of the desired isomer **187**, albeit only slightly (1.8:1 dr, entry 5). In an attempt to improve the diastereoselectivity, an elevated pressure of hydrogen gas was used under otherwise identical conditions. Upon switching from a H_2-filled balloon to running the reaction at 100 psi, the selectivity increased from 1.8:1 to an acceptable 5:1 (entries 5 and 6, respectively). Further increasing the pressure to 200 psi did not change the ratio (entry 7); increasing the pressure further still, to 500 psi, resulted in a surprising drop in selectivity (3.7:1) (entry 8). Other aromatic solvents (e.g., toluene), under otherwise identical conditions, provided lower selectivity (2.4:1 dr, entry 9). In an effort to identify conditions that would favor the desired

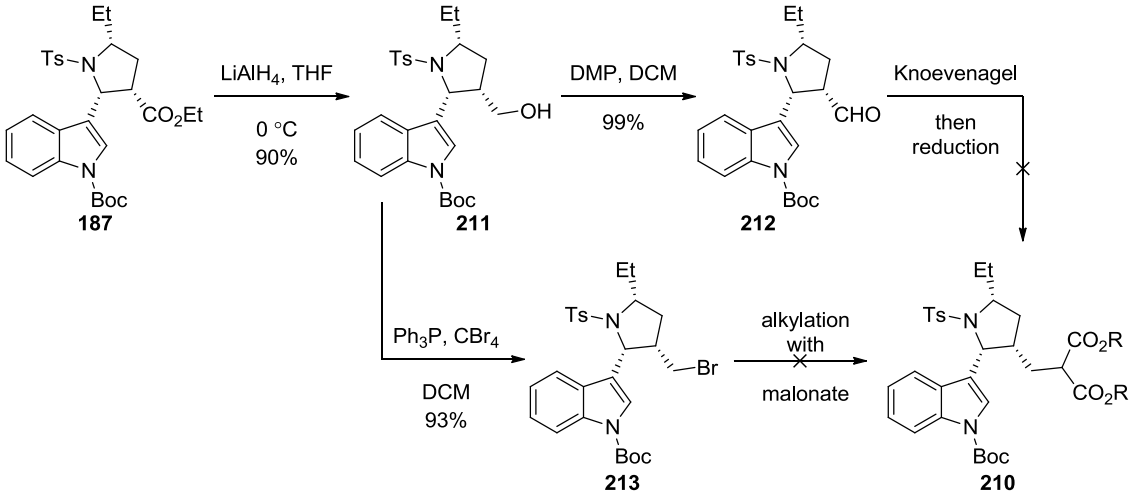
diastereoisomer with higher selectivity, other hydrogenation catalysts were explored. Homogeneous reduction with Wilkinson's catalyst provided mainly recovered starting material (entry 10). *In situ*–generated nickel boride provided little, if any, reduction products when employing two equivalents of $NaBH_4$ (entry 11). An increase to 10 equivalents of $NaBH_4$ did provide some of the desired pyrrolidine, along with recovered starting material; however, these conditions favored formation of the undesired diastereoisomer **209** in a ratio of 1:3 (entry 12). Simply using a large excess of $NaBH_4$ (50 equiv) in EtOH for three days resulted in a new compound, remarkably as a single diastereomer, later identified as the alcohol derived from reduction of the ester group of **209**. The best reducing agent identified for the desired transformation was Raney Ni (entries 14–17). Reacting pyrroline **202** with Raney Ni in EtOH favored formation of the desired diastereoisomer with dr of 8:1 (entry 14). Performing the reaction without external H_2 was not productive (entry 15). In an attempt to avoid some of the inconsistencies in conversion and selectivity when using Raney Nickel for the reduction, the reactions with were performed under elevated pressures of H_2. Not only did this provide more-reliable reaction times and conversions, but the diastereoselectivity increased as well (entries 16 and 17). When employing Raney Ni at 100 psi, the desired pyrrolidine **187** was isolated in a ratio of 9:1 favoring the desired isomer (entry 16). Further increasing the pressure to 200 psi, resulted in an additional improvement in selectivity to 16:1, the best selectivity obtained in this study. Under these optimized conditions (see below), the desired pyrrolidine **187** could be isolated consistently in 80% yield as a single diastereoisomer, the stereochemistry of which was determined by the NOE between the protons at C3 and C5 (pyrrolidine numbering, not ibophyllidine numbering (Scheme 37).



Scheme 37 Diastereoselective hydrogenation of pyrroline **202**

Section 3.10 Attempt to Functionalize Side Chain as Diester

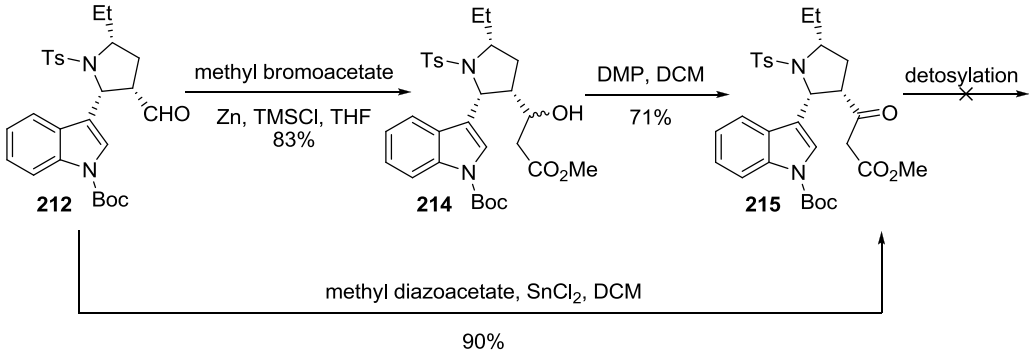
Our initial attempts to functionalize the side chain of pyrrolidine were to prepare diester **210** (Scheme 38). Lithium aluminum hydride reduction of the ester of **187** to alcohol **211** followed by Dess–Martin–Periodinane (DMP) oxidation provided aldehyde **212** in 90 and 99% yields, respectively. Attempts to carry out a Knoevenagel condensation, which upon reduction would provide the desired intermediate, failed. An alternative approach involving alkylation of malonate derivitives with bromide **213**, prepared in 93% yield from alcohol **211**, also failed.



Scheme 38 Failed attempt to produce diester **210**

Section 3.11 Attempt to Functionalize Side Chain as β-ketoester

While we were unable to identify a viable route to diester **210**, it was anticipated that a β-ketoester would also be suitable (Scheme 39). Reformatsky aldol reaction between aldehyde **212** and the zinc enolate derived from methyl bromoacetate provided alcohol **214** in 83% yield as an inconsequential mixture of diastereomers. Oxidation with the Dess–Martin periodinane provided the desired β-ketoester **215**, which existed as a mixture of keto and enol forms (judged by ^{1}H NMR) in 71% yield. It was eventually discovered that the same intermediate could be prepared in a single operation in 90% yield from aldehyde **212** by employing the Roskamp homologation protocol with methyl diazoacetate.[33] At this point it was necessary to cleave the pyrrolidine sulfonyl group in order to functionalize the amine with the necessary two carbon unit. However, all attempts to detosylate intermediate **215** failed to provide any of the desired amine. After several failed experiments, it was hypothesized that the ketone of the side chain β-ketoester was likely not stable to the strong single electron reduction conditions commonly employed in removing the tosyl group from secondary amines. In order to circumvent this problem, the synthetic strategy was modified. It was anticipated that detosylation of hydrogenation product

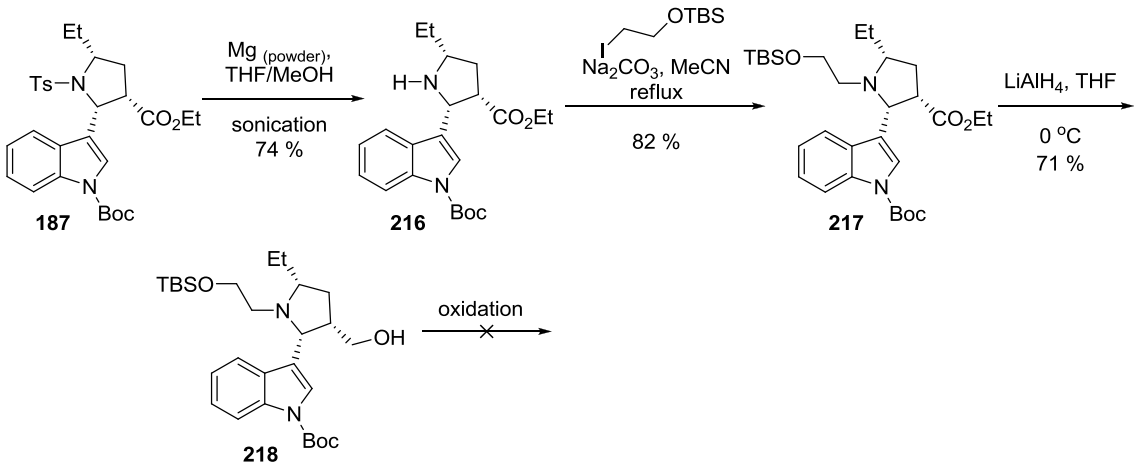


Scheme 39 Side chain functionalization as β-ketoester and difficulty with detosylation

187 followed by amine functionalization could be carried out prior to side chain functionalization.

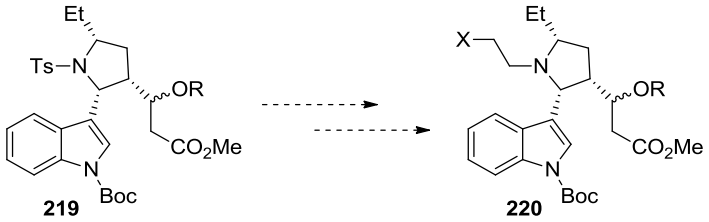
Section 3.12 Detosylation and Amine Functionalization From Hydrogenation Product 187

Although a number of conditions for detosylation of compound **187** were tried, in almost all cases either starting material or unidentified products from decomposition were observed. It was found that the strong reductant formed from samarium iodide, water, and pyrrolidine could effectively remove the tosyl group from **187** to provide secondary pyrrolidine **216** in 63% islolated yield (reaction with SmI_2 not shown).[34] These conditions required a large excess (10 equivalents) of freshly prepared samarium iodide and were operationally cumbersome. Upon further experimentation it was discovered that sonicating a solution of hydrogenation product **187** in a 9:1 MeOH/THF mixture in the presence of powdered magnesium metal provided a higher yielding (74%), less cumbersome, and more reproducible alternative to the reductive



Scheme 40 Amine functionalization prior to side chain homologation

cleavage of the sulfonamide with samarium diiodide (Scheme 40). *N*-Alkylation of the secondary amine of **216** with TBS protected 2-iodoethanol yielded 82% of tertiary amine **217**. Reduction with lithium aluminum hydride provided alcohol **218** in 71% yield. At this stage it was necessary to access the aldehyde derivative of **218** in order to perform an analogous homologation (either in one or two steps) to that performed previously (see Scheme 39). Despite our best efforts, **218** could not be oxidized to the corresponding aldehyde. Some aldehyde product was observed in the ^{1}H NMR of crude material, but any attempt at purification led to more extensive decomposition. Attempts to perform homologations on crude material failed. It was believed that the necessary aldehyde was unstable, for reasons unknown, and thus must be avoided as a synthetic intermediate. A third route was devised involving side chain homologation as a protected β-hydroxyester **219** which would be stable to the reductive cleavage of the tosyl group and amine functionalization providing an intermediate like that of **220**, which would allow for conversion to the desired β-ketoester later in the synthesis (Scheme 41).

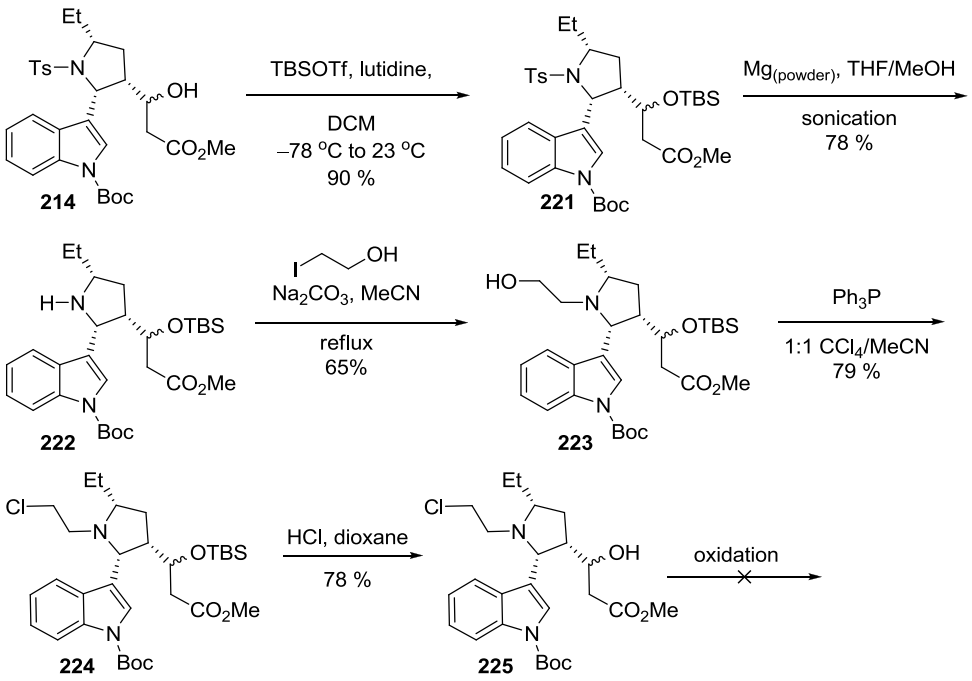


Scheme 41 Planned route to avoid intermediacy of an aldehyde side chain

Section 3.13 Route Avoiding an Aldehyde Side Chain

Implementation of this design plan is outlined in Scheme 42. Starting from the previously accessed `mixture of alcohols **214**, protection of the secondary carbinol as the TBS

ether **221** proceeded in 90% yield. Removal of the tosyl group, under the conditions previously described, gave *N*-H pyrrolidine **222** in 78% yield. *N*-alkylation with iodoethanol proceeded in 65% yield to give tertiary amine **223**. Conversion to chloride **224** followed by TBS removal yielded secondary alcohol **225** in 79 and 78% yields, respectively. All attempts to oxidize the alcohol of **225** failed to provide any of the desired β-ketoester and decomposition was the dominant pathway is most cases. The similarity in results obtained in the attempted oxidation intermediates **218** (see Scheme 40) and **225** led us to modify our previously established



Scheme 42 Attempt to access the desired β-ketoester side chain from the corresponding β-hydroxyester

hypothesis regarding the stability of the desired aldehyde derived from alcohol **218**. It was believed that the basicity of the amine may in fact be responsible for the observed decomposition

during oxidation. If in fact the case, it was hoped that we could utilize an alternative two carbon subunit on the pyrrolidine nitrogen that would also serve to deactivate the amine. It was felt that an α-haloamide would effectively serve this purpose (Figure 7).

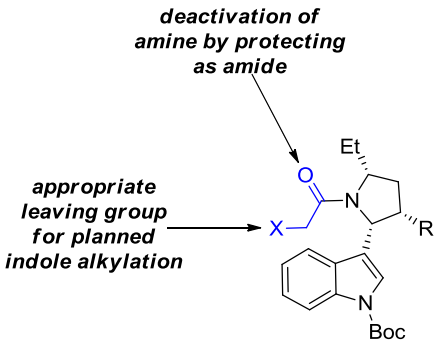
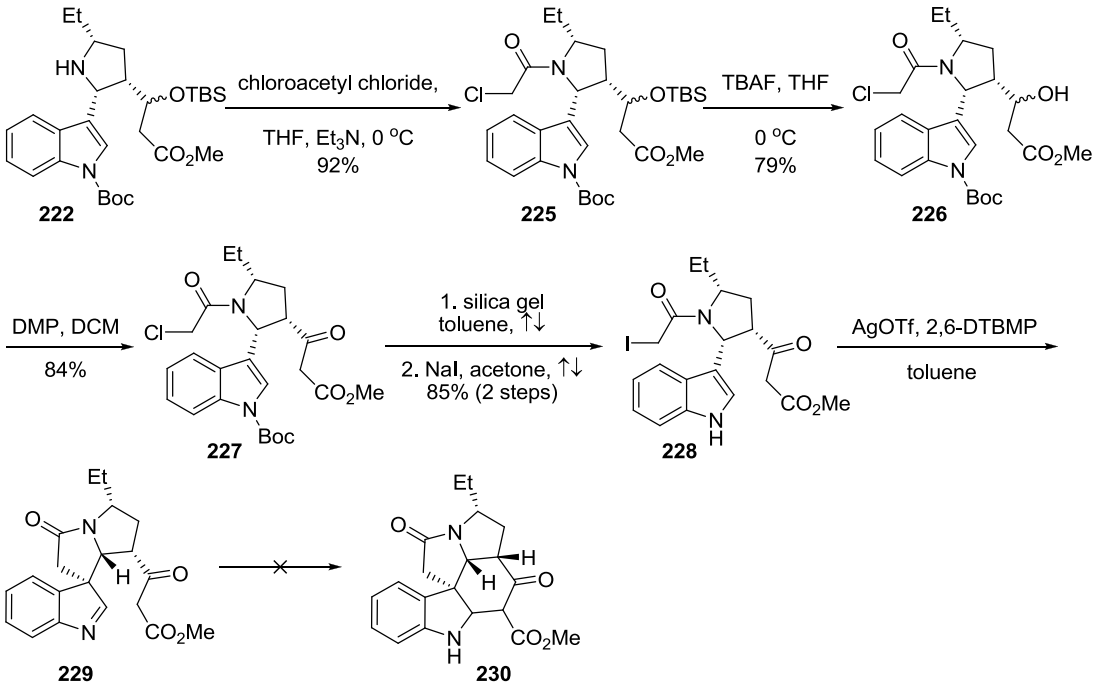


Figure 7 Planned use of haloamide

Section 3.14 Use of Haloamide

Investigating the potential benefits of using a haloamide like that depicted in Figure 7 required only a slight modification of the previously disclosed chemistry (Scheme 43). Free *N*-H pyrrolidine **222**, described previously (see Scheme 42), was acetylated with chloroacetyl chloride followed by cleavage of the silyl ether to provide chloroamide **225** then β-hydroxyester **226** in 92 and 79% yields, respectively. This intermediate underwent smooth oxidation with the Dess–Martin periodinane to provide the desired β-ketoester **227** in 84% yield. Although it cannot be definitively concluded, the ease of oxidation at this stage provides evidence in support of our hypothesis regarding the role of the pyrrolidine amines in the incompatibility of previous substrates in analogous oxidation reactions. Cleavage of the indole *N*-carbamate was facilitated by refluxing a toluene solution of **227** in the presence of silica gel. Treatment of the crude



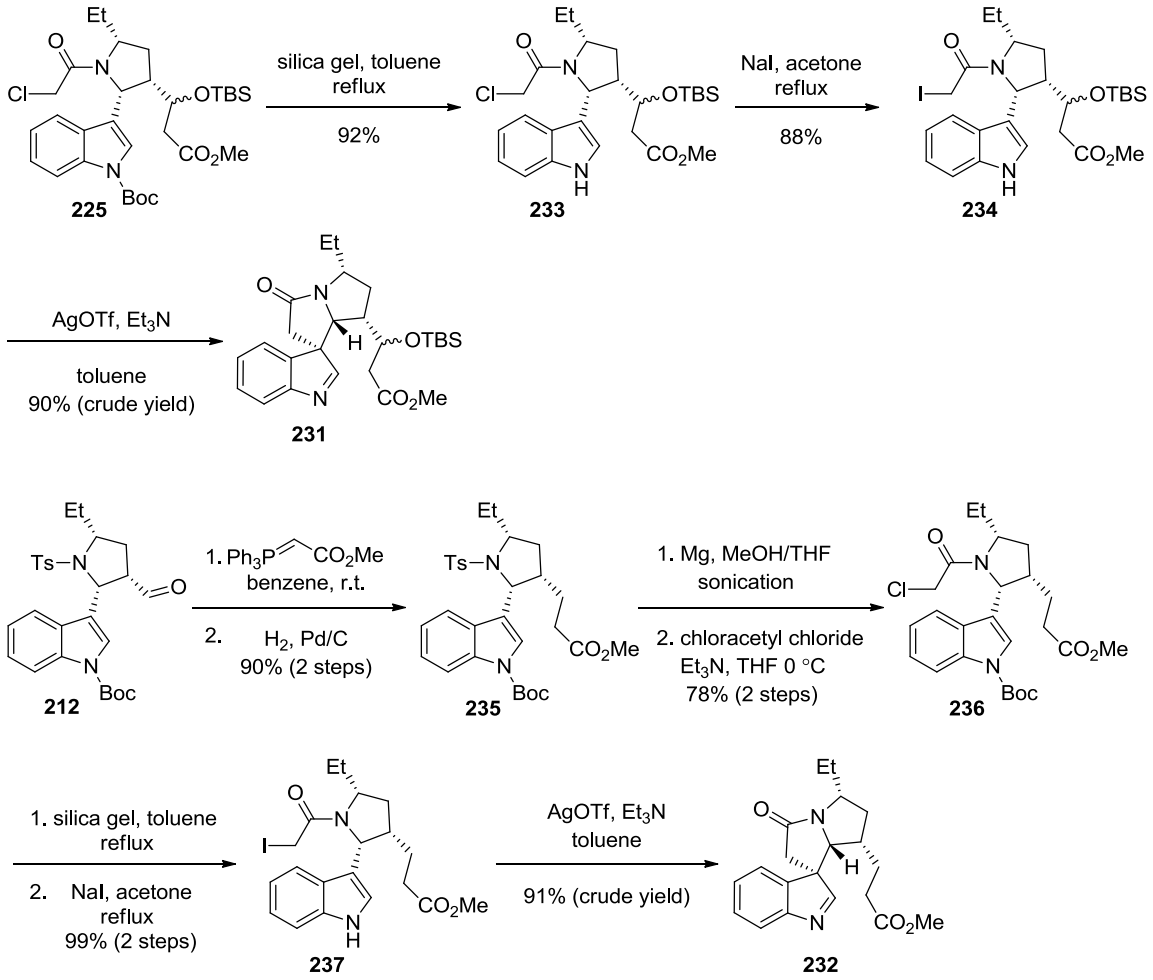
Scheme 43 Implementation of haloamide and the failed Mannich cyclization

Material, after filtration and concentration, under standard Finkelstein conditions provided the iodoamide cyclization precursor **228** in 85% yield over two steps. Adopting similar conditions to those reported by Heathcock, and later by Andrade, appeared to provide spirocyclic indolenine **229**.[35, 36] While the crude NMR spectra were difficult to decipher, and purification led to more extensive decomposition, there were key anticipated chemical shifts that led us to believe that the spirocyclization took place. The mass spectrum was also in agreement with this transformation having occurred. In accord with the literature, the use of the less reactive chloroamide directly in the spirocyclization was not effective. At this stage it was believed that if the spirocyclization had indeed occurred, the proximal β-ketoester was poised to undergo a facile intramolecular Mannich reaction with the imine of **229**. Despite our best efforts to facilitate such a transformation, none of the desired pentacycle **230** was identified.

Section 3.15 Use of Alternative Cyclization Substrates

In an attempt to explore alternative E-ring cyclization substrates and to obtain clearer data in order to confirm that spirocyclization is feasible in our system, we also prepared alternative spirocyclic indolenine substrates **231** and **232** bearing the TBS protected β-hydroxyester and a fully saturated side chain, respectively (Scheme 44). The Boc group of compound **225** was cleaved in 92% yield as previously described, followed by conversion to iodide **234** in 88% yield. Treatment of a single diastereomer of this cyclization precursor with silver trifluoromethanesulfonate and triethylamine provided the anticipated tetracycle **231** in 91% yield as the crude material. The saturated side chain substrate was prepared from aldehyde **212** via Wittig reaction followed by hydrogenation of the enoate double bond to provide homologate **235** in 90% yield over two steps. Tosyl group removal and *N*-acylation with chloroacetyl chloride, under the previously utilized conditions, provided chloroamide **236** in 78% yield over two steps. Boc group removal with silica gel in refluxing toluene and a subsequent Finkelstein reaction yielded the iodoamide **237** in 99% yield over two steps. Spirocyclization under the previously described conditions provided the anticipated tetracycle **232** in 91% crude yield.

Attempts to prepare an enolate from either of these precursors by deprotonation did not lead to any of the desired pentacycles. Attempts at generating the silyl ketene acetals from these substrates were also unsuccessful. These substrates were useful however, in confirming the success of the spirocyclization as they provided definitive data corresponding to the assigned structures. Although spirocyclization was believed to have taken place successfully with β-ketoester **229**, the keto/enol tautomeric mixture present in the ^{1}H NMR made the interpretation difficult. Interestingly, the spirocycles **231** and **232** were formed in a highly diastereoselective manner as judged by their crude ^{1}H NMR spectra after filtration and aqueous workup.



Scheme 44 Alternative spirocyclic indolenine substrates

A plausible rationale for this selectivity is proposed in Figure 8. Upon cylization the two orthogonally oriented ring systems can form in two ways. The more favorable way places the C2 hydrogen of the indolenine underneath the concave face of the 5,5-fused ring system (**238**), the less favorable way places the much larger benzene portion of the indolenine underneath the sterically more congested concave face of the 5,5-fused ring system (**239**). Satisfied that we had established a highly diastereo and enantioselective route to tetracyclic spirocycles like that of **231** and **232**, we felt that E-ring formation through this type of substrate would be ideal.

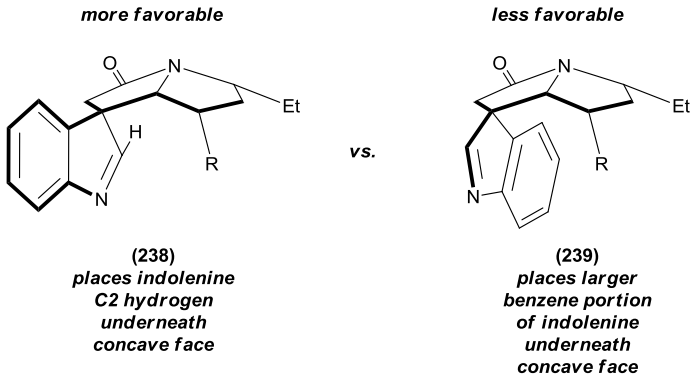
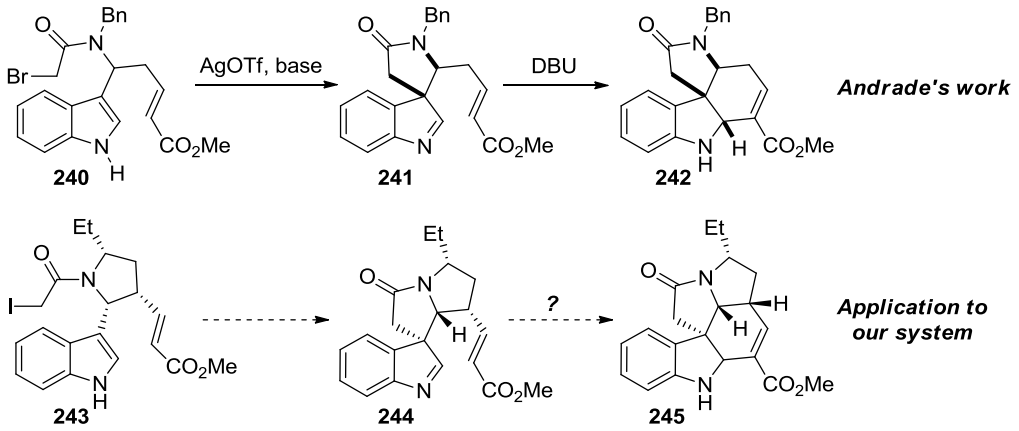


Figure 8 Plausible rationale for observed diastereoselectivity of spirocyclization

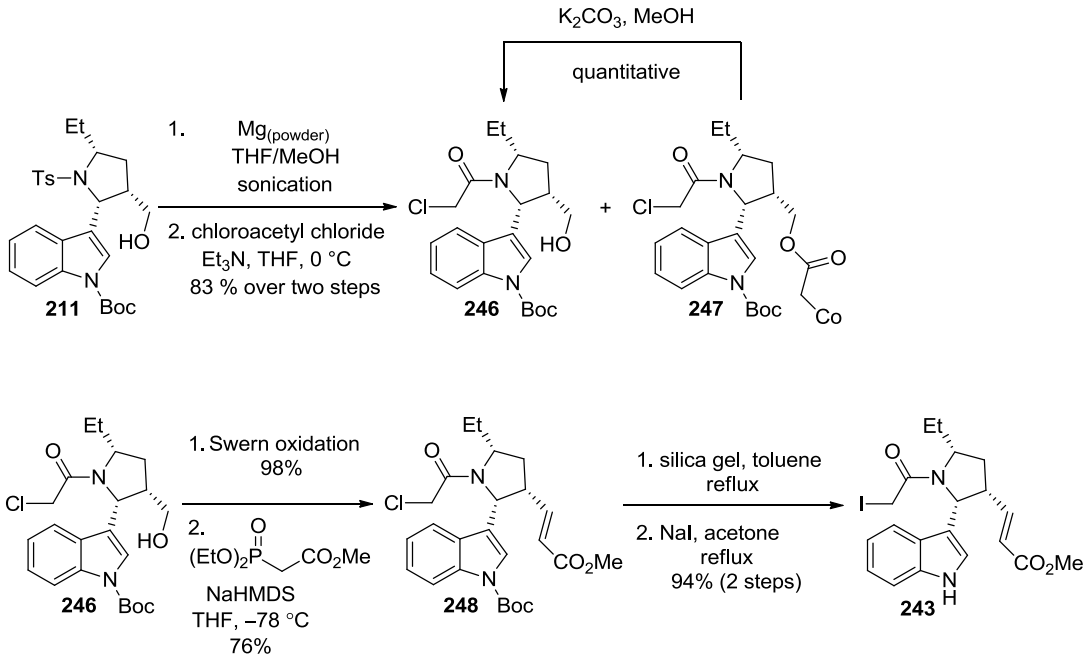
Section 3.16 Exploration of an Intramolecular aza-Morita–Baylis–Hillman reaction for E-ring Formation

Having had no success facilitating the desired Mannich-type cyclization initially envisioned, it was necessary to consider alternative methods for generating the desired carbon nucleophile capable of adding to the pendant imine. In this regard we took inspiration from the recent work of Andrade who has developed a useful intramolecular aza-Morita–Baylis–Hillman (MBH) reaction for forming the E-ring of a number of related alkaloids (**240** → **241** → **242**, Scheme 45).[36] It was hoped that we could exploit this type of reactivity for the formation of the E-ring of ibophyllidine (**244** → **245**, Scheme 45). In order to undertake such an investigation it was necessary to prepare a cyclization substrate bearing the requisite enoate double bond (**244**, Scheme 45) that was anticipated to arise from a spirocyclization, similar to that which we had previously observed, utilizing substrate **243**. Although we had previously functionalized the side chain in this manner via a Wittig olefination (**212** → **235**, Scheme 44), the olefin was immediately reduced prior to reductive cleavage of the sulfonamide protecting group. It was anticipated that with the α,β- unsaturated ester still in place, the double bond would almost



Scheme 45 Andrade's aza-MBH reaction and the potential application to our system

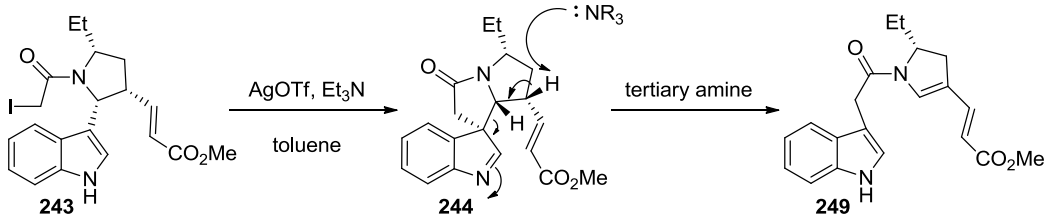
certainly be reduced under the detosylation conditions. In order to circumvent this problem, the modified synthetic strategy outlined in Scheme 46 was developed. Alcohol **211**, derived from LAH reduction of the hydrogenation product **187** (see Scheme 38) was detosylated under the conditions previously described. After aqueous workup, the crude amino alcohol was treated with chloroacetyl chloride to provide chloroamide **246** in 83% over two steps. During some runs of the acylation some of the bisacylation product derived from *N*- and *O*-acylation was isolated (**247**). In these instances, the *O*-acetyl group could be selectively cleaved with potassium carbonate in methanol in near quantitative yield to provide chloroamide **246**. Oxidation of the alcohol under Swern conditions followed by Horner–Wadsworth–Emmons olefination provided α,β-unsaturated ester **248** in 98 and 76% yields, respectively. It was necessary to employ the Horner–Wadsworth–Emmons olefination in place of the previously utilized Wittig reaction in order to minimize side reactions that presumably arise from the reactive chloroamide. Deprotection of the indole *N*-Boc group and Finkelstein reaction under the previously discussed conditions provided the cyclization precursor **243** in 94% yield over two steps.



Scheme 46 Preparation of the cyclization precursor bearing the desired α,β-unsaturated ester sidechain

With this key substrate in hand we readily facilitated the spirocyclization under analogous conditions utilized for previous substrates to provide the spirocyclic indolenine **244** (Scheme 47). Treatment of intermediate **244** under Andrade's conditions (DBU, toluene) failed to provide any of the desired pentacycle resulting from the desired intramolecular aza-MBH reaction. Instead, the formation of ring fragmentation product **249** was observed. Other tertiary amines known to catalyze MBH reactions were screened, but none facilitated the desired E-ring formation (see entries 1–4, Table 2). It was hypothesized that the fragmentation pathway was a result of the added steric encumbrance of the pyrrolidine ring at the enoate γ-position, in comparison to Andrade's system that bares only a methylene at the analogous position. The resulting impedement of catalyst addition favors an alternative pathway involving deprotonation γ to the enoate forming the cyclic enamine of **249** with concomitant C-ring fragmentation and

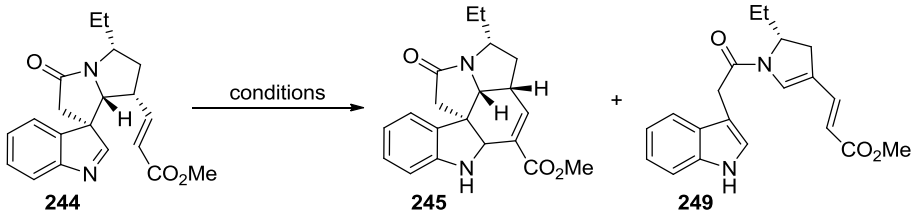
restoration of the aromatic indole nucleus. If this was indeed the case, it was rationalized that utilizing a highly nucleophilic, yet less Brønsted basic, catalysts may



Scheme 47 Results of attempted cylization utilizing nucleophilic amine catalysts

facilitate the desired pathway leading to E-ring formation. To this end, different conditions involving nucleophilic phosphines were screened (entries 5–14, Table 2). The initial results were promising, using tri-*n*-butylphosphine as catalyst in acetonitrile at 55 °C did provide some of the desired pentacycle, but as a near 1:1 mixture along with the undesired diene **249** (entry 5). Attempts to activate the imine nitrogen (entries 6–8) did not provide any improvement in the product distribution with acetic acid resulting in near identical results to the use of no additive (entries 6 and 7). Treating indolenine **244** with $BF_3{\cdot}Et_2O$ prior to catalyst addition resulted in only starting material (entry 8). It is possible that $BF_3{\cdot}Et_2O$ and the catalyst react to generate a catalytically inactive phosphonium borate complex resulting in recovered starting material. Switching to the more nucleophilic trimethylphosphine (10 equiv) with acetic acid as an additive in refluxing acetonitrile resulted largely in recovered starting material contaminated with small amounts of the undesired diene (entry 9). Employing 100 equivalents of trimethylphosphine at room temperature with no additives provided 51% islolated yield of the desired pentacycle along with the undesired diene (amount of diene undetermined, entry 10). Performing the reaction at 0 °C under otherwise identical conditions resulted in no product formation observable by TLC.

However upon warming to room temperature, the results were consistent with those obtained at room temperature (entry 11). Performing the reaction in benzene improved the yield of the desired product while suppressing fragmentation, however the



entry	catalyst	solvent	additive	temperature	result
1	DBU	PhMe	none	r.t.	Diene (50%)
2	DBU	PhMe	none	50 °C	diene
3	DABCO	DCM	none	r.t.	Starting material
4	3-quinuclidinol	MeCN	none	60 °C	unidentified
5	Bu_3P	MeCN	none	55 °C	~1:1 diene/pentac
6	Bu_3P	MeCN	AcOH	55 °C	~1:1 diene/pentac
7	Bu_3P	MeCN	AcOH	Reflux	~1:1 diene/pentac
8	Bu_3P	MeCN	$BF_3•Et_2O$	r.t.	Starting material
9	Me_3P (10 equiv.)	MeCN	AcOH	Reflux	Diene/s.m.
10	Me_3P (100 equiv.)	MeCN	None	r.t.	51%pent/+diene
11	Me_3P (100 equiv.)	MeCN	None	0 °C to r.t.	51%pent/+diene
12	Me_3P (100 equiv.)	PhH	MeOH[a]	r.t.	70% (2 steps)
13	Me_3P (10 equiv.)	PhH	MeOH	r.t.	80% (2 steps)
14	Me_3P (10 equiv.)	MeOH	None	r.t.	~50–60%

[a] Methanol was added to the reaction once it had been proceeding slowly for over 24 hours.

Table 2 Optimization of the intramolecular aza-MBH reaction for E-ring formation

reaction was exceedingly slow even with one hundred equivalents of trimethylphosphine. Upon addition of an aliquot of methanol to the progressing reaction, a substantial rate increase was observed resulting in the desired product being isolated in 70% yield (entry 12). These results are consistent with reports of alcoholic solvents increasing the rates of some MBH reactions.[37] According to the proposed model for acceleration, the alcoholic solvent facilitates the potentially rate determining proton transfer event that occurs after carbon-carbon bond formation (Figure 9).

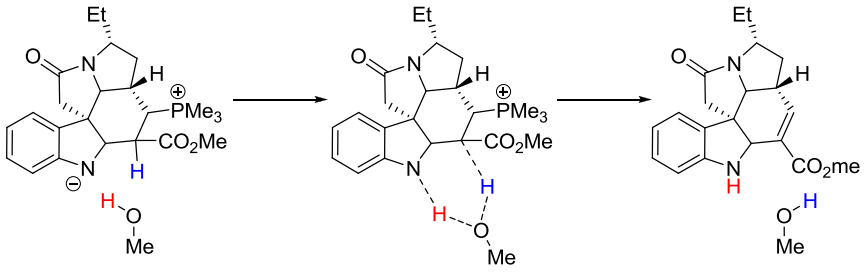
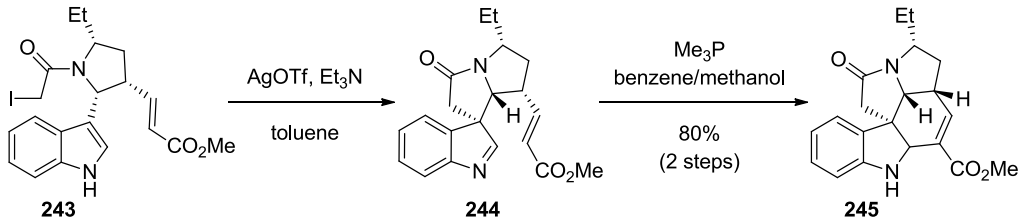


Figure 9 Potential role of methanol in the intramolecular aza-MBH reaction

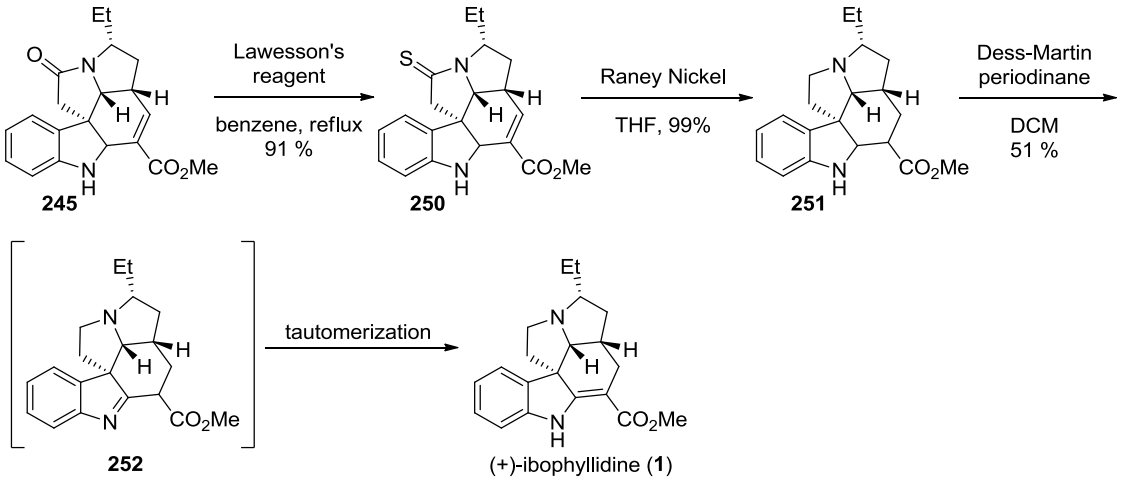
Further optimization revealed that performing the reaction in a 9:1 mixture of benzene/methanol with ten equivalents of trimethylphosphine for a few hours furnished the desired pentacycle in 80% islolated yield over two steps from iodoamide **243** (entry 13, Table 2, also see Scheme 48). The reaction could be performed in methanol as solvent leading to starting material consumption in only 5–10 minutes, however under these conditions the isolated yields tended to be lower (entry 14).



Scheme 48 Optimized two step sequence to pentacycle **245** from iodoamide **243**

Section 3.17 Completion of the Synthesis

With the pentacyclic skeleton of ibophyllidine in place, all that remained was reduction of the lactam to the amine and transposition of the enoate double bond into conjugation with the indoline nitrogen (Scheme 49). Cursory attempts to isomerize the double bond of **245** included treatment with *p*-toluenesulfonic acid, rhodium trichloride, and DBU. It was quickly realized, however, that thioamide formation (**250**) followed by reductive desulfurization with Raney nickel concomitantly reduced the double bond of the α,β-unsaturated ester to provide dihydroibophyllidine (**251**) in 99% yield as a single diastereomer, the stereochemistry of which was not determined.[38] It was speculated that upon oxidation of the indoline of **251** to the indolenine **252** a facile tautomerization to the natural product would occur. To this end a number of oxidants known to oxidize amines to imines were screened. DDQ,[39] Pd/C,[40] $(PhSeO)_2$,[41] *tert*-butyl hypochlorite,[42] MnO_2,[43] *N*-*tert*-butylbenzenesulfinimidoyl chloride,[44] IBX,[45] and PhIO[46] all failed to produce any of the desired compound. Oxidation under Swern conditions provided our first glimpse of the natural product, but it was produced as an inseparable mixture along with an unidentified side product.[47] Other methods for activating DMSO were screened, but none provided improved results. It was eventually discovered that treatment of dihdroibophyllidine with the Dess–Martin periodinane [48] in dichloromethatne at room temperature provided moderate



Scheme 49 Completion of the total synthesis

yields of (+)-ibophyllidine (**1**) , the spectral data of which was in accord with that reported in the literature.[1,2a, 13,17]

Section 3.18 Conclusions

The study described here resulted in the enantioselective total synthesis of the terpene indole alkaloid (+)-ibophyllidine. This work represents the first synthesis of this molecule to utilize asymmetric catalysis and the first non-formal total synthesis to utilize the phosphine-catalyzed allene–imine [3 + 2] annulation. The use of this reaction was very effective in controlling the relative stereochemistry between the C20 ethyl group and the C3 indole substituent. Diastereoselective hydrogenation of the [3 + 2] adduct provided the third stereocenter of ibophyllidine's D-ring. The C-ring was formed via intramolecular alkylation at C3 of indole which proceeded to construct the fourth and final stereocenter in the molecule with a high level of selectivity. The use of a haloamide as the electrophilic alkylation partner was necessary in order to serve a second purpose of protecting the reactive pyrrolidine nitrogen atom

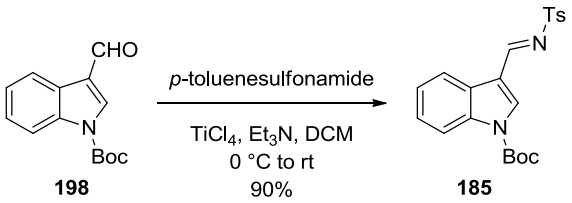
that made it difficult to manipulate the side chain at the pyrrolidine C3 position (pyrrolidine ring numbering). The strategy utilized is markedly different that previous syntheses of ibophyllidine alkaloids, which rely almost exclusively on the generation of a secodine-like analogue capable of undergoing an intramolecular Diels–Alder cyclization to form the C- and E-rings simultaneously.[49]

Section 3.19 Materials and Methods

Unless otherwise stated, all reactions were performed in flame-dried glassware fitted with a rubber septum, under an Ar atmosphere, and stirred with a Teflon-coated stirrer bar. All reaction solvents were distilled immediately prior to use [dichloromethane (DCM), acetonitrile (MeCN), benzene (PhH), and toluene (PhMe) were distilled from CaH_2; tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl; methanol (MeOH) was distilled from magnesium methoxide] and transferred with an oven-dried needle and a disposable syringe using standard Schlenk techniques. Thin layer chromatography (TLC) was performed using SiliCycle silica gel 60 F-254–precoated glass-backed plates (thickness: 0.25 mm) and visualized under UV light and through anisaldehyde or permanganate staining. Flash column chromatography was performed using SiliCycle Silica-P silica gel (particle size: 40–63 μm). Melting points were measured using an Electrothermal capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance-500, ARX-400, and ARX-500 MHz spectrometers, with ^{13}C operating frequencies of 125, 100, and 125 MHz respectively. Chemical shifts are reported in ppm (δ) with respect to the residual solvent ($CHCl_3$; δ = 7.26 ppm for ^{1}H; δ = 77 ppm for ^{13}C). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and number of protons. The following abbreviations are used for ^{1}H

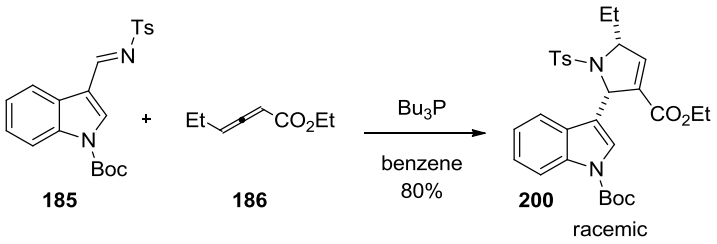
NMR multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; td = triplet of doublets; tdd = triplet of doublet of doublets; m = multiplet; br = broad; app = apparent. Data for ^{13}C NMR spectra are reported with respect to chemical shift (ppm). IR spectra were recorded using a Jasco FTIR-4100 spectrometer equipped with an ATR attachment. MALDI mass spectra were recorded using an AB/PerSpective DE-STR instrument. Samples for MALDI analysis were dissolved with 2,5-dihydroxybenzoic acid as the matrix. High-resolution mass spectra were recorded using a Waters LCT Premier instrument. Optical rotations were recorded using a Rudolph Autopol IV automatic polarimeter. Enantiomeric excess was measured using a Mettler Toledo SFC (supercritical fluid chromatography) instrument and a chiral OD-H column (20% EtOAc).

Section 3.20 Experimental Procedures



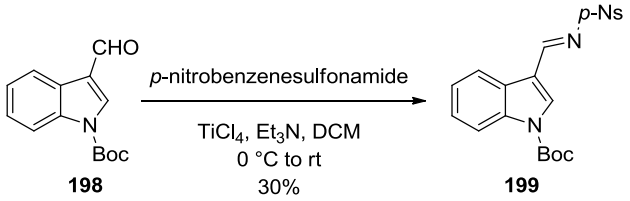
***N*-Tosyl-imine 185.** Indole-3-carboxaldehyde is commercially available or readily prepared via Vilsmeier–Haack formylation of indole, following the procedure of James and Snyder.[50] Indole-3-carboxaldehyde was then N-Boc–protected, following the procedure of Grehn and Ragnarsson, to provide **198**.[51] *N*-Boc-indole-3-aldehyde (**198**; 4.76 g, 19.4 mmol, 1 equiv) and *p*-toluenesulfonamide (3.36 g, 19.6 mmol, 1.01 equiv) were suspended in freshly distilled DCM (194 mL). The mixture was placed under a positive pressure of Ar and then freshly distilled triethylamine (8.12 mL, 58.2 mmol, 3 equiv) was introduced via syringe. The heterogeneous mixture was cooled to 0 °C and then 1 M $TiCl_4$ in DCM (9.71 mL, 9.71 mmol, 0.5 equiv) was

added via syringe pump over 1 h. The mixture was then stirred until the starting material was consumed (overnight, as determined by TLC; the mixture was slowly warmed to room temperature over the course of the reaction). The mixture was cooled to 0 °C and then the reaction was quenched through the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase extracted twice with DCM. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was recrystallized (DCM/hexanes) to provide a yellow crystalline solid (6.96 g, 90%). Mp: 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.29 (d, J = 7.9 Hz, 1H), 8.28 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 2H), 7.41 (td, J = 7.4, 1.4 Hz, 1H), 7.36–7.30 (m, 3H), 2.42 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 148.3, 144.0, 137.5, 136.1, 135.9, 129.6, 127.7, 126.2, 126.2, 124.6, 122.7, 116.4, 115.1, 85.9, 27.9, 21.5; IR (film): 3132, 1575, 1329, 1235, 1083, 811, 544 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{21}H_{22}N_2O_4SH$, 399.1378, found 399.1375.



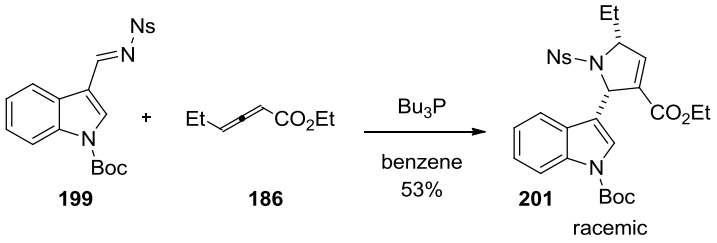
Racemic Pyrroline 200. A flame-dried round-bottom flask was charged with the imine **185** (150.0 mg, 0.38 mmol, 1 equiv), capped with a rubber septum and placed under a positive pressure of Ar. Imine **185** was dissolved in freshly distilled benzene (4.75 mL) and tri-*n*-butylphosphine (47 μL, 0.19 mmol, 05 equiv) was added. Allenoate **186** (79 mg, 0.56 mmol, 1.5 equiv), prepared using the method of Lang and Hansen was added.[52] The mixture was stirred

at room temperature until the starting imine **185** was consumed (4 h, as determined by TLC). The crude reaction product was loaded directly onto a column of SiO_2 and purified through flash column chromatography (30% Et_2O/pentanes) to yield a white solid (163 mg, 80%,). When employing the standard 20 mol% tri-*n*-butylphosphine, yields typically ranged from 69–75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.41 (s, 1H), 7.28 (td, *J* = 7.3, 1.1 Hz, 1H), 7.22 (td, *J* = 7.3, 1.0 Hz, 1H), 7.1 (d, *J* = 8.1 Hz, 2H), 6.79 (app t, *J* = 2.0 Hz, 1H), 5.98 (app t, *J* = 1.9 Hz, 1H), 4.66–4.60 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.14–2.03 (m, 1H), 1.89–1.77 (m, 1H), 1.66 (s, 9H), 1.06 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 162.1, 149.4, 143.4, 139.2, 135.3, 135.2, 133.9, 129.2, 128.9, 127.4, 125.3, 124.2, 122.4, 120.0, 119.7, 114.9, 83.7, 68.6, 61.3, 60.7, 29.3, 28.1, 21.3, 13.8, 10.4; IR (film) 2978, 2932, 2879, 1722, 1449, 1368, 1254, 1156, 1087 cm^{-1}



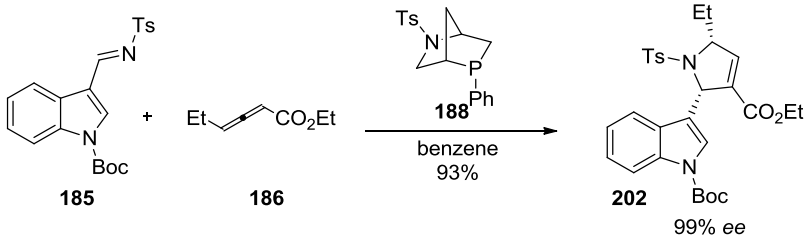
***N*-*p*-Nosyl-imine 199.** *N*-Boc-indole-3-aldehyde (**198**; 2.4 g, 9.8 mmol, 1 equiv) and *p*-nitrobenzenesulfonamide (2.2 g, 10.8 mmol, 1.01 equiv) were suspended in freshly distilled DCM (40 mL). The mixture was placed under a positive pressure of Ar and then freshly distilled triethylamine (4.1 mL, 29.4 mmol, 3 equiv) was introduced via syringe. The heterogeneous mixture was cooled to 0 °C and then 1 M $TiCl_4$ in DCM (4.9 mL, 4.9 mmol, 0.5 equiv) was added via syringe pump over 1 h. The mixture was then stirred until the starting material was consumed (overnight, as determined by TLC; the mixture was slowly warmed to room temperature over the course of the reaction). The mixture was cooled to 0 °C and then the

reaction was quenched through the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase extracted twice with DCM. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was recrystallized (DCM/hexanes) to provide a yellow solid (1.2 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.40–8.34 (m, 3H), 8.26–8.19 (m, 3H), 8.15 (d, J = 8.27 Hz), 7.43 (dd, J = 7.46, 1.32 Hz, 1H), 7.37 (dd, J = 7.98, 1.13 Hz, 1H), 1.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 150.4, 148.2, 145.1, 139.1, 136.4, 129.0, 126.7, 126.0, 125.0, 124.3, 122.7, 116.4, 115.4, 86.5, 28.0; IR (film): 3144, 3058, 2924, 1576 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{19}N_3O_6SH$, 430.1073, found 430.9.



***N*-nosyl-pyrroline 201.** A flame-dried round-bottom flask was charged with the imine **199** (429 mg, 1.00 mmol, 1 equiv), capped with a rubber septum and placed under a positive pressure of Ar. Imine X was dissolved in freshly distilled benzene (10 mL) and tri-*n*-butylphosphine (50 µL, 0.2 mmol, 0.2 equiv) was added. Allenoate **186** (168 mg, 1.2 mmol, 1.2 equiv) was added. The mixture was stirred at room temperature until the starting imine **199** was consumed (as determined by TLC). The crude reaction product was concentrated *in-vacuo* and purified through flash column chromatography (30% Et_2O/pentanes) to yield the desired product (294 mg, 53%,). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (app t, J = 9.0 Hz, 3H), 7.67–7.61 (m, 3H), 7.37 (s, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.87 (app t, J = 2.0 Hz, 1H), 6.08 (app

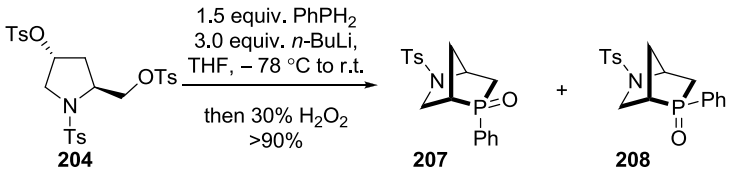
t, J = 2.2 Hz, 1H), 4.87–4.82 (m, 1H), 4.02 (q, J = 7.13 Hz, 2H), 2.24–2.15 (m, 1H), 1.91–1.88 (m, 1H), 1.66 (s, 9H), 1.10 (q, J = 7.4 Hz, 3H), 1.06 (t, J = 7.14 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 161.8, 149.3, 149.2, 145.0, 138.4, 134.9, 133.7, 128.4, 128.3, 125.7, 124.6, 123.1, 122.6, 119.3, 118.5, 115.0, 84.3, 68.6, 61.5, 60.9, 28.9, 28.0, 13.8, 10.3; IR (film) 3034, 2971, 2928, 2912, 1717, 1532, 1371, 1232, 746 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + Na]$^+$ calcd $C_{28}H_{31}N_3O_8SNa$, 592.1730, found 592.10.



Pyrroline 202. A flame-dried round-bottom flask was charged with the imine **185** (50.0 mg, 0.125 mmol, 1 equiv) and the phosphine **188** (4.30 mg, 0.0125 mmol, 0.1 equiv) in a glove box. The flask was capped with a rubber septum, transferred out of the glove box, and placed under a positive pressure of Ar. The solid mixture was dissolved in benzene (1 mL), followed by the addition of the allenoate **186** (23 mg, 0.163 mmol, 1.3 equiv). The mixture was stirred at room temperature until the starting imine **185** was consumed (4 h, as determined by TLC). The crude reaction product was loaded directly onto a column of SiO_2 and purified through flash column chromatography (30% Et_2O/pentanes) to yield a white solid (62.4 mg, 93%, 99% *ee* as determined by SFC). Mp: 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.41 (s, 1H), 7.28 (td, J = 7.3, 1.1 Hz, 1H), 7.22 (td, J = 7.3, 1.0 Hz, 1H), 7.1 (d, J = 8.1 Hz, 2H), 6.79 (app t, J = 2.0 Hz, 1H), 5.98 (app t, J = 1.9 Hz, 1H), 4.66–4.60 (m, 1H), 4.00 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 2.14–2.03 (m, 1H), 1.89–1.77 (m, 1H), 1.66 (s, 9H), 1.06 (t, J = 7.5 Hz, 3H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$): δ

162.1, 149.4, 143.4, 139.2, 135.3, 135.2, 133.9, 129.2, 128.9, 127.4, 125.3, 124.2, 122.4, 120.0, 119.7, 114.9, 83.7, 68.6, 61.3, 60.7, 29.3, 28.1, 21.3, 13.8, 10.4; IR (film) 2978, 2932, 2879, 1722, 1449, 1368, 1254, 1156, 1087 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{29}H_{34}N_2O_6SH$, 539.2216, found 539.2208; $[\alpha]^{24.2}_D$ +83.2° (*c* = 1.000, $CHCl_3$).

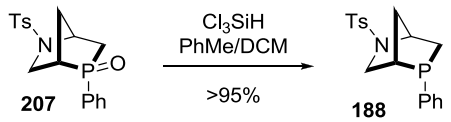
Large-Scale Synthesis of the Pyrroline 202. A flame-dried 1-L-round-bottom flask was charged with the imine **185** (28.8 g, 72.4 mmol, 1 equiv) and the phosphine **188** (2.5 g, 7.2 mmol, 0.1 equiv) in a glove box. The flask was capped with a rubber septum, transferred out of the glove box, and placed under a positive pressure of Ar. Benzene (576 mL) was added to the flask and then the mixture was stirred at room temperature until it became homogeneous (ca. 10 min). The allenoate **186** (13.2 g, 94.1 mmol, 1.3 equiv) was introduced via syringe and then the reaction mixture was stirred at room temperature until the starting imine **185** had been consumed (8 h, as determined by TLC). The crude reaction product was loaded directly onto a large column of SiO_2 and purified through flash column chromatography (30% Et_2O/pentanes). The impure fractions were subjected to a second round of column chromatography. The clean fractions were combined to yield a slightly yellow solid (36.7 g, 94% yield, 97% *ee* as determined by SFC).



Phosphine Oxides 207 and 208. A flame dried 500 mL Schlenk flask with a stir bar was placed under vacuum and refilled with argon three times then placed under a positive pressure of argon

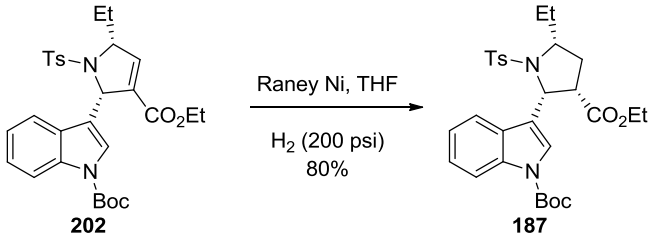
using a glass vacuum adapter attached to a Schlenk line. Freshly distilled THF (300 mL) was added via syringe through the side arm of the Schlenk flask as to avoid introduction of any oxygen into the system. Phenylphosphine (3.84 g, 34.9 mmol, 1 equiv.), freshly prepared by the reduction of dichlorophenylphosphine with lithium aluminum hydride and distilled, was added (Danger!! Phenylphosphine is pyrophoric and must be handled with extreme caution strictly avoiding contact with air.) The solution was cooled to –78 °C and *n*-BuLi (28.0 mL of a 2.5 M solution in hexanes, 69.9 mmol, 2.0 equiv.) was added dropwise over one hour. The solution was allowed to warm to room temperature and stir for one hour during which time a bright yellow precipitate was formed. Tritosylate **204**, prepared according to literature procedures, (13.5 g, 23.3 mmol, 0.67 equiv.) dissolved in freshly distilled THF (100 mL) was added and the reaction was left to stir overnight. The reaction was quenched with an aqueous solution of ammonium chloride followed by the addition of 30% H_2O_2 solution (10 mL) and was allowed to stir for thirty minutes. The aqueous layer was extracted three times with DCM. The combined organics were dried over sodium sulfate, filtered and concentrated *in-vacuo*. The crude material was purified via flash column chromatography (5% MeOH/DCM) to provide **207** (3.36 g, 40% yield) and **208**, (3.61 g, 43% yield). ***Endo* oxide 207.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (t, J = 10 Hz, 2H), 7.68 (d, J = 4Hz, 2H), 7.54 (d, J = 8Hz, 1H), 7.82 (t, J = 10 Hz, 2H), 7.46 (s, 2H), 7.30 (d, J = 8 Hz, 2H), 4.59 (d, J = 28 Hz, 1H), 3.08–2.92 (m, 2H), 2.62 (s, 1H), 2.60 (s, 1H), 2.37 (s, 3H), 2.33 (d, J = 12 Hz, 1H), 2.12 (t, J = 16 Hz, 1H), 1.50 (dd, J = 28, 12 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 134.4, 132.6, 131.2 (d, J_{CP} = 12.5 Hz), 129.9, 128.9, 128.7, 128.2, 127.3, 127.1, 58.9, 58.8, 47.8, 40.2, 39.5 (d, J_{CP} = 12.5 Hz), 38.8, 36.0 (d, J_{CP} = 12.5 Hz) 21.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.5; IR (film) 3061, 2978, 2877, 1595, 1438, 1343 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{18}H_{20}NO_3PSH$, 362.0974, found 362.0959. ***Exo* oxide 208.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.72–7.68 (m, 2H), 7.57–7.53 (m, 1H), 7.50–7.47 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 4.58 (d, J = 26.7 Hz, 1H), 4.14 (dd, J = 13.9, 9.5 Hz, 1H), 3.52 (ddd, J = 25.0, 9.5, 4.7 Hz, 1H), 2.82 (br s, 1H), 2.42 (s, 3H), 2.34–2.19 (m, 1H), 2.13–2.07 (m, 1H), 1.74–1.61 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 135.9, 132.4, (d, J_{CP} = 3 Hz), 131.7 (d, J_{CP} = 93 Hz), 130 (d, J_{CP} = 10 Hz, 2C), 129.9, 129.9, 129.0 (d, J_{CP} = 12 Hz), 127.4, 127.4, 59.0, 46.4 (J_{CP} = 7 Hz), 39.5 (d, J_{CP} = 66 Hz), 35.5 (d, , J_{CP} = 11 Hz), 34.5 (d, J_{CP} = 64 Hz), 21.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ 50.0; IR (film) 3059, 2990, 2881, 1595, 2360, 1436, 1341, 1223, 1180 cm^{-1}; HRMS–ESI (m/z) [M + Na]$^+$ calcd $C_{18}H_{20}NO_3PSNa$, 384.0794, found 384.0805.



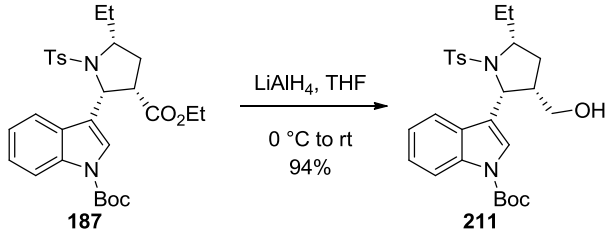
Chiral Phosphine 188. Phosphine oxide **207** (4.5 g, 12.5 mmol, 1 equiv.) was added to a flame dried round bottom flask and put under a positive pressure of argon. A 1:1 mixture of toluene and DCM (276 mL of each) was added to dissolve the phosphine oxide **207**. Freshly distilled trichlorosilane (6.3 mL, 62.4 mmol 5.0 equiv.) was added and the reaction was stirred at room temperature until the starting material had been consumed (as determined by TLC). The reaction was quenched with water (6 mL) while keeping the reaction under argon. After stirring for one hour, the mixture was treated with solid sodium bicarbonate and anhydrous Na_2SO_4 (quickly added and then the reaction was put back under argon). The organic solution was filtered via cannulationg through cotton into a clean flask. The solids were rinsed with DCM four times. The combined organic phases were concentrated *in-vacuo* with argon replenishing to yield the desired phosphine as a white solid (4.0 g, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J =

8.0 Hz, 2H), 7.40 (s, 2H), 7.28 (d, J = 4.0 Hz, 3H), 7.21 (d, J = 8.0 Hz, 1H), 4.48 (s, 1H), 3.09 (d, J = 8.0 Hz), 2.98 (d, J = 12.0 Hz, 1H), 2.62 (d, J = 28.0 Hz, 1H), 2.35 (s, 3H), 2.17 (d, J = 12.0 Hz, 1H). 1.98 (t, J = 18.0 Hz, 1H), 1.57 (t, J = 8.0 Hz, 1H), 1.36 (dd, J = 28.0, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 135.6, 132.0 (d, J_{CP} = 12.5 Hz), 129.6, 129.6, 128.7, 128.7, 128.4, 128.4, 127.1, 127.1, 60.5, 50.7, 37.8, 36.5, 36.3, 29.2, 12.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ -17.2; IR (film) 3053, 2970, 2915, 2864, 1594, 1433, 1340, 1170, 1151 cm^{-1}; HRMS–ESI (m/z) $[M + Na]^+$ calcd $C_{18}H_{20}NO_2PSH$, 346.1025, found 346.1016.



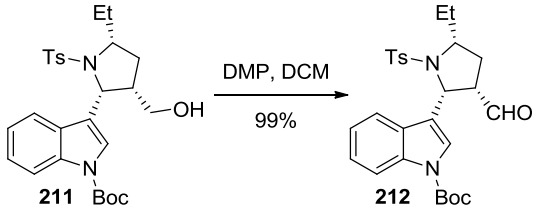
Pyrrolidine 187. The pyrroline **202** (10.0 g, 18.6 mmol) was added to a metal high-pressure reaction vessel equipped with a stirrer bar and then THF (400 mL) was added to form a solution. A suspension of Raney Ni in water [Raney Ni 4200 (Aldrich), 20 mL] was added directly to the solution without removal of the water. The reaction vessel was sealed and purged three times with H_2 gas (pressurized to 50 psi, followed by release of the H_2 gas). The vessel was then pressurized to 200 psi with H_2 gas and the mixture left to stir vigorously (to keep Raney Ni suspended) until no starting material remained (8 h, as determined from the crude NMR spectrum of a small aliquot). The reaction mixture was decanted from the solid Raney Ni into a separatory funnel containing saturated aqueous NaCl. The solids were rinsed three times with EtOAc and the rinses were added to the separatory funnel. After separation of the layers, the aqueous phase was extracted three times with EtOAc. The combined organic phases were

washed again with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude reaction product was recrystallized (by dissolving in boiling DCM and quickly diluting the mixture with a large amount of hexanes) to yield a white crystalline solid (8.3 g, 80%). Mp: 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.48 (s, 1H), 7.30–7.23 (m, 3H), 7.19 (td, J = 7.4, 1.0 Hz, 1H), 5.52 (d, J = 8.4 Hz, 1H), 3.67 (dq, J = 10.8, 7.1 Hz, 1H), 3.6 (tdd, J = 9.1, 8.9, 3.5 Hz, 1H), 3.47 (dq, 10.8, 7.1 Hz, 1H), 2.87–2.79 (m, 1H), 2.4 (s, 3H), 2.44–2.35 (m, 1H), 2.24–2.18 (m, 2H), 1.81–1.69 (m, 1H), 1.66 (s, 9H), 1.01 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 149.5, 143.6, 135.1, 129.7, 128.8, 127.6, 125.0, 124.5, 122.2, 119.6, 119.2, 115.1, 83.8, 62.0, 60.9, 57.9, 47.4, 32.2, 29.5, 28.2, 21.5, 13.5, 10.6; IR (film) 2978, 2936, 2899, 2879, 1726, 1458, 1372, 1343, 1266, 1152 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{29}H_{36}N_2O_6SH$, 541.2372, found 541.2370; $[\alpha]^{24.1}_D$ +88.6° (c = 1.000, $CHCl_3$).



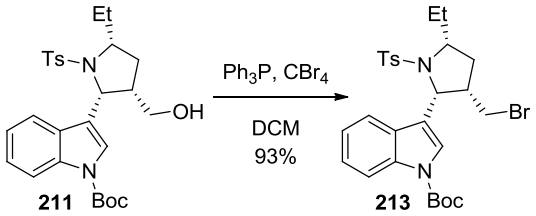
Alcohol 211. Freshly distilled THF (65 ml) was added to a flame-dried round-bottom flask charged with $LiAlH_4$ (710 mg, 18.7 mmol, 1 equiv). The flask was capped with an addition funnel and the setup was placed under a positive pressure of Ar. The heterogeneous mixture was cooled to 0 °C and then the pyrrolidine **187** (10.1 g, 18.7 mmol) was added to the addition funnel as a solution in THF (20 mL) over the course of 1 h. The mixture was then warmed to room temperature and stirred until the starting material had been consumed (2 h, as determined by

TLC). Once complete, the reaction was quenched through the dropwise addition of saturated aqueous sodium potassium tartrate at 0 °C. The mixture was stirred vigorously until the two phases were distinctly visible. The layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed once with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (30% EtOAc/hexanes) to yield a white solid (8.7 g, 94%). Mp: 81–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.50 (br s, 1H), 7.31–7.24 (m, 3H), 7.20 (td, J = 7.5, 1.04 Hz, 1H), 5.23 (d, J = 7.9 Hz, 1H), 3.54–3.45 (m, 1H), 3.28 (dd, J = 10.9, 7.0 Hz, 1H), 3.14 (dd, J = 10.8, 6.0 Hz, 1H), 2.53–2.42 (m, 1H), 2.40 (s, 3H), 2.13–2.00 (m, 2H), 1.81–1.70 (m, 1H), 1.67 (s, 9H), 1.58–1.45 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 143.5, 135.3, 134.8, 129.7, 129.1, 127.6, 125.0, 124.6, 122.6, 120.1, 119.0, 115.4, 83.9, 62.6, 62.1, 58.6, 44.9, 33.0, 29.7, 28.0, 21.6, 10.8; IR (film) 3547, 2978, 2916, 2875, 1722, 1453, 1372, 1254, 1152, 1087 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{27}H_{34}N_2O_5SH$, 499.2267, found 499.2273; $[\alpha]^{24.0}_D$ +123.8° (c = 1.000, $CHCl_3$).



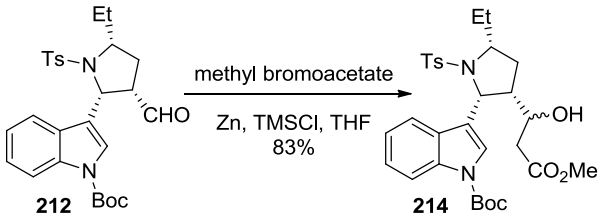
Aldehyde 212. Alcohol **211** (544 mg, 1.09 mmol, 1 equiv.) was weighed into a round bottom flask and dissolved in freshly distilled dichloromethane (5 mL). DMP (540 mg, 1.3 mmol, 1.2 equiv.) was added as a solid in a single portion. Upon consumption of the starting material (as determined by TLC) the crude mixture was filtered through a short pad of silica gel. The silica

gel was washed with 30% EtOAc/hexanes and the eluent was concentrated *in vacuo*. The crude material was redissolved in ethyl acetate and washed with a saturated solution of sodium bicarbonate$_{(aq)}$ then brine. Concentration of the volatiles and purification through flash column chromatography yielded the desired aldehyde (536 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (d, J = 3.06 Hz, 1H), 8.09 (br s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.59 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.34–7.27 (m, 3H), 7.22 (t, J = 7.6 Hz, 1H), 5.46 (d, J = 8.4 Hz, 1H), 3.67–3.60 (m, 1H), 2.77–2.69 (m, 1H), 2.42 (s, 3H), 2.40–2.31 (m, 1H), 2.19–2.10 (m, 1H), 2.10–2.02 (m, 1H), 1.78–1.70 (m, 1H), 1.68 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 149.3, 143.8, 135.4, 134.4, 129.7, 127.8, 127.5, 125.0, 124.8, 122.8, 118.8, 118.6, 115.4, 84.0, 62.4, 57.7, 53.7, 30.7, 29.6, 28.0, 21.4, 10.6; IR (film) 3059, 2978, 2936, 2875, 2741, 1726, 1453, 1372, 1254, 1156 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) [M + Na]$^+$ calcd $C_{27}H_{32}N_2O_5SNa$, 519.1930, found 519.38.



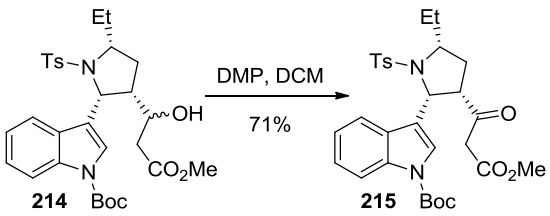
Bromide 213. A round bottom flask was charged with alcohol **211** (500 mg, 1 mmol, 1 equiv.) and triphenylphosphine (393 mg, 1.5 mmol, 1.5 equiv.) and the solids were dissolved in freshly distilled dichloromethane (10 mL). Carbon tetrabromide (497 mg, 1.5 mmol, 1.5 equiv.) was added as a solid in a single portion. After 20 minutes the starting material was consumed (as determined by TLC). The reaction was concentrated *in vacuo* and purified through flash column chromatography (10% EtOAc/hexanes) and isolated as a white solid (526 mg, 93%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.51 (s, 1H), 7.32 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.24 (dd, *J* = 7.3 Hz, 1H), 5.23 (d, *J* = 7.9 Hz, 1H), 3.59–3.52 (m, 1H), 3.22 (dd, *J* = 10.3, 5.2, 1H), 2.67 (t, *J* = 10.0 Hz, 1H), 2.50–2.43 (m, 1H), 2.42 (s, 3H), 2.38 (app quint, *J* = 6.1 Hz, 1H), 2.33–2.24 (m, 1H), 1.77–1.70 (m, 1H), 1.68 (s, 9H), 1.65–1.57 (m, 2H), 1.02 (t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ149.5, 143.6, 135.2, 134.8, 129.7, 129.0, 127.6, 125.1, 124.7, 122.7, 119.1, 119.0, 115.5, 84.0, 62.4, 59.0, 45.3, 35.7, 32.2, 29.6, 28.2, 21.6, 10.7; IR (film) 3055, 2978, 2936, 2879, 1731, 1453, 1372, 1156, 1083 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{27}H_{33}BrN_2O_4SNa$, 583.1242, found 583.31.

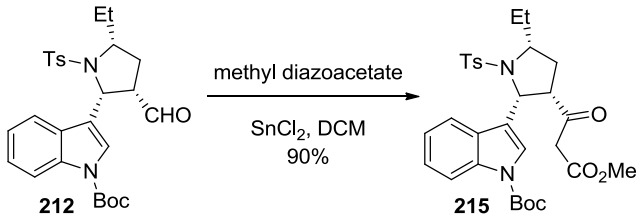


B-hydroxyester 214. An approximately 1M solution of the Reformatsky reagent derived from methyl bromoacetate was prepared using the following procedure: A round bottom flask was charged with zinc powder (470 mg, 7.2 mmol, 1.1 equiv.). The zinc powder was suspended in THF (3.5 mL) followed by the addition of freshly distilled TMS chloride (110 μL, 0.87 mmol, .14 equiv.). The solution was refluxed for fifteen minutes and then allowed to cool to room temperature. Methyl bromoacetate (600 μL, 6.3 mmol, 1 equiv.) was added dropwise at a rate that maintained a gentle reflux. After the addition was complete THF (2.3 mL) was added to provide an approximately 1M solution of the Reformatsky reagent that was used in the aldol reaction.

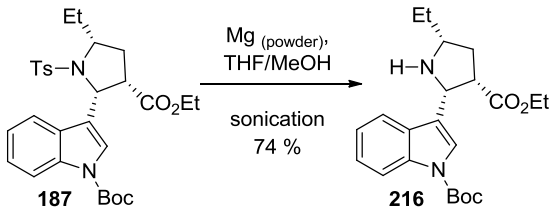
Aldehyde **212** (50 mg, 0.1 mmol, 1 equiv.), was dissolved in THF (1 mL) and cooled to 0 °C. 250 μL of the THF solution of Reformatsky reagent prepared as described above was added dropwise over 5 minutes. Within 5–10 minutes all of the starting material had been consumed (as determined by TLC). The reaction was quenched with aqueous ammonium chloride while still at 0 °C. The mixture was transferred to a separatory funnel and extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (30–40% EtOAc/hexanes) to yield the desired alcohol as an inseparable mixture of diastereomers (48 mg, 83%, ~1:0.7 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.00 (m, 1.7H), 7.74 (d, *J* = 7.8 Hz, 0.7H), 7.68 (d, *J* = 8.04 Hz, 1.4H) 7.65–7.58 (m, 3H), 7.49 (s, 1H), 7.46 (s, 0.7H), 7.34–7.16 (m, 7.2H), 5.38 (d, *J* = 7.8 Hz, 0.7H), 5.16 (d, *J* = 7.2 Hz, 1H), 3.76–3.71 (m, 1H), 3.65–3.56 (m, 1.7H), 3.56 (s, 2.1H), 3.55 (s, 3H), 3.44–3.34 (m, 0.7H), 2.70–2.62 (m, 0.7H), 2.56–2.49 (m, 1H), 2.38 (s, 2.1H), 2.37 (s, 3H), 2.01–1.90 (m, 3.4H), 1.68 (s, 6.3H), 1.67 (s, 9H), 1.00 (app t, *J* = 7.5 Hz, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.4, 149.4, 143.4, 135.4, 135.1, 134.9, 129.5, 129.5, 129.0, 127.6, 127.5, 125.1, 125.1, 124.8, 124.5, 123.0, 122.5, 120.4, 119.8, 119.4, 118.5, 115.3, 115.0, 84.1, 83.8, 67.5, 67.2, 62.5, 62.3, 58.7, 57.0, 51.7, 48.5, 47.8, 40.0, 39.6, 33.0, 32.6, 29.7, 29.6, 21.5, 21.5, 10.7, 10.6; IR (film) 3516, 2981, 2932, 2879, 1731, 1453, 1372, 1343, 1254, 1152 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{30}H_{38}N_2O_7SNa$, 593.2297, found 593.21.



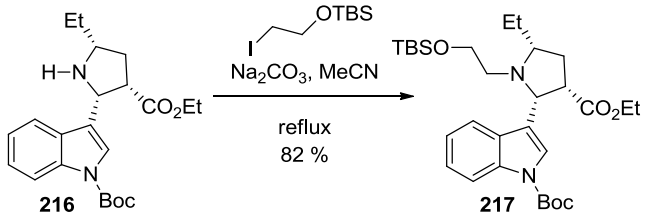
β-ketoester 215. B-hydroxyester **214** (48 mg, .084 mmol, 1 equiv.) was dissolved in freshly distilled dichloromethane (1 mL). The Dess–Martin periodinane (43 mg, 0.1 mmol, 1.2 equiv) was added as a solid in a single portion at room temperature. The reaction was stirred at room temperature until all of the starting material was consumed (as determined by TLC). The reaction was poured into water and the layers were separated. The aqueous phase was extracted twice more with DCM. The combined organic extracts were washed with brine and dried (Na_2SO_4). After filtration and concentratin *in vacuo*, the crude material was purified by flash column chromatography (20% EtOAc/hexanes) to provide the desired β-ketoester (34 mg, 71%) which existed as an equilibrium mixture of keto and enol forms (~1:0.42). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.64 (s, 0.42 H), 8.05 (s, 1.4 H), 7.76–7.74 (m, 3.9 H), 7.59 (d J = 7.7 Hz, 0.46 H), 7.48 (s, 0.44 H), 7.44 (s, 1H), 7.33–7.27 (m, 1.8 H), 7.27–7.21 (m, 2.8 H), 7.13 (t, J = 7.9 Hz, 0.49 Hz), 5.64 (d, J = 8.0 Hz, 1H), 5.46 (d, J = 7.6 Hz, 0.42 Hz), 4.71 (s, 0.41 H), 3.74–3.58 (m, 1.4 H), 3.56 (s, 3H), 3.53 (s, 1.2 H), 3.13–2.98 (m, 3H), 2.60–2.51 (m, 0.44 H), 2.42 (s, 1.2 H), 2.39 (s, 3H), 2.30–2.19 (m, 3H), 1.67 (s, 13 H), 1.03–0.90 (m, 4.8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 173.0, 171.9, 168.1, 166.8, 149.3, 143.6, 135.0, 129.6, 129.6, 127.5, 124.8, 124.7, 124.2, 122.8, 122.1, 119.3, 119.1, 118.8, 115.1, 114.7, 90.6, 84.0, 77.3, 62.0, 61.8, 56.8, 54.5, 52.2, 51.0, 48.4, 46.9, 32.1, 29.6, 28.0, 28.0, 21.4, 21.4, 10.7, 10.4; LRMS–MALDI-TOF (m/z) $[M + Na]^+$ calcd $C_{30}H_{36}N_2O_7SNa$, 591.2141, found 591.15.



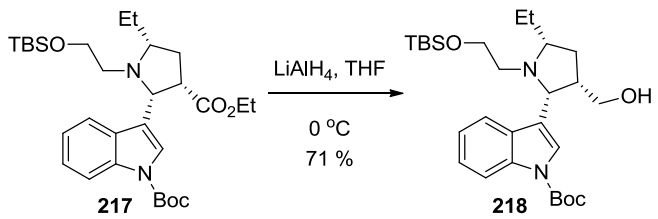
β-ketoester 215 via Roskamp homologation of 212. Freshly distilled dichloromethane (10 mL) was added to a round bottom flask charged with stannous chloride (227 mg, 1.2 mmol, 1.1 equiv.). Methyl diazoacetate (120 mg, 1.2 mmol, 1.1 equiv.) was added followed by aldehyde **212** (541 mg, 1.1 mmol, 1 equiv.) as a solution in dichloromethane. Once the starting material had been consumed (as determined by TLC), the reaction was concentrated *in vacuo* and the crude material was purified through flash column chromatography (20% EtOAc/hexanes) to yield the desired β-ketoester (558 mg, 90%) which existed as an equilibrium mixture of keto and enol forms (~1:0.42). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.64 (s, 0.42 H), 8.05 (s, 1.4 H), 7.76–7.74 (m, 3.9 H), 7.59 (d *J* = 7.7 Hz, 0.46 H), 7.48 (s, 0.44 H), 7.44 (s, 1H), 7.33–7.27 (m, 1.8 H), 7.27–7.21 (m, 2.8 H), 7.13 (t, *J* = 7.9 Hz, 0.49 Hz), 5.64 (d, *J* = 8.0 Hz, 1H), 5.46 (d, *J* = 7.6 Hz, 0.42 Hz), 4.71 (s, 0.41 H), 3.74–3.58 (m, 1.4 H), 3.56 (s, 3H), 3.53 (s, 1.2 H), 3.13–2.98 (m, 3H), 2.60–2.51 (m, 0.44 H), 2.42 (s, 1.2 H), 2.39 (s, 3H), 2.30–2.19 (m, 3H), 1.67 (s, 13 H), 1.03–0.90 (m, 4.8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 173.0, 171.9, 168.1, 166.8, 149.3, 143.6, 135.0, 129.6, 129.6, 127.5, 124.8, 124.7, 124.2, 122.8, 122.1, 119.3, 119.1, 118.8, 115.1, 114.7, 90.6, 84.0, 77.3, 62.0, 61.8, 56.8, 54.5, 52.2, 51.0, 48.4, 46.9, 32.1, 29.6, 28.0, 28.0, 21.4, 21.4, 10.7, 10.4; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{30}H_{36}N_2O_7SNa$, 591.2141, found 591.15.



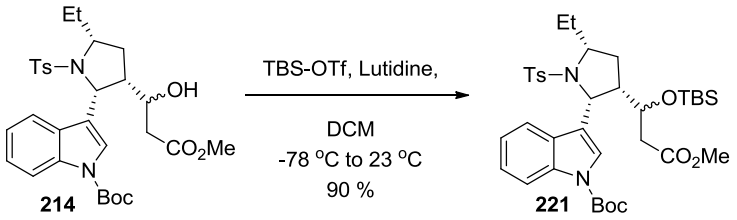
Secondary Amine 216. Pyrrolidine **187** (250 mg, 0.46 mmol, 1 equiv.) was dissolved in a minimal amount of THF (heating was used to aid in salvation of the starting material). Once the solution was homogeneous, methanol (about nine volume equivalents) was used to dilute the reaction mixture. Magnesium powder (225 mg, 9.3 mmol, 20 equiv.) was added in a single portion and the reaction was capped with a reflux condenser and sonicated for thirty minutes (stirring was not necessary). A second aliquot of magnesium (225 mg, 9.3 mmol, 20 equiv.) was added and the reaction was sonicated for an additional thirty minutes. The reaction was quenched with 1M HCl until all of the solids had dissolved. The aqueous phase was extracted with EtOAc five times. The combined organic extracts were washed with $K_2CO_{3(aq)}$ then brine. After drying (Na_2SO_4) and filtration, the crude material was purified through flash column chromatography (30→40% EtOAc/hexanes) to yield a light brown oil (133 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (bd, J = 7.4 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.30–7.26 (m, 1H), 7.23–7.18 (m, 1H), 4.57 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 3.64–3.50 (m, 2H), 3.47–3.41 (m, 1H), 3.16 (app pent, J = 7.3 Hz, 1H), 3.11 (bs, 1H), 2.33–2.27 (m, 1H), 1.89–1.78 (m, 2H), 1.71–1.66 (m, 1H), 1.64 (s, 9H), 1.04 (t, J = 7.3 Hz, 3H), 0.56 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 149.6, 135.5, 129.1, 124.5, 122.7, 122.3, 119.7, 118.8, 115.1, 83.7, 60.7, 60.1, 59.0, 48.5, 35.7, 28.2, 28.1, 13.3, 11.7; IR (film) 2978, 2932, 2875, 1735, 1453, 1372, 1254, 1160 cm^{-1}; LRMS–MALDI-TOF (m/z) $[M + Na]^+$ calcd $C_{22}H_{31}N_2O_4Na$, 387.2284, found 387.4925.



Tertiary Amine 217. Secondary amine **216** (638 mg, 1.65 mmol, 1.00 equiv.) was dissolved in acetonitrile (15.0 mL) followed by addition of anhydrous sodium carbonate (2.1 g, 19.8 mmol, 12 equiv.) and *O*-TBS-iodoethanol (1.9 g, 6.6 mmol, 4 equiv.). The round bottom was capped with a reflux condenser and the mixture was heated to reflux until the starting material had been consumed (as determined by TLC). The crude heterogeneous mixture was filtered over celite and concentrated to remove acetonitrile. The crude material was purified through flash column chromatography (0→20% EtOAc/hexanes) to yield the desired tertiary amine (739 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.51 (s, 1H), 7.24 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.4 Hz, 1H), 4.48 (d, J = 9.9 Hz, 1H), 3.58–3.50 (m, 2H), 3.47–3.40 (m, 1H), 3.35–3.22 (m, 2H), 2.84–2.74 (m, 2H), 2.72–2.65 (m, 1H), 2.15–2.02 (m, 2H), 1.89–1.80 (m, 1H), 1.66 (s, 9H), 1.56–1.48 (m, 1H), 1.00 (t J = 7.6 Hz, 3H), 0.79 (s, 9H), 0.65 (t, J = 7.2 Hz, 3H), -0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 149.8, 135.7, 129.6, 124.9, 124.1, 121.9, 121.7, 120.5, 114.9, 83.4, 64.8, 63.5, 61.6, 60.1, 54.0, 47.2, 32.3, 28.2, 26.7, 25.9, 18.2, 13.3, 10.2, -5.5, -5.5; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{30}H_{48}N_2O_5SiH$, 545.3411, found 545.16.

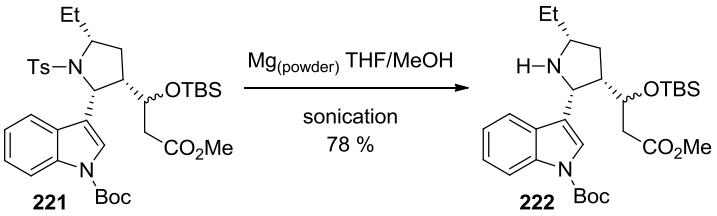


Alcohol 218. Lithium aluminum hydride (2.8 mg, .074 mmol, 2 equiv.) was suspended in THF (1 mL) and cooled to -40 °C. Ester **217** was dissolved in THF (1 mL) and added dropwise to the suspension of $LiAlH_4$. A second aliquot of $LiAlH_4$ was added and the reaction was allowed to warm to 0 °C. Once the starting material was consumed (as determined by TLC) the reaction was quenched with an aqueous solution of sodium potassium tartrate. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo* the crude material was purified through flash column chromatography (40% EtOAc/hexanes) to yield the desired alcohol (13 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.66–7.55 (m, 2H), 7.31 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 4.27 (d, J = 8.2 Hz, 1H), 3.60–3.3.47 (m, 2H), 3.36 (d, J = 4.5 Hz, 2H), 2.89–2.65 (m, 3H), 2.55–2.44 (m, 1H), 2.33–2.18 (m, 1H), 1.90–1.79 (m, 1H), 1.68 (s, 9H), 1.59–1.48 (m, 1H), 1.48–1.38 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H), 0.79 (s, 9H), -0.9 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 135.6, 125.6, 124.6, 124.2, 122.7, 122.4, 119.4, 115.4, 83.8, 65.7, 64.7, 64.0, 61.4, 42.1, 32.9, 29.7, 28.2, 27.0, 25.9, 18.3, 10.7, -5.5, -5.5; IR (film) 3387, 3049, 2956, 2845, 1730, 1444, 1356, 838 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{28}H_{46}N_2O_4SiH$, 503.3305, found 503.79.



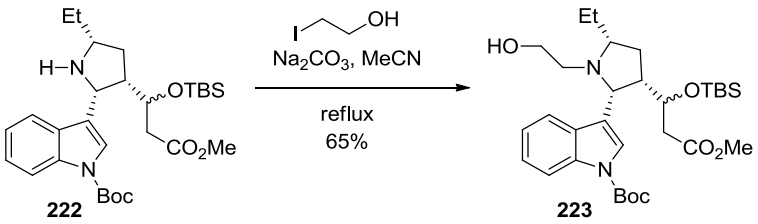
Silyl Ether 221. Alcohol **214** (1.1 g, 1.9 mmol, 1 equiv), was dissolved in freshly distilled dichloromethane (15 ml) and cooled to -78 °C. 2,6-lutidine (1.1 mL, 9.7 mmol, 5 equiv.), was added followed by dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.3 mL, 5.8 mmol, 3 equiv.). Upon completion of the addition the reaction was allowed to warm to room temperature. Upon consumption of the starting amterial (as determined by TLC) the reaction was quenched with an aqueous solution of sodium bicarbonate. The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic extracts were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo* the crude material was purified through flash column chromatography (20% EtOAc/hexanes) to provide the desired silyl ether (1.2 g, 90%). The diastereomers were separated and characterized independently. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.72–7.65 (m, 3H), 7.49 (s, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.26–7.19 (m, 3H), 5.27 (d, *J* = 7.9 Hz, 1H), 3.72–3.65 (m, 1H), 3.54–3.50 (m, 1H), 3.48 (s, 3H), 2.39 (s, 3H), 2.36–2.27 (m, 2H), 2.23–2.09 (m, 3H), 1.82–1.71 (m, 2H), 1.68 (s, 9H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.78 (s, 3H), -0.16 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 149.7, 143.3, 135.5, 129.6, 127.8, 124.8, 124.8, 127.7, 120.1, 119.2, 115.2, 84.1, 67.5, 62.3, 57.0, 47.8, 40.0, 35.4, 29.8, 28.3, 25.8, 21.6, 18.1, 10.7, -4.5, -4.8. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.50 (s, 1H), 7.34–7.22 (m, 4H), 5.19 (d, *J* = 7.6 Hz, 1H), 4.26–4.20 (m, 1H), 3.71–3.65 (m, 1H), 3.42 (s, 3H), 2.41 (s, 3H), 2.37–2.28 (m, 1H), 2.13–2.04 (m, 2H), 1.91–1.77 (m, 2H) 1.69 (s, 9H), 1.70–1.58 (m, 2H), 0.96 (t, *J* = 7.3 Hz,

3H), 0.91 (s, 9H), -0.16 (s, 3H), -0.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 149.8, 143.6, 135.0, 129.8, 129.7, 127.8, 125.0, 122.8, 119.7, 119.6, 115.2, 84.1, 69.5, 62.8, 57.6, 51.4, 49.6, 41.2, 31.7, 30.4, 28.3, 25.8, 21.6, 17.9, 11.0, -4.4, -5.4; LRMS–MALDI-TOF (data obtained on a sample containing a mixture of the two diastereomers) (*m*/*z*) $[M + Na]^+$ calcd $C_{36}H_{52}N_2O_7SSiNa$, 707.9476, found 707.27.



Amine 222. *N*-tosyl pyrrolidine **221** (359 mg, 0.52 mmol, 1 equiv.) was dissolved in THF (1 mL) and the homogeneous solution was diluted with methanol (9 mL). Magnesium powder (243 mg, 10 mmol, 19 equiv.) was added in a single portion and the reaction was capped with a reflux condenser and sonicated for thirty minutes (stirring was not necessary). A second aliquot of magnesium (243 mg, 10 mmol, 19 equiv.) was added and the reaction was sonicated for an additional thirty minutes. The reaction was quenched with 2M HCl until all of the solids had dissolved. The aqueous phase was extracted with EtOAc five times. The combined organic extracts were washed with $NaHCO_{3(aq)}$ then brine. After drying (Na_2SO_4) and filtration, the crude material was purified through flash column chromatography (5% MeOH/DCM) to yield a light brown oil (219 mg, 78%) as a mixture of diastereomers. The diastereomers could be separated if necessary and were characterized separately. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.45 (br s, 1H), 7.36–7.29 (m, 1H), 7.25–7.22 (m, 1H), 4.48 (dd, *J* = 8.1, 1.3 Hz, 1H), 3.90–3.83 (m, 1H), 3.43 (s, 3H), 3.10

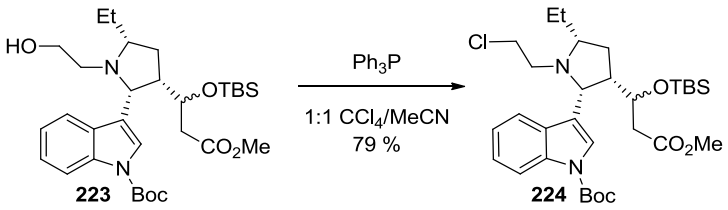
(app quint, J = 7.5 Hz, 1H), 2.84–2.75 (m, 1H), 2.72 (dd, J = 15.4, 2.2 Hz, 1H), 2.25 (dd, J = 15.4, 9.1 Hz, 1H), 2.19–2.08 (m, 1H), 1.69–1.52 (m, 4H), 1.66 (s, 9H), 1.00 (t, J = 7.4 Hz, 3H), 0.78 (s, 9H), -0.13 (s, 3H), -0.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 149.8, 135.8, 129.5, 124.6, 122.6, 122.5, 120.2, 118.9, 115.5, 83.5, 69.6, 59.0, 56.8, 51.1, 45.6, 40.1, 31.0, 28.8, 28.3, 25.7, 17.8, 11.8, -4.8, -5.0; IR (film) 2961, 2932, 2859, 1735, 1458, 1380, 1258, 1164, 1079 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + H]$^+$ calcd $C_{29}H_{46}N_2O_5SiH$ 531.3254, found 531.5167. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (br d, J = 7.1 Hz, 1H), 7.49 (br s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.34–7.30 (m, 1H), 7.26–7.21 (m, 1H), 4.35 (d, J = 7.9 Hz, 1H), 3.95 (td, J = 6.4, 3.3 Hz, 1H), 3.58 (s, 3H), 3.12–3.03 (m, 1H), 2.82–2.74 (m, 1H), 2.31 (d, J = 6.6 Hz, 2H), 2.24–2.15 (m, 1H), 1.84–1.74 (m, 1H), 1.67–1.61 (m, 2H), 1.64 (s, 9H), 1.59–1.50 (m, 1H), 1.05 (t, J = 7.4 Hz, 3H), 0.82 (s, 9H), -0.19 (s, 3H), -0.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 149.6, 135.7, 129.2, 124.5, 123.0, 122.4, 120.0, 119.6, 115.3, 83.4, 69.2, 60.7, 58.9, 51.5, 46.1, 41.9, 32.8, 28.3, 28.2, 26.1, 18.0, 11.9, -3.9, -5.1; IR (film) 2957, 2932, 2859, 1735, 1458, 1372, 1258, 1164, 837 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + H]$^+$ calcd $C_{29}H_{46}N_2O_5SiH$ 531.3254, found 531.59.



Amino Alcohcol 223. Secondary amine **222** (20 mg, 0.038 mmol, 1 equiv.) was dissolved in acetonitrile (3 mL). Iodoethanol (6 μL, 0.076 mmol, 2 equiv.) and sodium carbonate (12 mg,

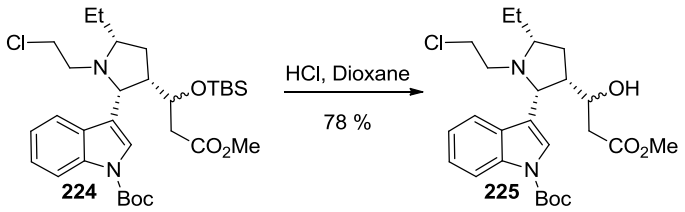
.114 mmol, 3 equiv.) were added and the flak was capped with a reflux condenser. The mixture was heated to refluxed overnight. A second aliquot of sodium carbonate and iodoethanol were added and the reaction was refluxed until all of the starting material had been consumed (as determined b TLC). The crude heterogeneous mixture was poured into water and extracet three times with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo* the crude material was purified through flash column chromatography (5% MeOH/DCM) to yield the desired amino alcohol (14 mg, 65%). The diastereomers were characterized separately. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.50 (br s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.17 (d, *J* = 9.0 Hz, 1H), 3.96–3.90 (m, 1H), 3.52–3.38 (m, 2H), 3.45 (s, 3H), 2.93–2.75 (m, 2H), 2.75–2.57 (m, 2H), 2.36–2.16 (m, 2H), 1.90–1.82 (m, 2H), 1.67 (s, 9H), 1.63–1.53 (m, 1H), 1.51–1.43 (m, 1H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.78 (s, 9H), -0.18 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 149.9, 135.9, 129.7, 124.6, 124.1, 122.5, 121.6, 119.3, 115.5, 83.7, 69.1, 67.3, 63.9, 60.8, 56.8, 51.3, 47.3, 40.1, 31.3, 28.3, 27.8, 25.8, 17.9, 10.9, -4.5, -5.0; IR (film) 3413, 2957, 2932, 2888, 2855, 1735, 1453, 1376, 1258, 1160, 1082, 744 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{31}H_{50}N_2O_6SiH$ 575.8319, found 475.31 corresponding to mass with loss of the Boc group. Expected mass with loss of Boc group (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{42}N_2O_4SiH$ 475.2992. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.48 (br s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 4.10 (d, *J* = 9.4 Hz, 1H), 3.67–3.61 (m, 1H), 3.48 (s, 3H), 3.34–3.27 (m, 1H), 3.26–3.17 (m, 1H), 3.02–2.94 (m, 1H), 2.81–2.64 (m, 3H), 2.29–2.14 (m, 3H), 1.91–1.78 (m, 1H), 1.68 (s, 9H), 1.65–1.54 (m, 2H), 1.50–1.38 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.81 (s, 9H), -0.95 (s, 3H), -0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 149.7, 135.8, 129.5,

124.6, 124.4, 123.3, 122.8, 119.6, 115.7, 83.9, 70.1, 66.3, 63.1, 60.5, 57.1, 51.2, 47.0, 41.7, 36.2, 28.2, 27.6, 25.8, 18.0, 10.7, -4.6, -4.7; IR (film) 3466, 2957, 2932, 2888, 2855, 1735, 1449, 1372, 1258, 1160, 1079, 916 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{31}H_{50}N_2O_6SiH$ 575.8319, found 475.19 corresponding to mass with loss of the Boc group. Expected mass with loss of Boc group (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{42}N_2O_4SiH$ 475.2992.



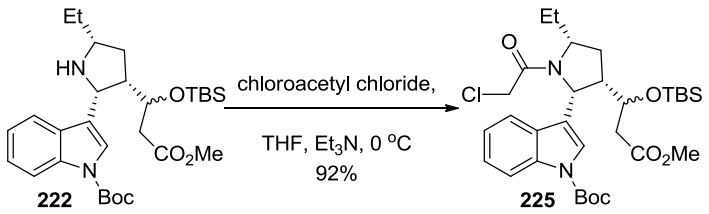
Chloride 224. Amino alcohol **223** (127 mg, 22 mmol, 1 equiv.) was dissolved in acetonitrile (1.6 mL) and carbon tetrachloride (1.6 mL). Triphenylphosphine (116 mg, 44 mmol, 2 equiv.) was added as a solid in a single portion at room temperature. After one hour the starting material had been consumed (as determined by TLC). The crude reaction mixture was concentrated *in vacuo* and purified through flash column chromatography (1% Et_3N/3% EtOAc/hexanes) to yield the desire dchloride (104 mg, 79%). The diastereomers were characterized separately. **Higher R_f diastereomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.49 (s, 1H), 7.31–7.26 (m, 1H), 7.18–7.13 (m, 1H), 4.05 (td, *J* = 6.4, 2.1 Hz, 1H), 3.68 (d, *J* = 9.0 Hz, 1H), 3.43 (s, 3H), 3.23–3.16 (m, 1H), 3.07–3.00 (m, 1H), 2.82 (t, *J* = 8.4 Hz, 2H), 2.72–2.62 (m, 1H), 2.45 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.40–2.33 (m, 1H), 2.32 (dd, *J* = 15.0, 6.62 Hz, 1H), 2.17–2.04 (m, 1H), 1.80–1.71 (m, 1H), 1.69 (s, 9H), 1.66–1.59 (m, 1H), 1.51–1.38 (m, 1H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 149.7, 136.5, 128.7, 124.5, 124.3, 122.2, 121.3, 121.1, 115.3, 83.6, 67.8, 65.7, 65.5, 54.3, 51.4, 48.0, 42.3, 42.0, 28.6, 28.3, 28.2, 26.0, 18.2, 10.1, -4.1, -4.4; IR (film) 2957, 2932, 2859, 1735,

1453, 1368, 1254, 1160, 1083, 907 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{31}H_{49}ClN_2O_5SiH$ 593.3178, found 593.55. **Lower R_f diastereomer:** ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 4.22–4.15 (m, 1H), 3.82 (d, *J* = 8.3 Hz, 1H), 3.37 (s, 3H), 3.26–3.17 (m, 1H), 3.10–3.01 (m, 1H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.75–2.66 (m, 1H), 2.63–2.55 (m, 1H), 2.40–2.35 (m, 2H), 1.98–1.88 (m, 1H), 1.81–1.73 (m, 2H), 1.70 (s, 9H), 1.48–1.35 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.87 (s, 9H), -.0.03 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 149.8, 136.2, 128.9, 124.4, 124.2, 122.7, 122.3, 120.8, 115.2, 83.7, 70.1, 65.3, 63.3, 54.3, 51.3, 47.8, 42.4, 40.0, 32.5, 28.3, 25.8, 18.0, 10.2, -4.7, -4.7; IR (film) 2957, 2932, 2884, 2859, 1731, 1453, 1368, 1250, 1160, 1083, 834 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{31}H_{49}ClN_2O_5SiH$ 593.3178, found 593.28.



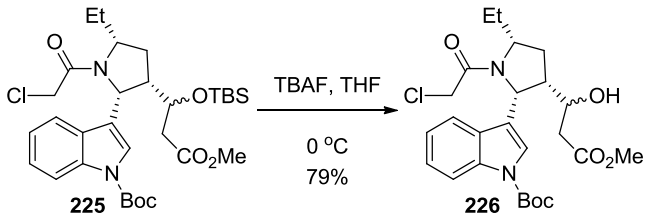
β-hydroxyester 225. Silyl ether **224** (161 mg, 0.27 mmol, 1 equiv.) was dissolved in dioxane (1.7 mL). HCl (338 μL of a 4M solution in dioxane, 1.35 mmol, 5 equiv.) was added at room temperature. After one hour the starting material had been consumed. Water was added and then the biphasic mixture was basified with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine and dried ($NaSO_4$). After filtration and concentration *in vacuo* the crude material was purified through flash column chromatography (2% Et_3N/20% EtOAc/hexanes) to

yield the desired β-hydroxyester (102 mg, 78%). The diastereomers were characterized separately. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 3.93 (app d, *J* = 10.3 Hz, 1H), 3.84 (d, *J* = 9.21 Hz, 1H), 3.61 (s, 3H), 3.28–3.20 (m, 1H), 3.13–3.07 (m, 1H), 3.03 (br s, 1H), 2.91–2.80 (m, 2H), 2.79–2.70 (m, 1H), 2.41 (dd, *J* = 16.7, 10.2 Hz, 1H), 2.29–2.20 (m, 2H), 2.16–2.10 (m, 1H), 1.80–1.73 (m, 1H), 1.69 (s, 9H), 1.51–1.45 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 149.7, 136.4, 128.8, 124.5, 124.4, 122.3, 121.2, 121.0, 115.4, 83.8, 66.3, 65.4, 65.3, 54.4, 51.8, 47.9, 42.4, 39.9, 28.6, 28.5, 28.3, 10.1; IR (film) 3492, 2972, 2930, 2879, 1734, 1453, 1368, 1255, 1159, 1092 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{35}ClN_2O_5H$ 479.2313, found 479.18. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.56 (s, 1H), 7.32–7.27 (m, 1H), 7.21–7.16 (m, 1H), 4.03 (app t, *J* = 8.2 Hz, 1H), 3.98 (d, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 3.28–3.19 (m, 1H), 3.14–3.05 (m, 1H), 2.90–2.85 (m, 2H), 2.82 (br s, 1H), 2.76 (qd *J* = 8.3, 3.1 Hz, 1H), 2.49–2.35 (m, 3H), 1.85–1.73 (m, 3H), 1.68 (s, 9H), 1.50–1.38 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 149.7, 136.2, 128.8, 124.5, 124.1, 123.3, 122.3, 120.8, 115.4, 83.7, 70.6, 65.1, 64.9, 54.3, 51.8, 48.1, 42.4, 39.6, 32.9, 28.2, 28.0, 10.1; IR (film) 3446, 2972, 2934, 2875, 1730, 1453, 1373, 1255, 1159, 1088 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{35}ClN_2O_5H$ 479.2313, found 479.13.



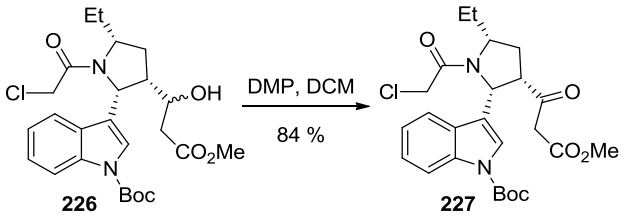
Chloroamide 225. NH pyrrolidine **222** (113 mg, 0.23 mmol, 1 equiv.) was dissolved in freshly distilled THF (2 mL), placed under a positive pressure of argon and cooled to 0 °C. Freshly distilled triethylamine (38 μL, 0.28 mmol, 1.2 equiv.) was added followed by the dropwise addition of chloroacetyl chloride (18.3 μL, 0.23 mmol, 1 equiv.). The reaction was stirred at 0 °C until the starting material was consumed then quenched with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in-vacuo*. The crude material was purified by flash column chromatography (35% EtOAc/hexanes) to provide the desired chloroamide (119 mg, 92%). The diastereomers were separated and characterized independently. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.46 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 5.46 (d, J = 7.3 Hz, 1H), 4.32–4.23 (m, 1H), 3.96–3.86 (m, 1H), 3.91 (d, J = 12.6 Hz, 1H), 3.67 (d, J = 12.4 Hz, 1H), 3.52 (s, 3H), 2.69–2.57 (m, 1H), 2.34–2.20 (m, 1H), 1.99 (dd, J = 14.9, 5.2Hz, 1H), 1.82–1.72 (m, 1H), 1.68 (s, 9H), 1.44–1.36 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H), 0.74 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 165.7, 149.4, 134.9, 129.1, 125.2, 124.6, 123.1, 119.2, 118.6, 115.5, 84.5, 67.9, 60.4, 55.3, 51.6, 49.3, 42.7, 40.2, 30.8, 28.2, 27.3, 25.6, 17.8, 10.9, -4.4, -4.7; IR (film) 2952, 2936, 2888, 2859, 1735, 1658, 1453, 1372, 1258, 1156, 1095, 1063, 916, 834 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + Na]$^+$ calcd $C_{31}H_{47}ClN_2O_6H$ 607.2970, found 607.24. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br d, J = 7.0 Hz, 1H), 7.69 (d, J = 7.8Hz, 1H), 7.52 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.30

(t, J = 7.5 Hz, 1H), 5.46, (d, J = 7.5 Hz, 1H), 3.95–3.86 (m, 1H), 3.90 (d, J = 12.4 Hz, 1H), 3.73–3.67 (m, 1H), 3.63 (d, J = 12.5 Hz, 1H), 3.60 (s, 3H), 2.79–2.70 (m, 1H), 2.67–2.58 (m, 1H), 2.50–2.43 (m, 1H), 2.29 (dd, J = 14.7, 4.9 Hz, 1H), 2.23 (dd, J = 14.7, 4.6 Hz, 1H), 1.82–1.72 (m, 1H), 1.69 (s, 9H), 1.43–1.34 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H), 0.81 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 165.5, 149.4, 134.7, 129.5, 125.2, 124.7, 123.4, 119.1, 118.1, 115.6, 84.6, 69.1, 60.4, 54.9, 51.6, 48.5, 42.8, 41.1, 33.6, 28.2, 27.3, 25.7, 17.9, 10.8, -4.6, -5.1; IR (film) 2978, 2957, 2932, 2884, 2859, 1739, 1661, 1453, 1372, 1258, 1156, 1087, 911, 834 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + H]$^+$ calcd $C_{31}H_{47}ClN_2O_6H$ 607.2970, found 607.27.



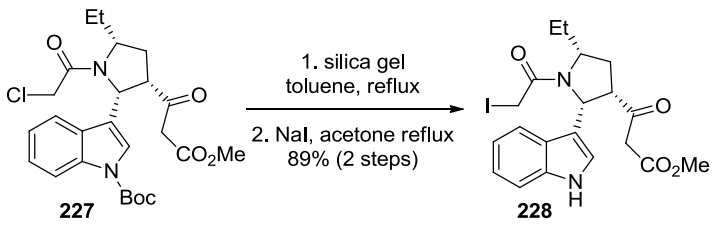
Alcohol 226. TBS-ether **225** (20 mg, 0.033 mmol, 1 equiv.) was dissolved in freshly distilled THF (0.5 mL), placed under a positive pressure of argon and cooled to 0 °C. TBAF (33 μL of a 1M solution in THF, 0.033 mmol, 1 equiv.) was added and the reaction was allowed to warm to room temperature. Upon consumption of the starting material the reaction was cooled back down to 0 °C and quenched with an aqueous solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and filtered. After concentration *in-vacuo*, the crude mixture was purified by flash column chromatography (30% EtOAc/hexanes) to provide the desired alcohol (12.8 mg, 79%) The diastereomers were separated and characterized independently. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.82 (d,

J = 7.9 Hz, 1H), 7.47 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 5.55 (d, J = 7.3 Hz, 1H), 3.98–3.91 (m, 1H), 3.91 (d, J = 12.6 Hz, 1H), 3.65 (d, J = 12.9 Hz, 1H), 3.62 (s, 3H), 3.47–3.39 (m, 1H), 2.89 (br s, 1H), 2.75–2.65 (m, 1H), 2.61–2.52 (m, 1H), 2.47–2.36 (m, 2H), 2.20–2.13 (m, 1H), 1.69 (s, 9H), 1.59–1.50 (m, 1H), 1.45–1.35 (m, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 165.7, 149.5, 134.9, 129.4, 125.1, 124.6, 123.0, 119.6, 119.3, 115.3, 84.5, 67.7, 60.9, 56.8, 51.9, 48.8, 42.7, 39.4, 31.6, 28.2, 27.1, 10.9; IR (film) 3437, 2978, 2932, 2879, 1735, 1653, 1453, 1376, 1258, 1160, 916, 744 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + H]$^+$ calcd $C_{25}H_{33}ClN_2O_6H$ 493.2105, found 493.16. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.53 (s, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 5.38 (d, J = 6.7 Hz, 1H), 3.96–3.88 (m, 1H), 3.85 (d, J = 12.5 Hz, 1H), 3.82–3.76 (m, 1H), 3.64 (d, J = 12.5 Hz, 1H), 3.61 (s, 3H), 2.69–2.59 (m, 1H), 2.59–2.46 (m, 3H), 2.46–2.41 (m, 2H), 1.99–1.89 (m, 1H), 1.68 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 165.5, 149.4, 134.7, 129.5, 125.2, 124.7, 123.4, 119.1, 118.1, 115.6, 84.6, 69.1, 60.4, 54.9, 51.6, 48.5, 42.8, 41.1, 33.7, 28.2, 27.4, 10.8; IR (film) 3441, 2978, 2932, 2875, 1735, 1653, 1453, 1372, 1254, 1156, 916, 744 cm^{-1}; LRMS–MALDI-TOF (m/z) [M + H]$^+$ calcd $C_{25}H_{33}ClN_2O_6H$ 493.2105, found 493.17.



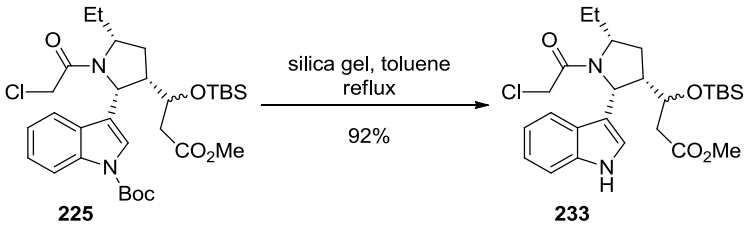
B-ketoester 227. A flame dried round bottom flask equipped with a stir bar was charged with alcohol **226** (12 mg, 0.024 mmol, 1.0 equiv.) and dissolved in freshly distilled dichloromethane (500 μL). Dess–Martin periodinane (11 mg, 0.026 mmol, 1.05 equiv.) was added in a single

portion at room temperature. The reaction was stirred at this temperature until the starting material had been consumed (as determined by TLC). The reaction was quenched with an aqueous solution of sodium bicarbonate and $Na_2S_2O_3$. The heterogeneous mixture was stirred at room temperature until homogeneous. The layers were separated and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over sodium sulfate. After concentration *in-vacuo*, the crude residue was purified by flash column chromatography (25% EtOAc/hexanes) to provide the desired β-ketoester (10 mg, 84%) which existed in solution as a mixture of the keto and enol forms (~1:0.5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.69 (s, 0.5H), 8.08 (br s, 1.8H), 7.67–7.54 (m, 1.4H), 7.51 (br s, 1H), 7.45 (s, 0.7H), 7.40–7.24 (m, 3H), 7.19 (t, *J* = 7.8 Hz, 0.5H), 5.83 (br s, 1H), 5.63 (d, *J* = 7.4 Hz, 0.5H), 4.85 (s, 0.5H), 4.01–3.86 (m, 3H), 3.76–3.64 (m, 3H), 3.62 (s, 3H), 3.55 (s, 1.5H), 3.32–3.18 (m, 1.5H), 3.12 (d, *J* = 15.7 Hz, 1H), 2.78–2.68 (m, 0.5H), 2.62 (br s, 1H), 2.42 (br s, 1H), 2.36–2.20 (m, 1.5H), 1.96 (app q, *J* = 12.2 Hz, 0.5H), 1.68 (s, 13.5H), 1.07–0.99 (m, 4.5H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 172.9, 172.1, 167.1, 165.8, 165.5, 149.5, 149.3, 135.0, 134.9, 129.0, 128.5, 125.3, 125.0, 124.8, 124.4, 123.3, 122.7, 119.0, 118.1, 115.7, 115.1, 90.9, 84.7, 84.4, 60.4, 55.2, 54.5, 52.5, 51.2, 48.8, 47.4, 42.5, 31.9, 30.8, 29.7, 29.7, 29.4, 28.1, 27.2, 22.7, 14.1, 13.7, 10.9, 10.7; IR (film) 3055, 2978, 2932, 2879, 1739, 1658, 1453, 1372, 1258, 1156, 1087, 911 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{31}ClN_2O_6H$ 491.1949, found 491.12.



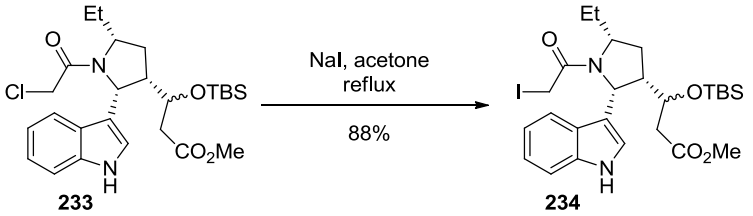
Iodoamide 228. Cloroamide **227** (100 mg, 0.2 mmol, 1 equiv. was dissolved in freshly distilled toluene (10 mL). Silica gel (1 g, 10 weight equiv.) was added and the reaction was heated to reflux until the starting material was consumed (as determined by TLC). The reaction was filtered and the silica gel was rinsed with ethyl acetate. The filtered solution was concentrated *in-vacuo* and purified by flash column chromatography (35% EtOAc/hexanes) to provide the deprotected indole (76 mg, 96%). The deprotected material (50 mg, 0.13 mmol, 1 equiv.) was dissolved in acetone 10 mL and sodium iodide (192 mg, 1.28 mmol, 10 equiv.) was added ad a solid in a single portion. The mixture was heated to reflux for 2 hours then cooled back down to room temperature and poured into water. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$ then brine. After filtration and concentration *in-vacuo*, the crude material was purified by flash column chromatography (35% EtOAc/hexanes) to provide the desired iodoamide (55.2 mg, 89%, or 85% over 2 steps) which existed in solution as a mixture of the keto and enol forms (~1:0.15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 0.15H), 8.91 (bs, 1H), 8.82 (br s, 0.15H), 7.60 (d, J = 8.1 Hz, 1.2H), 7.41 (d, J = 8.3 Hz, 1.3H), 7.23 (t, J = 7.5 Hz, 1.3H), 7.16–7.10 (m, 2.3H), 5.78 (br s, 0.15H), 5.60 (d, J = 6.2 Hz, 1H), 5.47 (d, J 5.3 Hz, 0.16H), 5.04 (s, 0.16H), 4.27–4.17 (m, 1.3H), 3.67–3.61 (m, 1.8H), 3.60 (s, 3H), 3.48 (d, J = 4.4 Hz, 2.6H), 2.32–2.25 (m, 1.15H), 2.24–2.15 (m, 1.3H), 2.11–2.05 (m, 1.3H), 1.62–1.51 (m, 1.3H), 1.00 (t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 201.5, 176.2, 172.8, 171.3, 167.9, 167.0, 136.9, 124.9, 124.6, 122.8, 122.8, 122.1, 121.8, 120.2, 120.1, 118.7, 118.6, 116.2, 116.0, 111.9, 111.8, 89.9, 60.8, 60.5, 58.3, 58.1,

52.5, 51.6, 51.4, 48.4, 32.5, 32.0, 28.0, 27.7, 14.2, 11.3, -0.73, -0.79; IR (film) 3287, 3051, 2961, 2932, 2875, 1742, 1711, 1625, 1433, 1400, 1233, 1156 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{23}IN_2O_4H$ 483.0781, found 483.04.



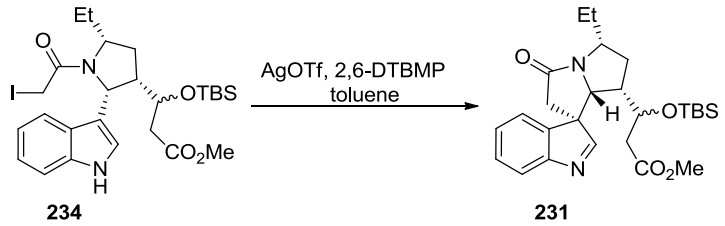
***N*-H Indole 233.** A flame dried round bottom flask with a stir bar was charged with chloroamide **225** (109 mg, 0.18 mmol, 1 equiv.). The starting material was dissolved in freshly distilled toluene (10 mL) and silica gel (1.09 g, 10 weight equiv.) was added. The mixture was heated to reflux until the starting material had been consumed (as determined by TLC) then allowed to cool to room temperature. The silica gel was filtered off and rinsed with ethyl acetate. The filtered solution was concentrated *in-vacuo* and purified via flash column chromatography (35% EtOAc/hexanes) to provide the desired *N*-H indole (84 mg, 94%). The diastereomers were characterized independently. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 9.3 Hz, 1H), 4.38–4.33 (m, 1H), 4.13–4.07 (m, 1H), 3.47 (d, *J* = 12.8 Hz, 1H), 3.38 (d, *J* = 12.8 Hz, 1H), 3.38 (s, 3H), 2.55–2.47 (m, 2H), 2.35 (dd, *J* = 15.3, 6.4 Hz, 1H), 2.21–2.10 (m, 1H), 2.04–1.95 (m, 1H), 1.90–1.79 (m, 1H), 0.94 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.20 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 167.4, 137.0, 123.8, 123.0, 119.2, 115.1, 111.9, 66.4, 60.6, 58.9, 51.5, 51.0, 43.7, 41.9, 27.5, 25.9, 24.8, 18.2, 8.6, -4.0, -4.4; IR (film) 3300, 2961, 2936, 2884, 2855, 1739, 1637, 1437, 1262, 911, 830, 744 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd

$C_{26}H_{39}ClN_2O_4H$ 507.2446, found 507.15. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 5.32 (d, *J* = 5.1 Hz, 1H), 4.32–4.17 (m, 2H), 3.79 (d, *J* = 12.8 Hz, 1H), 3.61 (d, *J* = 12.8 Hz, 1H), 3.51 (s, 3H), 2.73–2.62 (m, 1H), 2.52–2.40 (m, 2H), 2.40–2.30 (m, 1H), 2.24–2.16 (m, 1H), 1.71–1.64 (m, 1H), 1.55–1.44 (m, 1H), 0.95 (s, 9H), 0.93 (t, *J* = 8.0 Hz, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 167.4, 136.9, 124.5, 122.9, 121.7, 120.1, 119.3, 117.3, 111.7, 69.3, 60.6, 57.9, 51.9, 51.5, 43.3, 40.6, 29.6, 25.9, 25.8, 18.1, 10.1, -4.6, -4.6; IR (film) 3300, 3010, 2985, 2961, 2936, 2884, 2859, 1739, 1641, 1462, 1432 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{39}ClN_2O_4H$ 507.2446, found 507.17.



Iodoamide 234. Chloroamide **233** (84 mg, 0.17 mmol, 1 equiv.), was dissolved in acetone. Sodium iodide (248 mg, 1.7 mmol, 10 equiv.) was added as a solid in a single portion. The mixture was refluxed for two hours then allowed to cool to room temperature and poured into water. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$ then brine. After filtration and concentration *in-vacuo*, the crude material was purified by flash column chromatography (35% EtOAc/hexanes) to provide the desired iodoamide (87 mg, 88%, or 81% over 2 steps). The diastereomers were characterized separately. **Higher R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.37, (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 2.5 Hz, 1H), 7.19 (app t, *J* = 7.6 Hz, 1H), 7.06 (app t, *J* = 7.4 Hz, 1H), 4.83 (d, *J* = 9.5 Hz, 1H), 4.40–4.32 (m, 1H), 4.10 (td, *J* = 6.5,

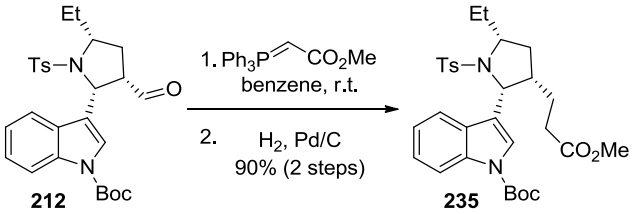
2.0 Hz, 1H), 3.36 (d, *J* = 10.2 Hz, 1H), 3.35 (s, 3H), 3.12 (d, *J* = 10.2 Hz, 1H), 2.55–2.46 (m, 2H), 2.36 (dd, *J* = 15.3, 6.5 Hz, 1H), 2.24–2.15 (m, 1H), 2.15–2.08 (m, 1H), 2.03–1.95 (m, 1H), 1.85–1.76 (m, 1H), 0.97–0.92 (m, 3H), (0.96, s, 9H), 0.24 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 168.4, 137.1, 123.6, 123.0, 122.6, 120.3, 119.4, 115.6, 111.9, 66.4, 60.6, 59.2, 51.4, 51.2, 41.9, 29.3, 27.4, 26.0, 24.6, 18.2, 8.9, -4.0, -4.2; IR (film) 3291, 3059, 2957, 2932, 2884, 2859, 1739, 1621, 1462, 1437, 1360, 1279, 1258, 1173, 1103, 911, 838 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{39}IN_2O_4SiH$ 599.1802, found 599.13. **Lower R_f diastereomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.44 Hz, 1H), 7.21 (app t, *J* = 7.7 Hz, 1H), 7.10 (app t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 5.19 (d, *J* = 5.5 Hz, 1H), 4.27 (q, *J* = 5.9 Hz, 1H), 4.25–4.18 (m, 1H), 3.57 (d, *J* = 10.4 Hz, 1H), 3.49 (s, 3H), 3.31 (d, *J* = 10.4 Hz, 1H), 2.72–2.65 (m, 1H), 2.47 (dd, *J* = 15.4, 6.2 Hz, 1H), 2.42 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.37–2.28 (m, 1H), 2.22–2.15 (m, 1H), 1.72–1.64 (m, 1H), 1.53–1.44 (m, 1H), 0.94 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 168.7, 136.9, 124.3, 122.9, 121.7, 120.1, 119.4, 117.7, 111.6, 60.5, 58.4, 53.8, 51.9, 51.5, 40.5, 29.3, 25.9, 25.2, 18.1, 10.0, -4.4, -4.6; IR (film) 3295, 3059, 2961, 2932, 2888, 2859, 1739, 1632, 1433, 1274, 1262, 911 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{39}IN_2O_4SiH$ 599.1802, found 599.11.



234 231

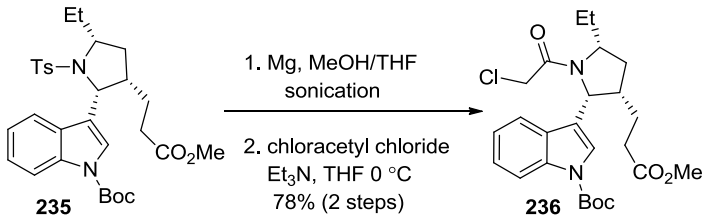
Tetracycle 231. A single diastereomer of iodoamide **234**, of unknown stereochemistry of the silyl ether (77 mg, 0.13 mmol, equiv.), was dissolved in toluene (10 mL). Triethylamine (53.8

μL, 0.39 mmol, 3 equiv.) was added followed by silver trifluoromethanesulfonate (99 mg, 0.34 mmol, 3 equiv.) as a solid at room temperature. The reaction was stirred at room temperature overnight resulting in a black precipitate. The crude material was filtered over celite (rinsed with ethyl acetate). The filtered solution was transferred to a separatory funnel and washed with an aqueous solution of sodium bicarbonate. The aqueous layer was extracted three additional times with ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate. After filtration and concentration *in-vacuo* the material was not purified further (54.7 mg, 90% crude yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 4.71 (d, J = 9.6 Hz, 1H), 3.89–3.78 (m, 1H), 3.53 (s, 3H), 3.43–3.35 (m, 1H), 3.02 (d, J = 15.6 Hz, 1H), 2.79–2.67 (m, 1H), 2.30 (d, J = 15.6 Hz, 1H), 2.09–2.02 (m, 1H), 2.02–1.88 (m, 1H), 1.81–1.67 (m, 1H), 1.65–1.54 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H), 0.78 (s, 9H), 0.88 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.1, 169.9, 155.4, 137.0, 129.1, 126.7, 122.0, 121.5, 67.3, 66.9, 63.6, 58.7, 51.6, 44.9, 44.5, 40.8, 36.4, 25.9, 24.2, 18.2, 11.1, -4.7, -4.8; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{26}H_{38}N_2O_4SiH$ 471.2679, found 471.22.



Ester 235. Aldehyde **212** (1 g, 2.0 mmol, 1 equiv.), was added to a round bottom flask and dissolved in freshly distilled benzene (20 mL). The Wittig reagent (820 mg, 2.4 mmol, 1.2 equiv.) was added as a solid in a single portion. The reaction was allowed to stir overnight at room temperature at which point the starting material had been consumed (as determined by

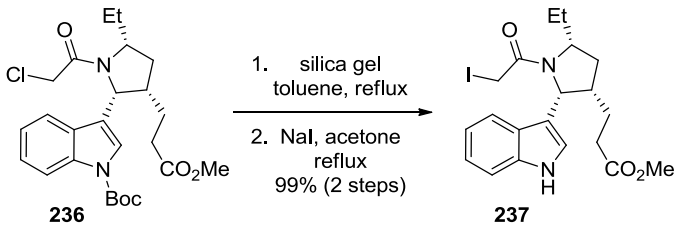
TLC). The reaction was concentrated *in-vacuo* and the crude material was purified via flash column chromatography (20% EtOAv/hexanes) to provide the homologated product (1.04 g, 94%). The homologated product (1.04 g, 1.88 mmol, 1 equiv.) was dissolved in freshly distilled benzene (50 mL) and 5% Pd/C was added (236 mg). The reaction was placed under a balloon of hydrogen and stirred at room temperature until the starting material had been consumed (as determined by TLC or NMR). The reaction was filtered through celite (rinsed with ethyl acetate), concentrated *in-vacuo* and purified via flash column chromatography (20% EtOAc/hexanes) to provide the desired ester (99 mg, 96%, or 90% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.32–7.27 (m, 1H), 7.25–7.20 (m, 3H), 5.18 (d, *J* = 8.2 Hz, 1H), 3.58–3.51 (m, 1H), 3.54 (s, 3H), 2.48–2.40 (m, 1H), 2.39 (s, 3H), 2.18–2.05 (m, 4H), 1.93–1.79 (m, 1H), 1.71–1.62 (m, 1H), 1.68 (s, 9H), 1.55–1.44 (m, 1H), 1.08–1.01 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 149.6, 143.3, 135.3, 135.1, 129.6, 129.5, 127.6, 124.8, 124.4, 122.6, 120.2, 119.1, 115.3, 83.8, 62.7, 59.7, 51.6, 42.1, 35.2, 32.4, 29.6, 28.2, 25.1, 21.5, 10.8; IR (film) 3051, 2974, 2932, 2875, 1731, 1453, 1372, 1343, 1250, 1152, 1087, 663, 581 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{30}H_{38}N_2O_6SNa$ 577.2348, found 577.18.



Chloroamide 236. *N*-tosyl-pyrrolidine **235** (1.68 g, 3.02 mmol, 1 equiv.) was dissolved in THF (10 mL). Once homogeneous, the solution was diluted with methanol (90 mL). Powdered magnesium (1.47 g, 60.4 mmol, 20 equiv.) was added and the mixture was capped with a reflux

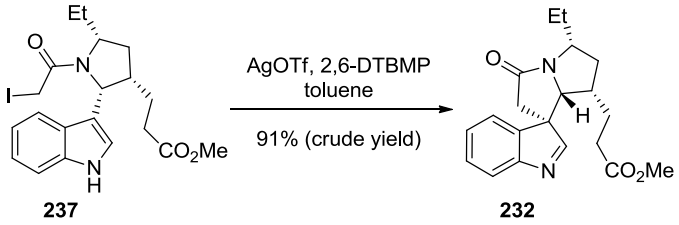
condenser. The reaction was sonicated for 30 minutes. A second aliquot of powdered magnesium (1.47 g, 60.4 mmol, 20 equiv.) was added and the reaction was sonicated for an additional 30 minutes. The reaction was diluted with ethyl acetate and cooled to 0 °C. 1M HCl was added until all of the magnesium was dissolved. The layers were separated and the aqueous phase was extracted four additional times with ethyl acetate. The combined organic phases were washed with an aqueous solution of sodium bicarbonate, washed with brine, dried over sodium sulfate and filtered. After concentration *in-vacuo* the crude material was used directly in the next step without further purification. The crude NH pyrrolidine was dissolved in THF (30 mL), placed under a positive pressure of argon and cooled to 0 °C. Triethylamine (468 μL, 3.4 mmol, 1.2 equiv. based on starting *N*-tosyl pyrrolidine) was added followed by dropwise addition of chloroacetyl chloride (223 μL, 2.8 mmol, 1 equiv. based on starting *N*-tosyl pyrrolidine). The reaction was stirred at 0 °C until all of the NH pyrrolidine had been consumed (as determined by TLC). The reaction was quenched with an aqueous solution of sodium bicarbonate and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentration *in-vacuo*. The crude material was purified by flash column chromatography (30% EtOAc/hexanes) to provide the desired chloroamide X (1.12 g, 72% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 5.36 (d, J = 7.6 Hz, 1H), 3.93–3.86 (m, 1H), 3.88 (d, J = 12.6 Hz, 1H), 3.67 (d, J = 12.6 Hz, 1H), 3.62 (s, 3H), 2.73–2.63 (m, 1H), 2.54–2.44 (m, 1H), 2.35 (app quint, J = 6.3 Hz, 1H), 2.30–2.17 (m, 1H), 1.84–1.75 (m, 1H), 1.68 (s, 9H), 1.53–1.44 (m, 1H), 1.44–1.35 (m, 1H), 1.12–1.04 (m, 1H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 165.7, 149.4, 135.1, 129.3, 125.1, 124.1, 123.1, 119.3, 118.6, 115.6, 84.4, 60.9, 57.9, 51.7, 42.7, 42.4, 34.3, 32.3, 28.2, 27.3, 25.2,

10.9; IR (film) 2974, 2932, 2875, 1731, 1658, 1449, 1368, 1246, 1147, 744 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{33}ClN_2O_5H$ 477.1732, found 477.17.



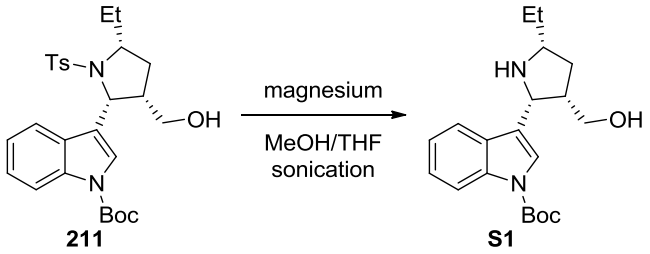
Iodoamide 237. Chloroamide **236** (250 mg, 0.52 mmol, 1 equiv.) was dissolved in freshly distilled toluene (50 mL) and silica gel (2.5 g, 10 weight equivalents) was added. The mixture was heated to reflux until the starting material had been consumed (as determined by TLC). The reaction was filtered over celite (rinsed with ethyl acetate) and concentrated *in*-vacuo. The crude material was purified via flash column chromatography (35% EtOAc/hexanes) to provide the Boc-deprotected chloroamide (197 mg, quantitative). The Boc-deprotected chloroamide (197 mg, 0.52 mmol, 1 equiv.) was dissolved in acetone (5 mL) and sodium iodide (785 mg, 5.2 mmol, 10 equiv.) was added as a solid in a single portion. The mixture was heated to reflux for two hours, allowed to allow to cool back down to room temperature, and poured into water. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with an aqueous solution of $Na_2S_2O_3$ then brine. The solution was dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The crude material was purified via flash column chromatography (35% EtOAc/hexanes) to provide the desired iodoamide (243 mg, 99%, or 99% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.4 (d, *J* = 8.0 Hz, 1H), 7.25–7.15 (m, 2H), 7.06 (app d, 2.4 Hz, 1H), 5.43 (d, 7.4 Hz, 1H), 3.89–3.78 (m, 1H), 3.61 (s, 3H), 3.50 (d, *J* = 9.8 Hz, 1H), 3.43 (d, *J* = 9.8 Hz, 1H), 2.76–2.63 (m, 1H), 2.54–2.38 (m, 1H), 2.37–2.28 (m, 1H), 2.78–2.16 (m, 2H), 1.82–1.66 (m, 1H), 1.56–1.45 (m, 1H),

1.45–1.34 (m, 1H), 1.20–1.07 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 167.5, 136.1, 126.9, 122.9, 122.4, 120.1, 118.1, 114.0, 111.8, 61.1, 59.8, 51.7, 42.4, 34.8, 32.4, 27.4, 25.3, 10.9, -0.06; IR (film) 3283, 3051, 2965, 2932, 2875, 1731, 1625, 1433, 1173, 1099 cm^{-1}; LRMS–ESI (m/z) $[M + H]^+$ calcd $C_{20}H_{25}IN_2O_3H$ 469.0988, found 469.10.



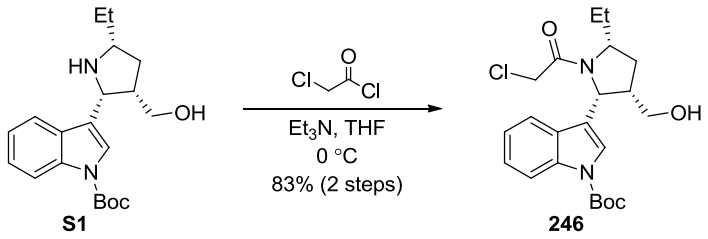
Tetracycle 232. Iodoamide **237** (32 mg, 0.07 mmol, 1 equiv.) was dissolved in freshly distilled toluene (2 mL) and freshly distilled triethylamine was added (19 µL, 0.14 mmol, 2 equiv.). Silver trifluoromethanesulfonate (35 mg, 0.14 mmol, 2 equiv.) was added as a solid in a single portion. The reaction was stirred at room temperature until all of the starting material had been consumed (as determined by TLC) resulting in the formation of a dark precipitate. The reaction was filtered over celite (rinsed with ethyl acetate). The filtered solution was washed with an aqueous solution of sodium bicarbonate. The aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated *in-vacuo* to provide the desired tetracycle that was used without further purification (21.5 mg, 91% crude yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.67 (d, 7.7 Hz, 1H), 7.46–7.37 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 4.65 (d, J = 8.8 Hz, 1H), 3.54 (s, 3H), 3.48–3.37 (m, 1H), 3.07 (d, J = 16.2 Hz, 1H), 2.77–2.66 (m, 1H), 2.33 (d, J = 16.2 Hz, 1H), 2.28–2.20 (m, 1H), 2.19–2.06 (m, 1H), 1.99–1.90 (m, 1H), 1.89–1.80 (m, 1H), 1.73–1.64 (m, 1H), 1.46–1.38 (m, 1H), 1.38–1.29 (m, 1H), 1.19–1.11 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 172.8, 169.6, 155.1, 136.3, 128.9, 126.9, 121.9, 121.4, 69.1,

63.9, 58.7, 51.4, 43.4, 39.0, 37.7, 32.4, 24.5, 23.1, 11.0; IR (film) 3051, 2961, 2928, 2875, 1735, 1689, 1551, 1413, 1274, 1193, 1169 cm^{-1}; LRMS–MALDI-TOF (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{24}N_2O_3H$ 341.1865, found 341.27.



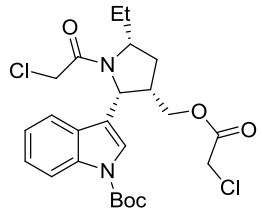
Amino Alcohol S1. The alcohol **211** (1.0 g, 20 mmol, 1 equiv) was dissolved in freshly distilled THF (7 mL) and then the homogeneous solution was diluted with freshly distilled MeOH (63 mL). Powdered Mg (980 mg, 40 mmol, 20 equiv) was added and then the flask was capped with a reflux condenser and placed under a positive pressure of Ar. The heterogeneous reaction mixture was sonicated for 30 min and then a second aliquot of Mg powder (980 mg, 40 mmol, 20 equiv) was added and sonication continued for another 30 min. The reaction was monitored (TLC) after each period of sonication. If starting material remained, then another 20 equiv of Mg was added and then the reaction mixture was sonicated for another 30 min (typically, the reaction was complete after 2–4 additions of Mg). Once the starting material had been consumed, the mixture was cooled to 0 °C and the reaction quenched through the dropwise addition of 2 M $HCl_{(aq)}$ until all of the solid Mg had dissolved to form a homogeneous solution, which was transferred to a separatory funnel. The aqueous phase was extracted five times with EtOAc; the combined organic phases were washed once with water then once with a saturated $NaHCO_3$. The organic phase was washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the resulting brown oil (crude amino alcohol **S1**) was used in the next

step without purification. Alternatively, **S1** could be purified through flash column chromatography (5% Et_3N in 35% EtOAc/hexanes) to give analytically pure material, isolated as a dark oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.59 (s, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 4.49 (d, J = 6.25 Hz, 1H), 3.33 (dd, J = 10.56, 3.25 Hz, 1H), 3.28 (dd, J = 10.6, 4.0 Hz, 1H), 3.13 (app quint, J = 7.3 Hz, 1H), 2.60–2.53 (m, 1H), 2.34 (dt, J = 13.0, 8.6 Hz, 1H), 1.72–1.59 (m, 4H), 1.67 (s, 9H), 1.00 (t, J = 7.46 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 135.6, 129.2, 124.4, 122.4, 122.3, 120.0, 118.9, 115.3, 83.6, 64.5, 58.6, 58.3, 41.4, 33.6, 28.7, 28.1, 11.5; IR (film) 3393, 3324, 2969, 2928, 2875, 1731, 1453, 1372, 1250, 1152, 1087 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{20}H_{28}N_2O_3H$, 345.2178, found 345.2166; $[\alpha]^{23.9}_D$ +72.6° (c = 1.000, $CHCl_3$).



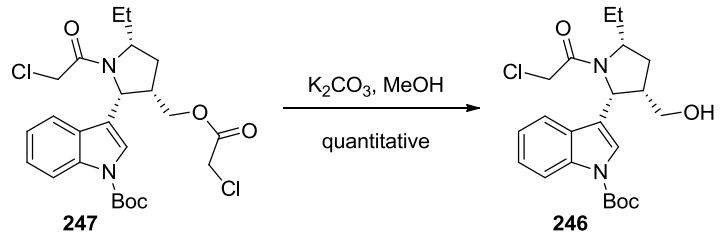
Chloroamide 246. The crude residue **S1** from the detosylation was dissolved in THF (7 mL) and placed under a positive pressure of Ar. Et_3N (279 μL, 2.00 mmol, 1 equiv) was added and then the reaction mixture was cooled to 0 °C. Chloroacetyl chloride (159 μL, 2.00 mmol, 1 equiv) was added dropwise over 5 min. The mixture was stirred at 0 °C until the starting material had been consumed (30 min, as determined by TLC) and then the reaction was quenched through the addition of saturated $NH_4Cl_{(aq)}$. The layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material

was purified through flash column chromatography (30%–50% EtOAc/hexanes) to yield a white solid (699 mg, 83% over two steps). Mp: 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.70 (d, *J* = 7.85 Hz, 1H), 7.45 (s, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 5.46 (d, *J* = 7.5 Hz, 1H), 3.96–3.88 (m, 2H), 3.67 (d, *J* = 12.4 Hz, 1H), 3.40–3.28 (m, 2H), 2.79–2.61 (m, 2H), 2.3 (app quint, *J* = 6.2 Hz, 1H), 1.68 (s, 9H), 1.53 (q, *J* = 12.1 Hz, 1H), 1.50–1.30 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 149.4, 135.2, 129.0, 125.2, 124.3, 123.0, 119.1, 118.9, 115.5, 84.5, 62.1, 60.8, 56.7, 45.5, 42.7, 32.0, 28.2, 27.3, 10.9; IR (film) 3454, 2985, 2965, 2921, 2879, 1735, 1653, 1458, 1376, 1258, 1147 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{22}H_{29}ClN_2O_4H$, 421.1894, found 421.1862; $[\alpha]^{23.9}_D$ +21.0° (*c* = 1.000, $CHCl_3$).

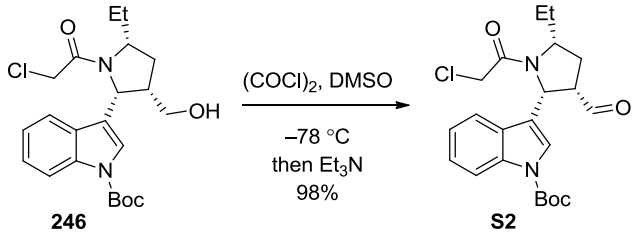


247

Bisacylation Product 247. During some trials of the acylation reaction, the bis-acylation product **247** was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 5.49 (d, *J* = 7.6 Hz, 1H), 4.00–3.83 (m, 5H), 3.74 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.69 (d, *J* = 12.6, 1H), 2.94–2.82 (m, 1H), 2.74–2.62 (m, 1H), 2.34 (app quint, *J* = 6.3 Hz, 1H), 1.69 (s, 9H), 1.66–1.54 (m, 1H), 1.48–1.35 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 165.8, 149.3, 135.1, 128.7, 125.4, 124.4, 123.0, 118.3, 118.2, 115.8, 84.7, 65.3, 60.6, 56.2, 42.6, 41.8, 40.6, 32.1, 28.2, 27.3, 10.9; IR (film) 2978, 2932, 2879, 1735, 1661, 1453, 1368, 1258, 1152 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd $C_{24}H_{30}Cl_2N_2O_5H$, 497.1610, found 497.1601.

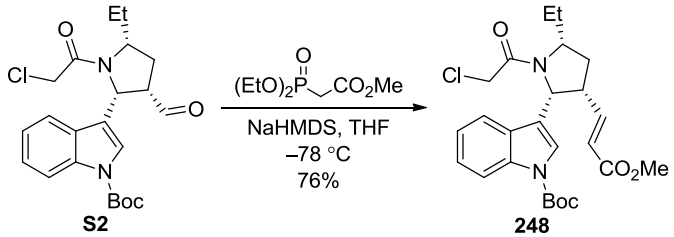


Cleavage of the O-Acetate 247. The bis-acylation product **247** (50.0 mg, 0.100 mmol, 1 equiv) was dissolved in freshly distilled MeOH (1 mL) and cooled to 0 °C. K_2CO_3 (138 mg, 1.00 mmol, 10 equiv) was added and then the heterogeneous mixture was stirred at 0 °C until the starting material had been consumed (10 min, as determined by TLC). The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (50% EtOAc/hexanes) to yield **246** (42 mg, quantitative) as a white solid, with spectroscopic data consistent with those for compound **246** isolated from the selective N-acylation of **S1**.



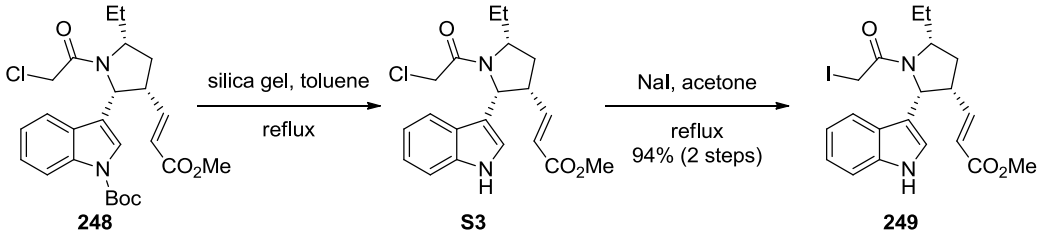
Aldehyde S2. Freshly distilled DCM (45 mL) was added to a flame-dried round-bottom flask under a positive pressure of Ar. DMSO (895 μL, 11.5 mmol, 3.5 equiv) was added and the solution cooled to –78 °C. 2 M oxalyl chloride in DCM (4.94 mL, 9.88 mmol, 3 equiv) was added dropwise and then the mixture was stirred at –78 °C for 20 min. A solution of the alcohol **246** (1.39 g, 3.29 mmol, 1 equiv) in freshly distilled DCM was then added to the mixture over 5

min. The solution was stirred at –78 °C for 20 min and then Et_3N (2.3 mL, 16.5 mmol, 5 equiv) was added. The cooling bath was removed and the reaction monitored (TLC) until the starting material had been consumed (5–10 min). The reaction was quenched through the addition of water and then the phases were separated. The aqueous phase was extracted twice with DCM. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (50% EtOAc/hexane) to yield a white solid (1.35 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.12 (br s, 1H), 7.54 (s, 1H), 7.50 (br s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 5.75 (br s, 1H), 4.08–4.00 (m, 1H), 3.89 (d, *J* = 11.5 Hz, 1H), 3.74 (d, *J* = 11.5 Hz, 1H), 3.40–3.31 (m, 1H), 2.61 (br s, 1H), 2.37 (app quint, *J* = 7 Hz, 1H), 2.27–2.13 (m, 1H), 1.68 (s, 9H), 1.50 (br s, 1H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 165.7, 149.3, 135.4, 127.7, 125.6, 124.2, 123.4, 118.3, 118.0, 115.8, 84.8, 60.6, 55.4, 54.1, 42.5, 29.6, 28.1, 27.5, 10.9; IR (film) 3055, 2978, 2936, 2879, 2835, 2741, 1726, 1661, 1453, 1372, 1254, 1152 cm^{-1}; MS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{22}H_{27}ClN_2O_4Na$, 441.1557, found 441.0644; $[\alpha]^{23.8}_D$ +77.4° (*c* = 1.000, $CHCl_3$).



***α,β*-Unsaturated Ester 248.** Freshly distilled THF (1.5 mL) and methyl diethylphosphonoacetate (55.2 mg, 0.26 mmol, 1.1 equiv) were added to a flame-dried round-bottom flask under a positive pressure of Ar. The solution was cooled to –78 °C and then NaHMDS (239 μL, 0.240 mmol, 1 equiv) was added. The mixture was stirred at –78 °C for 30

min and then a solution of the aldehyde **S2** (100 mg, 0.240 mmol, 1 equiv) in freshly distilled THF (1 mL) was added. The mixture was stirred at –78 °C for 5 min, at which point the starting material had been consumed (TLC). The reaction was quenched through the addition of saturated $NH_4Cl_{(aq)}$; the layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (25% EtOAc/hexanes) to yield a white solid (86 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (br s, 1H), 7.47 (s, 1H), 7.39–7.30 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.92 (d, *J* = 15.5 Hz, 1H), 5.43 (d, *J* = 7.5 Hz, 1H), 4.01–3.93 (m, 1H), 3.89 (d, *J* = 12.4 Hz, 1H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.55 (s, 3H), 3.33–3.21 (m, 1H), 2.76–2.63 (m, 1H), 2.29 (app quint, *J* = 6.2 Hz, 1H), 1.80 (q, *J* = 11.9 Hz, 1H), 1.68 (s, 9H), 1.51–1.40 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.8, 149.4, 145.6, 135.4, 128.4, 125.2, 124.3, 123.2, 122.9, 119.2, 118.6, 115.5, 84.5, 61.0, 58.6, 51.5, 46.0, 42.5, 35.0, 28.2, 27.4, 10.9; IR (film) 2969, 2932, 2879, 1735, 1653, 1458, 1376, 1254, 1147 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{31}ClN_2O_5H$, 475.2000, found 475.1994.

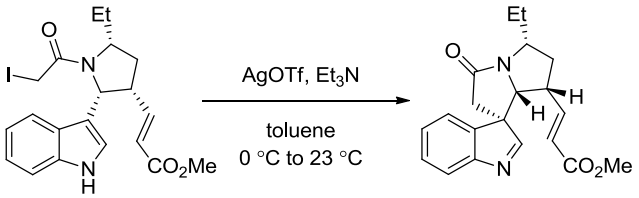


Iodoamide 249. The N-Boc–protected indole **248** (85 mg, 0.179 mmol, 1 equiv) was dissolved in freshly distilled toluene (2 mL). Silica gel (85 mg) was added and then the mixture was heated under reflux until the starting material had been consumed (TLC; typically 2–3 h). The

mixture was cooled to room temperature and filtered through a glass frit. The silica gel was washed three times with EtOAc. The solution obtained was concentrated *in vacuo* to give **S3** as a dark oil, which was used in the next reaction without purification. Alternatively, the crude material could be purified through flash column chromatography (20%–40% EtOAc/hexanes) to yield analytically pure **S3** as a white solid. Mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.38 (dd, *J* = 15.5, 9.1 Hz, 1H), 5.93 (dd, *J* = 15.5, 0.6 Hz, 1H), 5.51 (d, *J* = 7.4 Hz, 1H), 4.02–3.96 (m, 1H), 3.96 (d, *J* = 12.7 Hz, 1H), 3.72 (d, *J* = 12.7 Hz, 1H), 3.57 (s, 3H), 3.31–3.20 (m, 1H), 2.79–2.68 (m, 1H), 2.28 (app quint, *J* = 6.2 Hz, 1H), 1.79 (q, *J* = 12.1 Hz, 1H), 1.49–1.37 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 166.0, 146.5, 136.4, 125.7, 122.9, 122.8, 122.7, 120.1, 118.9, 113.5, 111.6, 60.9, 59.3, 51.5, 46.4, 42.6, 35.2, 27.5, 11.0; IR (film) 3291, 3059, 2969, 2932, 2879, 1718, 1649, 1458, 1421, 1262, 1233, 137 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{23}ClN_2O_3H$, 375.1476, found 375.1472.

The crude material **S3** was dissolved in acetone (3 mL). NaI (255 mg, 1.79 mmol, 10 equiv) was added and then the mixture was heated under reflux for 2 h, at which point the starting material had been consumed (determined from the NMR spectrum of a removed aliquot). The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (20%–40% EtOAc/hexanes) to yield the iodoamide **249** (78.6 mg, 94% over two steps) as a light-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.40

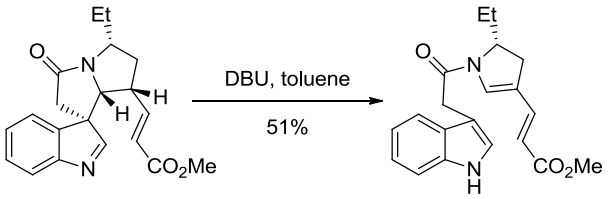
(dd, J = 15.6, 9.1 Hz, 1H), 5.94 (d, J = 15.5 Hz, 1H), 5.49 (d, J = 7.5 Hz, 1H), 3.95–3.86 (m, 1H), 3.57 (s, 3H), 3.48 (s, 2H), 3.32–3.21 (m, 1H), 2.78–2.66 (m, 1H), 2.30–2.22 (m, 1H), 1.84–1.75 (m, 1H), 1.50–1.34 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.2, 146.6, 136.4, 125.9, 122.8, 122.8, 122.7, 120.1, 118.9, 113.6, 111.6, 61.2, 60.6, 51.5, 46.1, 35.4, 27.6, 11.0, –0.5; IR (film) 3288, 3053, 2964, 2932, 2875, 1718, 1629, 1431, 1232, 739 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{20}H_{23}IN_2O_3H$, 467.0832, found 467.0818; $[\alpha]^{23.9}_D$ +77.4° (c = 1.000, $CHCl_3$).



243 **244**

Spirocyclic Indolenine 244. The iodoamide **243** (20.0 mg, 0.428 mmol, 1 equiv) was dissolved in freshly distilled toluene (8 mL) and placed under a positive pressure of Ar. Et_3N (112 μL, 0.856 mmol, 2 equiv) was added and the solution cooled to 0 °C. Silver trifluoromethanesulfonate (206 mg, 0.856 mmol, 2 equiv) was added as a solid in a single portion and then the mixture was removed from the ice bath and warmed to room temperature. Once the starting material had been consumed (TLC; typically within 30 min), the mixture was filtered through a short pad of Celite, which was rinsed three times with EtOAc. The solution was transferred to a separatory funnel and washed with a 1:1 solution of saturated $NaHCO_{3(aq)}$ and saturated $Na_2S_2O_3$ and then with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude spirocyclic indolenine **244** as a dark oil, which was used for the next reaction without purification. Alternatively, the crude material could be purified

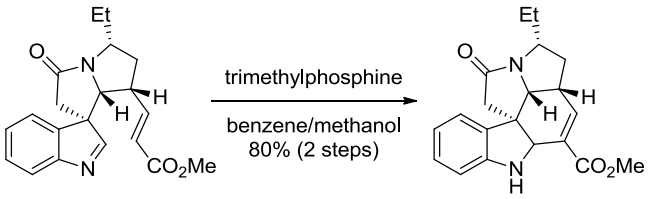
through flash column chromatography (5% Et_3N in 35% EtOAc/hexanes) to yield the analytically pure spirocyclic indolenine **244** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.4, 0.9 Hz, 1H), 6.52 (dd, *J* = 15.4, 8.9 Hz, 1H), 5.47 (dd, *J* = 15.6, 1.1Hz, 1H), 4.64 (d, *J* = 7.7 Hz, 1H), 3.64 (s, 3H), 3.57–3.49 (m, 1H), 3.04 (dd, *J* = 16.7, 1.2 Hz, 1H), 2.82–2.67 (m, 2H), 2.48 (d, *J* = 16.6 Hz, 1H), 2.43 (dt, *J* = 13.0, 7.2 Hz, 1H), 1.76 (app quint, *J* = 6.5 Hz, 1H), 1.69–1.58 (m, 1H), 0.99 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.0, 165.7, 155.2, 144.2, 136.7, 129.1, 126.9, 122.8, 121.8, 121.3, 70.0, 61.7, 57.2, 51.7, 42.9, 39.8, 39.2, 25.1, 11.1; IR (film) 3041, 2973, 2948, 2883, 2846, 1718, 1682, 1641, 1548, 1442, 1415, 1273 cm^{-1}; HRMS–ESI (*m*/*z*) [M + H] calcd $C_{20}H_{22}N_2O_3H$, 339.1709, found 339.1718; $[\alpha]^{23.8}_D$ +245.8° (*c* = 1.000, $CHCl_3$).



244 **249**

Diene 249. DBU (24.3 μL, 0.162 mmol, 1.5 equiv) was added to a solution of the spirocyclic indolenine **244** (38.0 mg, 0.112 mmol, 1 equiv) in toluene (2 mL) and then the homogeneous mixture was stirred for 60 h. The resulting mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*; the crude residue was purified using preparatory TLC (EtOAc/hexanes, 1:1) to give a light-yellow solid (19.4 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 15.8 Hz, 1H), 7.34 (s, 1H), 7.21 (td, *J* = 7.1, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.1, 1.1 Hz,

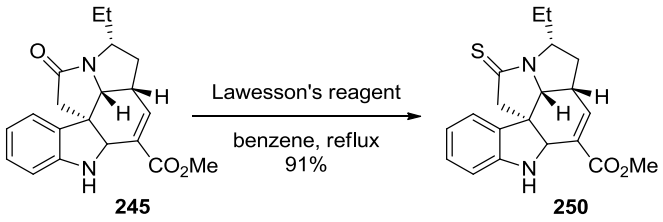
1H), 7.00 (d, J = 2.5 Hz, 1H), 6.92 (s, 1H), 5.63 (d, J = 15.4 Hz, 1H), 4.56–4.47 (m, 1H), 3.89 (d, J = 3.5 Hz, 2H), 3.74 (s, 3H), 2.83 (dd, J = 15.5, 10.5 Hz, 1H), 2.32 (dd, J = 15.9, 3.6 Hz, 1H), 1.93–1.83 (m, 1H), 1.66–1.56 (m, 1H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.6, 138.5, 136.1, 134.5, 126.9, 122.5, 122.3, 121.3, 119.7, 118.6, 115.7, 111.2, 108.2, 59.8, 51.4, 32.5, 32.0, 26.1, 8.3; IR (film) 3328, 3104, 3059, 2957, 2879, 1701, 1661, 1612, 1596, 1421, 1156, 732 cm^{-1}; MS–MALDI-TOF $[M + Na]^+$ (m/z) calcd $C_{20}H_{22}N_2O_3Na$, 361.1528, found 361.1049.



244 245

Pentacycle 245. Trimethylphosphine (55 μL, 0.536 mmol, 10 equiv) was added to a solution of the crude spirocyclic indolenine **244** (18.13 mg, 0.0536 mmol, 1 equiv) in freshly distilled benzene (700 μL) and MeOH (50 μL). The mixture was stirred at room temperature until the starting material had been consumed (2 h, as determined by TLC). Once complete, the mixture was concentrated and purified through flash column chromatography (EtOAc/hexanes, 1:1) to yield a white solid (14.6 mg, 80% over two steps). Mp: 149–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 7.5 Hz, 1H), 7.04 (td, J = 7.7, 1.2 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.71 (td, J = 7.5, 1.0 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 4.65 (br s, 1H), 4.44 (d, J = 5.7 Hz, 1H), 4.38 (s, 1H), 3.80 (s, 3H), 3.53 (t, J = 9.7 Hz, 1H), 3.02 (dd, J = 16.5, 1.2 Hz, 1H), 2.87 (d, J = 16.5 Hz, 1H), 3.73–3.66 (m, 1H), 2.60 (dt, J = 17.4, 8.8 Hz, 1H), 2.48–2.39 (m, 1H), 2.02 (d, J = 13.5 Hz, 1H), 1.16–1.05 (m, 1H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3,

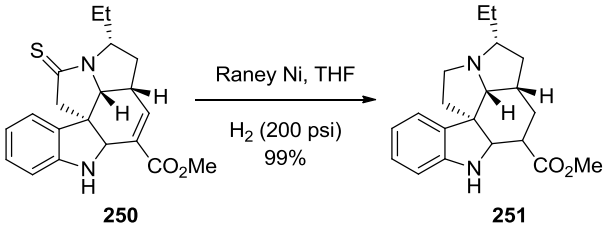
166.7, 149.8, 141.0, 130.2, 129.1, 128.6, 122.8, 118.4, 109.1, 67.1, 60.4, 54.7, 53.5, 52.2, 49.3, 38.1, 33.3, 24.3, 10.8; IR (film) 3401, 3051, 2965, 2879, 1678, 1608, 1490, 1482, 1416, 1254, 1095, 911, 732 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{22}N_2O_3H$, 339.1709, found 339.1707; $[\alpha]^{23.9}_D$ +181.0° (*c* = 1.000, $CHCl_3$).



245 **250**

Thioamide 250. A solution of the pentacycle **245** (20.0 mg, 0.0590 mmol, 1 equiv) in freshly distilled benzene (2 mL) was placed under a positive pressure of Ar. Lawesson's reagent (14.3 mg, 0.0350 mmol, 0.6 equiv) was added and then the mixture was heated under reflux. The reaction was closely monitored (TLC) until the starting material had been consumed (typically 1 h; continued heating under reflux after consumption of the starting material decreased the yields). The mixture was poured into water and the phases separated. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed successively with water and brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (25% EtOAc/hexanes) to yield a yellow solid (19.1 mg, 91%). Mp: 222–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.05 (td, *J* = 7.7, 1.2 Hz, 1H), 6.90–6.86 (m, 1H), 6.69 (td, *J* = 7.5, 0.8 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.71 (d, *J* = 5.5 Hz, 1H), 4.67 (br s, 1H), 4.35 (s, 1H), 3.81 (s, 3H), 3.78 (t, *J* = 9.6 Hz, 1H), 3.53 (d, *J* = 17.4 Hz, 1H), 3.40 (dd, *J* = 17.4, 1.5 Hz, 1H), 3.04–2.94 (m, 1H), 2.82–2.77 (m, 1H), 2.73 (dt, *J* = 13.4, 8.5 Hz, 1H), 2.19 (d, *J* = 13.5 Hz, 1H), 1.09–0.98 (m, 1H), 0.87 (t, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 166.4, 149.7, 139.5, 131.3, 129.2, 126.4,

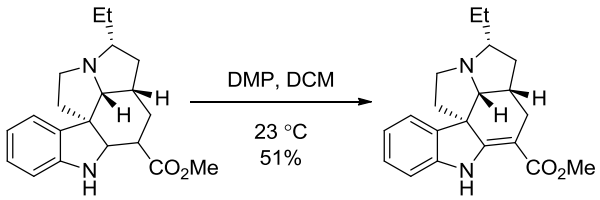
122.5, 118.2, 109.0, 72.9, 65.8, 59.2, 57.7, 52.1, 50.8, 38.0, 32.9, 22.6, 10.6; IR (film) 3275, 3047, 2965, 2936, 2899, 2875, 2855, 1711, 1498, 1482, 1250, 1091 cm^{-1}; HRMS–ESI (*m*/*z*) [M + H]$^+$ calcd $C_{20}H_{22}N_2O_2SH$, 355.1480, found 355.1486; $[\alpha]^{22.6}_D$ +235.8° (*c* = 1.000, $CHCl_3$).



250 **251**

Dihydroibophyllidine (251). A suspension of Raney Ni [Raney Ni 4200 (Aldrich)] in water was added to a solution of the thioamide **250** (31.1 mg, 0.088 mmol, 1 equiv.) in freshly distilled THF (1 mL). The mixture was placed in a high-pressure reaction vessel, which was then sealed. The reactor was purged with H_2 gas (pressurized to 50 psi with H_2 gas, followed by release of the pressure) three times and then pressurized to 200 psi with H_2 gas. The mixture was stirred vigorously (to keep the Raney Ni suspended) for 2 h, at which point the starting material had been consumed (1 h, as determined by TLC). The mixture was decanted from the solid Raney Ni into a separatory funnel containing brine. The solids were rinsed three times with EtOAc; these washings were added to the separatory funnel. The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration of the volatiles, dihydroibophyllidine (**251**, 28.4 mg, 99%) was isolated as a colorless oil that required no further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.5 Hz, 1H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 6.73 (td, *J* = 7.5, 0.9 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 4.37 (br s, 1H), 3.72 (s, 3H), 3.65 (d, *J* = 10.3 Hz, 1H), 3.29 (d, *J* = 6.4 Hz, 1H), 2.97–2.86 (m, 1H), 2.62–2.45 (m, 3H), 2.39–2.20 (m,

2H), 2.10–1.90 (m, 3H), 1.82–1.69 (m, 1H), 1.51–1.32 (m, 3H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 148.7, 134.6, 127.7, 122.6, 118.8, 109.2, 72.6, 68.0, 61.6, 51.8, 51.4, 46.4, 45.9, 45.4, 40.0, 33.6, 31.8, 26.6, 11.4; IR (film) 3389, 3051, 2957, 2928, 2868, 2782, 1726, 1462 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{20}H_{26}N_2O_2H$, 327.2072, found 327.2067; $[\alpha]^{22.2}_D$ +101.6° (c = 1.000, $CDCl_3$).

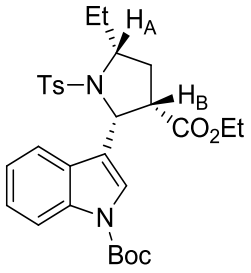


251 (+)-ibophyllidine (**1**)

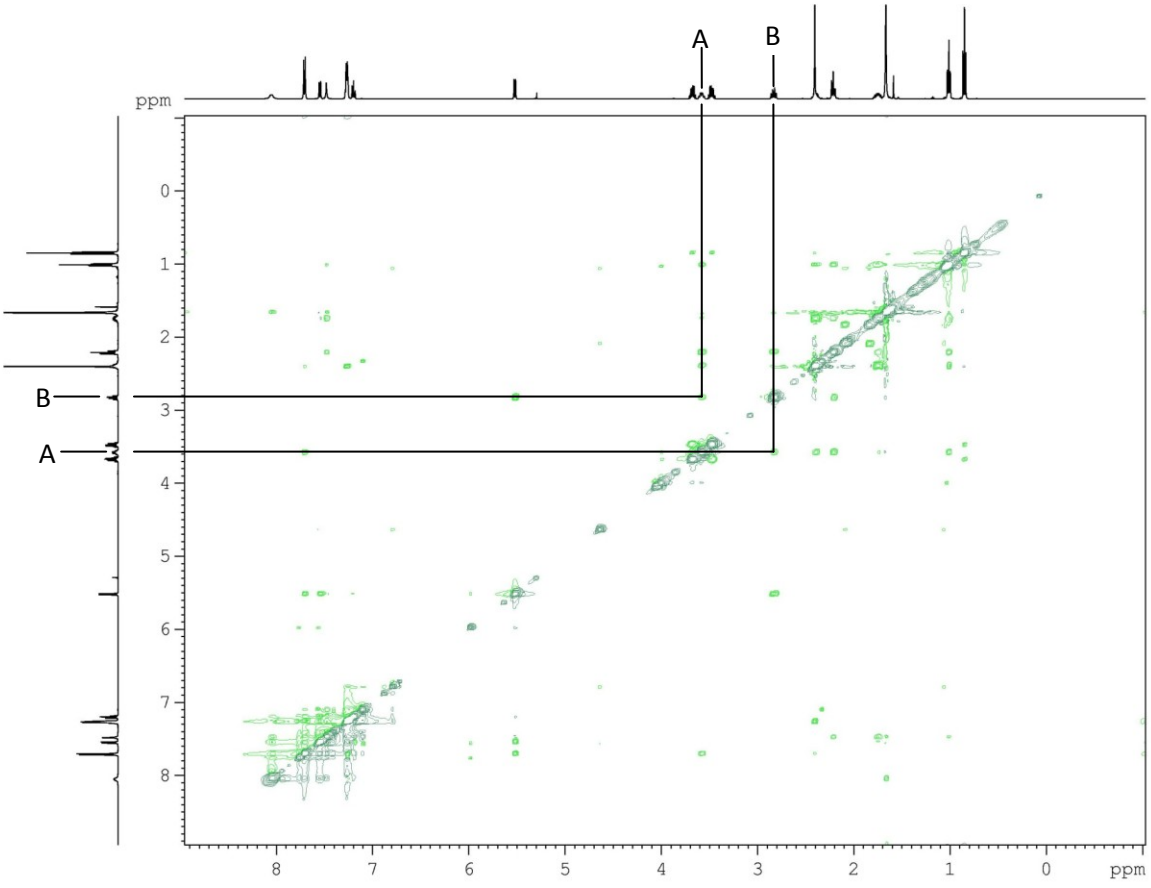
(+)-Ibophyllidine (1). The Dess–Martin periodinane (12 mg, 1.1 equiv) was added to a solution of the dihydroibophyllidine (**251**, 8.4 mg, 0.026 mmol, 1 equiv) in DCM (2 mL) and then the mixture was stirred for 5 min. The reaction was quenched through the addition of a 1:1 solution of saturated $NaHCO_{3(aq)}$ and saturated $Na_2S_2O_{3(aq)}$. The mixture was diluted with EtOAc and the phases separated. The aqueous phase was extracted twice more with EtOAc and then the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was passed through a short pad of basic alumina and eluted with Et_2O. The NMR spectrum of the crude product revealed that some starting material remained. The crude product was redissolved in DCM and then a second aliquot of the Dess–Martin periodinane (8 mg, 0.019 mmol, 0.73 equiv) was added. The mixture was stirred for 5 min and then worked up as before to yield (+)-ibophyllidine (**1**, 4.2 mg, 51%) as a thin film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (br s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 6.92 (td, J = 7.5, 1.0 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 3.76 (s, 3H), 3.49 (d, J = 8.7 Hz, 1H), 3.25–3.13 (m, 2H), 3.11 (dd, J =

15.5, 6.9 Hz, 1H), 2.77 (app q, J = 9.6 Hz, 1H), 2.29–2.22 (m, 1H), 2.21–2.11 (m, 2H), 2.07–1.96 (m, 1H), 1.94–1.85 (m, 1H), 1.81 (dd, J = 15.3, 11.2 Hz, 1H), 1.61–1.51 (m, 1H) 1.32–1.22 (m, 1H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 165.2, 143.2, 138.8, 127.7, 123.2, 121.3, 108.8, 92.1, 75.7, 65.8, 55.9, 51.0, 47.8, 41.4, 37.9, 34.9, 31.9, 25.7, 12.5; IR (film) 3377, 2957, 2925, 2863, 1674, 1608, 1466, 1437, 1282, 1246 cm^{-1}; HRMS–ESI (m/z) $[M + H]^+$ calcd $C_{20}H_{24}N_2O_2H$, 325.1916, found 325.1905; $[\alpha]^{24.3}_D$ +140° (c = 1.000, $CHCl_3$).

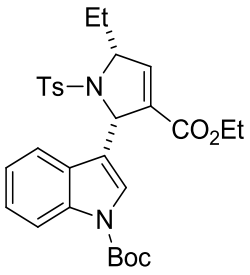
NOESY spectrum of pyrrolidine 187



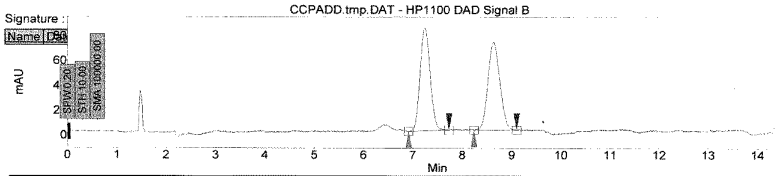
187



SFC trace for racemic pyrroline 200



200 (racemic)



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2	UNKNOWN	8.24	8.65	9.10	0.00	50.43	70.7	19.9	50.429
Total						100.00	153.4	39.4	100.000

CHROMATOGRAM METHOD REPORT :

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Multipliplier factor : 1.00
Analysis : Sample
Injection volume : 5.00
Sample mass : 0.00

Run Log :

Injection occured at 11/14/2011 12:10:17 PM

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11/14/2011 12:09:07 PM Event 109 (Status change to Ready)
11/14/2011 12:09:12 PM Event 202 (Home parameters modified)
11/14/2011 12:09:14 PM Event 201 (Sysvar modified)
11/14/2011 12:09:26 PM Event 108 (Status change to Not Ready)
11/14/2011 12:09:26 PM Event 7200 (Balance started)
11/14/2011 12:09:33 PM Event 109 (Status change to Ready)
11/14/2011 12:09:33 PM Event 7090 (Device idle)
11/14/2011 12:10:17 PM Event 104 (Status change to Run)
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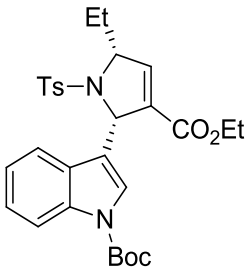
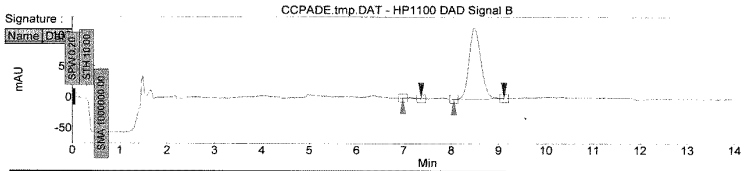
11/14/2011 12:11:26 PM Event 1039 (Unknown Event)

SFC trace for optically active pyrroline 202



202 (optically active)



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
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2	UNKNOWN	8.06	8.49	9.12	0.00	99.65	115.6	33.2	99.650
Total						100.00	117.0	33.3	100.000

CHROMATOGRAM METHOD REPORT :

No calibration file found.

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Run Id. : 19
Run Time : 15.00
Scale :
Autoscale
Vial : 2
Rack : 0
Divisor factor : 1.00
Multipliplier factor : 1.00
Analysis : Sample
Injection volume : 5.00
Sample mass : 0.00

Run Log :

Injection occured at 11/14/2011 1:00:31 PM

DAD [Agilent G1315A/B Diode Array Detector]
HP1100 G1315A Events occurred
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11/14/2011 12:59:40 PM Event 108 (Status change to Not Ready)
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11/14/2011 1:01:40 PM Event 1039 (Unknown Event)

Section 3.21 References

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