Abstract

Synthetic Studies Toward the Securamine Alkaloids

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Three new approaches toward the phomoidride ring system are described; employing an oxy-Cope rearrangement, and Wharton fragmentation of norbornane-based as well as isotwistane-based ring systems.

Three different model studies towards constructing an appropriately functionalized isotwistane skeleton are described. The first focuses on using an intramolecular C-H insertion reaction as the key step , the second employs a Wessely oxidation – intramolecular Diels-Alder sequence as the key steps to assemble in only five steps a heavily functionalized isotwistane ring system. The third uses as key steps a one pot phenolic oxidation – trapping – intramolecular Diels-Alder sequence followed by two substrate controlled radical cyclization to furnish in only six steps an isotwistane ring system containing most of the functionalities needed for the total synthesis. The complete side-chains and the anhydride unit of the phomoidrides have been efficiently assembled.

Synthetic Studies Toward the Securamine Alkaloids

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To the members of the Wood lab

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To my friends and family I owe whatever measure of success I've managed to achieve. My accomplishments are theirs.

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List of Abbreviations

aq	aqueous
$BF_3 \bullet Et_2O$	boron trifluoride diethyl etherate
Bn	benzyl
Boc	*t*-butoxycarbonyl
BORSM	based on recovered starting material
Bu	butyl
$(Bu)_4NHSO_3$	tetrabutyl ammonium hydrogen sulfate
C	carbon
°C	degrees Celsius
calcd	calculated
CCl_4	carbon tetrachloride
$CDCl_3$	chloroform-*d*
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CI	chemical ionization
CuI	copper iodide
Cy	cyclohexyl
δ	chemical shift in ppm downfield from Me_4Si
d	doublet
dba	dibenylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ea	each
EI	electron impact
equiv	equivalent
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
EtMgBr	ethyl magnesium bromide
Et_2NH	diethylamine
Et_3N	triethylamine
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
h	hour(s)
H_2	hydrogen
H_2O	water

H_2O_2	hydrogen peroxide
HCl	hydrochloric acid
$HgCl_2$	mercury(II) chloride
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrum
Hz	hertz
hν	irradiation
J	coupling constant
KF	potassium fluoride
L	liter(s), ligand
lit.	literature
μ	micro
m	medium (FTIR), multiplet (NMR)
mm	millimeters
mmol	millimole
M	moles per liter
Me	methyl
MeOH	methanol
mg	milligrams
$MgSO_4$	magnesium sulfate
mp	melting point
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
m/z	mass to charge ratio
Na	sodium
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_4$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH_3	ammonia
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
[O]	oxidation
O_3	ozone
OAc	acetate
p	para
$P(Bu)_3$	tri(*n*-butyl)phosphine
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium

$Pd(PPh_3)_2Cl_2$	dichlorobis(triphenylphosphine)palladium
pH	hydrogen ion concentration
P(*o*-tolyl)$_3$	tri(*ortho*-tolyl)phosphine
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet
$RuCl_3$	ruthenium(III) chloride
s	singlet (NMR), strong (FTIR)
SiO_2	silicon dioxide, silica gel
soln	solution
t	triplet
td	triplet of doublets
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tri(methyl)silyl
Ts	toluenesulfonyl
TsOH	toluenesulfonic acid
ttmpp	tris(trimethoxyphenyl)phosphine
w	weak

Chapter One

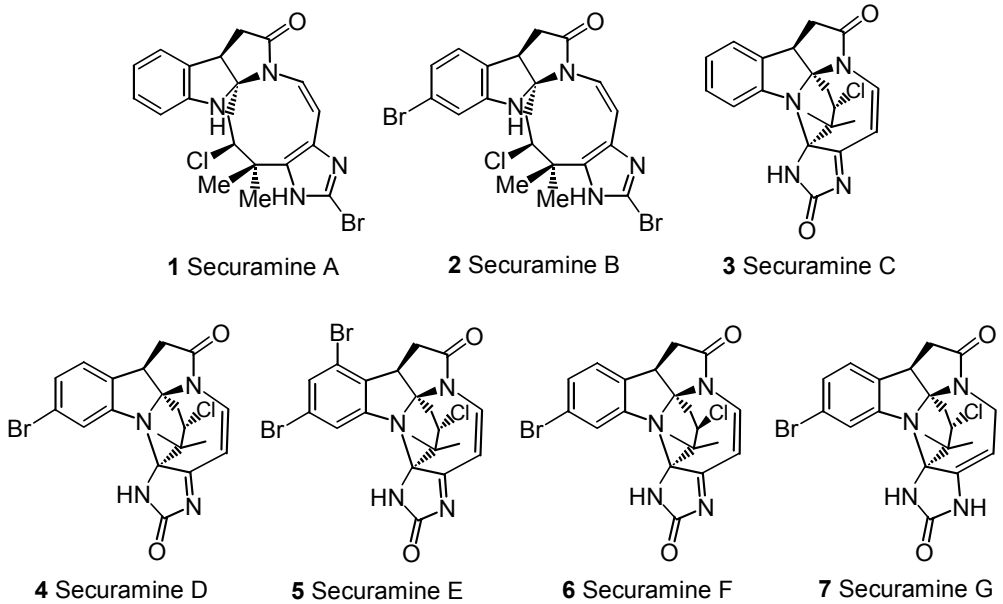
The Securamines: A New Class of Indole Alkaloid Natural Products

1.1 Isolation

In 1994, Christophersen and coworkers reported the isolation and characterization of four new alkaloids from the marine bryozoan *Securiflustra securifrons*.[1] Within a year, three more alkaloids had been identified and characterized, completing a family of seven unprecedented indole alkaloid natural products.[2] Owing both to their structure and taxonomic heritage, the natural products were fittingly named securamines A-G (**1-7**).

The alkaloids originated from the lyophilized extracts of bryozoan material collected at a depth of 70 meters off the west coast of Denmark.[3] Silica gel chromatography of the extracts afforded fractions containing pure material, to which structures were assigned based on NMR and mass spectrometry experiments.[1,2]

Figure 1.1.1



1.2 Structure

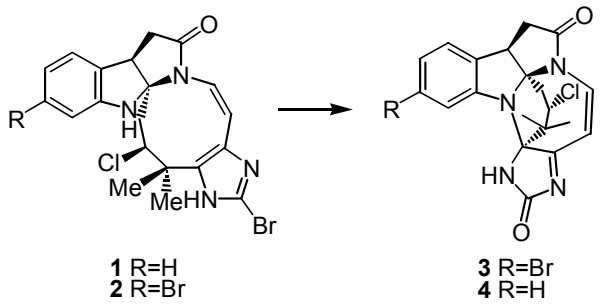
1.2.1 A Compact Fusion of Heterocycles

The Securamine structure is defined by a unique combination of functionalities. The alkaloids all contain a central tricyclic pyrroloindole core and highly substituted imidazole ring. Two quaternary centers serve as junction points, connecting the heterocyclic fragments through a modified isoprene unit containing a neopentyl chlorine atom. A rare enamide moiety links the two heterocyclic fragments again, completing the compact fusion of heterocycles that defines the securamines.

A few subtle variations mark the differences between the individual members of the securamine family of natural products. Notably, securamines A (**1**) and B (**2**) differ just in the presence or absence of a bromine substituent at the indole 6-position. The

remaining five alkaloids, although appearing very different from the previous two, can formally be derived from the ring-closure of the indole nitrogen to the imidazole 5-position (Scheme 1.2.1). Formation of this C-N bond in securamines A (**1**) and B (**2**) provides the hexacyclic structure of alkaloids D (**4**) and C (**3**), respectively. Securamine E (**5**) possesses another bromine substituent on the aromatic ring, while alkaloid F (**6**) contains the opposite chlorine stereochemistry. Finally, securamine G (**7**) appears to be a hydrogenated form of alkaloid C (**3**).

Scheme 1.2.1

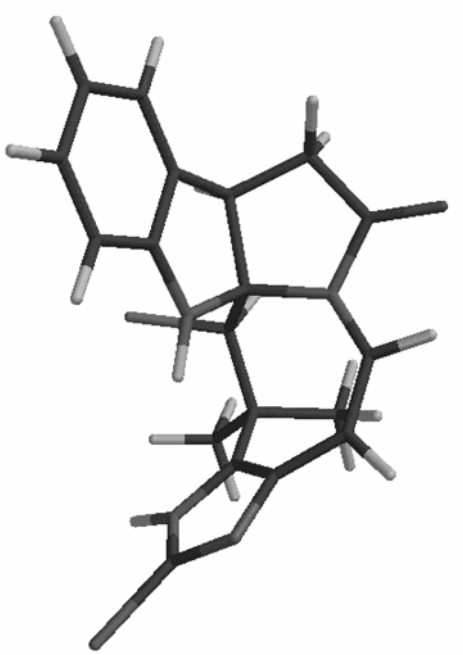


1.2.2 3-Dimensional Structure

The compact fusion of heterocycles possessed by the securamines creates an intricate 3-dimensional structure, not suggested by their 2-dimensional representation. Although the structures were solved primarily on the basis of NMR data, the crystal structure of a related natural product helped to confirm the suspected geometry as that depicted in Figure 1.2.1.[4] The central nonadiene core takes on a boat-like configuration, folding the imidazole ring directly beneath the indole moiety. Interestingly, the cavity created by this folded shape is lined with all four nitrogen atoms present in the natural

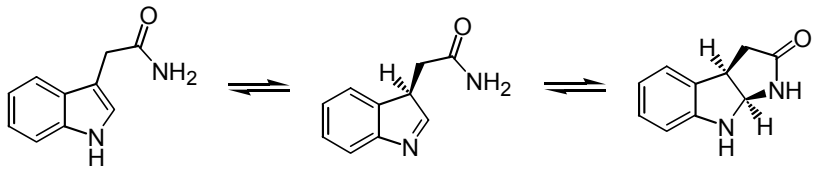
products. In alkaloids A (**1**) and B (**2**), it is apparent that the indole nitrogen is juxtaposed immediately above the imidazole 5-position, poised to form the bond responsible for the hexacyclic structure of alkaloids C-G (**3**-**7**). Curiously, there seems to be essentially no overlap in the π system extending from the amide carbonyl through the imidazole ring.

Figure 1.2.1



1.2.3 An Isomeric Equilibrium

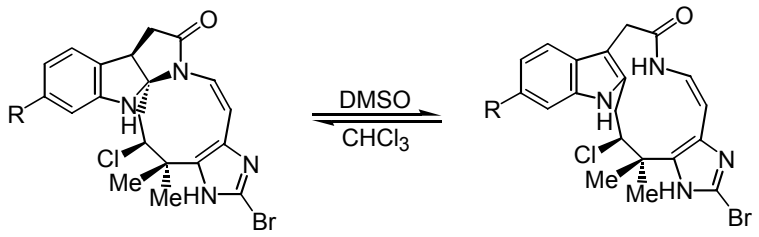
Scheme 1.2.2



8 **9** **10**

It is well known that tryptophan and tryptamine derivatives often exist in equilibrium between three isomeric forms: the indole (**8**), the indolinine (**9**) and the pyrroloindole (**10**).[5-12] A similar isomeric equilibrium is apparently present in the securamines as well. Upon solvation in DMSO, alkaloids A and B undergo a ring-opening process to form the corresponding macrolactams securines A (**11**) and B (**12**), respectively (Scheme 1.2.3). After concentration and redissolution in $CDCl_3$, the macrolactams undergo the reverse ring-closing process to reform the parent natural products.[1]

Scheme 1.2.3



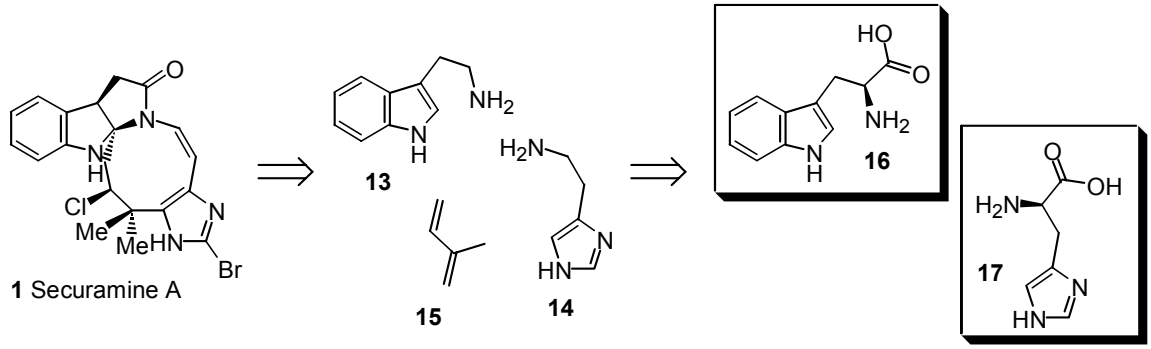
1 R=H, Securamine A
2 R=Br, Securamine B

11 R=H, Securine A
12 R=Br, Securine B

1.3 Biological Activity

Biogenetically, the securamine alkaloids are composed of modified tryptamine and histamine residues linked by an isoprene subunit (Scheme 1.3.1). The tryptamine and histamine residues are undoubtedly derived from the corresponding amino acids tryptophan (**16**) and histidine (**17**). Although the biological activity of the securamines has not been revealed to date, clues about their function may be gleaned from secondary sources. A significant number of alkaloids derived from the Flustridae family of bryozoans (of which *securiflustra securifrons* is a member) that contain structural units similar to the securamines exhibit potent biological activity. Notably, mixtures of extracts from these bryozoans display antifouling activity comparable with commercially available additives, strong antibiotic and antiviral activity, and potent muscle relaxant activity.[13]

Scheme 1.3.1



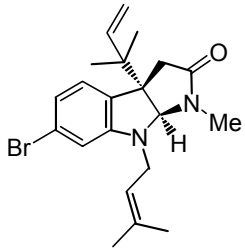
There is evidence to suggest that the securamines are likely secondary metabolites of an associated microorganism and are produced by species-specific bacteria in defense against local predators. The flustramines, for example, exhibit strong larvotoxicity against location-specific predators.[13]

1.4 Related Natural Products

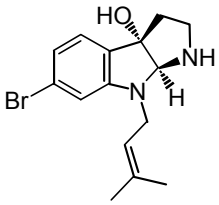
1.4.1 The Flustra Alkaloids

Although their complete architecture is unique, the securamine natural products appear to combine the structural features of two other families of alkaloids. Like the securamines, the flustramines[14,15] and the chartellines (**18**, **19**)[4,16-18] are both isoprene-containing, halogenated tryptamine derivatives. The chartellines (**20-24**), unlike the flustramines, share with the securamines additional structural features including a macrolactam and a brominated histamine subunit (Figure 1.4.1). It is noteworthy that all three families of natural products are derived from the same class of marine bryozoan.

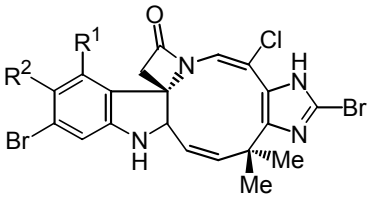
Figure 1.4.1



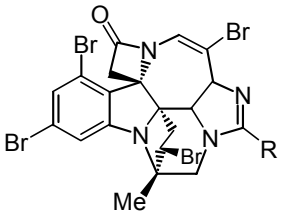
18 Flustramide A



19 Flustraminol B



20 R^1=R^2=Br, Chartelline A
21 R^1=Br, R^2=H, Chartelline B
22 R^1=R^2=H, Chartelline C

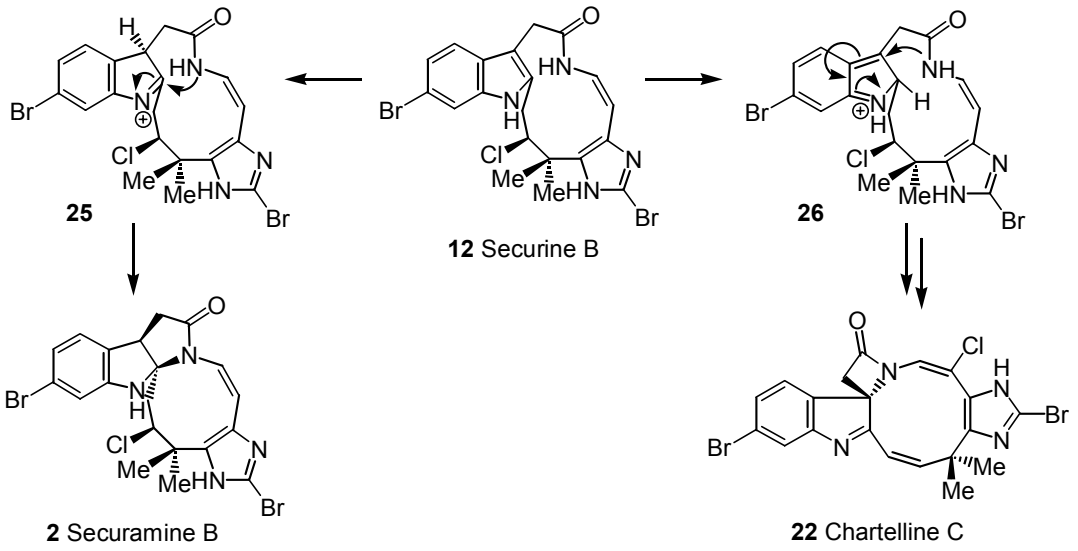


23 R=H, Chartellamide A
24 R=Br, Chartellamide B

1.4.2 A Common Precursor

It seems reasonable to speculate that the securines might serve as biogenetic precursors to both the securamines and the chartellines (Scheme 1.4.1). Protonation of the indole at the 3-position would activate the 2-position toward electrophilic attack. Cyclization of the proximal amide into the resulting positively charged iminium ion (**25**) would form the pyrroloindole skeleton of the securamines. Alternatively, protonation of the indole 2-position would similarly activate the 3-position toward reactivity with the amide. Closure of the C-N bond in that case (**26**) would provide, after loss of a proton, the β-lactam skeleton found in the chartellines.

Scheme 1.4.1



1.5 Relevant Synthetic Efforts

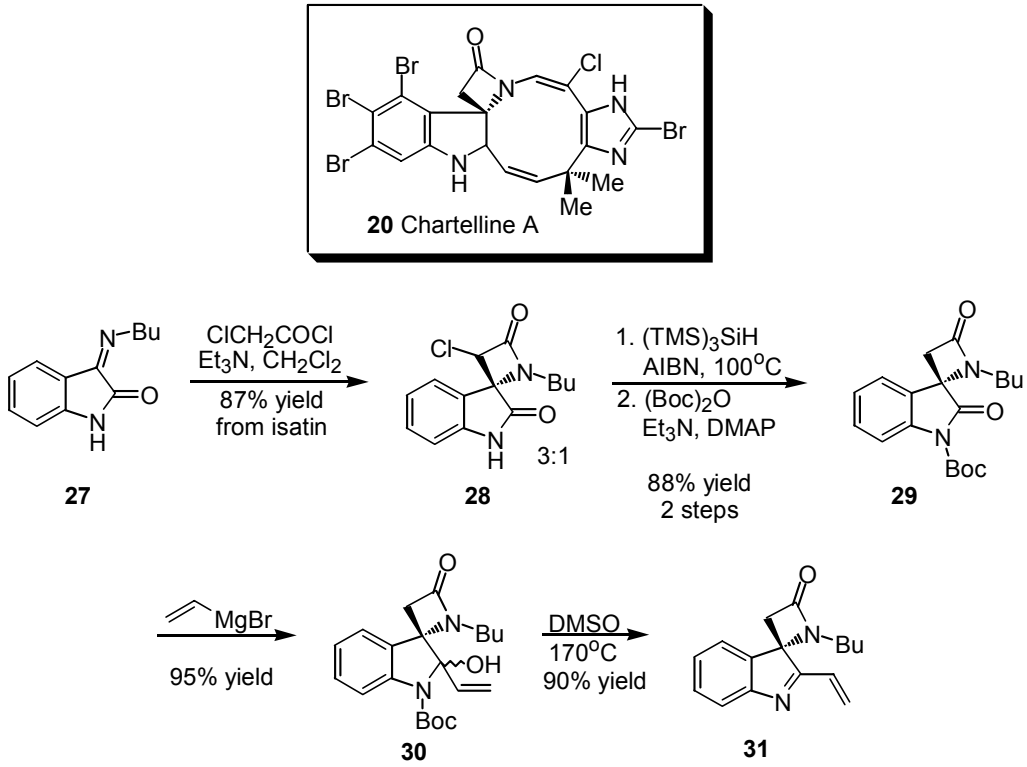
1.5.1 Synthetic Studies Toward the Flustra Alkaloids

Because of their uniquely complex architecture, the securamines have been a favorite topic of recent natural product reviews.[19-25] In spite of this attention there have been no reported efforts toward their total synthesis to date. There have, however, been several reports regarding syntheses of the other flustra alkaloids, the chartellines and the flustramines.

1.5.1.1 Efforts Toward the Chartellines

In 2001, Weinreb published an account of his efforts toward the chartelline skeleton (Scheme 1.5.1).[26] Envisioning the spyrocyclic β-lactam as the major synthetic challenge, a model study was completed aimed at its construction. Staudinger ketene-imine cycloaddition[27-29] of **27** (available from isatin) with chloroketene provided the desired α-chloro β-lactam **28** as a mixture of stereoisomers. Reductive removal of the chlorine under radical conditions followed by Boc protection of the oxindole yielded spirocycle **29**. With **29** in hand, attention was focused on introduction of a suitable carbon fragment that would eventually become the C-10,11 olefin of the α,β-unsaturated imine.

Scheme 1.5.1



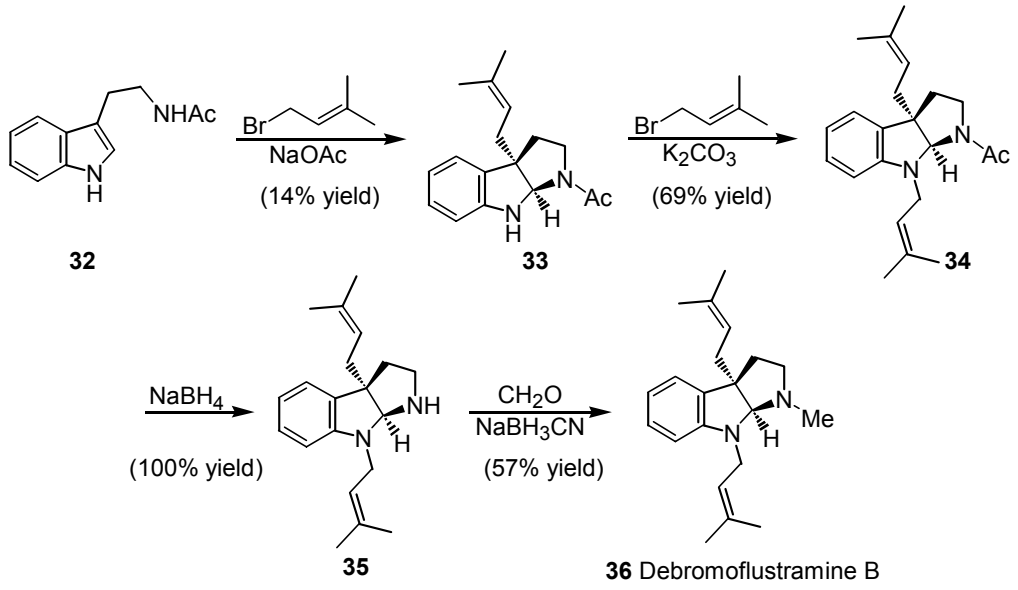
To this end, vinyl grignard addition proceeded smoothly to afford **30**. Thermolysis of **30** at 170°C in DMSO provided the desired α,β-unsaturated imine **31**. Although successful in forming the spirolactam found in the chartellines, instability of the β-lactam proved to be a contentious issue throughout the effort and may hint toward the benefits of a late-stage introduction of this sensitive functionality.

1.5.1.2 Synthesis of Debromoflustramine B and Debromoflustramide B.

Debromoflustramide B (**36**) contains the pyrroloindole core of the securamines. In 1983, Christophersen and coworkers completed the synthesis of the cyclotryptamine

analog, debromoflustramine B (Scheme 1.5.2).[30] They were later able to apply the same chemistry to the synthesis of the oxidized version, debromoflustramide B.[31]

Scheme 1.5.2



Treatment of N-acetyltryptamine (**32**) with prenyl bromide in an acetate buffer facilitated nucleophilic attack of the indole 3-position, followed by cyclization to the desired pyrroloindole (**33**). Further exposure to prenyl bromide in the presence of K_2CO_3 resulted in alkylation of the remaining nitrogen. Avoiding strongly acidic or basic reagents, $NaBH_4$ proved to be the best reagent for removal of the acetate protecting group. The final methylation was achieved with formaldehyde and $NaBH_3CN$ to afford the desired product.

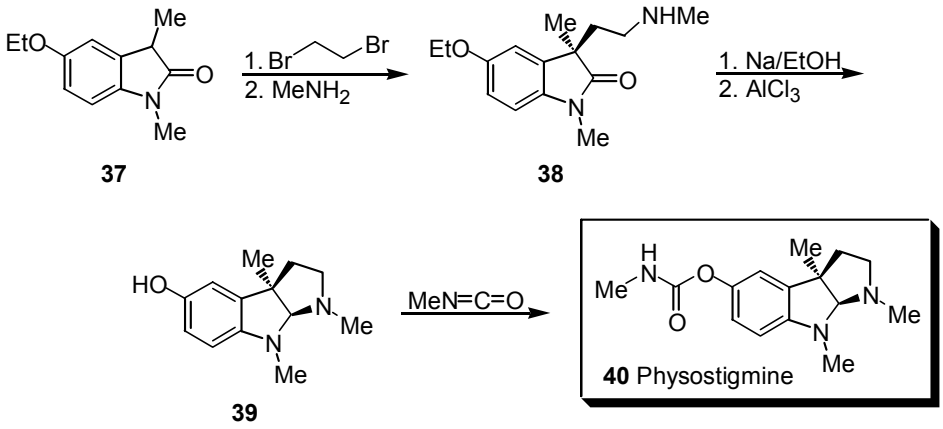
1.5.2 Construction of Pyrroloindoles

The pyrroloindole core of the securamines has been found in natural products dating back to the structure elucidation of physostigmine in 1925.[32] Owing to the intriguing therapeutic effects of these natural products,[33-35] construction of the physostigmine skeleton has been the target of a variety of synthetic endeavors.

1.5.2.1 Reductive Cyclization: Synthesis of Physostigmine

Julian and Pikl completed the first formal synthesis of physostigmine (**40**) in 1935 employing a reductive cyclization as the key ring-forming step (Scheme 1.5.3).[36] Treatment of oxindole **37** with ethylene dibromide followed by heating with methylamine afforded amine **38**. Sodium reduction led directly to the tricylcic skeleton, after which deprotection of the aryl ether yielded alcohol **39**. Final treatment with methyl isocyanate provided the natural product.

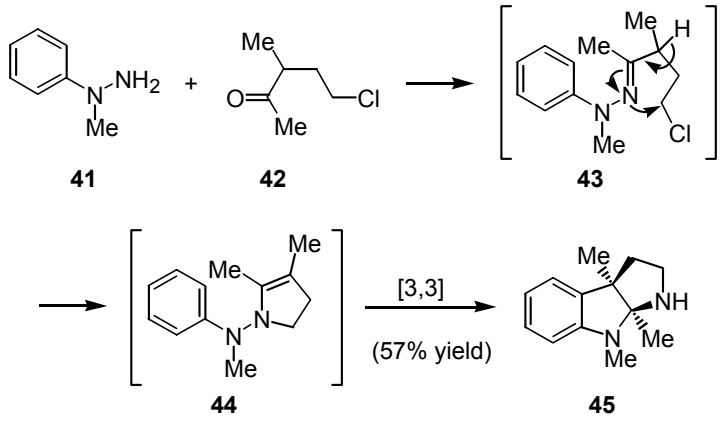
Scheme 1.5.3



1.5.2.2 Fischer Indole Cyclization

Most methods for the preparation of pyrroloindoles utilize a 3-substituted indole as the starting material. Grandberg and Ivanova circumvented this potential restriction by employing a Fischer indole synthesis[37] for the construction of the physostigmine skeleton (Scheme 1.5.4).[38]

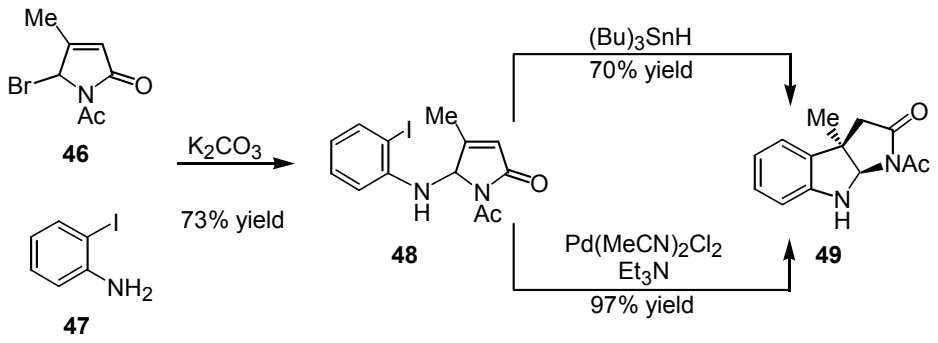
Scheme 1.5.4



1.5.2.3 Transition-Metal Catalyzed Cyclization

A bond disconnection similar to that shown in Scheme 1.5.4 provided for the construction of pyrroloindole **49** through palladium catalysis.[39] 5-exo-trig cyclization of aminal **48** afforded a remarkable yield of the desired tricyclic physostigmine skeleton. The reaction could also be carried out under radical conditions, though the yield was slightly lower.

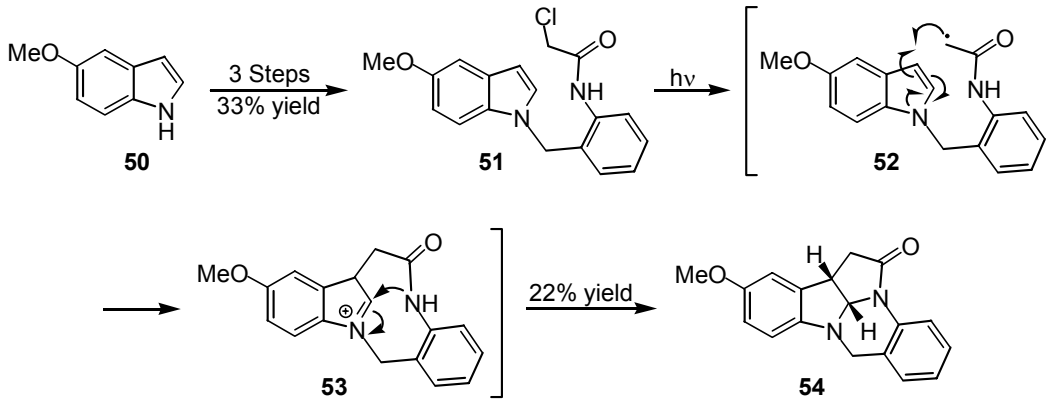
Scheme 1.5.5



1.5.2.4 Radical Cyclization

A recent pharmacological effort to access novel indoles uncovered a synthesis of fused pyrroloindoles similar to those found in the securamines.[40] Photocyclization of chloroacetamide derivative **51** (available in 3 steps, 33% yield from methoxyindole **50**) led to the unexpected pyrroloindole **54** in modest yields. The proposed mechanism leading to the product involves a photo-induced single electron transfer followed by chloride ion loss to intermediate **52**. Cyclization of **53** afforded pentacycle **54**, which contains a considerable amount of the securamine skeleton.

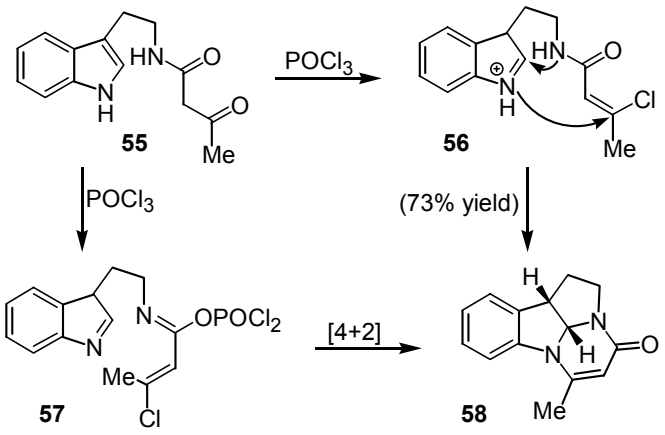
Scheme 1.5.6



1.5.2.5 Electrophilic Cyclization

Under Bischler-Napierski[41] type conditions, Shannon and coworkers were able to construct a tetracyclic pyrroloindole system in one step from a simple tryptamine derivative.[42,43] Initial reaction of ketone **55** with phosphoryl chloride liberated HCl, which led to protonation of the indole 3-position. The resulting iminium ion was satisfied by closure of the amide to pyrroloindole, followed by final cyclization of the indoline to tetracycle (**56**→**58**). An alternative electrocyclic ring closure was also proposed that would lead to the same product (**57**→**58**).

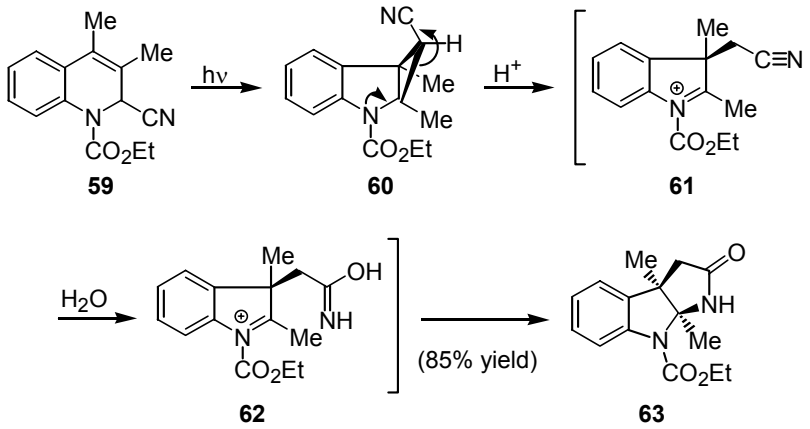
Scheme 1.5.7



1.5.2.6 Cyclopropane Fragmentation

Ring fragmentation of cyclopropanes provided Ikeda and coworkers a direct route to the physostigmine skeleton from known compounds.[44] Photolysis of dihydroquinoline **59** afforded cyclopropane **60**, which upon treatment with HCl, rearranged to pyrroloindole **63**. The indole nitrogen lone pair likely participated in the ring fragmentation step, followed by cyclization of the amide to the resulting iminium ion.

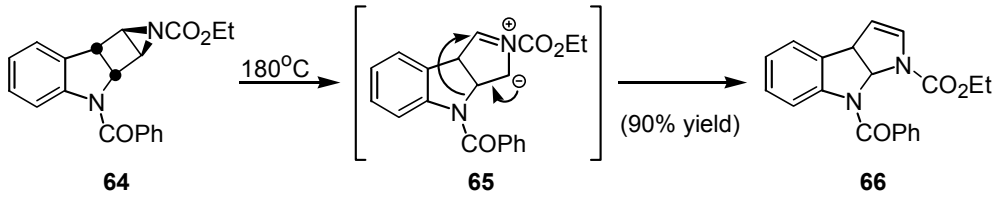
Scheme 1.5.8



1.5.2.7 Aziridine Thermolysis

Thermolysis of aziridine **64** was proposed to proceed through an ionic intermediate (**65**), which after migration of the aniline moiety, yielded pyrroloindole **66** in 90% yield.[45]

Scheme 1.5.9



1.6 Conclusions

The wide variety of synthetic methods surrounding pyrroloindoles offered the benefit of flexibility to any synthetic effort. Compelled by the fascinating complexity of the securamine structure as well as the allure of potential biological activity, it was with great enthusiasm that this lab initiated a synthesis of the securamine alkaloids. The following chapters outline some of the work toward this end.

1.7 Notes and References

(1) "Marine alkaloids 18. Securamines and securines, halogenated indole-imidazole alkaloids from the marine bryozoan Securiflustra securifrons", Rahbaek, L.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Petersen, B. O., *Journal of Organic Chemistry* **1996**, *61*, 887-889.

(2) "Marine alkaloids 19. Three new alkaloids, securamines E-G, from the marine bryozoan Securiflustra securifrons", Rahbaek, L.; Christophersen, C., *Journal of Natural Products* **1997**, *60*, 175-177.

(3) The bryozoan material was collected on two separate occasions, and varied in the relative amounts of natural products present.

(4) "Marine Alkaloids 14. Prototropy of Chartellines from Chartella-Papyracea", Nielsen, P. H.; Anthoni, U.; Christophersen, C., *Acta Chemica Scandinavica Series B-Organic Chemistry and Biochemistry* **1988**, *42*, 489-491.

(5) "Cyclization of Tryptophans 3. The Crystal-Structure of a Product Derived from Trifluoroacetylation of N-B- Methoxycarbonyl-L-Tryptophan Methyl-Ester in Pyridine", Anthoni, U.; Christophersen, C.; Obel, A.; Nielsen, P. H., *Acta Chemica Scandinavica* **1994**, *48*, 334-339.

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Chapter Two

Construction of the Carbon Framework

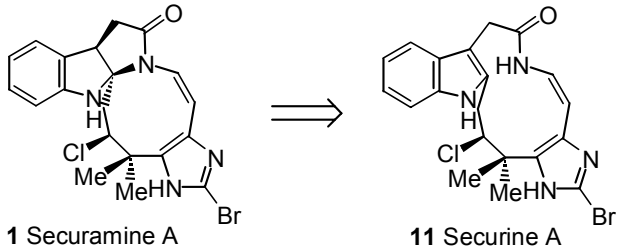
2.1 Initial Considerations

Before designing a synthetic plan for the construction of the securamines, there were several important points that, when kept in mind, would help guide a synthetic approach.

2.1.1 The Isomeric Equilibrium

The presence of the isomeric equilibrium in the pyrroloindole core, although noted only as a subtle side point in the isolation paper,[1] seemed worthy of particular attention from a synthetic standpoint. Pyrroloindoles unsubstituted at C-3 are generally unstable and tend to exist as the ring-opened aromatic indole outside a narrow range of conditions.[2-6] Certainly this is the case with the securamines, as indicated by the solvent-specific isomeric shift discussed in Chapter 1. Early construction of the pyrroloindole in the synthetic sequence might likely prove futile upon exposure to a variety of reaction and workup conditions. It therefore stood to reason that the synthetic target should actually be the ring-opened isomer, securine A (**11**) (Scheme 2.1.1), and that upon its construction, conditions could be found to effect the final equilibration to the natural product.

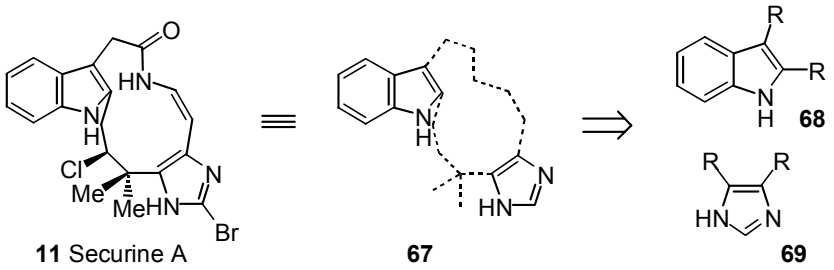
Scheme 2.1.1



2.1.2 Visualizing a Disconnection

The securines were viewed by this lab primarily as the union of two heterocyclic subunits (indole and imidazole) joined into a macrocyle by two short tethers (the isoprene and the enamide) (Scheme 2.1.2). Because the chemistries of the two heterocycles have been fairly well explored, this seemed to be a logical picture of the securamine alkaloids from a synthetic standpoint. This visualization allowed for the dissection of the molecule into roughly two aromatic pieces with the remaining "tethers" acting as bridges between the heterocycles (Scheme 2.1.2). The synthetic plan would focus on the independent construction of these two heterocycles (**68** and **69**) in a manner that would allow for flexible functionalization at their connecting junctions.

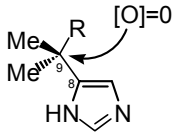
Scheme 2.1.2



2.1.3 A Rational Starting Point

The chemistries of both indoles and imidazoles have been explored for well over a century, and consequently, there are scores of methods in the literature for their construction. Unlike indoles, however, the synthetic methods surrounding imidazoles generally suffer from harsh reaction conditions, low yields, and poor functional group tolerance. Because of these potential limitations, it was decided to focus first on construction of the imidazole and to build appropriate linking tethers off this heterocycle from which the indole could later be coupled. The geminal dimethyl carbon α to the imidazole, however, presented a concern with this type of disconnection. Without any oxidation states associated with this carbon, it posed a challenge in the formation of the C8-C9 bond between the quaternary center and the heterocycle (Figure 2.1.1). It therefore seemed appropriate to try to incorporate this carbon-carbon bond directly into the imidazole construction rather than subsequent to its formation. Alkylated imidazole **70** became the initial synthetic goal.

Figure 2.1.1

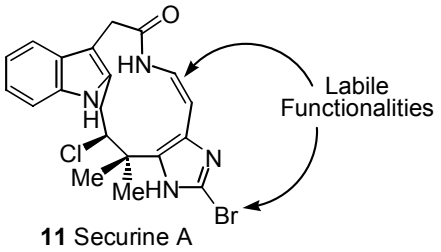


70

2.1.4 An Endgame Strategy

One of the most notable features of the securamine alkaloids is the presence of an enamide moiety. Likely the most unstable part of the molecule, it was decided to introduce this functionality as late as possible in the sequence, shielding it from possibly destructive reaction conditions.

Figure 2.1.2



11 Securine A

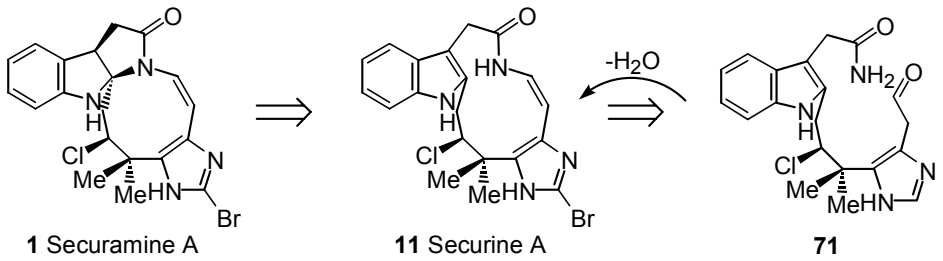
Also of particular concern was the halogenated imidazole. Imidazoles brominated at the 2-position are notoriously prone to nucleophilic attack.[7-9] It therefore seemed prudent to also postpone the introduction of that halogen until late in the synthesis and avoid potential problems with reactivity.

With the above considerations in mind, it was possible to devise a retrosynthetic analysis.

2.2 Retrosynthetic Analysis

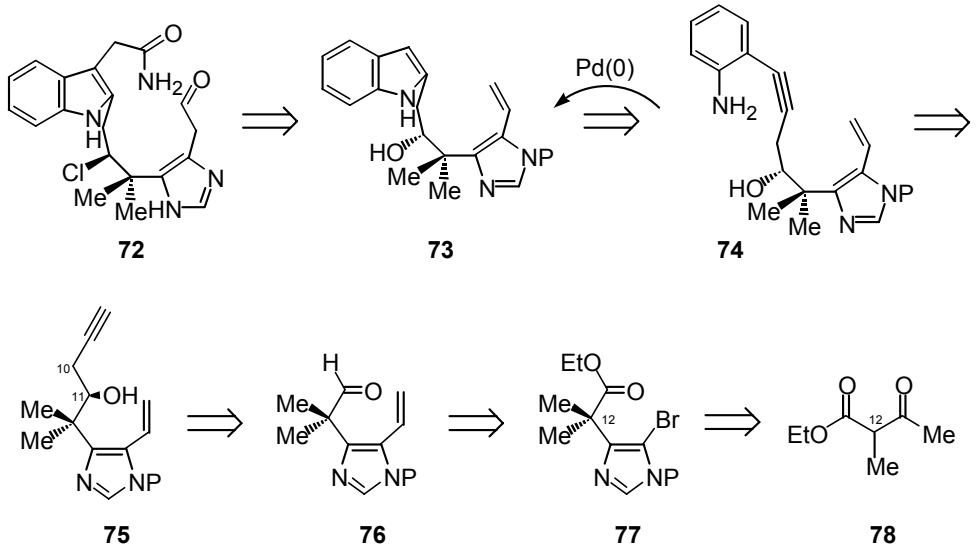
Allowing for equilibrium control of the final pyrroloindole cyclization, the synthetic target becomes securine A (**11**). As discussed, the reactive aromatic bromine would be introduced late with an electrophilic halogen source. The other labile functionality, the enamide, was envisioned to arise through the acid-catalyzed condensation of a primary amide with an aldehyde (**71**).

Scheme 2.2.1



The amide sidechain would be introduced through the alkylation of indole at the more reactive 3-position, while hydroboration and oxidation of a vinyl imidazole was envisioned to provide the requisite aldehyde (Scheme 2.2.2). The secondary alcohol of **73** was imagined to serve as a chlorine precursor, while formation of the indole heterocycle, was envisaged to arise from the cyclization of an aniline derivative into an alkyne (**74**).

Scheme 2.2.2



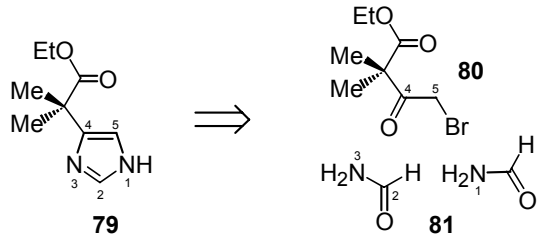
Aniline **74** could be constructed via a coupling reaction with an aryl halide and acetylene **75**. Employment of a 2° alcohol as a chlorine precursor allows for the disconnection of C_{10}-C_{11} bond in **75**, presenting the addition of a propargylic anion into an aldehyde and simplifying the initial target to imidazole **76** (Scheme 2.2.2). A cross-coupling reaction would be employed to install the vinyl group of **76** from an aryl halide. Finally, β-keto ester **78** was seen as an appropriate imidazole precursor that would allow for early installation of the potentially problematic geminal dimethyl carbon center at C-12.

2.3 Construction of the Imidazole Subunit

The Benzimidazole Rule[10] states that given the right number of carbons and nitrogens, any starting material would ultimately end up as a benzimidazole. At the

outset of this work, it was hoped that the same rule would apply to uncondensed imidazoles as well. Imidazole **79** was envisioned to arise from the condensation of α-halo ketone **80** with two molecules of formamide (**81**) in what would be a modified Bredereck reaction. [11,12]

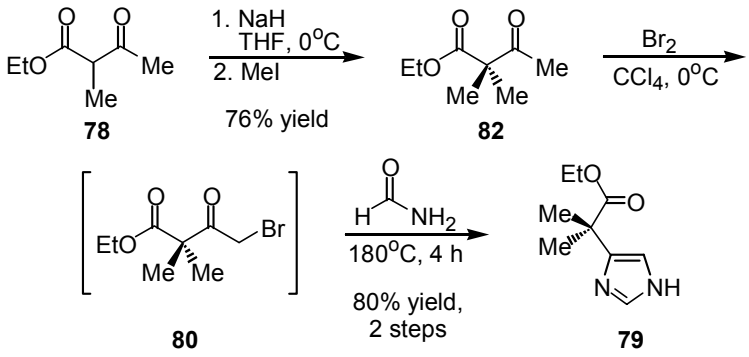
Scheme 2.3.1



2.3.1 Imidazole Formation

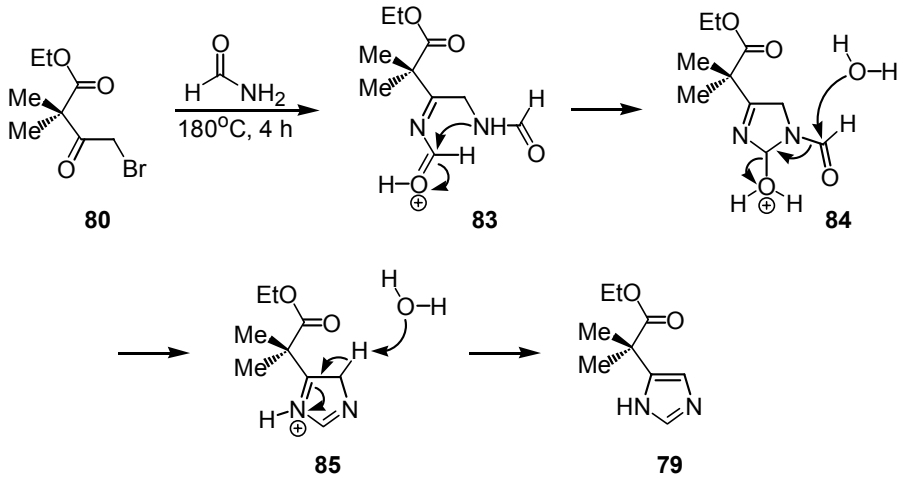
Imidazole construction commenced with commercially available β-keto ester **78**, which was deprotonated with sodium hydride followed by addition of methyl iodide, affording the geminal dimethyl carbon center found in the natural product (Scheme 2.3.2). Slow addition of Br_2 to the methyl ketone of **82** provided for smooth monohalogenation to α-bromo ketone **80**, the proposed imidazole precursor. Crude bromoketone **80** was treated with neat formamide followed by a short period of heating, allowing for formation of desired imidazole **79**.

Scheme 2.3.2



Scheme 2.3.3 outlines the likely sequence of events leading to heterocycle formation. Two equivalents of formamide add to the α-bromo ketone; the first equivalent displaces the halogen while the second condenses with the ketone. Condensation of one formamide onto the other (**83**) forms the requisite 5-membered ring, allowing aromatization to drive the reaction to completion. To that end, water presumably deformylates the tertiary amine (**84**) yielding a molecule of formic acid, followed by elimination of a proton to afford the fully aromatic heterocycle (**79**).[13]

Scheme 2.3.3



2.3.2 Imidazole Isolation

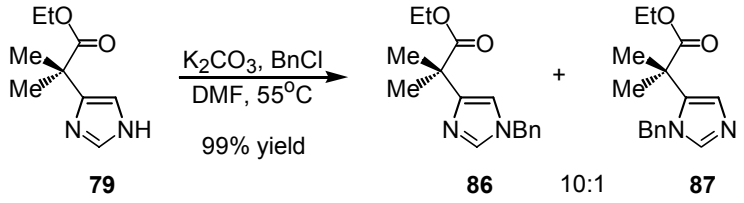
The isolated yield of the Bredereck reaction ranged from 5% to 80% depending almost entirely on workup conditions. Of difficulty was the separation of the imidazole from polymeric side products, presumably derived from formamide. The polymers seemed to share many physical characteristics with the imidazole product, rendering most purification methods ineffective.[14] To our delight, however, it was found that the desired product could be efficiently isolated by slow crystallization from the crude reaction mixture.

2.4 Elaboration of the Heterocycle

2.4.1 Imidazole Protection

Imidazole **79** contained a free amine, which was expected to be problematic as the synthesis advanced. It was therefore decided to protect the amine early on to avoid any complications that might arise.[15] Treatment of **79** with K_2CO_3 and benzyl chloride afforded a 10:1 mixture of regioisomeric benzyl imidazoles **86** and **87** (Scheme 2.4.1). While the regiochemistry of the protection would ultimately be of no consequence, to avoid further mixtures of products it was decided to carry only the major regioisomer through the sequence. The minor isomer could later be deprotected and recycled.

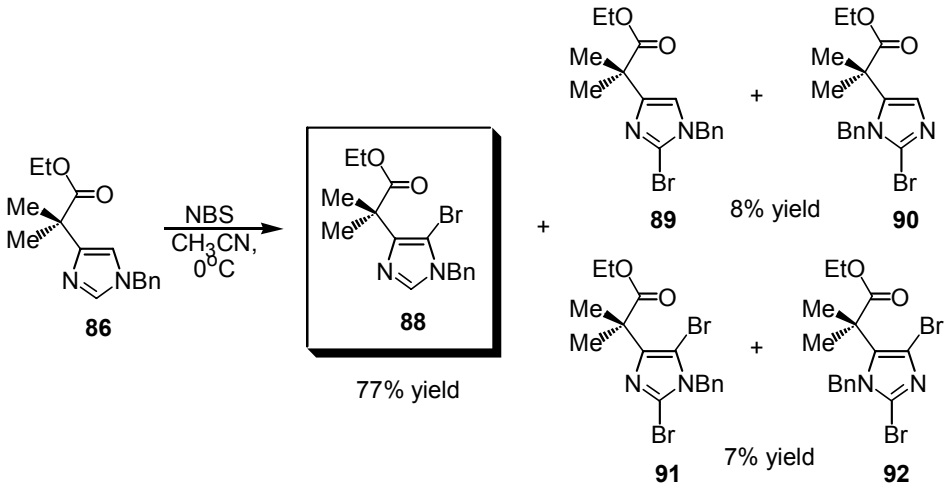
Scheme 2.4.1



2.4.2 Stille Coupling

NBS bromination of benzyl imidazole **86** furnished a mixture of five brominated imidazoles. Fortunately, the desired 5-bromo product (**88**) was the major component and was easily separable from the others by column chromatography.

Scheme 2.4.2

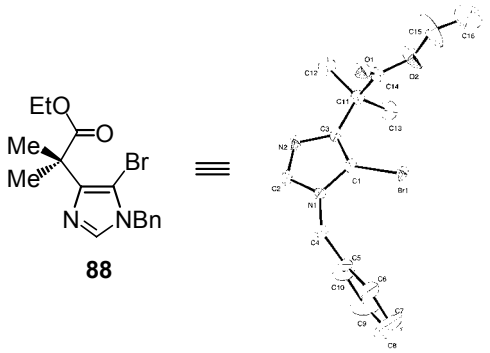


Although 2- and 2,5-bromoimidazoles **89** and **91** were not unexpected, it was surprising to isolate the brominated imidazoles **90** and **92**, regioisomeric at the site of benzyl protection. Since the benzyl regioisomer had been carefully removed in the

previous step, the transfer of the benzyl protecting group must have occurred during bromination. It was also interesting to note that the benzyl transfer did not occur in the 5-bromo compound (**88**), but rather only in the compounds brominated at the 2-position. It is possible that bromination at the 2-position increases the nucleophilicity of the imidazole nitrogen, allowing for benzyl transfer. This observation only reinforced earlier concerns about potential difficulties associated with halogenation at this position.

With just one aromatic proton, the regioisomeric monobromoimidazoles **88, 89** and **90** were difficult to distinguish spectroscopically, and although the NMR shifts were in accord with the regiochemical assignment of **88**, X-ray analysis provided more concrete verification (Figure 2.4.2).

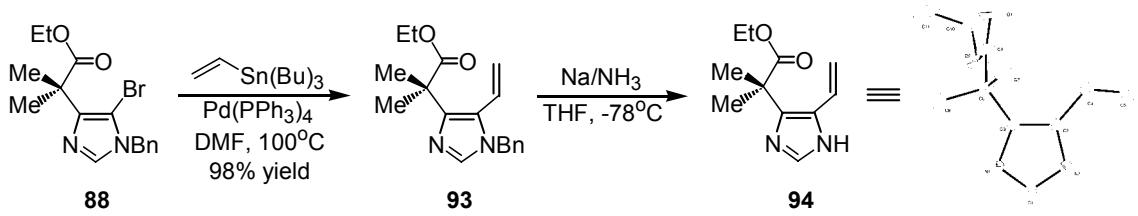
Figure 2.4.2



Upon separation of **88** from the reaction mixture, Stille coupling of the aryl halide with vinyl(tributyl)tin proceeded in excellent yield to afford the desired vinyl imidazole (**93**) (Scheme 2.4.3).[16,17] Some concern was developed over possible exchange of the metal complex to the 2-position of imidazole during Stille coupling. In order to confirm

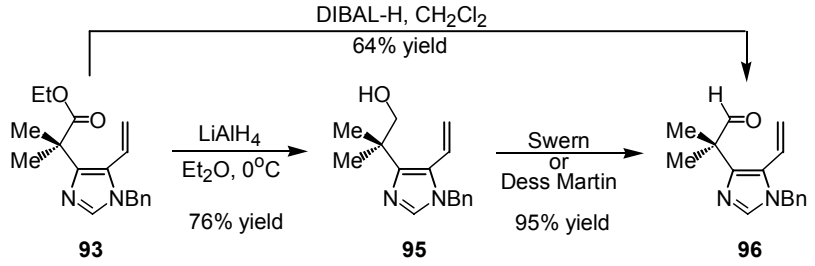
the regiochemistry of the coupling reaction, the benzyl protecting group was removed to afford crystalline **94**, the structure of which was verified by X-ray crystallography.

Scheme 2.4.3



With the appropriately functionalized 4,5-disubstituted imidazole in hand, attention was turned toward construction of the indole portion of the natural product. The ethyl ester of **93** was originally intended to serve not only as the handle on to which the indole would be assembled, but was also earmarked for eventual chlorine introduction. To accomplish these transformations, the oxidation state of that carbon would need to be adjusted. Direct reduction to the aldehyde with DIBAL-H proved to be problematic as the product was invariably accompanied by significant amounts of alcohol and starting material. This problem was circumvented by a two-step oxidation/reduction procedure wherein the ester was reduced to the alcohol (**95**) and then oxidized to the aldehyde (**96**) with either Dess-Martin periodinane[18,19] or Swern conditions.[20]

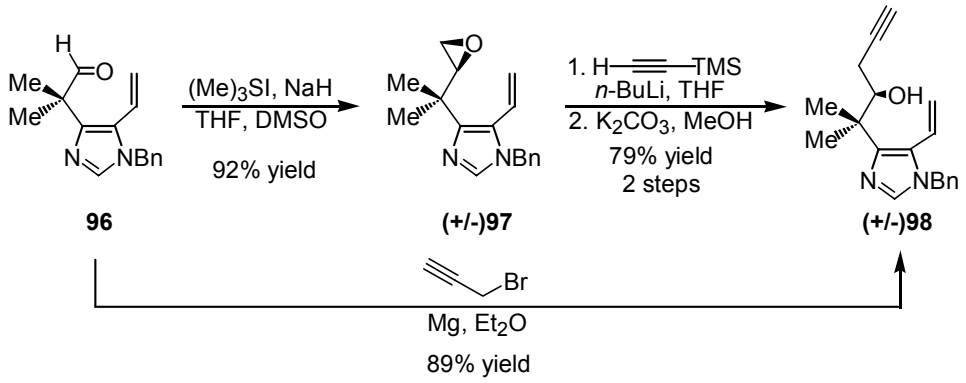
Scheme 2.4.4



2.4.3 A Chlorination Precursor

A Corey-Chaykovsky[21-27] reaction was used to homologate aldehyde **96** to terminal epoxide **97** (Scheme 2.4.5). Addition of the anion derived from TMS-acetylene to the less-sterically hindered terminus of the epoxide unmasked the secondary alcohol chlorine precursor, which after removal of the silyl group with K_2CO_3 in MeOH, cleanly afforded terminal acetylene **98**. Alternatively, aldehyde **96** could be treated with the grignard reagent derived from propargyl bromide to afford alcohol **98** directly.

Scheme 2.4.5

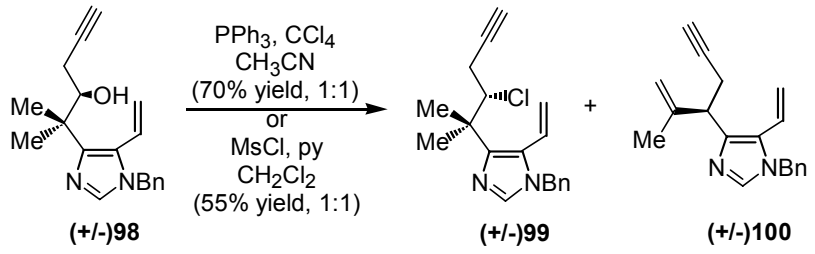


2.5 Chlorination of the Alcohol

2.5.1 An Unexpected Side Product

With secondary alcohol **98** in hand, efforts were turned toward the introduction of the neopentyl chlorine found in the natural product. Because of the steric hindrance involved, halogen incorporation was not expected to be trivial. Screening results of various chlorination reaction conditions confirmed these concerns, as dozens of reaction conditions[28] led to little more than decomposition of starting material. Two sets of conditions, however, did provide the desired neopentyl chlorine **99** (Scheme 2.5.1).

Scheme 2.5.1

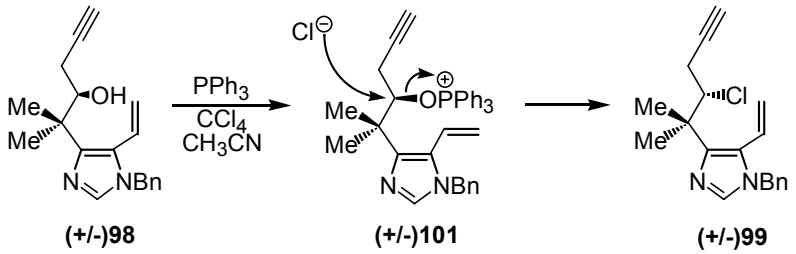


In both cases of successful chlorine introduction, however, the product was accompanied by a significant amount of an unexpected side product (**100**), the apparent result of rearrangement of the carbon side chain.

2.5.1.1 Proposed Mechanism of Rearrangement

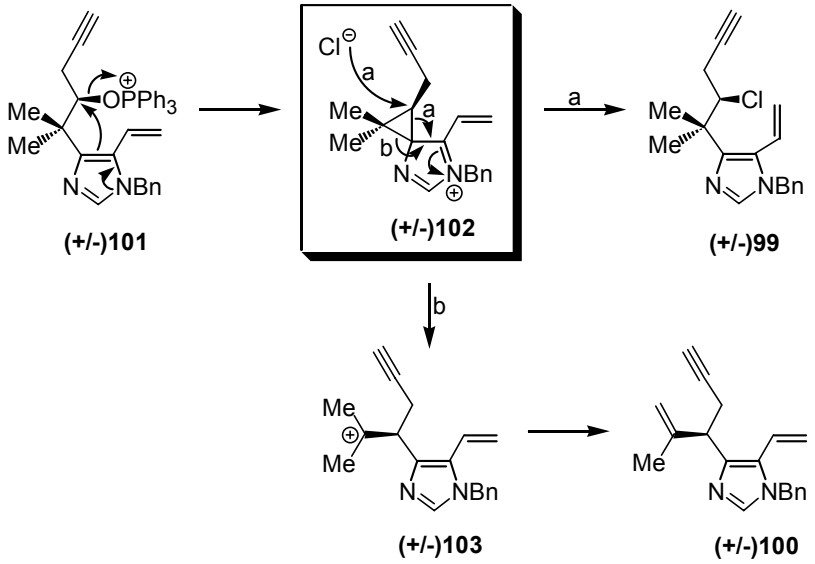
The obvious mechanism for the formation of **99** was through a simple S_N2 displacement of the phosphonium intermediate by chloride ion (**98→101→99**) (Scheme 2.5.2). That mechanism, however, did not account for the formation of olefin **100**.

Scheme 2.5.2



Scheme 2.5.3 outlines an alternative mechanism to explain the observed products. Rather than displacement of the phosphonium intermediate by chloride, the imidazole ring might act as a nucleophile, affording cyclopropyl intermediate **102**. The strained cyclopropyl ring could then be opened by attack of the chloride ion (path a) producing the desired neopentyl chlorine product. Alternatively, the cyclopropane might ring-fragment (path b), restoring aromaticity to the imidazole and yielding tertiary carbocation **103**. Elimination of a proton from **103** would then afford the observed olefinic side product (**100**).

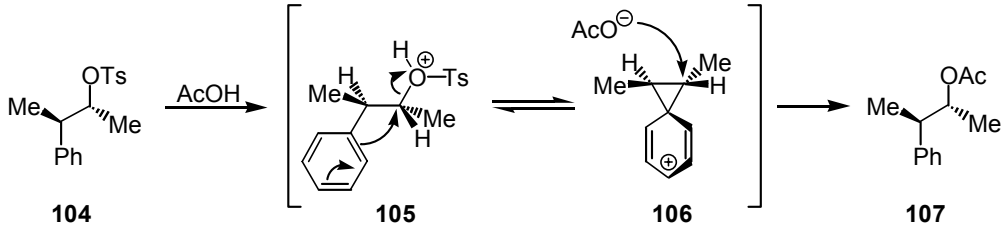
Scheme 2.5.3



2.5.1.2 Mechanistic Precedent

A series of papers published in 1949 by Cram[29-31] outlined mechanistic studies that offer support for the above mechanism. Cram's work dealt with establishing the mechanistic course of the Wagner-Meerwein rearrangement of 3-phenyl-2-butanol through the distribution of products (Scheme 2.5.4). To explain the product distribution, Cram proposed a cyclopropyl intermediate (**106**) resulting from the addition of the neighboring aromatic substituent into the carbon center bearing a leaving tosylate.

Scheme 2.5.4



Although cyclopropane **106** at first appears to be a very strained intermediate, there are several important factors contributing to its feasibility. Of note is the fact that the effective concentration of the attacking neighboring group is always very high, since by definition it is always adjacent to the leaving group. In addition, very little atom movement is required to achieve such an intermediate, and therefore the entropic demands on the reaction are low. Enthalpically, the energy lost in forming a strained 3-membered ring is counterbalanced by the formation of an additional C-C bond. Finally, Cram noted that more electron-rich neighboring groups (*para*-methoxyphenyl) tended to accelerate this type of reaction. The imidazole system that is the subject of this study is very electron rich as well, and thus the proposed mechanism seemed reasonable.

2.5.2 Optimization of Chlorination

As interesting as this unique rearrangement was, there was no way envisioned by this lab to advance **100** toward the securamines. Efforts were therefore made to direct the course of the reaction toward desired chloride **99** and away from the deleterious rearrangement. Based on the proposed mechanism, several factors were manipulated toward this end.

2.5.2.1 Chloride Ion Concentration and Source

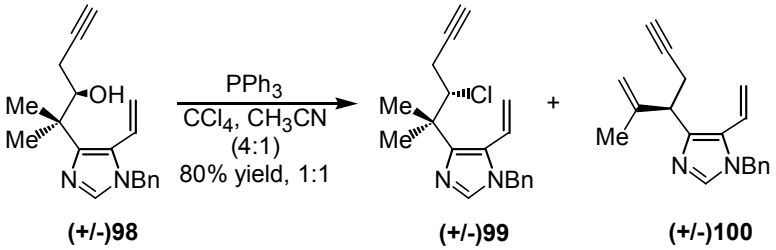
It was reasoned that if the concentration of chloride ion could be increased, it might be possible to shift the reaction toward either of the S_N2 chlorination mechanisms. Several chloride sources were added to the reaction without positive effect.[32] Since most of the chloride sources were salts, they were fairly insoluble under the anhydrous reactions conditions and therefore likely could not participate in the reaction.

The original source of chloride in the reaction was altered as well.[33] Although both hexachloroethane and NCS afforded the desired chloride product, there was no improvement in either product ratio or yield.

2.5.2.2 Solvent

The nature of the solvent had some measurable effect on the reaction, but mostly, it seemed, on the rate rather than product distribution. This appeared to be a manifestation of changes in solubility. Neither the starting alcohol nor the products were soluble in neat CCl_4, and the polarity therefore had to be increased by addition of CH_3CN. The rate, and ultimately the yield of the reaction, however, were inversely proportional to the amount of CH_3CN used in the reaction, and so solubility had to be tempered with reactivity. Ultimately it was found that a ratio of CCl_4 to CH_3CN of 4:1 afforded the best conversion (Scheme 2.5.5). Interestingly, in this solvent mixture neither the starting material nor the products were completely soluble.

Scheme 2.5.5



2.5.2.3 Phosphine

The only reaction condition manipulation that had a measurable effect on the ratio of products was the nature of the phosphine employed. It seemed that the course of reaction was, at least in part, dependent on the size of the phosphine. The results of using different phosphines are summarized in Table 2.5.1.

Scheme 2.5.6

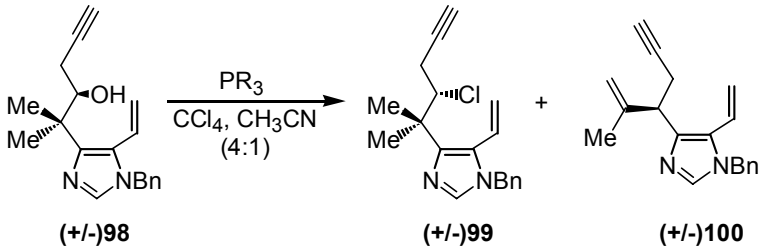


Table 2.5.1

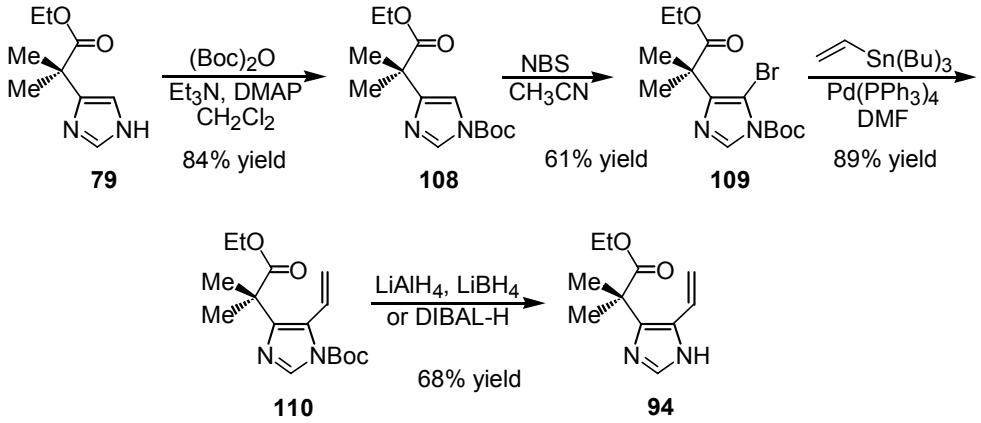
Phosphine	Cone Angle	**99**:**100**
$P(Cy)_3$	170°	No Reaction
$P(Ph)_2Cy$	162°	1:5 + s.m.
$P(Ph)_3$	145°	1:1
$P(Bu)_3$	135°	2:1

Larger phosphines tended to produce not only longer reaction times, but also more rearranged product. Smaller phosphines, conversely, reacted quickly and afforded more of the desired chlorinated product. Although an explanation for this effect is not entirely straightforward, it may suggest a steric dependence in the reaction pathway.

2.5.2.4 Imidazole Protecting Group

If the reaction products (**99** and **100**) arose through the proposed cyclopropanation mechanism (Scheme 2.5.3), altering the electronic nature of the imidazole (acting as a nucleophile) should have an effect on the reaction. A more electron-deficient heterocycle should be less nucleophilic and therefore should retard formation of the cyclopropane intermediate. To this end, efforts were made to replace the benzyl moiety with a more electron-withdrawing protecting group.

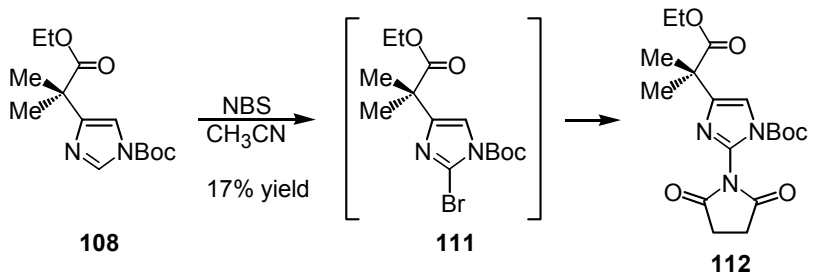
Scheme 2.5.7



Free imidazole **79** was first protected as its Boc derivative (Scheme 2.5.7) with $(Boc)_2O$, followed by bromination with NBS. Stille coupling of aryl halide **109** with vinyl(tributyl)stannane cleanly afforded vinyl imidazole **110**, however subsequent exposure to hydride reductants[34] (to reduce the ester) led to exclusive removal of the Boc protecting group. A curious result, the unfortunate lability of the carbonate did not seem unreasonable in retrospect given the ability of imidazole to act as a leaving group.

This sequence provided another exceptional result in the formation of succinimide **112** (Scheme 2.5.8). Bromination of **108** likely occurred to a minor extent at the 2-position to afford bromide **111**. Never isolated, bromide **111** was apparently the target of a nucleophilic displacement by succinimide to deliver **112**, further confirming earlier speculation as to the instability of such compounds.

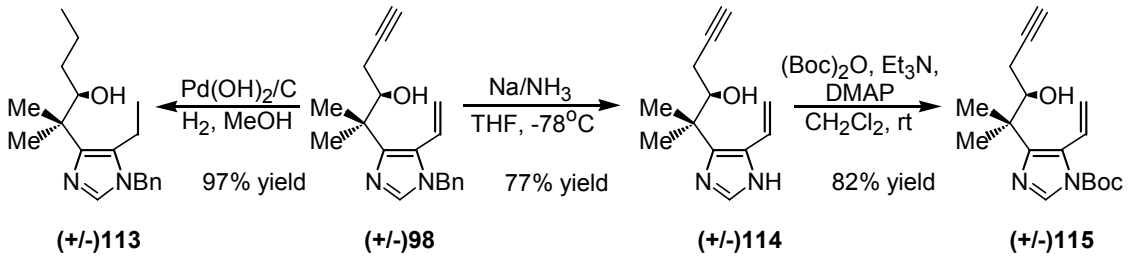
Scheme 2.5.8



Thwarted by the lability of the Boc protecting group to reducing agents, a more effective solution was sought. While palladium-catalyzed hydrogenolysis of the benzyl protecting group unfortunately exhibited a chemoselective preference for reduction of the vinyl and acetylenic fragments (**98**→**113**), **98** could be deprotected under carefully monitored dissolving metal conditions to afford **114**. Reprotection as the Boc derivative

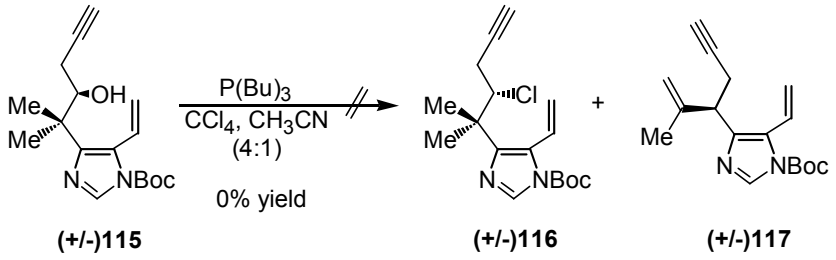
proceeded without incident to provide the more electron-deficient chlorination substrate **115** (Scheme 2.5.9).

Scheme 2.5.9



Subjection of the Boc-protected imidazole (**115**) to the same chlorination conditions (Scheme 2.5.10) interestingly afforded neither the chlorinated or rearranged products even under forcing conditions. These results strongly suggest an electronic influence on the course of the chlorination reaction and support the proposed theory of neighboring group participation. In addition, because neither of the products were formed in the reaction, these result also seem to imply a common intermediate in their formation, perhaps cyclopropane **102**.

Scheme 2.5.10



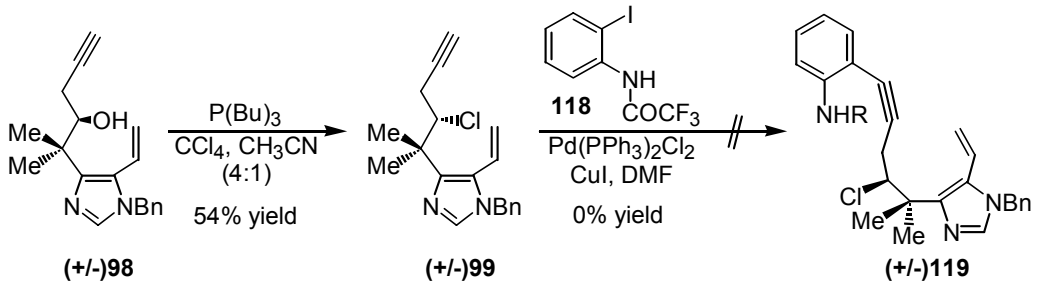
2.6 Indole Construction

With a better understanding of the chlorination reaction and an optimized 54% (80%, 2:1) yield of chlorinated product in hand, focus was returned to advancing material toward an indole substrate.

2.6.1 Sonogashira Coupling

Sonogashira[35,36] coupling of the terminal acetylene (**99**) with aniline derivative **118** (Scheme 2.6.1),[37] however, met with disappointing failure. Extensive efforts directed at optimizing the reaction also met with no success.[38] Together with the mediocre chlorination results, the failed coupling forced a reconsideration of the synthetic sequence.

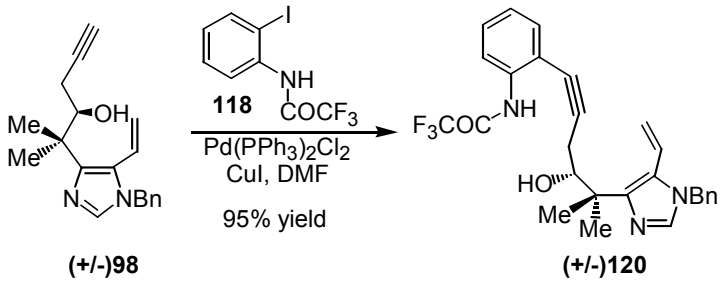
Scheme 2.6.1



Hoping that a change in the order of events would provide more promising results, it was decided to carry the synthesis through on the preceding alcohol (**98**) and to chlorinate later in the sequence. To this end, terminal acetylene **98** was treated with

iodoaniline derivative **118** under Sonagashira coupling conditions, affording an excellent yield of acetanilide **120** (Scheme 2.6.2). With an indole precursor in hand, efforts turned to an efficient method of cyclization and alkylation to provide the desired disubstituted indole.

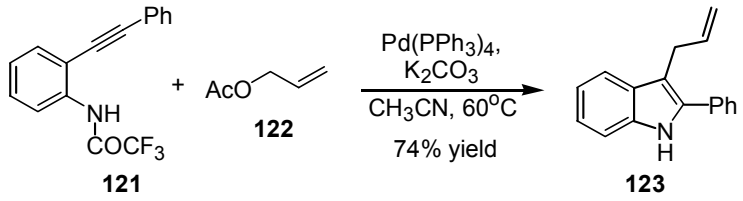
Scheme 2.6.2



2.6.2 Cacchi Indole Synthesis

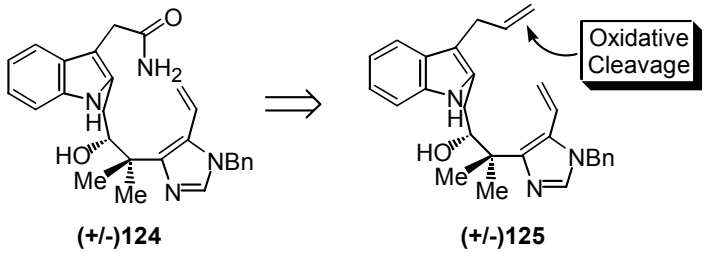
While the cyclization of aniline derivatives into alkynes was not a new method for indole construction[39-45], there were few methods available that allowed for direct functionalization of the 3-position.[46,47] Because most methods utilize transition metal catalysis, those that were available typically allowed for the introduction of only sp^2 centers at that carbon. This synthetic plan, however, required the introduction of an sp^3 methylene unit at that position.

Scheme 2.6.3



To our fortune, Cacchi and coworkers had recently published work detailing a new tandem palladium-catalyzed cyclization/alkylation protocol that seemed well suited to the task at hand.[48] Their procedure employed π-allyl palladium chemistry to introduce an allyl group to the 3-position of indole (Scheme 2.6.3). Employed in the securamine synthesis, it would provide the required methylene, as well as an olefin that could be oxidatively cleaved and advanced to the amide of the securamines (Scheme 2.6.4).

Scheme 2.6.4

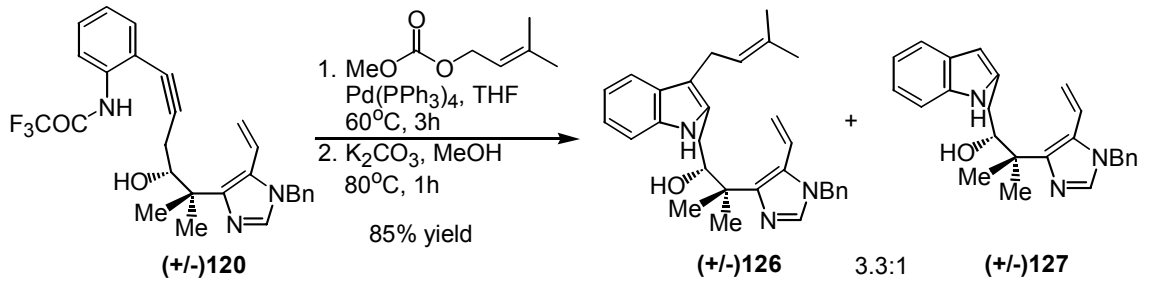


2.6.3 Indole Cyclization/Alkylation

Treatment of acetanilide **120** with a prenyl carbonate[49] under Cacchi's conditions afforded a good yield of the fully cyclized and alkylated indole **126**, accompanied by a

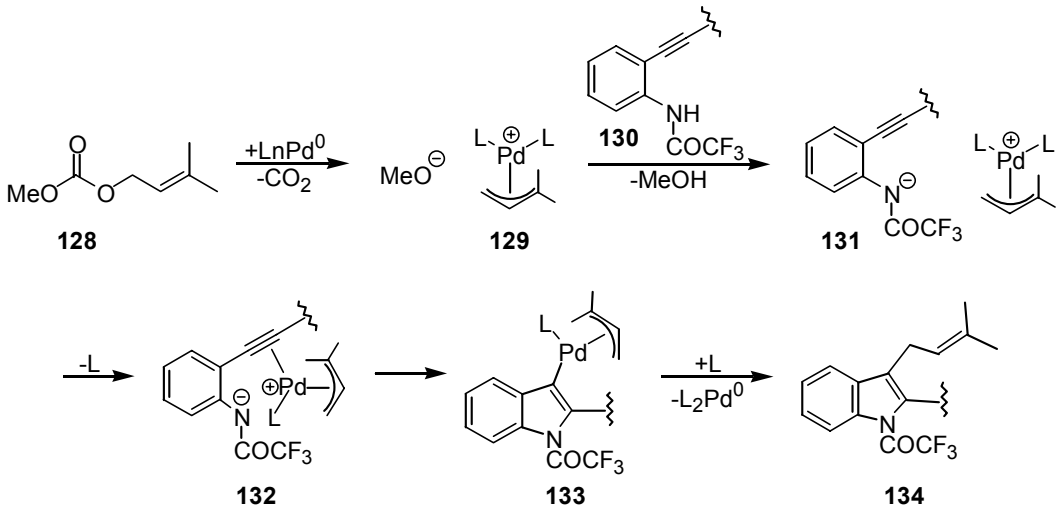
small amount of unalkylated indole **127**. Indole **126** now contained every carbon-carbon bond found in the natural product.

Scheme 2.6.5



The proposed mechanism of the tandem cyclization/alkylation reaction is shown in Scheme 2.6.6. Initial reaction of the catalyst with the allylic carbonate (**128**) furnishes a π-allyl palladium complex (**129**) and an equivalent of methoxide ion. Methoxide deprotonation of the acidic aniline, followed by coordination of the acetylene to the metal produces ionic intermediate **132**. Activation of the triple bond by metal coordination facilitates nucleophilic addition of the anilide nitrogen to what ultimately is the indole 2-position, leaving palladium at the 3-position (**133**). Reductive transfer of the allylic group occurs specifically at the least sterically hindered carbon to afford the alkylated indole **134** and the active palladium catalyst.

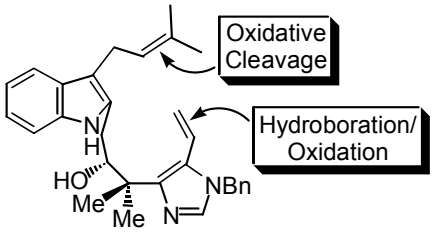
Scheme 2.6.6



2.7 Oxidation of the Olefin Side Chains

Now all that remained was to elaborate the olefin side chains to an amide and an aldehyde for the macrocyclic condensation. The original synthetic plan called for the oxidative cleavage of the prenyl olefin and hydroboration and oxidation of the vinyl olefin (Figure 2.7.1). Given the preferential reaction of ozone with more highly substituted olefins, and the preference of hydroboration for less sterically hindered double bonds, chemoselectivity was anticipated between the two olefins. Unfortunately, chemoselectivity never became an issue, as neither of these reaction proceeded as expected.

Figure 2.7.1



(+/-)126

2.7.1 Oxidative Cleavage of the Prenyl Olefin

Treatment of indole **126** with a variety of oxidants invariably resulted in complete decomposition of starting material. A partial list of oxidative conditions that were employed is shown in Table 2.7.1.

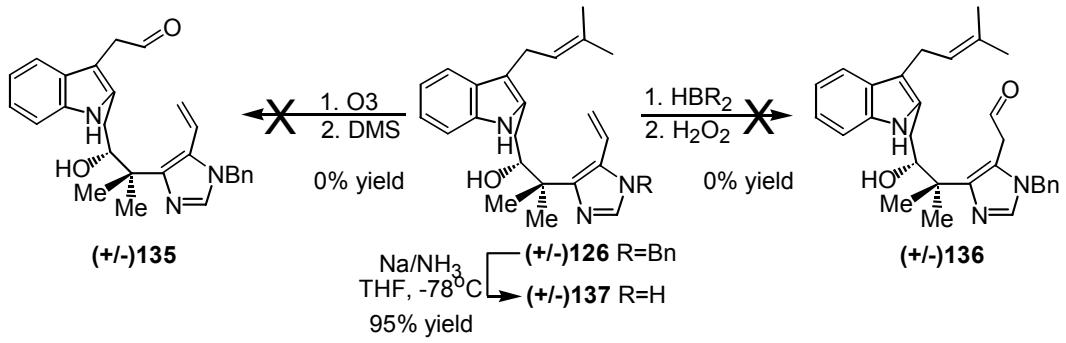
Table 2.7.1

Oxidant	Results
O_3, various solvents	Decomposition
$KMnO_4$	Decomposition
$NaIO_4$ +/- cat. $KMnO_4$	Decomposition
$NaIO_4$, cat. OsO_4	Decomposition
OsO_4	Decomposition
$NaIO_4$ cat. $RuCl_3$	Decomposition

It's known that electron rich heterocycles are often easily oxidized, an issue that perhaps should have been anticipated. It was suspected that either one or both of the heterocycles present in this system were being oxidized before the olefins, followed by an unknown decomposition pathway. In no case could any identifiable products be discerned.

In the hope that a less sterically congested environment might enhance reactivity of the vinyl moiety, the benzyl protecting group was removed under dissolving metal conditions to afford the free imidazole **137**. No favorable effect was realized.[50]

Scheme 2.7.1



2.7.2 Hydroboration of the Vinyl Olefin

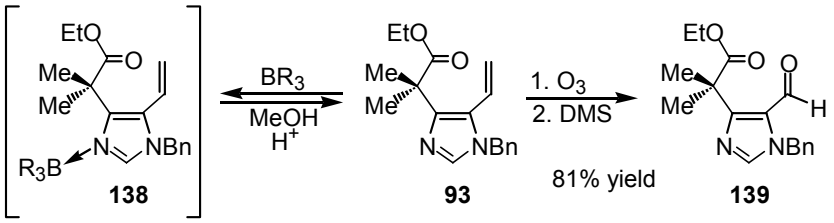
Hydroboration of the vinyl group met with less disastrous, though equally unsuccessful results. Although a variety of hydroboration conditions were employed,[51] in no case was there determined to be reaction with either of the olefins present in the system. It was suspected that the boron reagents were coordinating to one or both of the heterocycles, rendering the system unreactive.

2.7.3 Olefin Reactivity

Faced with these disappointing results, it was decided to investigate the reactivity of a simpler system in the hopes of finding suitable oxidation conditions. Efforts were focused on an earlier substrate in the synthetic sequence, vinyl imidazole **93**.

As before, any attempt at hydroboration of the olefin proceeded without success. In several cases, what appeared to be short-lived boron complexes of the starting material were isolated (i.e. **138**), supporting the theory of heterocycle complexation. Upon treatment with dilute acid in MeOH, these complexes would return to starting material.

Scheme 2.7.2



While treatment of **93** with a wide range of oxidants met with the same disastrous results as previously, it was found that ozonolysis in MeOH at -78°C afforded the corresponding aldehyde (**139**) in good yield. Interestingly, this was the only solvent and temperature with which the aldehyde was formed. Applied to the fully elaborated system, however, these conditions were as ineffective as before.

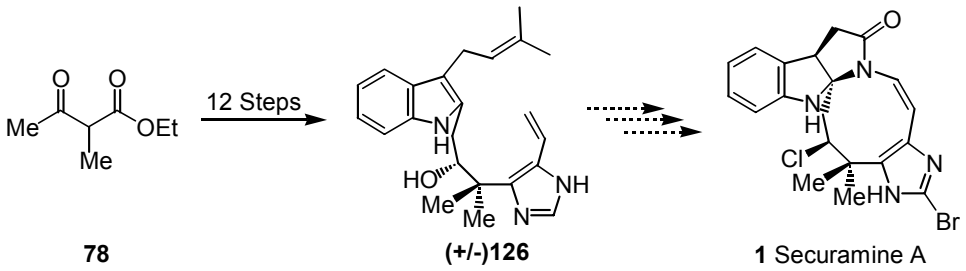
To gage further the reactivity of the vinyl olefin, several other reactions were employed. Azyridination, aminohydroxylation, epoxidation, iodolactonization, and

oxymercuration all met with similar failure, providing no indication of any reaction with the vinyl olefin.

2.8 Conclusions

In a very efficient sequence, this lab has been able to advance commercially available β-keto ester **78** to intermediate **126** toward the total synthesis of the securamine family of natural products.

Scheme 2.8.1



The unanticipated resistance with which olefin **126** met oxidation conditions called for the abandon of this synthetic approach. Owing to the efficiency and flexibility with which the securamine carbon skeleton had been constructed, however, it was with great anticipation that efforts were redirected toward a more suitably functionalized system.

2.9 Experimental

2.9.1 Materials and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

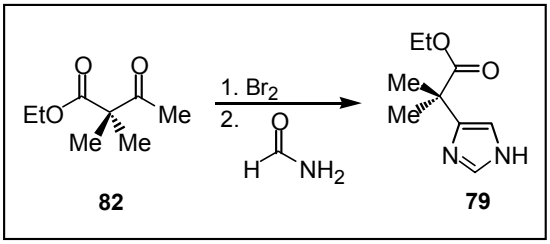
Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Bodman. In general, the chromatography guidelines reported by Still et al. were followed

All melting points were obtained on a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500, Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.0 ppm). High-resolution mass spectra were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters 510 solvent delivery system

using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 solvent delivery system with a Rainin Microsorb 80-120-C5 column.

2.9.2 Preparative Procedures.

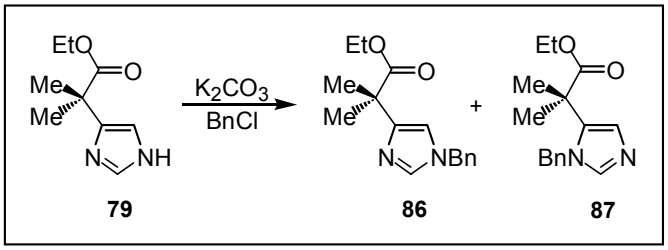
Preparation of Imidazole 79:



Imidazole 79. To a stirred solution of **82** (90 g, 568.9 mmol, 1.0 equiv.) in CCl_4 (200 mL) at 0°C was added Br_2 (26.4 mL, 512 mmol, 0.9 equiv.) in CCl_4 (75 mL) dropwise over 1 hour. The mixture was stirred for and additional 2 hours at 0°C and then concentrated *in vacuo*, maintaining the bath temperature below 30°C. Formamide (300 mL) was added and the solution was heated at 180°C for 4 hours. Excess formamide was removed by vacuum distillation (170°C, 3 mm Hg) until solid formation. After cooling to room temperature, the solid was dissolved in a minimum amount of H_2O and the solution made basic by addition of solid K_2CO_3. The solution was refrigerated for 12 hours, allowing crystallization of the product. The crystalline product was filtered and washed with Et_2O (2 x 100 mL) to afford nearly pure **79** (74.6g, 80% yield) as a white solid. Silica gel chromatography (100% EtOAc) provided an analytical sample of **79**.

Imidazole 79. m.p. 94-95°C; FTIR (thin film/NaCl) 2988 (m), 2842 (m), 2628 (m), 1718 (s), 1466 (m), 1264 (m), 1173 (m), 1161 (m), 1138 (m), 982 (m), 631 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J*=1.0 Hz, 1H), 6.91 (d, *J*=1.2Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 1.60 (s, 6H), 1.21 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 134.9, 60.9, 42.3, 25.7, 14.0; HRMS (EI) *m/z* 183.1133 [calculated for $C_9H_{14}N_2O_2$ (M^+) 183.1133].

Preparation of Benzyl Imidazoles 86 and 87:

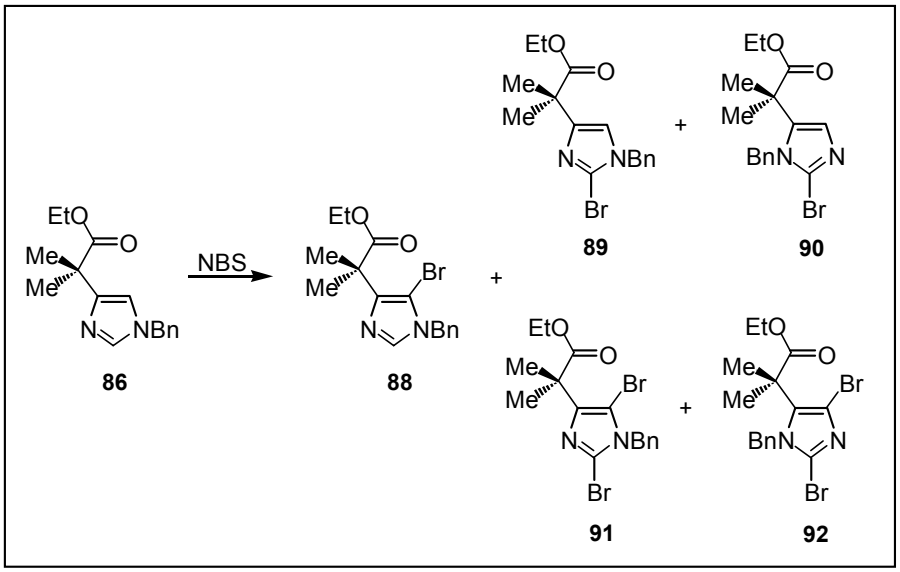


Benzyl Imidazoles 86 and 87. To a stirred solution of **79** (500 mg, 2.74 mmol, 1.0 equiv.) in DMF (25 mL) at room temperature was added K_2CO_3 (1.90 g, 13.72 mmol, 5.0 equiv.). The heterogeneous mixture was stirred vigorously for 30 minutes, at which time benzyl chloride (474 μL, 4.12 mmol, 1.5 equiv.) was added in one portion, and the mixture was heated at 55°C for 12 hours. The reaction was filtered through a fritted funnel and the filtrates washed with EtOAc (2 x 25 mL). The solution was reduced *in vacuo* and chromatographed on silica gel (70% EtOAc/Hexanes) to afford **86** (672 mg, 90% yield) and **87** (67 mg, 9% yield) as white solids.

Benzyl Imidazole 86. m.p. 72-73°C; FTIR (thin film/NaCl) 2978 (m), 2935 (w), 1725 (s), 1498 (m), 1455 (m), 1382 (w), 1361 (w), 1256 (m), 1213 (m), 1146 (s), 1113 (m), 1027 (m), 972 (w), 728 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J*=1.4 Hz, 1H) 7.37-7.28 (m, 3H), 7.16-7.13 (m, 2H), 6.75 (d, *J*=1.4 Hz, 1H), 5.05 (s, 2H), 4.12 (q, *J*=7.1 Hz, 2H), 1.55 (s, 6H), 1.19 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 146.8, 136.4, 136.1, 128.8, 128.0, 127.2, 114.8, 77.3, 77.0, 76.8, 60.5, 50.7, 43.0, 25.4, 14.0; HRMS (EI) *m/z* 273.1602 [calculated for $C_{16}H_{20}N_2O_2$ (M^+) 273.1603].

Benzyl Imidazole 87. m.p. 90-91°C; FTIR (thin film/NaCl) 2981 (m), 2937 (w), 1725 (s), 1496 (m), 1453 (m), 1387 (w), 1363 (w), 1255 (m), 1147 (m), 1026 (w), 916 (w), 730 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.27 (m, 4H), 7.04 (d, *J*=7.4Hz, 2H), 7.00 (s, 1H), 5.06 (s, 2H), 3.88 (q, *J*=7.2 Hz, 2H), 1.58 (s, 6H), 1.14 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 139.5, 136.3, 135.2, 128.8, 129.9, 126.7, 126.4, 61.1, 48.8, 41.2, 26.1, 13.9; HRMS (EI) *m/z* 273.1602 [calculated for $C_{16}H_{20}N_2O_2$ (M^+) 273.1603].

Preparation of Bromoimidazoles 88, 89, 90, 91, 92:



Bromoimidazoles 88, 89, 90, 91, 92. To a stirred solution of **86** (500 mg, 1.84 mmol, 1.0 equiv.) in CH_3CN (20 mL) at 0°C was added NBS (327 mg, 1.84 mmol, 1.0 equiv.) in 5 equal portions over 1 hour. The solution was then allowed to warm to room temperature and stirred for an additional 30 minutes. After removal of the solvent *in vacuo*, the mixture was dissolved in $CHCl_3$ (50 mL) and washed with water (3 x 20 mL). The organic layer was dried with $MgSO_4$, filtered and chromatographed on silica gel (30% EtOAc/Hexanes) to afford **88** (498 mg, 77% yield), an inseparable mixture of **89** and **90** (50 mg, 8% yield), and an inseparable mixture of **91** and **92** (48 mg, 7% yield) as white solids.

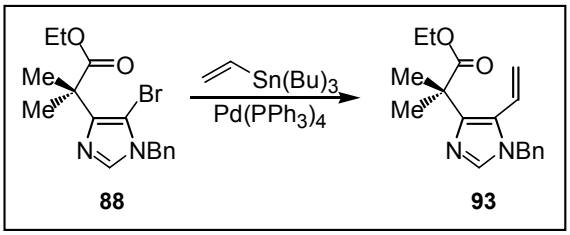
Bromoimidazole 88. m.p. 80-81°C; FTIR (thin film/NaCl) 2980 (m), 2934 (w), 1727 (s), 1486 (m), 1454 (m), 1299 (w), 1254 (m), 1227 (m), 1147 (m), 1028 (w), 996 (w), 733 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.38-7.30 (m, 3H), 7.11

(d, *J*=7.2 Hz, 2H), 5.11 (s, 2H), 4.16 (q, *J*=7.2 Hz, 2H), 1.62 (s, 6H), 1.20 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 143.4, 136.4, 135.8, 129.3, 128.6, 127.4, 61.3, 50.0, 43.8, 25.7, 14.6; HRMS (EI) *m/z* 351.0706 [calculated for $C_{16}H_{19}BrN_2O_2$ (M^+) 351.0708].

Bromoimidazoles 89 and 90. m.p. 110-111°C; FTIR (thin film/NaCl) 3142 (w), 2975 (w), 1724 (s), 1473 (w), 1438 (w), 1376 (w), 1259 (m), 1222 (w), 1153 (m), 1108 (w), 1027 (w), 980 (w), 938 (w), 799 (w), 715 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 6H), 7.18-7.13 (m, 4H), 6.81 (s, 1H), 6.75 (s, 1H), 5.06 (s, 2H), 5.05 (s, 2H), 4.12 (q, *J*=7.2 Hz, 2H), 4.11 (q, *J*=7.2 Hz, 2H), 1.52 (s, 6H), 1.51 (s, 6H), 1.20 (t, *J*=7.2 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 147.2, 145.5, 135.5, 135.4, 128.9, 128.8, 128.2, 128.1, 127.2, 127.1, 118.7, 117.8, 116.6, 60.7, 51.2, 50.1, 43.2, 43.1, 25.3, 25.2, 14.0; HRMS (EI) *m/z* 351.0706 [calculated for $C_{16}H_{19}BrN_2O_2$ (M^+) 351.0708].

Bromoimidazoles 91 and 92. m.p. 89-90°C; FTIR (thin film/NaCl) 2990 (w), 2979 (m), 1729 (s), 1526 (w), 1454 (m), 1381 (m), 1249 (m), 1175 (m), 1138 (m), 1027 (w), 1009 (m), 716 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 6H), 7.14-7.08 (m, 4H), 5.20 (s, 2H), 5.17 (s, 2H), 4.16 (q, *J*=7.2 Hz, 2H), 4.15 (q, *J*=7.2 Hz, 2H), 1.61 (s, 6H), 1.60 (s, 6H), 1.21 (t, *J*=7.2 Hz, 3H), 1.20 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 144.6, 143.0, 135.3, 135.2, 129.3, 129.2, 128.5, 128.4, 127.1, 127.0, 118.0, 101.4, 100.4, 61.4, 50.4, 49.4, 44.0, 43.9, 25.7, 14.6; HRMS (EI) *m/z* 428.9814 [calculated for $C_{16}H_{18}Br_2N_2O_2$ (M^+) 428.9813].

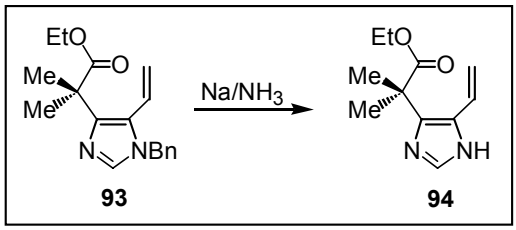
Preparation of Vinylimidazole 93:



Vinylimidazole 93. To a stirred solution of **88** (5.0 g, 14.23 mmol, 1.0 equiv.) in DMF (100 mL) was added vinyl(tributyl)tin (6.24 mL, 21.35 mmol, 1.5 equiv.) and tetrakis(triphenylphosphine)palladium(0) ($P(PPh_3)_4$) (822 mg, 0.71 mmol, 0.05 equiv.). The mixture was heated to 100°C for 4 hours, at which time the solvent was removed *in vacuo*. The reaction was then chromatographed on silica gel (40% EtOAc/Hexanes) to afford **93** (4.2 g, 98% yield) as a colorless oil.

Vinylimidazole 93. FTIR (thin film/NaCl) 2980 (m), 2935 (w), 1725 (s), 1632 (w), 1497 (m), 1454 (m), 1381 (w), 1632 (w), 1255 (m), 1138 (m), 1028 (w), 734 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.33-7.23 (m, 3H), 7.00 (d, *J*=7.2 Hz, 2H), 6.41 (dd, *J*=12Hz, 18Hz, 1H), 5.21 (dd, *J*=1 Hz, 12 Hz, 1H), 5.13 (dd, *J*=1 Hz, 18 Hz, 1H), 5.12 (s, 2H), 4.09 (q, *J*=7.2 Hz, 2H), 1.60 (s, 6H), 1.15 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 143.5, 136.8, 136.3, 128.7, 127.7, 126.2, 124.9, 124.0, 117.7, 60.5, 48.9, 43.5, 26.1, 14.0; HRMS (EI) *m/z* 299.1759 [calculated for $C_{18}H_{22}N_2O_2$ (M^+) 299.1759].

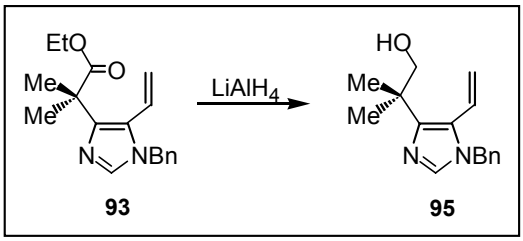
Preparation of Vinylimidazole 94.



Vinylimidazole 94. To a stirred solution of **93** (200 mg, 0.67 mmol, 1 equiv.) in THF (4 mL) and NH_3 (4 mL) at -78°C was added Na (~30 mg, 2.0 equiv.). The reaction was stirred at -78°C and monitored by TLC. Upon consumption of starting material (as indicated by TLC), NH_4Cl (sat., aq.) (1 mL) was added to quench the reaction. H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 x 5 mL). The organics were dried with $MgSO_4$, filtered, and the solvent removed *in vacuo*. Silica gel chromatography of the mixture afforded **94** (112 mg, 80% yield) as a colorless oil.

Vinylimidazole 94. FTIR (thin film/NaCl) 3116 (m), 2980 (s), 2936 (m), 2874 (m), 2707 (w), 1728 (s), 1634 (w), 1544 (w), 1465 (m), 1365 (w), 1351 (w), 1253 (s), 1151 (s), 1136 (s), 1025 (m), 988 (w), 902 (w), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.61 (dd, *J*=11.3 Hz, 17.4 Hz, 1H), 5.46 (d, *J*=17.4 Hz, 1H), 5.03 (d, *J*=11.3 Hz, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 1.59 (s, 3H), 1.16 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 133.5, 125.1, 111.6, 61.1, 43.0, 26.4, 14.1; HRMS (EI) *m/z* 209.1289 [calculated for $C_{11}H_{16}N_2O_2$ (M^+) 209.1290].

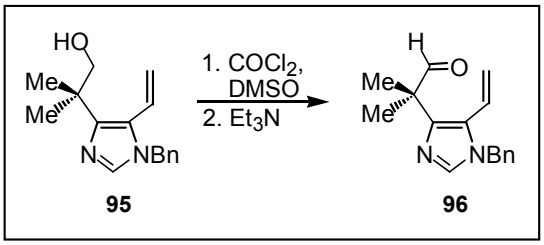
Preparation of Alcohol 95:



Alcohol 95. To a stirred solution of $LiAlH_4$ (789 mg, 20.78 mmol, 2.0 equiv.) in Et_2O (100 mL) at 0°C was added dropwise **93** (3.10 g, 10.39 mmol, 1.0 equiv.) in Et_2O (20 mL). The solution was allowed to warm to room temperature and stirred for 1 hour. H_2O (3.1 mL), NaOH (aq., 1N) (6.2 mL), and KF (sat., aq.) (9.3 mL) were added dropwise sequentially. The solution was decanted off and the solid precipitate washed with EtOAc (5 x 20 mL). The organic layers were combined, dried with $MgSO_4$ and reduced *in vacuo*. The mixture was chromatographed on silica gel (80% EtOAc/Hexanes) to afford **95** (2.02 g, 76% yield) as a white solid.

Alcohol 95. m.p. 67-68°C; FTIR (thin film/NaCl) 3353 (s), 2961 (s), 2926 (m), 2867 (m), 1631 (m), 1497 (s), 1454 (s), 1359 (m), 1243 (m), 1153 (w), 1053 (s), 996 (m), 917 (w), 732 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 4H), 7.04 (d, *J*=7.2 Hz, 2H), 6.63 (dd, *J*=11.7 Hz, 18.1 Hz, 1H), 5.36 (dd, *J*=1.3 Hz, 11.7 Hz, 1H), 5.21 (dd, *J*=1.3 Hz, 18.1 Hz, 1H), 5.12 (s, 2H), 4.67 (bs, 1H), 3.69 (s, 2H), 1.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 136.4, 136.0, 128.8, 127.8, 126.5, 125.3, 125.1, 119.3, 73.1, 48.9, 37.4, 25.3; HRMS (EI) *m/z* 257.1654 [calculated for $C_{16}H_{20}N_2O$ (M^+) 257.1654].

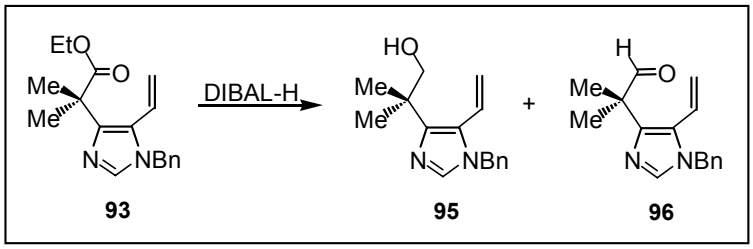
Preparation of Aldehyde 96:



Aldehyde 96. To a solution of oxalyl chloride (664 μL, 7.61 mmol, 1.3 equiv.) in CH_2Cl_2 (60 mL) at -78°C was added DMSO (830 μL, 11.70 mmol, 2.0 equiv.) dropwise. The solution was stirred for 10 minutes, followed by the addition of **95** (1.5 g, 5.85 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) dropwise. Stirring of the solution for another 10 minutes, was followed by the addition of Et_3N (4.08 mL, 29.25 mmol, 5.0 equiv.). After being allowed to warm to room temperature, H_20 (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the organic layers combined and dried with $MgSO_4$. Removed of the solvent *in vacuo* provided an oil that was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **96** (1.40 g, 95% yield) as a colorless oil.

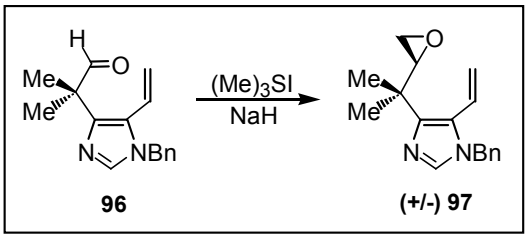
Aldehyde 96. FTIR (thin film/NaCl) 2976 (w), 2931 (w), 1721 (s), 1498 (s), 1454 (m), 1359 (m), 1235 (w), 1143 (w), 989 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.48 (s, 1H), 7.36-7.27 (m, 3H), 7.04 (d, *J*=7.2 Hz, 2H), 6.38 (dd, *J*=11.8 Hz, 17.8 Hz, 1H), 5.31 (dd, *J*=1.0 Hz, 11.8 Hz, 1H), 5.18 (dd, *J*=1.0 Hz, 17.8 Hz, 1H), 5.14 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 140.2, 137.5, 136.1, 129.0, 128.0, 126.7, 126.4, 123.8, 119.7, 49.1, 48.0, 22.0; HRMS (EI) *m/z* 255.1522 [calculated for $C_{16}H_{18}N_2O$ (M^+) 255.1497].

Preparation of Alcohol 95 and Aldehyde 96:



Alcohol 95 and Aldehyde 96. To a stirred solution of **93** (1.0 g, 3.35 mmol, 1.0 equiv.) in CH_2Cl_2 (35 mL) at -78°C was added DIBAL-H (1.0 M in CH_2Cl_2) (3.35 mL, 3.35 mmol, 1.0 equiv.). The solution was stirred for 30 min. at -78°C and then allowed to warm to room temperature. NH_4Cl (sat., aq.) (5 mL) was added and the solution was poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layers combined and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the resulting oil was chromatographed on silica gel (80% EtOAc/Hexanes) to afford **95** (100 mg, 12% yield) as a white solid, **96** (545 mg, 64% yield) as a colorless oil, and recovered **93** (70 mg, 7% yield) as a colorless oil.

Preparation of Epoxide 97:

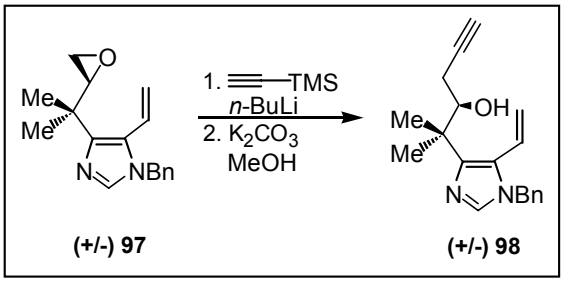


Epoxide 97. To a suspension of NaH (60% in mineral oil) (838 mg, 20.84 mmol, 2.0 equiv.) in THF (40 mL) and DMSO (40 mL) at room temperature was added trimethylsulfonium iodide (Me_3SI) (4.25 g, 20.84 mmol, 2.0 equiv.). The mixture was stirred for 1 hour and then cooled to 0°C. Aldehyde **96** (2.65 g, 10.42 mmol, 1.0 equiv.) was added dropwise in THF (10 mL), followed by warming to room temperature. The reaction was allowed to stir until completion as indicated by TLC (2-3 hours) and then quenched by pouring into H_2O (100 mL). The mixture was extracted with Et_2O (3 x 50 mL), the organic layers washed with brine and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (50% EtOAc/Hexanes) to afford **97** (2.55 g, 92% yield) as a colorless oil.

Epoxide 97. FTIR (thin film/NaCl) 2972 (m), 2930 (m), 2871 (w), 1631 (w), 1497 (m), 1454 (m), 1359 (m), 1238 (w), 996 (w), 881 (m), 731 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37-7.26 (m, 3H), 7.05 (d, *J*=7.2 Hz, 2H), 6.73 (dd, *J*=11.7 Hz, 18.0 Hz, 1H), 6.35 (dd, *J*=1.5 Hz, 11.7 Hz, 1H), 5.21 (dd, *J*=1.5 Hz, 18.0 Hz, 1H), 5.14 (s, 2H), 3.17 (dd, *J*=2.8 Hz, 4.1 Hz, 1H), 2.73 (dd *J*=4.1 Hz, 4.7 Hz, 1H), 2.64 (dd, *J*=2.8 Hz, 4.7 Hz, 1H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4,

136.8, 136.7, 128.9, 127.8, 126.5, 126.0, 125.9, 119.2, 59.3, 48.9, 45.1, 36.4, 24.5, 23.7; HRMS (EI) *m/z* 269.1653 [calculated for $C_{17}H_{20}N_2O$ (M^+) 269.1654].

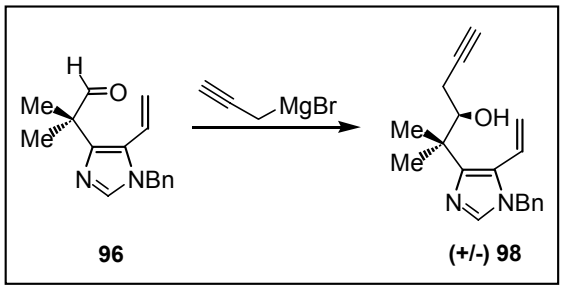
Preparation of Acetylene 98:



Acetylene 98. To a stirred solution of tri(methyl)silylacetylene (1.69 mL, 11.96 mmol, 1.5 equiv.) in THF (100 mL) at -78°C was added *n*-BuLi (2.5 M in hexanes) (4.78 mL, 11.96 mmol, 1.5 equiv.). The reaction was stirred for 10 minutes, at which time BF_3•Et_2O (1.52 mL, 11.96 mmol, 1.5 equiv.) was added dropwise. The reaction was stirred for another 10 minutes at -78°C followed by the dropwise addition of **97** (2.14 g, 7.97 mmol, 1.0 equiv.) in THF (10 mL). The reaction was stirred for 1 hour and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the organic layers combined. The solvent was removed *in vacuo* and the resulting oil was then dissolved in THF (50 mL). MeOH (1.0 mL) and K_2CO_3 (1.0 g) were added and the suspension stirred for another hour at room temperature, at which time the reaction was filtered and the solvent removed *in vacuo*. Silica gel chromatography (30 % EtOAc/Hexanes) afforded **98** (1.86 g, 79% yield) as a colorless oil.

Acetylene 98. FTIR (thin film/NaCl) 3296 (s), 2970 (m), 2931 (m), 2116 (w), 1631 (w), 1497 (s), 1453 (m), 1359 (m), 1238 (m), 1156 (w), 1068 (s), 995 (m), 932 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.38-7.28 (m, 3H), 7.03 (d, *J*=7.2 Hz, 2H), 6.61 (dd, *J*=11.4 Hz, 18.0 Hz, 1H), 5.42 (dd, *J*=1.6 Hz, 11.5 Hz, 1H), 5.22 (dd, *J*=1.6 Hz, 18.0 Hz, 1H), 5.10 (s, 2H), 3.81 (dd, *J*=3.1 Hz, 9.2 Hz, 1H), 2.33 (ddd, *J*=2.7, 9.2 Hz, 12.0 Hz, 1H), 2.30 (ddd, *J*=2.7 Hz, 9.2 Hz, 12.0 Hz, 1H), 1.98 (t, *J*=2.7 Hz, 1H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 136.6, 136.3, 128.9, 127.9, 126.5, 125.9, 125.8, 120.9, 83.1, 78.9, 69.1, 48.7, 40.3, 26.8, 24.3, 23.0; HRMS (EI) *m/z* 295.1809 [calculated for $C_{19}H_{22}N_2O$ (M^+) 295.1810].

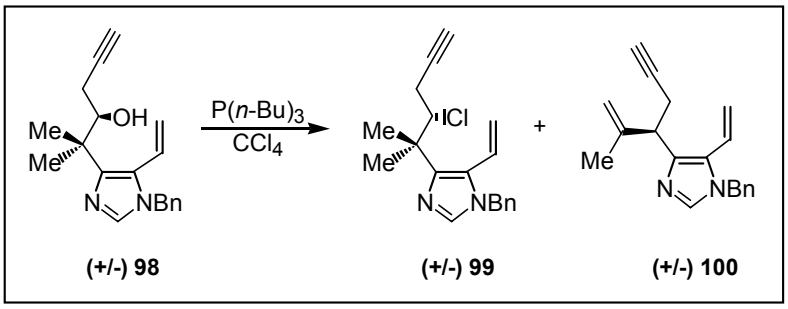
Preparation of Acetylene 98:



Acetylene 98. To a stirred suspension of dry Mg turnings (260 mg, 10.62 mmol, 3.0 equiv.) in Et_2O (100 mL) at room temperature was added propargyl bromide (80 wt. % solution in toluene) (1.18 mL, 10.62 mmol, 3.0 equiv.) and $HgCl_2$ (144 mg, 0.53 mmol, 0.15 equiv.). The suspension was fitted with a reflux condenser and heated with a heat gun to the point of a self-sustaining reflux. After consumption of most of the Mg turnings, the solution was cannulated into a stirred solution of **96** (900 mg, 3.54 mmol,

1.0 equiv.) in Et_2O (35 mL). The reaction was stirred at room temperature for 15 minutes and then quenched by addition of H_20 (100 mL). The mixture was extracted with EtOAc (3 x 75 mL), washed with brine (50 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* and the resulting oil chromatographed on silica gel (50% Acetone/Hexanes) to afford **98** (930 mg, 89% yield) as a colorless oil.

Preparation of Chloride 99 and Olefin 100:



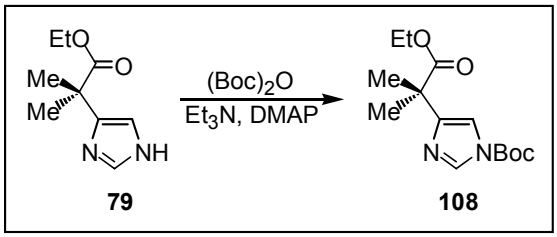
Chloride 99 and Olefin 100. To a stirred solution of **98** (1.0 g, 3.40 mmol, 1.0 equiv.) in CCl_4 (40 mL) and CH_3CN (10 mL) at 75°C was added tri-*n*-butylphosphine ($P(n\text{-}Bu)_3$) (1.69 mL, 6.60 mmol, 2.0 equiv.) dropwise. The reaction was refluxed for 10 minutes, cooled to room temperature, and the solvent removed *in vacuo*. The mixture was chromatographed on silica gel (30% Acetone/Hexanes) to afford **99** (567 mg, 53% yield) and **100** (258 mg, 27% yield) as colorless oils.

Chloride 99. FTIR (thin film/NaCl) 3296 (m), 2980 (m), 2930 (m), 1633 (w), 1496 (s), 1454 (m), 1385 (w), 1370 (m), 1275 (w), 1215 (m), 1144 (w), 1105 (m), 985 (w), 933 (w), 732 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (s, 1H), 7.36-7.27 (m, 3H), 7.00 (d, *J*=7.3 Hz, 2H), 6.44 (dd, *J*=11.7 Hz, 17.7 Hz, 1H), 5.52 (dd, *J*=1.2 Hz, 17.7 Hz,

1H), 5.29 (dd, *J*=1.2 Hz, 11.7 Hz, 1H), 5.20 (d, *J*=16.3 Hz, 1H), 5.16 (d, *J*=16.3 Hz, 1H), 3.50 (dd, *J*=3.5 Hz, 11.1 Hz, 1H), 2.99 (m, 2H), 1.82 (t, *J*=2.5 Hz, 1H), 1.74 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 137.5, 136.5, 129.1, 128.9, 127.9, 126.1, 123.5, 118.0, 83.4, 73.9, 68.8, 49.3, 49.0, 32.1, 28.6, 20.7; HRMS (EI) *m/z* 313.1473 [calculated for $C_{19}H_{21}ClN_2$ (M^+) 313.1471].

Olefin 100. FTIR (thin film/NaCl) 3296 (s), 3067 (w), 3030 (w), 2969 (w), 2915 (w), 2116 (w), 1630 (m), 1496 (s), 1453 (m), 1372 (w), 1357 (w), 1301 (w), 1227 (m), 1076 (w), 1029 (w), 984 (w), 894 (s), 732 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.36-7.27 (m, 3H), 7.04 (d, *J*=7.0 Hz, 2H), 6.44 (dd, *J*=11.7 Hz, 18.0 Hz, 1H), 5.39 (dd, *J*=1.3 Hz, 18.0 Hz, 1H), 5.25 (dd, *J*=1.3 Hz, 11.7 Hz, 1H), 5.15 (s, 2H), 4.94-4.90 (m, 2H), 3.70 (t, *J*=7.6 Hz, 1H), 2.84 (dd, *J*=2.5 Hz, 7.6 Hz, 2H), 1.92 (t, *J*=2.5 Hz, 1H), 1.74 (s, 3H), ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 141.2, 137.3, 136.3, 128.9, 127.9, 126.7, 126.3, 123.3, 116.8, 111.6, 83.6, 68.8, 49.0, 44.4, 22.5, 20.6; HRMS (EI) *m/z* 277.1704 [calculated for $C_{19}H_{20}N_2$ (M^+) 277.1704].

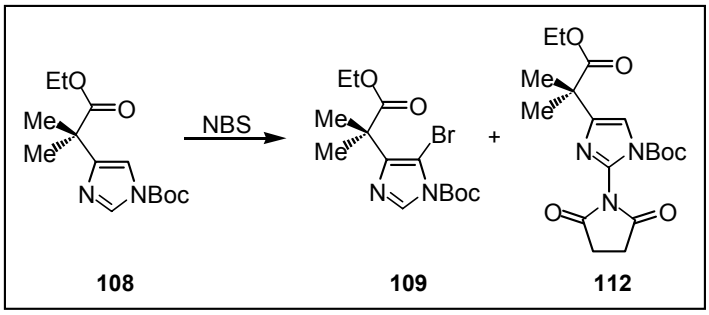
Preparation of Boc-Imidazole 108.



Boc-Imidazole 108. To a stirred solution of **79** (500 mg, 2.74 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) at room temperature was added Et_3N (423 μL, 3.02 mmol, 1.1 equiv.) and DMAP (17 mg, 0.14 mmol, 0.05 equiv.) followed by di-*t*-butyl dicarbonate (628 mg, 2.88 mmol, 1.05 equiv.). The solution was warmed to 45°C and stirred for 8 hours, at which time the reaction was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (20 mL) and dried with $MgSO_4$. The resulting oil was chromatographed on silica gel (20% EtOAc/Hexanes) to afford **108** (648 mg, 84% yield) as a colorless oil.

Boc-Imidazole 108. FTIR (thin film/NaCl) 3161 (w), 3132 (w), 2981 (s), 2937 (m), 2875 (s), 1755 (s), 1732 (s), 1568 (w), 1471 (m), 1389 (s), 1329 (w), 1274 (s), 1256 (s), 1154 (s), 1098 (m), 1011 (s), 969 (w), 841 (m), 773 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J*=1.3 Hz, 1H), 7.17 (d, *J*=1.3 Hz, 1H), 4.13 (q, *J*=7.0 Hz, 2H), 1.59 (s, 9H), 1.53 (s, 6H), 1.20 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 147.5, 147.0, 136.5, 112.4, 85.3, 60.9, 43.0, 27.8, 25.1, 14.0; HRMS (EI) *m/z* 283.1659 [calculated for $C_{14}H_{22}N_2O_4$ (M^+) 283.1658].

Preparation of Bromoimidazole 109 and Succinimide 112:



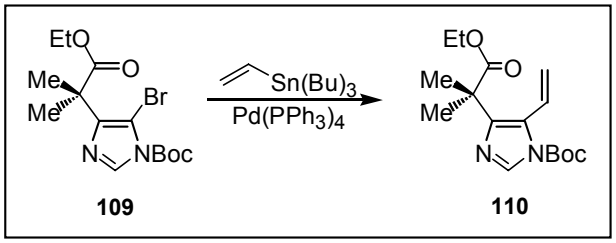
Bromoimidazole 109 and Succinimide 112. To a stirred solution of **108** (1.0 g, 3.54 mmol, 1.0 equiv.) in CH_3CN (35 mL) at room temperature was added NBS (630 mg, 3.54 mmol, 1.0 equiv.) in 5 equal portions over 1 hour. The reaction was stirred at room temperature for 12 hours, at which time the solvent was removed *in vacuo* and the mixture chromatographed on silica gel (20% EtOAc/Hexanes) to afford **109** (386 mg, 61% yield) and **112** (234 mg, 17% yield) as white solids.

Bromoimidazole 109. m.p. 97-98°C; FTIR (thin film/NaCl) 3135 (w), 2982 (m), 2936 (m), 2872 (w), 1758 (s), 1733 (s), 1538 (w), 1466 (m), 1360 (s), 1312 (m), 1244 (s), 1153 (s), 1060 (m), 1029 (w), 986 (w), 928 (w), 845 (m), 768 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 1.63 (s, 9H), 1.30 (s, 6H), 1.25 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 146.3, 145.6, 137.4, 97.2, 86.6, 61.1, 43.4, 27.9, 25.1, 14.2; HRMS (EI) *m/z* 361.0763 [calculated for $C_{14}H_{21}BrN_2O_4$ (M^+) 361.0763].

Succinimide 112. m.p. 109-110°C; FTIR (thin film/NaCl) 2982 (w), 1758 (m), 1732 (s), 1535 (w), 1470 (w), 1412 (w), 1363 (m), 1294 (w), 1249 (m), 1168 (m), 1141

(m), 1025 (w), 844 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 2.84 (s, 4H), 1.52 (s, 6H), 1.51 (s, 9H), 1.19 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 174.7, 145.7, 144.6, 132.0, 115.2, 86.2, 60.9, 42.9, 28.6, 27.6, 24.9, 13.9; HRMS (EI) *m/z* 380.1822 [calculated for $C_{18}H_{25}N_3O_6$ (M^+) 380.1822].

Preparation of Vinylimidazole 110:

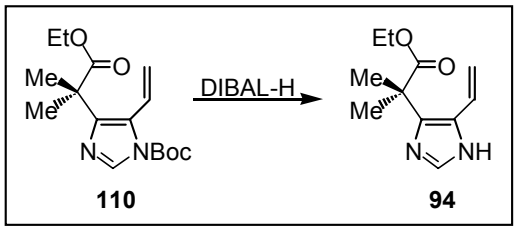


Vinylimidazole 110. To a stirred solution of **109** (1.0 g, 2.77 mmol, 1.0 equiv.) in DMF (30 mL) was added vinyl(tributyl)tin (1.20 mL, 4.15 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (160 mg, 0.14 mmol, 0.05 equiv.). The reaction was heated at 100°C for 90 minutes, at which time the solvent was removed *in vacuo* and the mixture chromatographed on silica gel (50% Et_2O/petroleum ether) to afford **110** (760 mg, 89% yield) as a colorless oil.

Vinylimidazole 110. FTIR (thin film/NaCl) 2982 (m), 2936 (w), 1756 (s), 1731 (s), 1468 (m), 1364 (s), 1299 (s), 1243 (m), 1163 (s), 1149 (s), 1055 (m), 1030 (w), 984 (m), 929 (w), 847 (m), 773 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.67 (dd, *J*=11.4 Hz, 17.8 Hz, 1H), 5.39 (dd, *J*=1.5 Hz, 11.4 Hz, 1H), 5.24 (dd, *J*=1.5 Hz, 17.8 Hz, 1H), 4.08 (q, *J*=7.2 Hz, 2H), 1.57 (s, 9H), 1.56 (s, 6H), 1.20 (t, *J*=7.2 Hz, 3H);

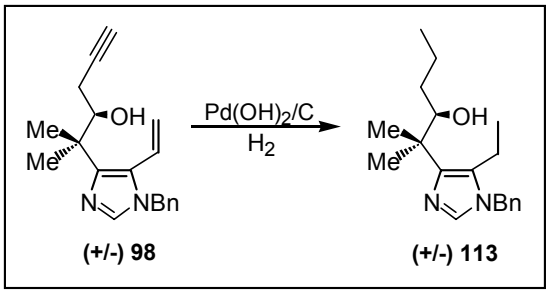
^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 147.4, 144.0, 135.9, 125.9, 125.1, 120.3, 85.4, 60.7, 43.5, 27.8, 26.7, 14.0; HRMS (EI) *m/z* 309.1813 [calculated for $C_{16}H_{24}N_2O_4$ (M^+) 309.1814].

Preparation of Vinylimidazole 94.



Vinylimidazole 94. To a Stirred solution of **110** (200 mg, 0.65 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added DIBAL-H (1.0 M in CH_2Cl_2) (650 μL, 0.65 mmol, 1.0 equiv.) dropwise at 0°C. The reaction was allowed to warm to room temperature and monitored by TLC. Upon consumption of starting material (as indicated by TLC), NH_4Cl (sat., aq.) (1 mL) was added and the mixture was poured into H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the organic layers combined and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel to afford **94** (92 mg, 68% yield) as a colorless oil.

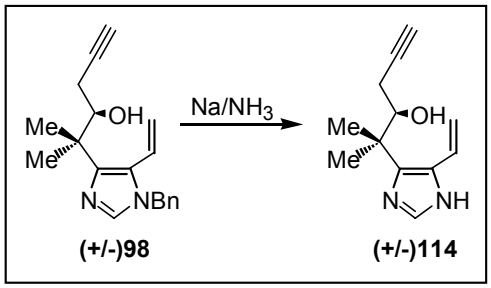
Preparation of Ethylimidazole 113:



Ethylimidazole 113. To a stirred solution of **98** (100 mg, 0.340 mmol, 1.0 equiv.) in MeOH (5 mL) at room temperature was added $Pd(OH)_2$ (20 wt % on carbon) (24 mg, 0.017 mmol, 0.05 equiv.). The reaction was flushed with H_2 gas and positive H_2 pressure was continued with vigorous stirring for 2 hours. The solvent was removed *in vacuo* and the reaction filtered through a plug of silica gel (100% EtOAc) to afford **113** (99 mg, 97% yield) as a colorless oil.

Ethylimidazole 113. FTIR (thin film/NaCl) 3324 (s), 2957 (s), 2932 (m), 2870 (m), 1505 (m), 1454 (m), 1381 (w), 1357 (w), 1231 (m), 1117 (w), 1075 (w), 979 (w), 726 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.37-7.28 (m, 3H), 7.04 (d, *J*=7.0 Hz, 2H), 5.04 (s, 2H), 3.58 (dd, *J*=1.6 Hz, 10.1 Hz, 1H), 2.61 (q, *J*=7.6 Hz, 2H), 1.66 (m, 1H), 1.49-1.33 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.21 (m, 1H), 1.04 (t, *J*=7.6 Hz, 3H), 0.92 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7, 136.6, 134.9, 128.9, 128.3, 127.9, 126.5, 79.8, 48.2, 40.2, 34.1, 27.2, 23.2, 20.0, 17.1, 15.3, 14.3; HRMS (EI) *m/z* 301.2281 [calculated for $C_{19}H_{28}N_2O$ (M^+) 301.2280].

Preparation of Acetylene 114:

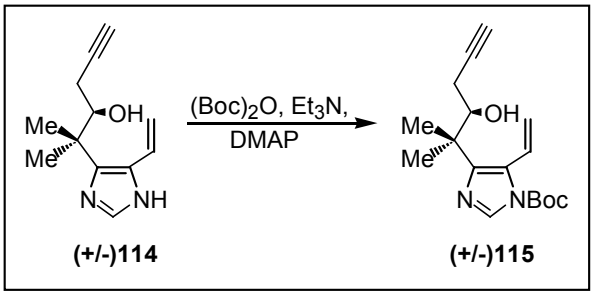


Acetylene 114. To a solution of **98** (100 mg, 0.34 mmol, 1.0 equiv.) in THF (5 mL) and NH3 (5 mL) at -78°C was added Na (~17mg, 0.68 mmol, 2.0 equiv.). The reaction was stirred at -78°C and monitored by TLC. Upon consumption of the starting material (as indicated by TLC), NH_4Cl (sat., aq.) (1 mL) was added to quench the reaction. The mixture was allowed to warm to room temperature and then stirred for an additional hour, at which time H_2O (5 mL) was added and the mixture was extracted with EtOAc (3 x 5mL). The organic layers were combined, dried with MgSO4, and reduced *in vacuo*. The resulting oil was chromatographed on silica gel to afford **114** (55 mg, 77% yield) as a colorless oil.

Acetylene 114. FTIR (thin film/NaCl) 3295 (s), 2977 (s), 2916 (m), 2118 (w), 1631 (m), 1542 (m), 1463 (s), 1387 (m), 1347 (m), 1280 (m), 1246 (w), 1069 (s), 1048 (s), 985 (m), 950 (m), 907 (s), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.88 (dd, *J*=11.3 Hz, 17.4 Hz, 1H), 5.59 (d, *J*=17.4 Hz, 1H), 5.12 (dd, *J*=1.0 Hz, 11.3 Hz, 1H), 3.81 (dd, J=3.2 Hz, 9.8 Hz, 1H), 2.42 (dt, *J*=2.7 Hz, 16.9 Hz, 1H), 2.15 (ddd, *J*=2.7 Hz, 9.8 Hz, 16.9 Hz, 1H), 2.00 (t, *J*=2.7 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 139.2, 134.4, 129.4, 126.8, 112.8, 82.9, 79.2, 70.3, 40.5, 27.7, 25.1, 23.5; HRMS (EI) *m/z* 205.13 [calculated for $C_{12}H_{16}N_2O$ (M^+) 205.13].

Preparation of Boc-Imidazole 115.

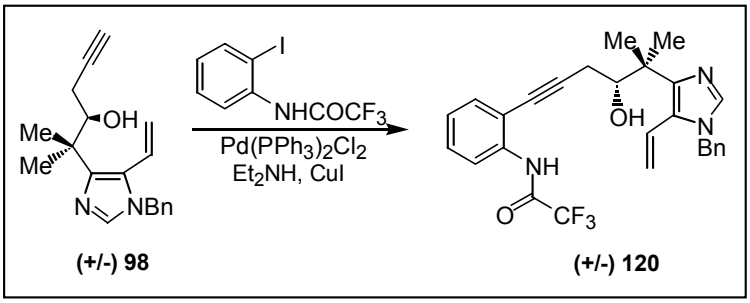


Boc-Imidazole 115. To a stirred solution of **114** (50 mg, 0.24 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at room temperature was added Et_3N (51 μL, 0.37 mmol, 1.5 equiv.), DMAP (3 mg, 0.02 mmol, 0.1 equiv.) and di-*t*-butyldicarbonate (58 mg, 0.26 mmol, 1.1 equiv.). The reaction was allowed to stir for 3 hours at room temperature, at which time H_2O (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL) and the organics combined. After drying with $MgSO_4$, the solvent was removed *in vacuo* and the mixture was chromatographed on silica gel to afford **115** (60 mg, 82 % yield) as a white solid.

Boc-Imidazole 115. m.p. 121-122°C; FTIR (thin film/NaCl) 3306 (m), 2979 (m), 2936 (w), 2118 (w), 1758 (s), 1501 (w), 1469 (w), 1370 (s), 1279 (m), 1156 (s), 1112 (m), 1067 (w), 979 (w), 935 (w), 847 (m), 773 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 6.71 (dd, *J*=11.1 Hz, 17.7 Hz, 1H), 5.55 (dd, *J*=1.8 Hz, 11.1 Hz, 1H), 5.38 (dd, *J*=1.8 Hz, 17.7 Hz, 1H), 4.81 (bs, 1H), 3.80 (bd, *J*=8.1 Hz), 2.40 (dt, *J*=3.0 Hz, 16.7

Hz, 1H), 2.20 ddd J=2.8 Hz, 9.4 Hz, 16.8 Hz, 1H), 2.00 (t, J=2.7 Hz, 1H), 1.60 (s, 9H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 145.9, 136.4, 127.3, 126.3, 123.1, 86.1, 83.3, 79.4, 69.7, 40.8, 28.3, 27.3, 25.2, 23.5; HRMS (EI) *m/z* 305.18 [calculated for $C_{17}H_{24}N_2O_3$ (M^+) 305.18].

Preparation of Acetanilide 120:

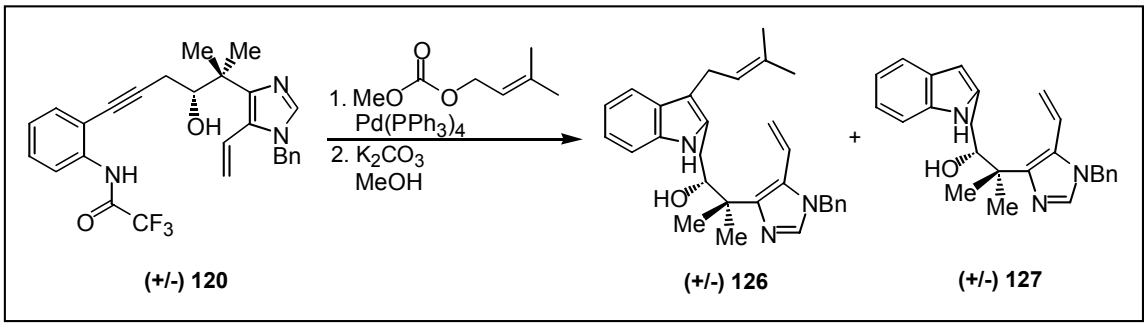


Acetanilide 120. To a solution of **98** (600 mg, 2.04 mmol, 1.0 equiv.) in DMF (10 mL) and Et_2NH (10 mL) was added 2-iodotrifluoroacetanilide (963 mg, 3.06 mmol, 1.5 equiv.), dichlorobis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_2Cl_2$) (72 mg, 0.10 mmol, 0.05 equiv.), and CuI (19 mg, 0.10 mmol, 0.05 equiv.). The mixture was stirred at room temperature for 8 hours at which time the solvent was removed *in vacuo*. The reaction was then chromatographed on silica gel (20% Acetone/Hexanes) to afford **120** (934 mg, 1.94 mmol, 95% yield) as a colorless oil.

Acetanilide 120. FTIR (thin film/NaCl) 3350 (m), 2970 (w), 2225 (w), 1730 (s), 1583 (m), 1541 (m), 1497 (m), 1453 (m), 1359 (w), 1286 (m), 1194 (m), 1153 (s), 1069 (w), 900 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (bs, 1H), 8.34 (d, J=8.4 Hz, 1H), 7.43-7.31 (m, 6H), 7.13 (dt, J=1.0 Hz, 7.6 Hz, 1H), 7.03 (d, J=6.6 Hz, 1H), 6.61 (dd,

J=11.6 Hz, 17.9 Hz, 1H), 5.46 (dd, *J*=1.3 Hz, 11.6 Hz, 1H), 5.25 (dd, *J*=1.3 Hz, 17.9 Hz, 1H), 5.07 (q, *J*=15.9 Hz, 23.8 Hz, 2H), 3.87 (dd, *J*=3.4 Hz, 9.4 Hz, 1H), 2.72 (dd, *J*=3.4 Hz, 17.0 Hz, 1H), 2.53 (dd, *J*=9.4 Hz, 17.0 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (q, *J*=37.6 Hz), 144.4, 136.8, 136.2, 136.1, 131.3, 129.0, 128.8, 128.0, 126.6, 126.0, 125.6, 125.1, 121.4, 119.6, 115.7 (q, *J*=289.1 Hz), 114.3, 98.2, 78.9, 48.9, 40.2, 27.3, 24.1, 24.0; HRMS (EI) *m/z* 482.2057 [calculated for $C_{27}H_{26}F_3N_3O_2$ (M^+) 482.2057].

Preparation of Prenyl Indole 126 and Indole 127:



Prenyl Indole 126 and 127. To a mixture of acetanilide **120** (250 mg, 0.519 mmol, 1.0 equiv.) in THF (15 mL) was added prenyl methyl carbonate (82 mg, 0.571 mmol, 1.1 equiv.) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (30 mg, 0.026 mmol, 0.05 equiv.). The reaction was heated at 60°C for 3 hours at which time K_2CO_3 (360 mg, 2.60 mmol, 5.0 equiv.) and MeOH (1.0 mL) were added and the temperature was increased to 80°C. After 2 hours the solvent was removed *in vacuo* and

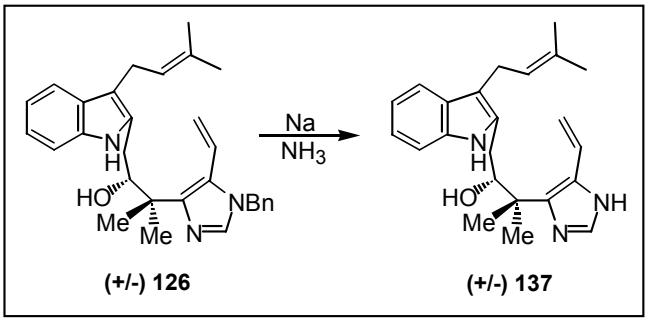
the mixture was chromatographed on silica gel (25% EtOAc/Hexanes) to afford **126** (153 mg, 65%yield) and **127** (41 mg, 20% yield) as waxy solids oils.

Prenyl Indole 126. FTIR (thin film/NaCl) 3288 (s), 3110 (m), 3060 (m), 2974 (s), 2924 (m), 2860 (m), 2748 (s), 1631 (w), 1497 (m), 1460 (s), 1356 (m), 1243 (m), 1124 (w), 1062 (m), 994 (m), 737 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (bs, 1H), 7.51 (d, *J*=7.7 Hz, 1H), 7.42 (s, 1H), 7.39-7.28 (m, 4H), 7.13-7.03 (m, 4H), 6.66 (dd, *J*=11.4 Hz, 17.9 Hz, 1H), 6.00 (bs, 1H), 5.47 (dd, *J*=1.3 Hz, 11.4 Hz, 1H), 5.30 (tt, *J*=1.4 Hz, 6.9 Hz, 1H), 5.27 (dd, *J*=1.3 Hz, 17.9 Hz, 1H), 5.11 (s, 2H), 3.91 (d, *J*=10.3 Hz, 1H), 3.40 (d, *J*=6.9 Hz, 2H), 3.08 (dd, *J*=1.6 Hz, 15.1 Hz, 1H), 2.56 (dd, *J*=10.3 Hz, 15.1 Hz, 1H), 1.81 (s, 3H), 1.70 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 136.5, 136.2, 135.4, 134.6, 130.0, 129.0, 128.1, 128.0, 126.5, 125.8, 125.7, 124.5, 121.0, 120.6, 118.5, 118.0, 110.5, 110.4, 80.8, 48.8, 40.3, 27.9, 27.1, 25.7, 24.1, 23.2, 17.8; HRMS (EI) *m/z* 454.2856 [calculated for $C_{30}H_{25}N_3O$ (M^+) 454.2858].

Indole 127. FTIR (thin film/NaCl) 3274 (s), 2972 (m), 2928 (m), 1723 (m), 1631 (w), 1584 (w), 1548 (w), 1497 (m), 1455 (s), 1358 (w), 1288 (m), 1198 (m), 1156 (s), 1063 (m), 932 (w), 780 (m), 735 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (bs, 1H), 7.51 (d *J*=7.8 Hz, 1H), 7.41 (s, 1H). 7.40-7.29 (m, 5H), 7.10 (t, *J*=7.2 Hz, 1H), 7.06-7.01 (m, 2H), 6.63 (dd, *J*=11.6 Hz, 17.9 Hz, 1H), 6.20 (s, 1H), 5.46 (dd, *J*=1.0 Hz, 11.6 Hz, 1H), 5.25 (dd, *J*=1.0 Hz, 17.9 Hz, 1H), 5.11 (d, *J*=16.3 Hz, 1H), 5.07 (d, *J*=16.3 Hz, 1H), 3.93 (dd, *J*=1.3 Hz, 10.2 Hz, 1H), 3.01 (dd, *J*=1.3 Hz, 15.2 Hz, 1H), 2.69 (dd, *J*=10.2 Hz, 15.2 Hz, 1H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 139.1, 136.4, 136.1, 129.0, 128.3, 128.0, 126.6, 126.5, 125.8, 121.2, 120.6, 119.5, 119.1, 110.6,

99.5, 80.8, 50.8, 48.8, 40.15, 30.6, 27.2, 24.1; HRMS (EI) *m/z* 386.2232 [calculated for $C_{25}H_{27}N_3O$ (M^+) 386.2232].

Preparation of Imidazole 137:

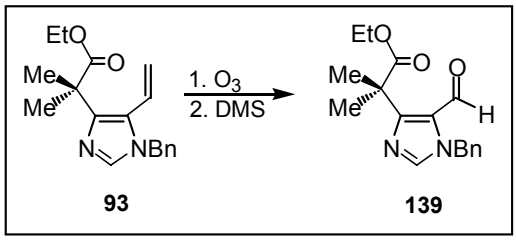


Imidazole 137. To a stirred solution of **126** (100 mg, 220 mmol, 1.0 equiv.) in THF (5 mL) and NH_3 (5 mL) at -78°C was added a small piece of Na metal (roughly 50 mg, 10 equiv.). The solution was allowed to stir until the appearance of a deep purple color (about 10 minutes) at which time NH_4Cl (saturated, aq.) was added to quench the reaction. The mixture was allowed to warm to room temperature and stirred until the NH_3 had boiled off, at which time H_20 (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the organic layers were washed with brine (5 mL), dried with MgSO4, and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel (100% EtOAc) to afford **137** (76 mg, 95% yield) as a colorless oil.

Imidazole 137. FTIR (thin film/NaCl) 3287 (s), 3055 (m), 2937 (s), 2926 (m), 1653 (w), 1615 (m), 1523 (m), 1461 (s), 1376 (m), 1266 (m), 1163 (w), 1046 (m), 903 w), 739 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.97 (bs, 1H), 7.49 (d, *J*=7.5 Hz, 1H),

7.42 (s, 1H), 7.27 (d, *J*=7.9 Hz, 1H), 7.10 (dt, *J*=1.3 Hz, 7.2 Hz, 1H), 7.05 (dt, *J*=1.3 Hz, 7.0 Hz, 1H), 6.93 (dd, *J*=11.4 Hz, 17.4 Hz, 1H), 5.41 (bs, 1H), 5.26 (tt, *J*=1.6 Hz, 7.3 Hz, 1H), 5.17 (d, *J*=11.4 Hz, 1H), 3.86 (dd, *J*=1.6 Hz, 10.5 Hz, 1H), 3.37 (d, *J*=7.0 Hz, 2H), 3.02 (dd, *J*=1.6 Hz, 15.2 Hz, 1H), 2.50 (dd, *J*=10.5 Hz, 15.2 Hz, 1H), 1.80 (s, 3H), 1.69 (d, *J*=1.3 Hz, 3H), 1.47 (s, 3H, 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 133.8, 133.4, 130.3, 128.2, 125.9, 124.3, 120.8, 118.7, 118.2, 112.0, 111.0, 110.5, 80.6, 40.3, 28.2, 27.3, 25.6, 24.3, 23.2, 17.9; HRMS (EI) *m/z* 364.2389 [calculated for $C_{23}H_{29}N_3O$ (M^+) 364.2389].

Preparation of Aldehyde 139:



Aldehyde 139. A solution of vinyl imidazole **93** (100 mg, 0.34 mmol) was stirred at -78°C in MeOH (5 mL). Ozone was passed over the reaction until consumption of the starting material as indicated by TLC, at which time dimethyl sulfide (500 μL) was added. The reaction was allowed to warm to room temperature and stirred for 12 hours. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **139** (83 mg, 81% yield) as a colorless oil.

Aldehyde 139. FTIR (thin film/NaCl) 3109 (w), 3032 (w), 2982 (m), 2936 (w), 2768 (w), 1728 (s), 1665 (s), 1517 (m), 1499 (m), 1455 (m), 1353 (m), 1323 (m), 1256 (m), 1139 (m), 1027 (m), 858 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (d, *J*=0.9 Hz, 1H), 7.56 (s, 1H), 7.36-7.26 (m, 3H), 7.15 (d, *J*=6.7 Hz, 2H), 5.48 (s, 2H), 4.15 (q, *J*=7.1 Hz, 2H), 1.68 (s, 6H), 1.17 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 175.9, 140.6, 135.6, 128.9, 128.2, 127.3, 125.7, 77.3, 77.0, 76.7, 61.3, 50.8, 44.6, 27.0, 13.9; HRMS (EI) *m/z* 301.1553 [calculated for $C_{17}H_{20}N_2O_3$ (M^+) 301.1552].

2.10 Notes and References

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(13) The reaction mixture contains residual HBr from the previous bromination step which likely serves to catalyze the reaction.

(14) Although chromatography could be used to separate the material, the reaction was typically performed on molar scale, making this option unattractive.

(15) Several different protecting groups were evaluated for their applicability to the synthesis including benzyl, *p*-methoxybenzyl, Boc, benzenesulfonamide and *o*-nitrobenzyl. Based on the ease of both protection and deprotection, benzyl was chosen as that best suited to the synthetic goals.

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(32) A partial list of chloride ion sources employed includes LiCl, LiCl/18-crown-6, KCl, NaCl and $(Bu)_4NCl$.

(33) A partial list of chloride sources employed includes CCl_4, C_2Cl_6, $(CCl_3)_2CO$ and NCS.

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(38) A list of reaction conditions employed is includes combinations of CuI and catalysts ($Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$,) ligands (PPh_3, $P(o\text{-}tol)_3$) bases (Et_3N, Et_2NH, *i*-Pr_2NH) and solvents (PhH, DMF, THF, CH_3CN) at various temperatures.

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(50) Compound **122** was also triply protected as both its Boc and benzene sulfonamide derivatives without any improvement in the oxidation reactions.

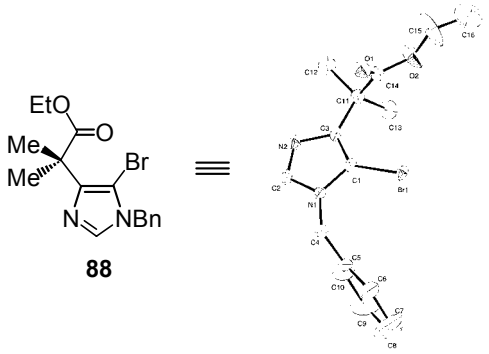
(51) A partial list of hydroboration reagents employed includes $BH_3 \cdot THF$, $BH_3 \cdot DMS$, $BH_3 \cdot Et_3N$, catecholborane, 9-BBN, and disiamylborane in various solvents at various temperatures.

Appendix One: Spectra Relevant to Chapter Two

Appendix Two: X-ray Structures Relevant To Chapter Two

X-ray Crystallography Report for Bromoimidazole **88**

Figure A.2.1



A.2.1.1 Crystal Data

Empirical Formula	$C_{16}H_{19}N_2O_2Br$
Formula Weight	351.24
Crystal Color, Habit	colorless, cut column
Crystal Dimensions	0.10 X 0.14 X 0.35 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 10.5967(3)Å b = 7.0396(2) Å c = 22.577(1) Å V = 93.587(2)^o V = 1680.84(9) Å^3
Space Group	$P2_1/n$ (#14)
Z value	4
Dcalc	1.388 g/cm^3
F000	720.00
μ(MoKα)	24.58 cm^{-1}

A.2.1.2 Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å) graphite
monochromated	
Take-off Angle	2.8^o
Crystal to Detector Distance	35 mm

Temperature	-90.0^{o}C
Scan Type	ω
Scan Rate	30s/frame
Scan Width	1.5^{o}/frame
$2\theta_{max}$	55.0^{o}
No. of Reflections Measured	Total: 10098 Unique: 4119 (R_{int} = 0.036)
Corrections	Lorentz-polarization SORTAV absorption

A.2.1.3 Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>5.00\sigma(I)$)	2439
No. Variables	190
Reflection/Parameter Ratio	12.84
Residuals: R; Rw	0.035 ; 0.040
Goodness of Fit Indicator	2.17
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.65 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.55 $e^-/Å^3$

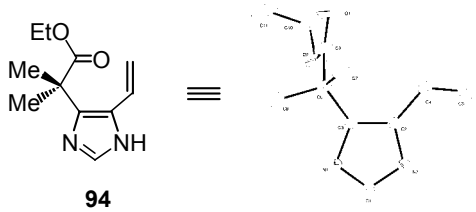
Atomic coordinates and B_{iso}/B_{eq}

Table A.2.1

atom	x	y	z	Beq
Br(1)	0.87484(3)	0.44044(4)	1.06601(2)	2.876(8)
O(1)	1.1058(2)	0.1602(4)	1.1510(1)	4.24(6)
O(2)	1.0005(2)	0.2625(5)	1.2260(1)	6.31(8)
N(1)	0.8435(2)	0.1003(3)	0.9994(1)	2.41(6)
N(2)	0.8619(2)	-0.1372(4)	1.0634(1)	2.81(6)
C(1)	0.8642(2)	0.1765(4)	1.0549(1)	2.30(7)
C(2)	0.8434(3)	-0.0907(4)	1.0074(2)	2.79(8)
C(3)	0.8748(3)	0.0310(4)	1.0947(1)	2.37(7)
C(4)	0.8272(3)	0.2013(5)	0.9427(1)	2.77(7)
C(5)	0.7021(3)	0.3007(5)	0.9337(1)	2.82(7)
C(6)	0.6984(4)	0.4767(6)	0.9062(2)	4.8(1)
C(7)	0.5869(5)	0.5701(8)	0.8934(2)	7.6(2)
C(8)	0.4780(5)	0.488(1)	0.9087(3)	8.8(2)
C(9)	0.4770(4)	0.3176(9)	0.9371(2)	7.7(2)
C(10)	0.5909(3)	0.2222(6)	0.9494(2)	4.8(1)
C(11)	0.8948(3)	0.0407(5)	1.1611(1)	2.95(8)
C(12)	0.9242(4)	-0.1573(6)	1.1866(2)	5.0(1)
C(13)	0.7746(3)	0.1178(6)	1.1877(2)	4.62(10)
C(14)	1.0120(3)	0.1601(5)	1.1775(2)	3.44(9)
C(15)	1.1176(5)	0.3665(10)	1.2486(3)	10.5(2)
C(16)	1.0920(5)	0.4707(9)	1.2963(3)	9.7(2)
H(1)	0.8314	-0.1801	0.9760	3.3458
H(2)	0.8925	0.2934	0.9412	3.3204
H(3)	0.8343	0.1121	0.9115	3.3204
H(4)	0.7753	0.5341	0.8961	5.7926
H(5)	0.5859	0.6901	0.8741	9.1043
H(6)	0.4001	0.5516	0.8994	10.5614
H(7)	0.3997	0.2643	0.9483	9.2167
H(8)	0.5913	0.1024	0.9688	5.7634
H(9)	0.8538	-0.2385	1.1782	5.9546
H(10)	0.9962	-0.2077	1.1690	5.9546
H(11)	0.9409	-0.1485	1.2283	5.9546
H(12)	0.7606	0.2453	1.1752	5.5387
H(13)	0.7848	0.1136	1.2298	5.5387
H(14)	0.7041	0.0420	1.1746	5.5387
H(15)	1.1823	0.2773	1.2594	12.6140
H(16)	1.1452	0.4477	1.2184	12.6140
H(17)	1.1669	0.5324	1.3115	11.6544
H(18)	1.0613	0.3901	1.3259	11.6544
H(19)	1.0297	0.5631	1.2851	11.6544

X-ray Crystallography Report for Vinylimidazole **94**

Figure A.2.2



A.2.2.1 Crystal Data

Empirical Formula	$C_{22}H_{32}N_4O_4$
Formula Weight	416.52
Crystal Color, Habit	colorless, prism
Crystal Dimensions mm	0.17 X 0.18 X 0.25
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 8.8769(3)Å b = 15.701(1) Å c = 17.1699(4) Å V = 91.564(2)^o V = 2392.2(1) Å^3
Space Group	$P2_1/c$ (#14)
Z value	4
Dcalc	1.156 g/cm^3
F000	896.00
μ(MoKα)	0.80 cm^{-1}

A.2.2.2 Intensity Measurements

Diffractometer	Nonius KappaCCD
Radiation	MoKα (λ = 0.71069 Å)
monochromated	graphite
Take-off Angle	2.8^o
Crystal to Detector Distance	33 mm

Temperature	-90.0^{o}C
Scan Rate	48s/frame
Scan Width	1.6^{o}/frame
$2\theta_{max}$	55.0^{o}
No. of Reflections Measured	Total: 5715
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 1.97596e-06)

A.2.2.3. Structure Solution and Refinement

Structure Solution (SIR92)	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\ w\ (\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo)$
p-factor	0.0100
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I>5.00\sigma(I)$)	3195
No. Variables	399
Reflection/Parameter Ratio	8.01
Residuals: R; Rw	0.037 ; 0.041
Goodness of Fit Indicator	2.71
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.21 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.15 $e^-/Å$

A.2.2.4 Atomic coordinates and B_{iso}/B_{eq}

Table A.2.2

atom	x	y	z	Beq
O(1)	0.7889(1)	0.51649(9)	0.30487(7)	4.85(4)
O(2)	0.6313(1)	0.49499(8)	0.20341(7)	4.31(3)
O(3)	0.9422(1)	0.21565(9)	0.61179(7)	4.31(3)
O(4)	1.1569(1)	0.22301(7)	0.54811(6)	3.54(3)
N(1)	0.2573(1)	0.55155(8)	0.27488(7)	2.33(3)
N(2)	0.2121(1)	0.42122(9)	0.31618(7)	2.47(3)
N(3)	1.0020(1)	0.29264(8)	0.35513(7)	2.70(3)
N(4)	0.8570(1)	0.18277(8)	0.32382(7)	2.36(3)
C(1)	0.1545(2)	0.4920(1)	0.28428(9)	2.47(4)
C(2)	0.3640(2)	0.43502(10)	0.32989(8)	2.27(3)
C(3)	0.3900(2)	0.51650(10)	0.30406(8)	2.09(3)
C(4)	0.4655(2)	0.3710(1)	0.36404(10)	3.05(4)
C(5)	0.4273(3)	0.2955(1)	0.3890(1)	4.00(5)
C(6)	0.5336(2)	0.56823(10)	0.31131(9)	2.49(4)
C(7)	0.5719(2)	0.5855(1)	0.3977(1)	3.41(5)
C(8)	0.5160(2)	0.6536(1)	0.2681(1)	3.66(5)
C(9)	0.6662(2)	0.5232(1)	0.27497(10)	3.04(4)
C(10)	0.7554(3)	0.4605(2)	0.1590(2)	5.78(7)
C(11)	0.8372(3)	0.5289(2)	0.1184(2)	6.74(8)
C(12)	0.9508(2)	0.2424(1)	0.29841(10)	2.87(4)
C(13)	0.8443(2)	0.19452(9)	0.40314(8)	2.13(3)
C(14)	0.9338(2)	0.26358(9)	0.42147(8)	2.13(3)
C(15)	0.7534(2)	0.1378(1)	0.45117(10)	2.59(4)
C(16)	0.6770(2)	0.0734(1)	0.4286(1)	3.51(5)
C(17)	0.9547(2)	0.30871(10)	0.49938(8)	2.46(4)
C(18)	0.8032(2)	0.3440(2)	0.5254(1)	3.81(5)
C(19)	1.0667(2)	0.3827(1)	0.4942(1)	3.03(4)
C(20)	1.0139(2)	0.2444(1)	0.55943(9)	2.74(4)
C(21)	1.2240(2)	0.1626(2)	0.6034(1)	4.50(6)
C(22)	1.3858(3)	0.1547(2)	0.5871(2)	5.19(7)
H(1)	0.049(2)	0.4979(9)	0.2733(8)	2.6(3)
H(2)	0.156(2)	0.376(1)	0.330(1)	4.3(4)
H(3)	0.568(2)	0.388(1)	0.3654(9)	4.2(4)
H(4)	0.503(2)	0.259(1)	0.413(1)	5.1(5)
H(5)	0.323(2)	0.274(1)	0.384(1)	4.8(5)
H(6)	0.590(2)	0.528(1)	0.428(1)	4.7(4)
H(7)	0.661(2)	0.624(1)	0.4018(9)	3.7(4)
H(8)	0.487(2)	0.614(1)	0.4226(9)	4.0(4)
H(9)	0.496(2)	0.645(1)	0.210(1)	5.0(5)

H(10)	0.611(2)	0.685(1)	0.2740(9)	4.3(4)
H(11)	0.437(2)	0.691(1)	0.292(1)	5.0(5)
H(12)	0.706(2)	0.426(1)	0.124(1)	6.5(6)
H(13)	0.821(2)	0.426(1)	0.197(1)	6.3(6)
H(14)	0.916(3)	0.503(1)	0.089(1)	7.5(6)
H(15)	0.888(2)	0.568(1)	0.157(1)	6.6(6)
H(16)	0.760(3)	0.567(2)	0.089(1)	8.9(8)
H(17)	0.975(2)	0.2466(9)	0.2434(9)	2.8(3)
H(18)	0.811(2)	0.143(1)	0.2926(9)	3.1(4)
H(19)	0.756(2)	0.1554(10)	0.499(1)	3.0(4)
H(20)	0.625(2)	0.042(1)	0.466(1)	4.4(4)
H(21)	0.676(2)	0.055(1)	0.375(1)	3.6(4)
H(22)	0.725(2)	0.297(1)	0.5275(10)	4.9(5)
H(23)	0.814(2)	0.374(1)	0.575(1)	5.1(4)
H(24)	0.766(2)	0.386(1)	0.488(1)	4.7(5)
H(25)	1.078(2)	0.412(1)	0.5466(10)	3.8(4)
H(26)	1.025(2)	0.427(1)	0.4573(10)	3.7(4)
H(27)	1.173(2)	0.3625(10)	0.4776(9)	3.1(3)
H(28)	1.210(2)	0.190(1)	0.658(1)	6.9(6)
H(29)	1.162(2)	0.110(1)	0.5938(10)	4.6(4)
H(30)	1.430(2)	0.114(1)	0.624(1)	6.7(6)
H(31)	1.440(2)	0.211(1)	0.591(1)	6.2(5)
H(32)	1.402(2)	0.132(1)	0.531(1)	6.9(6)

Chapter Three

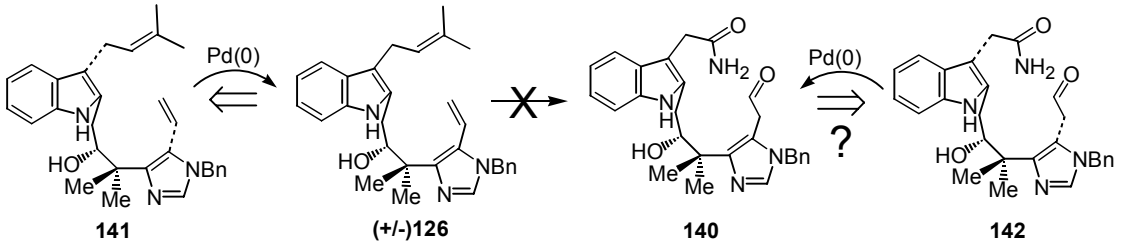
Evolution of a Synthetic Approach

3.1 A New Synthetic Strategy

Unable to advance the previous system toward the securamines, it was evident that the synthetic approach would have to be altered.

The breakdown of the preceding approach arose from the inability to affect any oxidation of the advanced olefinic system (**126→140**). This difficulty suggested the development of a new synthetic strategy devoid of late stage oxidation chemistry; one that would incorporate the correct oxidation states directly into the synthetic sequence. Because of its modular nature, it was believed that the previous approach could be adapted to accommodate these requirements. Both problematic olefins from the previous approach had been introduced through palladium coupling chemistry (**141→126**), therefore if the electrophilic component in each case could be altered to incorporate the correct oxidation state, the strategy would still be viable (**142→140**).

Scheme 3.1.1

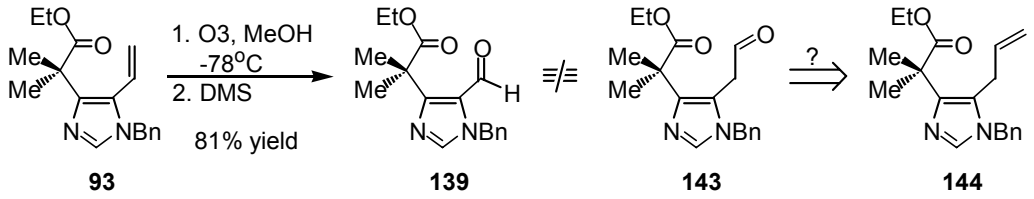


3.2 Addressing the Aldehyde

3.2.1 Reevaluating Ozonolysis

The first impasse addressed was that of the chemically resistant vinyl olefin. It was shown previously that a carefully employed ozonolysis of the vinyl imidazole would afford the corresponding aldehyde (**93**→**139**). Unfortunately, the resulting aldehyde (**139**) was one carbon short of that needed for eventual macrocyclic condensation (i.e. **143**). The homologous allylic imidazole (**144**), therefore, should provide the correct aldehyde after ozonolysis.

Scheme 3.2.1

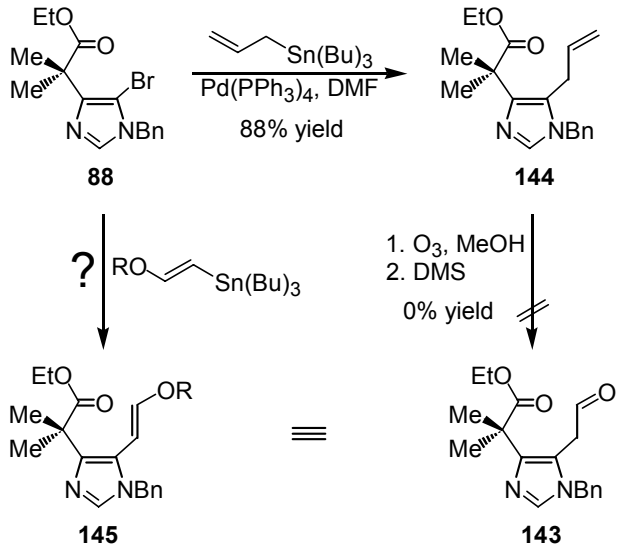


3.2.2 An Aldehyde Equivalent

To this end, Stille coupling of aryl bromide **88** with allyl(tributyl)tin afforded an excellent yield of the requisite allylic imidazole (**144**) (Scheme 3.2.2). Careful ozonolysis at –78°C in MeOH, however, yielded an intractable mixture of products. Although optimization may have possible,[1] the desired aldehyde (**143**) would require protection and later deprotection if it were to survive the impending nucleophilic reaction

conditions. Considering these options, the idea of an enol ether protecting group presented the possibility of direct introduction of a protected aldehyde equivalent (i.e. **145**). Furthermore, the consistent success with which Stille coupling had occurred on bromoimidazole **88** offered the prospect of coupling a stannyl enol ether to provide the protected aldehyde directly (**88**→**145**).

Scheme 3.2.2

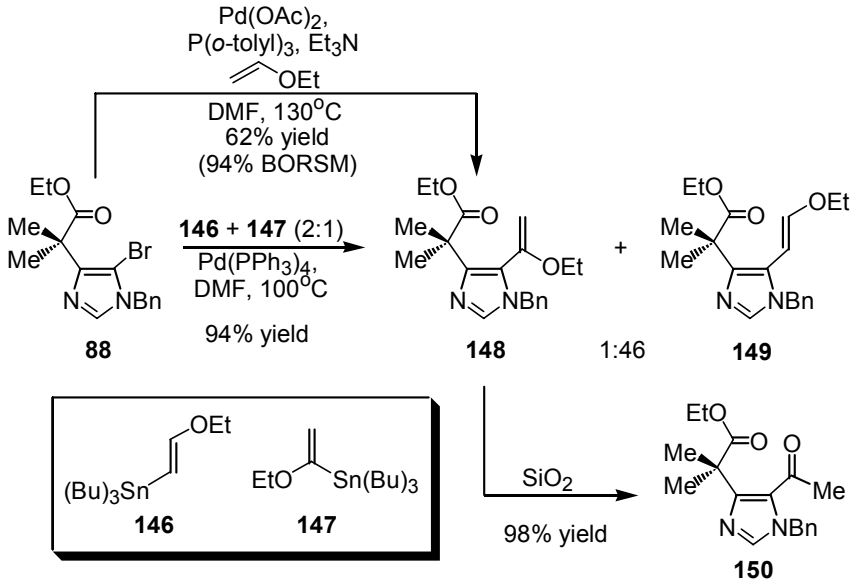


3.2.3 Selective Stille Coupling

While stannylcupration of acetylenes is a common method for the preparation of vinyl tin compounds,[2] the ethereal form of the product presents some difficulty. Outside of carefully controlled conditions, the major stannylcupration product of alkyl acetylenic ethers is the corresponding alcohol, resulting from an elimination process. Nevertheless, using conditions developed by Oehlschlager and Cabezas, it was possible to generate a

mixture of α- and β-tin enol ethers **146** and **147**. The two tin compounds were inseparable by any methods employed by this lab, and concern developed over the potential coupling of the undesired α product (**147**) with the aryl halide.[3-5] Fortunately, these concerns were quickly allayed by the almost exclusive preference for Stille coupling with the desired β-tin compound. Reaction of readily available ethyl vinyl ether with aryl halide **88** under Heck-type conditions afforded exclusively undesired coupling product **148**. [6,7]

Scheme 3.2.3



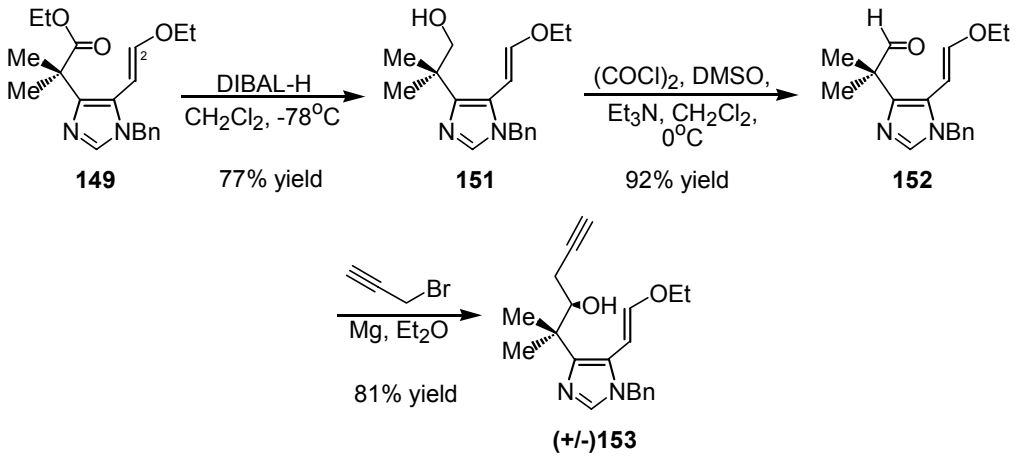
Due to conjugation with the imidazole, the desired enol ether product (**149**) was surprisingly stable, and could be handled without concern for hydrolysis. Interestingly, however, the same stability was not true of minor Stille product **148**. Even the mildly acidic conditions of silica gel chromatography effected hydrolysis of enol ether **148** to ketone **150**.

3.3 Toward Indole Construction

3.3.1 Elaboration of the Ester

With the correct oxidation state now installed at C-2 (Scheme 3.3.1), efforts were again shifted towards construction of the indole heterocycle. Employing the successful chemistry of the earlier approach to elaborate the ethyl ester, DIBAL-H reduction afforded alcohol **151**. Oxidation of the alcohol to the aldehyde proceeded without incident under Swern conditions, followed by addition of propargyl grignard to yield terminal acetylene **153**.

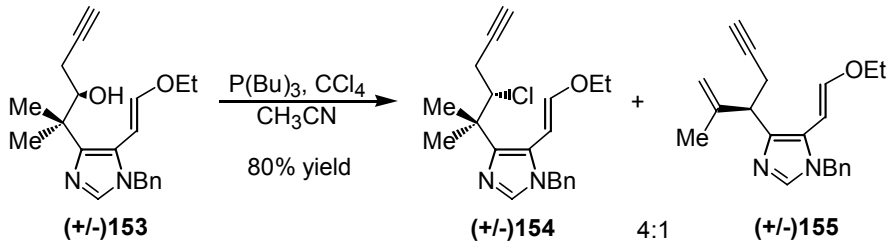
Scheme 3.3.1



3.3.2 Improved Chlorination

Given the limited success of chlorination in the previous vinyl system, this critical transformation was again explored. The optimized chlorination conditions, applied to **153**, afforded a very gratifying 4:1 mixture of chlorinated (**154**) and rearranged (**155**) products. The improved ratio of products was difficult to rationalize given the minor differences between the vinyl and enol ether systems.[8]

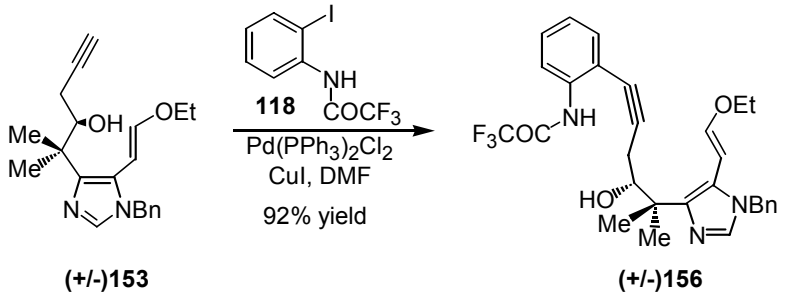
Scheme 3.3.2



3.3.3 A Cyclization Precursor

Encouraged by the chlorination results, material was advanced toward the natural product. Sonagashira coupling[9,10] of the chlorinated substrate **154** was again unsuccessful, but coupling of the preceding alcohol with iodoaniline **118**[11] cleanly produced the cyclization precursor (**156**).

Scheme 3.3.3



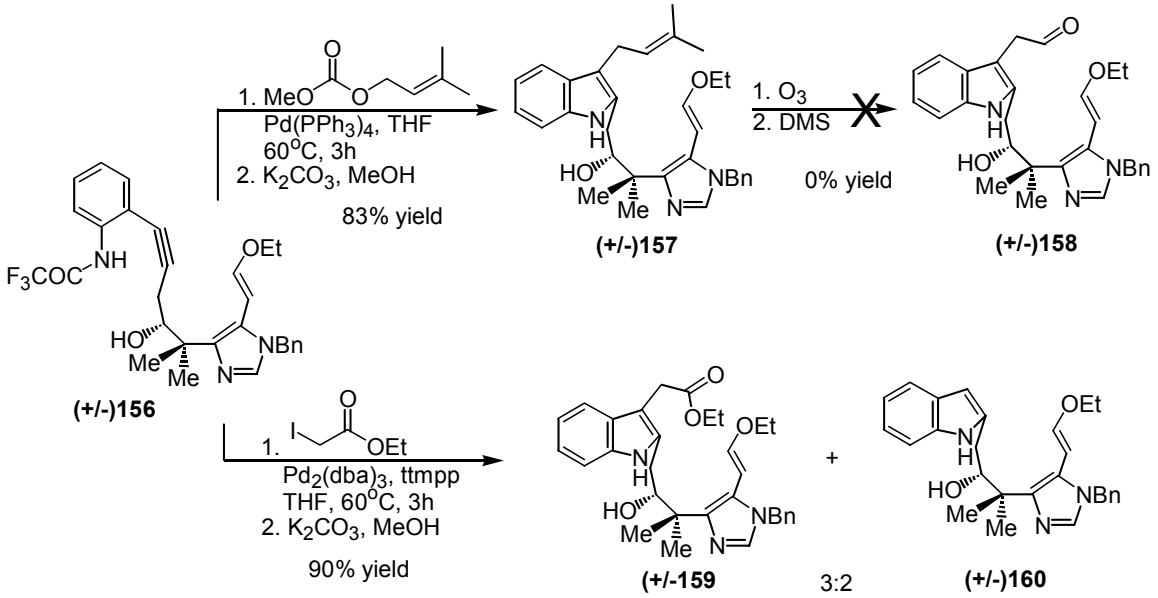
3.4 Addressing The Amide

3.4.1 Electrophile Replacement

The efficiency with which the previous indole cyclization took place mandated a return to the Cacchi reaction. The issue to be addressed at this juncture, however, was the oxidation state of the indole side chain.

Reemployment of Cacchi's indole protocol to the new system reliably afforded fully alkylated indole **157**. As expected, however, attempted oxidative cleavage of the trisubstituted olefin once again resulted in decomposition. With sights set on direct installation of the correct side chain oxidation state, the allylic carbonate was replaced with ethyl iodoacetate as the electrophile. A careful screening of catalyst systems[12] revealed a set of conditions affording a good yield of alkylated indole **159**, incorporating every carbon in the natural product with the correct oxidation states in place.

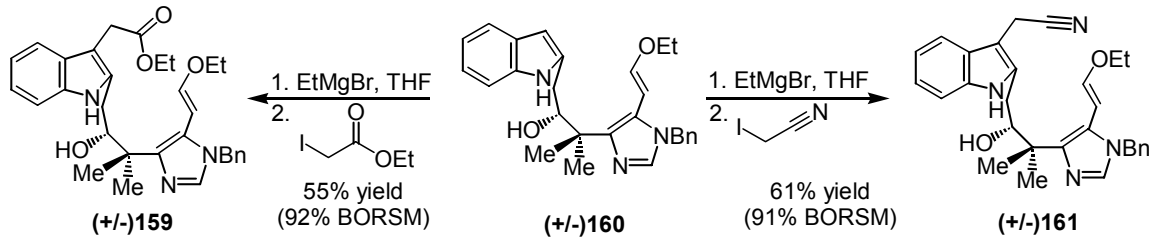
Scheme 3.4.1



3.4.2 Salvaging the Byproduct

Indole **159** was invariably accompanied by unalkylated indole **160**, the apparent product of reduction in the palladium-catalyzed cyclization. At such a late stage in the synthetic sequence, discarding this unalkylated indole was not acceptable. In an effort to salvage this material, the alkylation of indole **160** was explored.

Scheme 3.4.2



Treatment of indole **160** with ethyl magnesium bromide as a base, followed by addition of ethyl iodoacetate provided a 55% yield of alkylated indole **159** (92% based on recovered starting material). Similarly, iodoacetonitrile could be employed as the electrophile, affording the corresponding nitrile as the product (**161**) in 61% yield.

3.4.3 An Alternative Cyclization

Separation of indole ester **159** from unalkylated indole **160** proved a hopelessly tedious task.[13] In an effort to avoid this separation, the indole cyclization was optimized toward unalkylated indole **160**, which could then be alkylated to the nitrile. Although the unalkylated indole had always been a byproduct in the previous cyclization reactions, the mechanism of its formation was unclear. For example, simple exclusion of the electrophile from the reaction, while affording a fair yield of indole **160**, resulted in the formation of significant quantities of several byproducts (**162, 163** and **164**). After extensive experimentation, it was found that addition of ethylene glycol to the reaction mixture suppressed the formation of these byproducts and afforded a much-improved yield of indole **160** (Table 3.4.1).[14] **160** was then alkylated as previously described.

Scheme 3.4.3

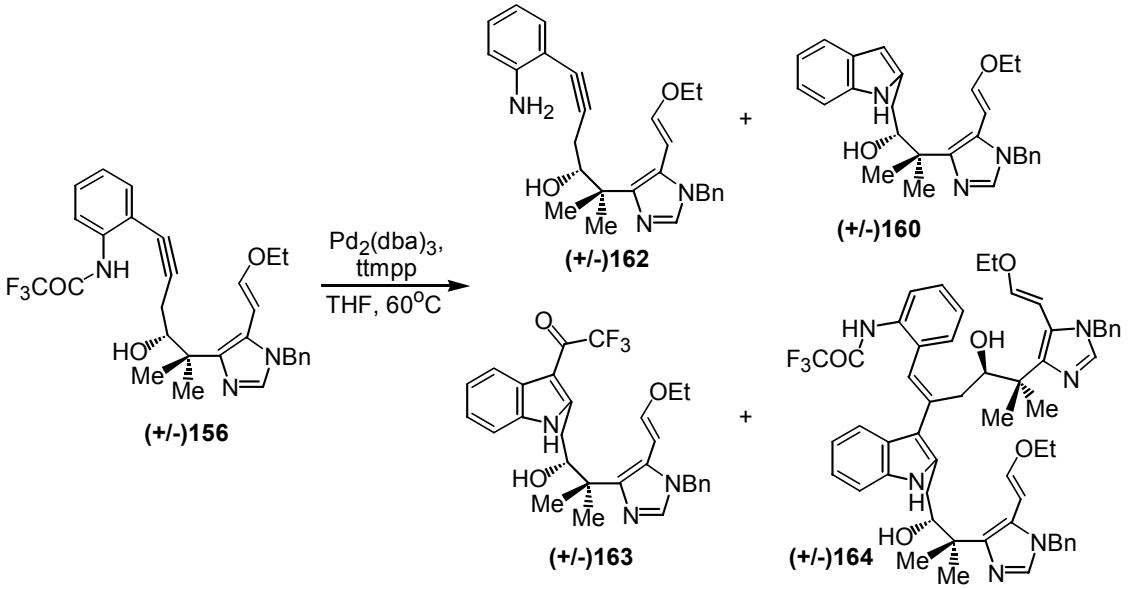


Table 3.4.1

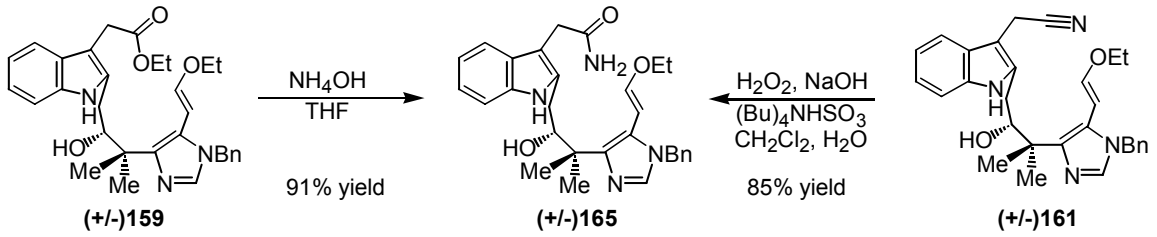
	160	**162**	**163**	**164**
w/o ethylene glycol	35%	12%	15%	10%
w/ ethylene glycol	71%	4%	9%	3%

3.5 Toward Macrocyclization

3.5.1 Acetal Formation

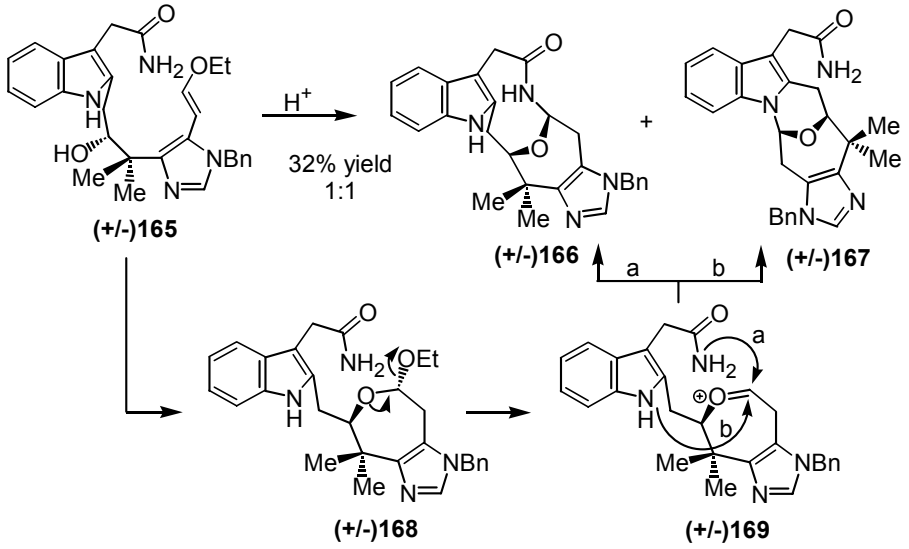
Conversion of nitrile **161** to the corresponding amide was achieved with basic peroxide under phase-transfer conditions. The same amide could be formed from ester **159** by treatment with refluxing ammonium hydroxide.

Scheme 3.5.1



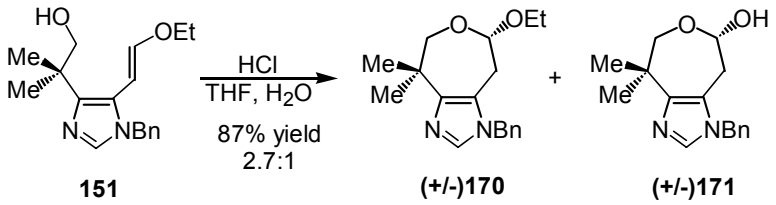
With the amide in place, the prospect of macrocyclic condensation had reached fruition. Under acidic catalysis, the previously formed enol ether should function as an appropriate electrophile for a nucleophilic amide. Toward this end, amide **165** was treated with a variety of acidic conditions. Unfortunately, reactivity appeared to be directed toward the secondary alcohol rather than the amide. Isolated products were identified as aminals **166** and **167**.[15] Presumably these aminals had been formed via initial formation of acetal **168**, followed by closure of either the amide nitrogen (path a) or the indole nitrogen (path b) onto oxonium intermediate **169**. Interestingly, **166** contains the correct C-N bond found in the natural products with the enamide olefin and neopentyl chlorine masked as an ether.

Scheme 3.5.2



The reactivity of the alcohol toward the enol ether was supported by experiments on earlier analogous substrates (Scheme 3.5.3). Thus, alcohol **151**, when subjected to similarly acidic conditions, afforded a mixture of acetal **170** and hemiacetal **171**.

Scheme 3.5.3

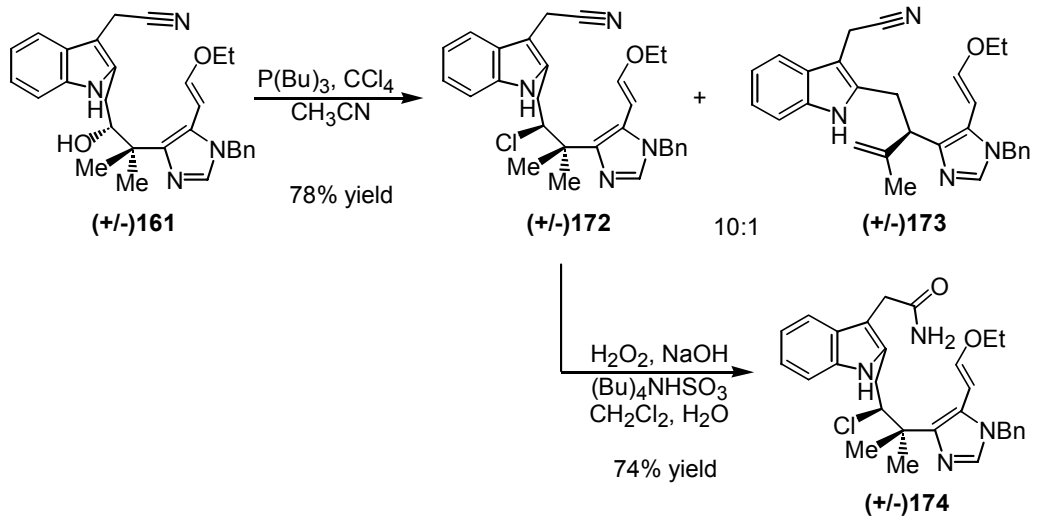


3.5.2 Chlorine Introduction

The enhanced reactivity of the alcohol with respect to the suggested that the reaction conditions chosen for cyclization might be better suited to the corresponding

chlorinated substrate. The free amide, however, presented complications in chlorination, and focus therefore briefly reverted to nitrile **161**. When the optimized chlorination conditions were employed, halogenation proceeded with a gratifying 10:1 product distribution favoring the desired chloride. Basic peroxide hydration of the nitrile ensued without incident to afford an excellent yield of amide **174**.

Scheme 3.5.4

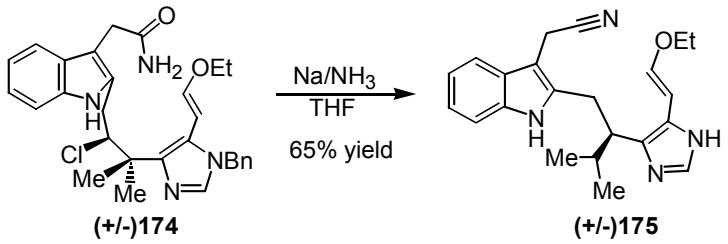


3.5.3 Rearrangement Revisited

In an effort to alter the reactivity of the heterocyclic system to yield products more closely resembling securamine A, the benzyl protecting group was removed. The product of the deprotection, surprisingly, was not simply the expected free imidazole, but apparently the result of a rearrangement reminiscent of that realized during chlorination. Under the dissolving metal conditions, however, the product was not the terminal methylene, but rather the corresponding isopropyl compound (**175**) (Scheme 3.5.5). The

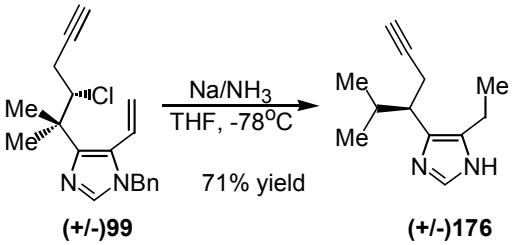
reduced product suggests either a radical or anionic version of the rearrangement mechanism proposed earlier.

Scheme 3.5.5



Identical reaction conditions were applied to vinyl imidazole **99** with the same curious results.

Scheme 3.5.6

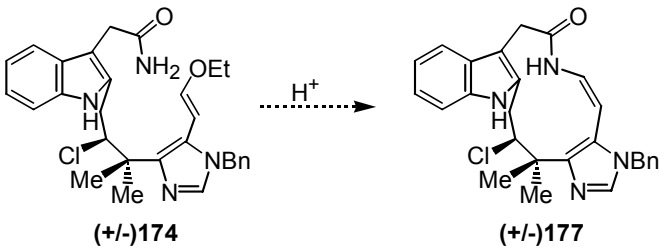


3.5.4 Attempts at Cyclization

Efforts are currently focused on the acid-catalyzed condensation of amide **174** to macrocycle **177**. Of particular difficulty has been the issue of solubility. Upon exposure to acidic conditions **174** tends to precipitate out of solution, the likely result of

protonation of the imidazole. Ironically, the protonated material becomes soluble only in polar protic solvents such as MeOH or H_2O, conditions seemingly prohibitive of enamide formation. While several reaction conditions have produced as-yet unidentified products, their crude spectra do not suggest the formation of the desired enamide.

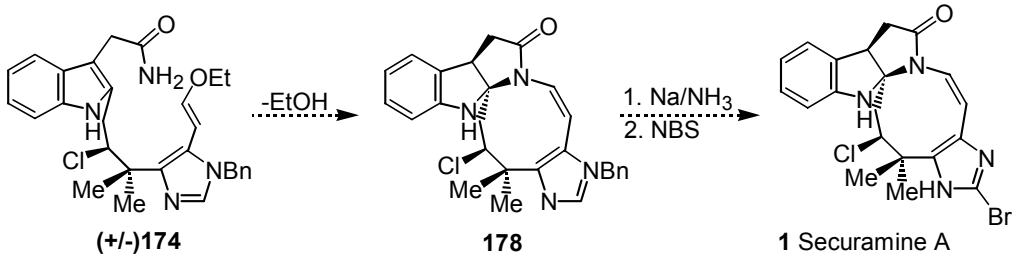
Scheme 3.5.7



3.6 Conclusions

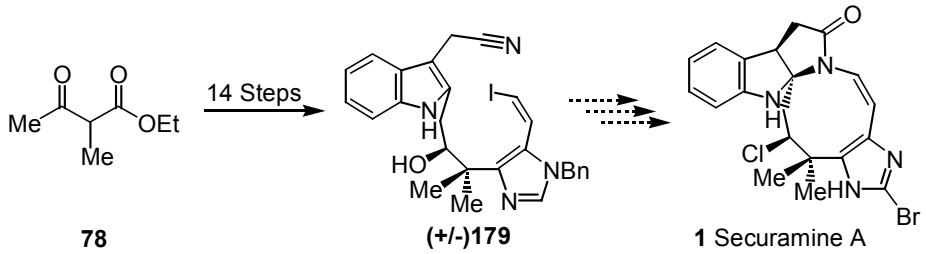
Applying knowledge gained from previous approaches, this lab has designed and carried out a flexible and efficient 15-step synthesis of advanced intermediate **174** towards the total synthesis of the securamines. Advanced intermediate **174** contains both appropriately substituted heterocycles of the natural product, the geminal dimethyl and neopentyl chlorine centers, and incorporates every carbon of the natural product in the correct oxidation state. Currently the work stands with just three synthetic steps remaining for the completion of securamine A: macrocyclic condensation, benzyl deprotection and bromination (Scheme 3.6.1).

Scheme 3.6.1



While work continues toward the planned acid-catalyzed condensation to the enamide, the difficulties presented by the acidic conditions have spawned alternative macrocyclization initiatives. Although some of these efforts are very advanced, their progress will not be discussed in detail here as they will be the subject of a future dissertation. It can be said, however, that through the employment of an adapted synthetic approach, material has been advanced to intermediate **179**, which will be the subject of a copper-mediated coupling reaction.[16] Early model studies predict the success of this method.

Scheme 3.6.2



Upon completion of securamine A, efforts will be advanced toward introduction of stereoselectivity into the sequence and completion of the remaining members of the securamine family of natural products.

3.7 Experimental

3.7.1 Materials and Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using freshly distilled solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride. All other commercially obtained reagents were used as received.

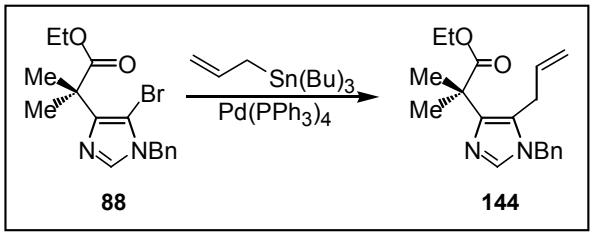
Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (230-400 mesh) purchased from Bodman. In general, the chromatography guidelines reported by Still et al. were followed

All melting points were obtained on a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M1200 FTIR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500, Bruker Avance DPX-500 or Bruker Avance DPX-400 spectrometer. Chemical shifts are reported relative to internal chloroform (^1H, δ 7.26 ppm; ^{13}C, δ 77.0 ppm). High resolution mass spectra

were performed at the University of Illinois Mass Spectrometry Center. Single-crystal X-ray analyses were performed by Susan DeGala of Yale University. High performance liquid chromatography (HPLC) was performed on a Waters 510 solvent delivery system using a Rainin Microsorb 80-199-C5 column, or a Rainin Dynamax SD-200 solvent delivery system with a Rainin Microsorb 80-120-C5 column.

3.7.2 Preparative Procedures.

Preparation of Allyl Imidazole 144:

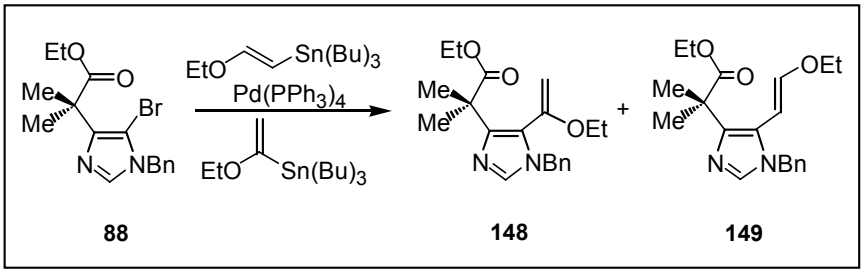


Allyl Imidazole 144. To a stirred solution of bromoimidazole **88** (250 mg, 0.71 mmol, 1.0 equiv.) in DMF (10 mL) was added allyl(tributyl)tin (331 μL, 1.07 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (41 mg, 0.036 mmol, 0.05 equiv.). The reaction was heated at 100°C for 4 hours and then the solvent removed *in vacuo*. The mixture was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **144** (196 mg, 88% yield) as a colorless oil.

Allyl Imidazole 144. FTIR (thin film/NaCl) 3080 (w), 3030 (w), 2978 (m), 2934 (m), 2870 (w), 1724 (s), 1638 (w), 1498 (m), 1454 (m), 1382 (m), 1360 (w), 1256 (s), 1136 (s), 1029 (m), 913 (w), 729 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H),

7.35-7.28 (m, 3H), 7.00 (d, *J*=7.3 Hz, 2H), 5.76 (ddt, *J*=5.3 Hz, 10.1 Hz, 17.1 Hz, 1H), 5.05 (dd, *J*=1.6 Hz, 10.1 Hz, 1H), 4.88 (dd, *J*=1.6 Hz, 17.0 Hz, 1H), 4.10 (q, *J*=7.0 Hz, 2H), 1.60 (s, 3H), 1.17 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 142.0, 136.4, 135.5, 134.7, 128.9, 127.9, 126.5, 123.5, 116.2, 60.6, 48.4, 43.3, 27.6, 26.3, 14.1; HRMS (EI) *m/z* 313.1915 [calculated for $C_{19}H_{24}N_2O_2$ (M^+) 313.1916].

Preparation of Enol Ethers 148 and 149:



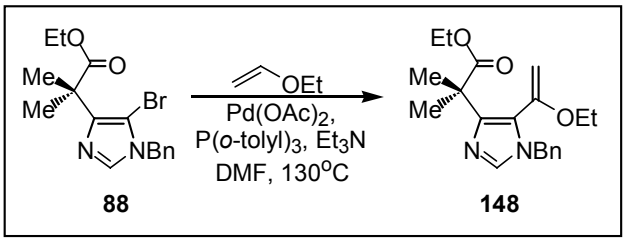
Enol Ethers 148 and 149. To a solution of **88** (19.0 g, 53.33 mmol, 1.0 equiv.) in DMF (500 mL) was added a 2:1 mixture of **146** and **147** (38.5 g, 106.7 mmol, 2.0 equiv.) and $Pd(PPh_3)_4$ (3.08 g, 2.67 mmol, 0.05 equiv.). The mixture was stirred at 100°C for 4 hours at which time the solvent was removed *in vacuo* and the mixture chromatographed on silica gel (30% EtOAc/Hexanes) to afford **149** (16.76 g, 92% yield) and **148** (297 mg, 2% yield) as colorless oils.

Enol Ether 149. FTIR (thin film/NaCl) 2980 (s), 2934 (m), 1725 (s), 1663 (m), 1644 (m), 1496 (m), 1455 (m), 1380 (w), 1361 (w), 1318 (w), 1255 (m), 1193 (s), 1177 (s), 1134 (s), 1029 (m), 932 (w), 853 (w), 729 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.35-7.26 (m, 3H), 7.03 (d, *J*=7.2 Hz, 2H), 6.28 (d, *J*= 13.0 Hz, 1H), 5.24

(d, J=13.0 Hz, 1H), 5.02 (s, 2H), 4.10 (q, J=7.0 Hz, 2H), 3.75 (q, J=7.3 Hz, 2H), 1.60 (s, 6H), 1.26 (t, J=7.0 Hz, 3H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 152.4, 142.5, 136.8, 135.3, 128.8, 127.7, 126.5, 122.3, 91.7, 65.4, 60.5, 48.4, 43.5, 26.3, 14.6, 14.1; HRMS (EI) *m/z* 343.2021 [calculated for $C_{20}H_{26}N_2O_3$ (M^+) 343.2022].

Enol Ether 148. FTIR (thin film/NaCl) 2979 (m), 2932 (w), 1728 (s), 1635 (w), 1557 (w), 1455 (m), 1322 (w), 1253 (m), 1220 (m), 1173 (w), 1138 (m), 1056 (m), 1029 (w), 973 (w), 819 (w), 733 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.34-7.26 (m, 3H), 7.09 (d, J=6.9 Hz, 2H), 5.06 (s, 2H), 4.38 (d, J=2.3 Hz, 1H), 4.15 (d, J=2.2 Hz, 1H), 4.09 (q, J=7.3 Hz, 2H), 3.72 (q, J=7.0 Hz, 2H), 4.60 (s, 6H), 1.26 (t, J=7.3 Hz, 3H), 1.20 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 151.6, 143.8, 137.0, 135.9, 129.0, 128.2, 127.5, 125.1, 91.3, 63.7, 60.9, 49.4, 44.1, 26.6, 14.6, 14.5; HRMS (EI) *m/z* 343.2021 [calculated for $C_{20}H_{26}N_2O_3$ (M^+) 343.2022].

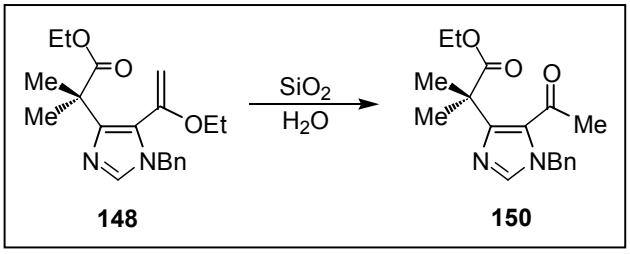
Preparation of Enol Ether 148:



Enol Ether 148. To a stirred solution of **88** (830 mg, 2.36 mmol, 1.0 equiv.) in DMF (25 mL) was added ethyl vinyl ether (1.36 mL, 14.24 mmol, 5.0 equiv.), palladium acetate ($Pd(OAc)_2$) (27 mg, 0.118 mmol, 0.05 equiv.), tri(*o*-tolyl)phosphine (P(*o*-tol)$_3$)

(72 mg, 0.236 mmol, 0.10 equiv.) and Et_3N (493 μL, 3.54 mmol, 1.5 equiv.). The mixture was fitted with a reflux condenser and heated at 130°C for 2 hours. The solvent was removed *in vacuo* and silica gel chromatography of the mixture afforded **148** (500 mg, 62% yield, (94% yield based on recovered starting material)) as a colorless oil.

Preparation of Ketone 150:

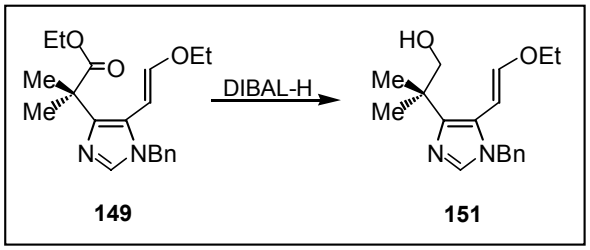


Ketone 150. To a solution of **148** (100 mg, 0.32 mmol) in MeOH (5 mL) was added SiO_2 (1.0g) and H_20 (200 μL). The mixture was stirred at room temperature for 10 minutes, at which time the solvent was removed *in vacuo*, and the mixture chromatographed on silica gel (30% EtOAc/Hexanes) to afford **150** (98 mg, 98% yield) as a colorless oil.

Ketone 150. FTIR (thin film/NaCl) 3107 (w), 2981 (m), 2935 (w), 1727 (s), 1656 (s), 1512 (m), 1453 (m), 1364 (s), 1323 (m), 1256 (m), 1216 (w), 1172 (w), 1135 (m), 1029 (w), 949 (w), 859 (w), 734 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36-7.27 (m, 3H), 7.02 (d, *J*=7.0 Hz, 2H), 5.40 (s, 2H), 4.12 (q, *J*=7.1 Hz, 2H), 2.24 (s, 3H), 1.64 (s, 6H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7,

176.5, 152.9, 139.4, 136.1, 129.0, 128.1, 127.5, 126.4, 60.8, 51.0, 45.0, 30.3, 26.5, 14.0; HRMS (EI) *m/z* 315.1709 [calculated for $C_{18}H_{22}N_2O_3$ (M^+) 315.1709].

Preparation of Alcohol 151:

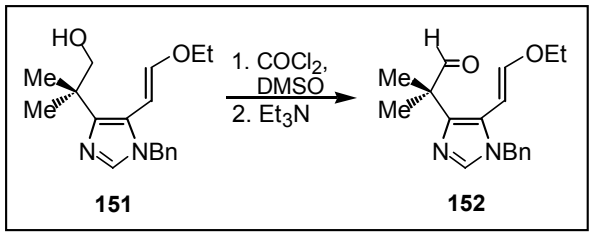


Alcohol 151. To a stirred solution of **149** (10.0 g, 29.2 mmol, 1.0 equiv.) in CH_2Cl_2 (300 mL) at -78°C was added DIBAL-H (20.82 mL, 116.81 mmol, 4.0 equiv.) dropwise. The reaction was stirred at -78°C for 1 hour, at which time it was quenched by the slow addition of H_2O (10 mL, then 100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the organic layers combined. The organic layers were washed with brine (100 mL), dried with MgSO4, and the solvent removed *in vacuo*. The resultant oil was chromatographed on silica gel (75% EtOAc/Hexanes) to afford **151** (6.76 g, 77% yield) as a waxy solid.

Alcohol 151. FTIR (thin film/NaCl) 3361 (s), 3031 (w), 2977 (s), 2929 (m), 2870 (m), 1663 (m), 1644 (s), 1541 (w), 1497 (s), 1454 (m), 1358 (w), 1323 (w), 1237 (m), 1187 (s), 1052 (s), 946 (w), 853 (w), 802 (w), 728 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.37-7.27 (m, 3H), 7.05 (d, *J*=7.1 Hz, 2H), 6.31 (d, *J*=13.1 Hz, 1H), 5.37 (d, *J*=13.1 Hz, 1H), 5.02 (s, 2H), 4.86 (t, *J*=6.4 Hz, 1H), 3.79 (q, *J*=7.1 Hz, 2H), 3.67 (d,

J=6.4 Hz, 2H), 1.29 (s, 6H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 146.3, 136.8, 134.9, 128.8, 127.7, 126.7, 122.0, 92.5, 73.4, 65.3, 48.3, 37.2, 25.6, 14.6; HRMS (EI) *m/z* 301.1916 [calculated for $C_{18}H_{24}N_2O_4$ (M^+) 301.1916].

Preparation of Aldehyde 152:

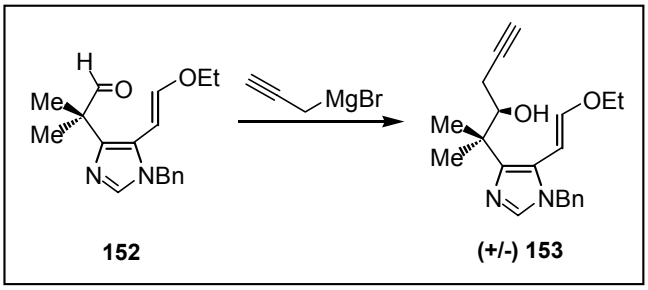


Aldehyde 152. To a stirred solution of oxalyl chloride (1.13 mL, 12.98 mmol, 1.3 equiv.) in CH_2Cl_2 (100 mL) at -78°C was added DMSO (1.42 mL, 20.0 mmol, 2.0 equiv.) dropwise. The solution was stirred for 10 minutes, followed by the dropwise addition of **151** (3.0 g, 9.99 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL). The reaction was stirred for another 10 minutes at -78°C, followed by the addition of Et_3N (6.97 mL, 50.0 mmol, 5.0 equiv.). The mixture was allowed to warm to room temperature and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layers combined. The organic layers were washed with brine (50 mL), dried with $MgSO_4$, and the solvent removed *in vacuo*. The resulting oil was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **152** (2.73 g, 92% yield) as a colorless oil.

Aldehyde 152. FTIR (thin film/NaCl) 3062 (w), 3031 (w), 2977 (m), 2930 (m), 2805 (w), 2706 (w), 1721 (s), 1662 (m), 1643 (s), 1496 (m), 1455 (m), 1391 (w), 1318

(w), 1237 (m), 1191 (s), 1114 (m), 1029 (w), 946 (w), 852 (s), 838 (w), 731 (m), 701 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.49 (s, 1H), 7.35-7.25 (m, 3H), 7.04 (d, *J*=7.2 Hz, 2H), 6.25 (d, *J*=13.1 Hz, 1H), 5.20 (d, *J*=13.1 Hz, 1H), 5.01 (s, 2H), 3.75 (q, *J*=7.0 Hz, 2H), 1.45 (s, 6H), 1.25 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.4, 153.2, 139.6, 136.5, 136.4, 128.9, 127.8, 126.6, 124.0, 91.2, 65.6, 48.5, 47.8, 22.2, 14.6; HRMS (EI) *m/z* 299.1759 [calculated for $C_{18}H_{22}N_2O_2$ (M^+) 299.1760].

Preparation of Acetylene 153:

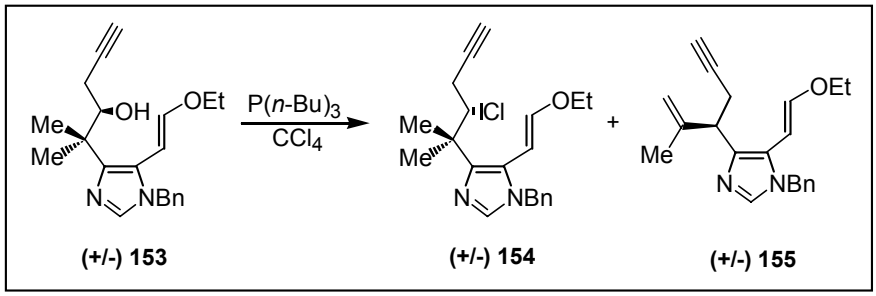


Acetylene 153. To a suspension of Mg turnings (2.46 g, 101.37 mmol, 5.5 equiv.) in Et_2O (500 mL) was added propargyl bromide (80 wt. % solution in toluene) (10.27 mL, 92.16 mmol, 5.0 equiv.) and $HgCl_2$ (250 mg, 0.92 mmol, 0.05 equiv.). The reaction was fitted with a reflux condenser and heated with a heat gun to the point of a self-sustained reflux. After most of the Mg turnings were consumed, the reaction was cannulated into a solution of **152** (5.5 g, 18.43 mmol, 1.0 equiv.) in Et_2O (200 mL). The reaction was stirred at room temperature for 10 minutes, and then quenched by the addition of H_2O (100 mL). The organic layer was separated, washed with brine (100 mL), and dried with $MgSO_4$. The solvent was removed and the resulting oil was

chromatographed on silica gel (100% EtOAc) to afford **153** (5.10 g, 81% yield) as a colorless oil.

Acetylene 153. FTIR (thin film/NaCl) 3295 (s), 2978 (m), 2932 (m), 1662 (m), 1644 (m), 1558 (w), 1497 (m), 1455 (m), 1359 (w), 1235 (m), 1185 (s), 1111 (m), 1067 (m), 1029 (w), 947 (w), 850 (w), 730 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.36-7.26 (m, 3H), 7.02 (d, *J*=7.3 Hz, 2H), 6.25 (d, *J*=13.1 Hz, 1H), 5.32 (d, *J*=13.1 Hz, 1H), 5.00 (s, 2H), 3.77 (m, 1H), 3.76 (q, *J*=7.0 Hz, 2H), 2.40 (ddd, *J*=2.6 Hz, 3.3 Hz, 16.7 Hz, 1H), 2.17 (ddd, *J*=2.6 Hz, 9.2 Hz, 16.7 Hz, 1H), 1.97 (t, *J*=2.6 Hz, 1H), 1.38 (s, 3H), 1.30 (s, 3H), 1.27 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 144.6, 136.8, 135.3, 128.8, 127.8, 126.6, 122.7, 92.5, 83.2, 79.0, 70.0, 65.4, 48.3, 40.0, 27.1, 24.5, 23.0, 14.6; HRMS (EI) *m/z* 339.2074 [calculated for $C_{21}H_{26}N_2O_2$ (M^+) 339.2072].

Preparation of Chloride 154 and Olefin 155:



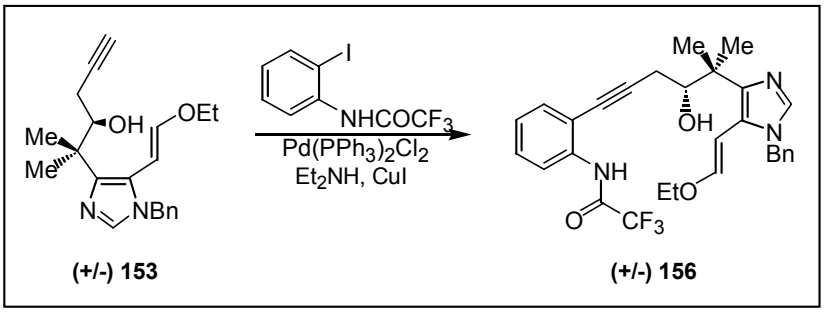
Chloride 154 and Olefin 155. To a stirred solution of **153** (200mg, 0.591 mmol, 1.0 equiv.) in CCl_4 (5 mL) and CH_3CN (5 mL) at 75°C was added P(*n*-Bu)$_3$ (294 μL, 1.82 mmol, 2.0 equiv.). The mixture was refluxed for 10 minutes, then cooled to room temperature and the solvent removed *in vacuo*. Chromatography of the crude reaction on

silica gel (30% Acetone/Hexanes) afforded **154** (135 mg, 64% yield) and **155** (30 mg, 16% yield) as colorless oils.

Chloride 154. FTIR (thin film/NaCl) 3294 (m), 3031 (w), 2979 (m), 2929 (m), 2117 (w), 1660 (m), 1642 (s), 1496 (s), 1454 (m), 1370 (m), 1327 (m), 1276 (w), 1184 (s), 1106 (s), 1029 (w), 942 (m), 805 (w), 728 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.35-7.26 (m, 3H), 7.00 (d, *J*=7.0 Hz, 2H), 6.74 (d, *J*=13.0 Hz, 1H), 5.25 (d, *J*=13.0 Hz, 1H), 5.09 (d, *J*=16.1 Hz, 1H), 5.04 (d, *J*=16.1 Hz, 1H), 3.80 (q, *J*=7.0 Hz, 2H), 3.42 (dd, *J*=3.2 Hz, 11.4 Hz, 1H), 3.05-2.91 (m, 2H), 1.83 (t, *J*=2.5 Hz, 1H), 1.73 (s, 3H), 1.45 (s, 3H), 1.29 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 137.2, 136.9, 136.4, 128.8, 127.7, 127.1, 126.2, 91.2, 83.9, 74.2, 68.8, 65.6, 49.0, 48.5, 32.1, 28.4, 20.7, 14.6; HRMS (EI) *m/z* 357.1733 [calculated for $C_{21}H_{25}ClN_2O$ (M^+) 357.1734].

Olefin 155. FTIR (thin film/NaCl) 3297 (m), 2977 (m), 2928 (m), 1722 (w), 1659 (m), 1642 (s), 1496 (m), 1453 (m), 1227 (w), 1183 (s), 1113 (w), 726 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.37-7.27 (m, 3H), 7.03 (d, *J*=7.3 Hz, 2H), 6.62 (d, *J*=13.0 Hz, 1H), 5.32 (d, *J*=13.0 Hz, 1H), 5.04 (d, *J*=2.4 Hz, 2H), 4.91 (s, 1H), 4.88 (s, 1H), 3.79 (q, *J*=7.0 Hz, 2H), 3.60 (t, *J*=7.5 Hz, 1H), 2.82 (dd, *J*=2.5 Hz, 7.6 Hz, 2H), 1.92 (t, *J*=2.5 Hz, 1H), 1.74 (s, 3H), 1.58 (s, 3H), 1.29 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 146.8, 138.9, 136.7, 136.3, 128.9, 127.8, 126.5, 124.7, 111.2, 91.8, 84.0, 68.8, 65.7, 48.5, 44.3, 22.6, 20.6, 14.7; HRMS (EI) *m/z* 321.1967 [calculated for $C_{21}H_{24}N_2O$ (M^+) 321.1967].

Preparation of Acetanilide 156:

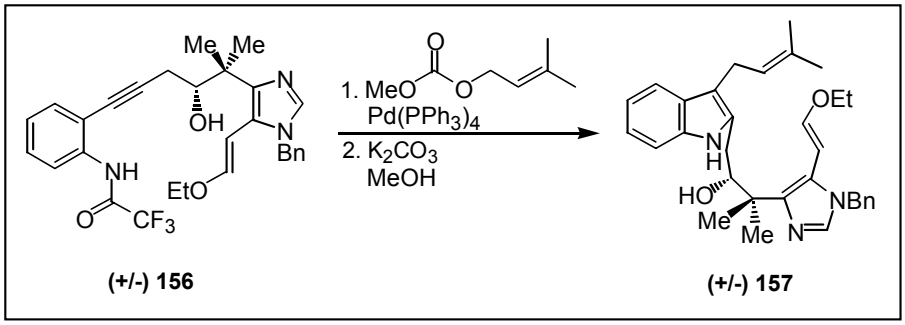


Acetanilide 156. To a solution of **153** (1.16 g, 3.43 mmol, 1.0 equiv.) in benzene (20 mL) and Et_3N (20 mL) at room temperature was added 2-iodotrifluoroacetanilide (1.62 g, 5.14 mmol, 1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (120 mg, 0.17 mmol, 0.05 equiv.) and CuI (65 mg, 0.34 mmol, 0.10 equiv.). The mixture was stirred at room temperature for 4 hours, at which time the solvent was removed *in vacuo*. The reaction was chromatographed on silica gel (30% EtOAc/Hexanes) to afford **156** (1.65 g, 92% yield) as a colorless oil.

Acetanilide 156. FTIR (thin film/NaCl) 3345 (s), 2980 (w), 2879 (w), 2226 (w), 1730 (s), 1643 (m), 1583 (m), 1543 (m), 1498 (m), 1453 (m), 1386 (s), 1360 (w), 1330 (w), 1287 (m), 1189 (s), 1153 (s), 1067 (w), 1030 (w), 898 (w), 851 (w), 763 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.14 (bs, 1H), 8.34 (d, *J*=8.3 Hz, 1H), 7.42 (s, 1H), 7.40 (dd, *J*=1.6 Hz, 7.9 Hz, 1H), 7.36-7.26 (m, 4H), 7.12 (t, *J*=7.3 Hz, 1H), 7.02 (d, *J*=7.3 Hz, 2H), 6.27 (d, *J*=13.0 Hz, 1H), 5.95 (bs, 1H), 5.34 (d, *J*=13.0 Hz, 1H), 5.0 (d, *J*=15.7 Hz, 1H), 4.95 (d, *J*=15.7 Hz, 1H), 3.83 (bd, *J*=7.3 Hz, 1H), 3.77 (q, *J*=6.9 Hz, 2H), 2.69 (dd, *J*=3.5 Hz, 16.9 Hz, 1H), 2.49 (dd, *J*=9.4 Hz, 16.9 Hz, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.28 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (q, *J*=37.5 Hz), 152.9,

144.5, 136.8, 136.7, 135.2, 131.2, 128.8, 128.6, 127.8, 127.1, 126.6, 125.0, 122.8, 115.7 (q, *J*=288.1 Hz), 114.3, 98.5, 92.3, 79.1, 75.7, 65.4, 48.3, 39.9, 27.5, 24.3, 24.0, 14.6; HRMS (EI) *m/z* 526.2320 [calculated for $C_{29}H_{30}F_3N_3O_3$ (M^+) 526.2237].

Preparation of Prenyl Indole 157:

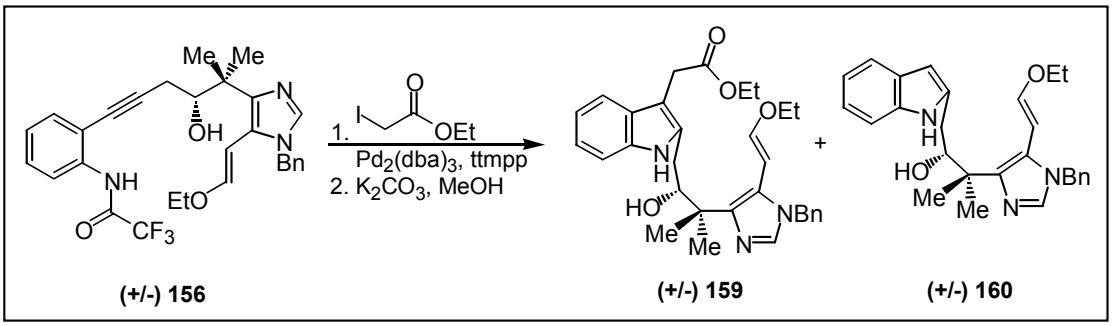


Prenyl Indole 157. To a mixture of **156** (600 mg, 1.14 mmol, 1.0 equiv.) in THF (30 mL) was added prenyl methyl carbonate (180 mg, 1.37 mmol, 1.2 equiv.) and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol, 0.05 equiv.). The reaction was heated to 60°C for 3 hours, at which time K_2CO_3 (790 mg, 5.70 mmol, 5.0 equiv.) and MeOH (200 μL) were added and the temperature was increased to 80°C. After 1 hour the solvent was removed *in vacuo* and the crude reaction chromatographed on silica gel (50% EtOAc/Hexanes) to afford **157** (475 mg, 83% yield) as a waxy solid.

Prenyl Indole 157. FTIR (thin film/NaCl) 3287 (s), 2977 (s), 2926 (m), 1660 (w), 1643 (m), 1499 (m), 1461 (s), 1378 (w), 1241 (w), 1185 (s), 1123 (w), 1061 (m), 1009 (w), 865 (w), 738 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (bs, 1H), 7.49 (d, *J*=7.9 Hz, 1H), 7.45 (s, 1H), 7.38-7.27 (m, 4H), 7.12-7.01 (m, 4H), 6.29 (d, *J*=13.1 Hz,

1H), 6.16 (bs, 1H), 5.37 (d, *J*=13.1, 1H), 5.27 (t, *J*=7.0 Hz, 1H), 5.02 (s, 2H), 3.85 (d, *J*=9.4 Hz, 1H), 3.79 (q, *J*=7.0 Hz, 2H), 3.38 (m, 2H), 3.05 (dd, *J*=1.3 Hz, 15.2 Hz, 1H), 2.51 (dd, *J*=10.3 Hz, 15.2 Hz, 1H), 1.80 (s, 3H), 1.68 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.30 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 145.3, 136.8, 135.3, 135.2, 134.8, 130.0, 128.9, 128.1, 127.9, 126.7, 126.6, 124.5, 122.7, 120.5, 118.4, 118.0, 110.5, 110.3, 92.5, 80.9, 65.4, 48.4, 40.0, 27.9, 27.4, 25.7, 24.3, 23.2, 17.8, 14.7; HRMS (EI) *m/z* 498.3123 [calculated for $C_{32}H_{39}N_3O_2$ (M^+) 498.3121].

Preparation of Ester 159 and Indole 160:

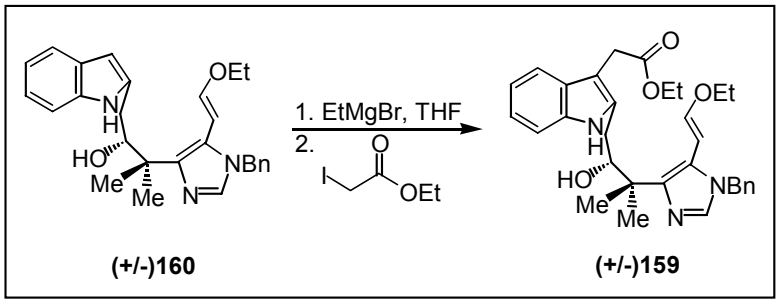


Ester 159 and Indole 160. To a stirred solution of **156** (500 mg, 0.95 mmol, 1.0 equiv.) in THF (10 mL) was added ethyl iodoacetate (169 μL, 1.43 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (43 mg, 0.048 mmol, 0.05 equiv.), and ttmpp (tris(trimethoxyphenyl)phosphine) (102 mg, 0.19 mmol, 0.20 equiv.). The mixture was heated to 60°C for 3 hours, at which time K_2CO_3 (394 mg, 2.85 mmol, 3.0 equiv.) and MeOH (100 μL) were added and the reaction temperature was increased to 80°C for 1 hour. The solvent was removed *in vacuo* and the crude mixture chromatographed on

silica gel (20-50% Acetone/Hexanes) to afford an inseparable mixture of **159** (264 mg, 54% yield) and **160** (149 mg, 36% yield) (based on NMR) as a colorless oil.

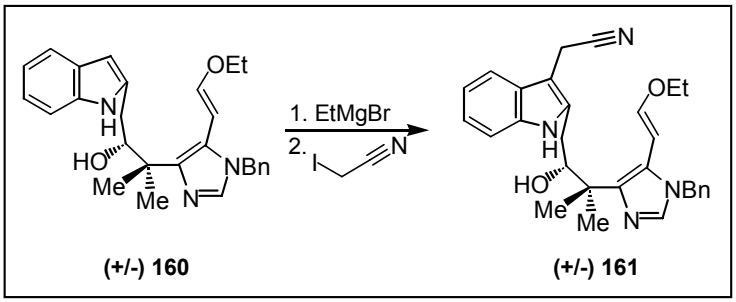
Ester 159 and Indole 160. FTIR (thin film/NaCl) 3271 (s), 3058 (m), 2978 (s), 2929 (m), 1732 (s), 1663 (m), 1644 (m), 1550 (w), 1498 (m), 1457 (s), 1358 (w), 1302 (w), 1238 (w), 1184 (s), 1061 (m), 1030 (m), 946 (w), 853 (m), 780 (m), 736 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (bs, 1H), 9.45 (bs, 1H), 7.55 (d, *J*=7.5 Hz, 1H), 7.52 (d, *J*=7.9 Hz, 1H), 7.46 (s, 1H), 7.44 (s, 1H), 7.38-7.28 (m, 8H), 7.13-7.01 (m, 8H), 6.32 (d, *J*=13.0 Hz, 1H), 6.29 (d, *J*=13.0 Hz, 1H), 6.20 (s, 1H), 5.37 (d, *J*=13.0 Hz, 1H), 5.35 (d, *J*=13.0 Hz, 1H), 5.00 (s, 2H), 4.98 (s, 2H), 4.10 (q, *J*=7.0 Hz, 2H), 3.92 (m, 2H), 3.80 (m, 4H), 3.70 (d, *J*=15.3 Hz, 1H), 3.65 (d, *J*=15.3 Hz, 1H), 3.09 (dd *J*=1.5 Hz, 15.3 Hz, 1H), 3.00 (dd, *J*=1.6 Hz, 15.1 Hz, 1H), 2.67 (dd, *J*=10.3 Hz, 15.2 Hz, 1H), 2.61 (dd, *J*=10.3 Hz, 15.2 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (t, *J*=7.0 Hz, 3H), 1.30 (t, *J*=7.0 Hz, 3H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 153.0, 152.9, 145.0, 144.9, 136.7, 136.6, 136.2, 136.1, 135.2, 135.1, 135.0, 128.9, 128.3, 128.0, 127.9, 126.7, 126.6, 122.9, 122.8, 120.9, 120.6, 119.4, 119.1, 118.9, 117.9, 110.7, 110.6, 103.7, 99.4, 92.4, 80.8, 80.5, 65.5, 65.4, 60.6, 48.4, 48.4, 40.1, 40.1, 30.6, 30.5, 28.2, 27.4, 27.1, 24.5, 24.3, 14.7, 14.2; HRMS (EI) *m/z* 516.2862 [calculated for $C_{31}H_{37}N_3O_4$ (M^+) 516.2862].

Preparation of Ester 159:



Ester 159. To a stirred solution of EtMgBr (1.0 M in THF) (2.79 mL, 2.79 mmol, 3.0 equiv.) in THF (20 mL) at room temperature was added **160** (400mg, 0.93 mmol, 1.0 equiv.) in THF (5 mL). The reaction was stirred for 10 minutes and then ethyl iodoacetate (550 μL, 4.65 mmol, 5.0 equiv.) was added. The reaction was then quenched by addition of NH_4Cl (aq. sat.) (1.0 mL). Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (25 mL), and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel (25% Acetone/Hexanes) to give an inseparable mixture of **159** (265 mg, 55% yield) and **160** (165 mg, 40% yield) (based on NMR) as a colorless oil.

Preparation of Nitrile 161:

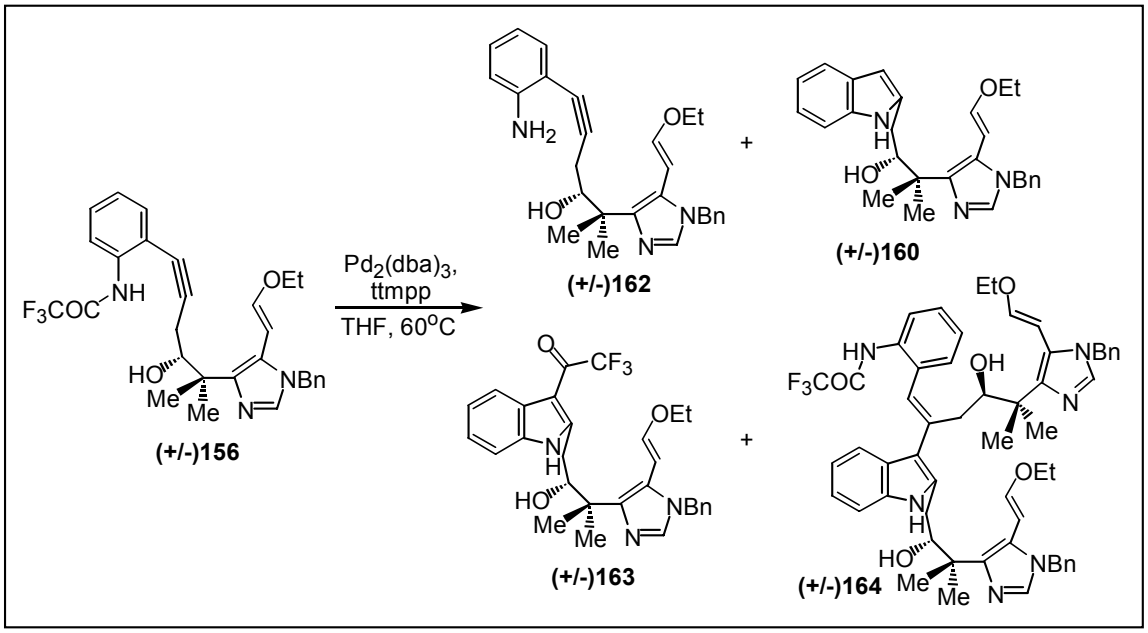


Nitrile 161. To a stirred solution of EtMgBr (1.0 M) (460 μL, 0.46 mmol, 2.0 equiv.) in THF (3 mL) at room temperature was added **160** (100mg, 0.23 mmol, 1.0 equiv.) in THF (2 mL) dropwise. The mixture was stirred for 10 minutes, at which time iodoacetonitrile (51 μL, 0.69 mmol, 3.0 equiv.) was added. The reaction was stirred for another 10 minutes and then quenched by addition of NH_4Cl (sat. aq.) (1.0 mL). H_2O (20 mL) was added and the reaction was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL) and dried with $MgSO_4$. Silica gel chromatography (25% Acetone/Hexanes) afforded **161** (66 mg, 61% yield) and **160** (32 mg, 32% yield) as white solids.

Nitrile 161. m.p. 129-130°C; FTIR (thin film/NaCl) 3281 (s), 2978 (m), 2247 (w), 1644 (s), 1500 (s), 1464 (s), 1357 (m), 1311 (w), 1240 (m), 1181 (s), 1061 (s), 1033 (m), 944 (w), 855 (w), 738 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.54 (d, *J*=7.2 Hz), 1H, 7.44 (s, 1H), 7.39-7.29 (m, 4H), 7.19-7.10 (m, 2H), 7.06 (d, *J*=7.0 Hz), 6.33 (d, *J*=13.0 Hz, 1H), 5.38 (d, *J*=13.0 Hz, 1H), 5.02 (s, 2H), 3.91 (dd, *J*=1.6 Hz, 10.4 Hz, 1H), 3.81 (q, *J*=7.0 Hz, 2H), 3.77 (d, *J*=18.0 Hz, 1H), 3.72 (d, *J*=18.0 Hz, 1H), 3.04 (dd, *J*=1.6 Hz, 15.4 Hz, 1H), 2.63 (dd, *J*=10.5 Hz, 15.4 Hz, 1H), 1.47 (s, 3H), 1.40 (s,

3H), 1.31 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 144.8, 136.7, 136.6, 135.1, 135.0, 128.9, 127.9, 126.8, 126.7, 122.9, 121.5, 119.5, 118.4, 117.1, 110.9, 99.0, 92.2, 80.5, 65.5, 48.4, 39.9, 27.9, 27.5, 24.5, 14.7, 12.9; HRMS (EI) *m/z* 469.2602 [calculated for $C_{29}H_{32}N_4O_2$ (M^+) 469.2603].

Preparation of Indole 160, Aniline 162, Trifluoroacetate 163 and Dimer 164:



Indole 160, Aniline 162, Trifluoroacetate 163 and Dimer 164. To a stirred solution of **156** (1.0 g, 1.90 mmol, 1 equiv.) in DMF (20 mL) and ethylene glycol (5 mL) was added Et_2NH (2.0 mL, 19.0 mmol, 10.0 equiv.) and $Pd(PPh_3)_4$ (110 mg, 0.1 mmol, 0.05 equiv.). The mixture was heated to 60°C for 12 hours and then poured into EtOAc (100 mL). The reaction was washed with H_2O (3 x 50 mL), brine (25 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* and the crude mixture chromatographed

on silica gel (25% Acetone/Hexanes) to afford **160** (580 mg, 71% yield) as a white solid, **162** (33 mg, 4% yield) as a white solid, **163** (91 mg, 9% yield) as a white solid and **164** (54 mg, 3% yield) as a waxy solid.

Indole 160. m.p. 98-99°C; FTIR (thin film/NaCl) 3268 (s), 2978 (s), 2928 (m), 1661 (w), 1642 (m), 1551 (w), 1499 (m), 1455 (s), 1357 (w), 1290 (m), 1239 (w), 1185 (s), 1061 (m), 1030 (w), 946 (w), 852 (w), 782 (m), 734 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (bs, 1H), 7.52 (d, *J*=7.6 Hz, 1H), 7.44 (s, 1H), 7.39-7.27 (m, 4H), 7.13-7.01 (m, 4H), 6.29 (d, *J*=13.0 Hz, 1H), 6.28 (bs, 1H), 6.20 (s, 1H), 5.36 (d, *J*=13.0 Hz, 1H), 5.00 (s, 2H), 3.90 (dd, *J*=1.6 Hz, 10.4 Hz, 1H), 3.79 (q, *J*=7.0 Hz, 2H), 3.00 (dd, *J*=1.6 Hz, 15.2 Hz, 1H), 2.67 (dd, *J*=10.4 Hz, 15.2 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.30 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 145.2, 139.3, 136.7, 136.0, 135.1, 128.9, 128.2, 127.9, 126.7, 122.7, 120.6, 119.4, 119.0, 110.6, 99.4, 92.5, 80.9, 65.4, 48.3, 39.9, 30.6, 27.5, 24.4, 14.7; HRMS (EI) *m/z* 430.2493 [calculated for $C_{27}H_{31}N_3O_2$ (M^+) 430.2495].

Aniline 162. m.p. 138-139°C; FTIR (thin film/NaCl) 33.48 (s), 2977 (m), 2929 (m), 1661 (w), 1642 (m), 1614 (m), 1549 (w), 1493 (s), 1454 (s), 1358 (w), 1308 (w), 1236 (w), 1185 (s), 1065 (w), 1029 (w), 947 (w), 850 (w), 730 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.36-7.26 (m, 4H), 7.20 (d, *J*=7.6 Hz, 1H), 7.09-6.99 (m, 3H), 6.66 (d, *J*=8.0 Hz, 1H), 6.62 (t, *J*=7.6 Hz, 1H), 6.27 (d, *J*=13.0 Hz, 1H), 5.53 (bs, 1H), 5.35 (d, *J*=13.0 Hz, 1H), 4.99 (d, *J*=15.3 Hz, 1H), 4.94 (d, *J*=15.3 Hz, 1H), 4.37 (bs, 2H), 3.84 (dd, *J*=3.5 Hz, 8.9 Hz, 1H), 3.77 (q, *J*=7.0 Hz, 2H), 2.67 (dd, *J*=3.5 Hz, 16.9 Hz, 1H), 2.46 (dd, *J*=8.9 Hz, 16.9 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.27 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 148.8, 145.0, 137.2, 135.8, 131.8, 129.3,

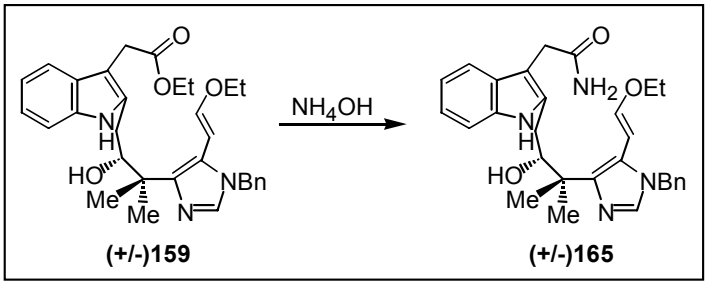
129.1, 128.2, 127.1, 123.2, 117.7, 114.3, 109.2, 94.9, 93.0, 79.9, 78.6, 65.8, 48.7, 40.5, 28.0, 25.2, 24.7, 15.1; HRMS (EI) *m/z* 430.2493 [calculated for $C_{27}H_{31}N_3O_2$ (M^+) 430.2494].

Trifluoroacetate 163. m.p. 129-130°C; FTIR (thin film/NaCl) 3061 (m), 2979 (m), 2932 (w), 2881 (w), 1659 (m), 1644 (m), 1499 (w), 1456 (m), 1387 (w), 1358 (w), 1273 (w), 1174 (s), 1056 (m), 927 (w), 853 (w), 731 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.05 (bs, 1H), 8.02 (d, *J*=7.7 Hz, 1H), 7.42 (s, 1H), 7.40-7.24 (m, 5H), 7.05 (d, *J*=7.0 Hz, 2H), 6.35 (d, *J*=13.0 Hz, 1H), 5.37 (d, *J*=13.0 Hz, 1H), 5.02 (s, 2H), 4.00 (dd, *J*=1.6 Hz, 10.8 Hz, 1H), 3.84 (dd, *J*=1.6 Hz, 17.2 Hz, 1H), 3.82 (q, *J*=7.0 Hz, 1H), 2.77 (dd, *J*=10.8 Hz, 17.2 Hz, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.31 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 153.7, 153.3, 144.6, 136.5, 135.0, 130.0, 128.0, 126.7, 125.2, 123.3, 123.2, 122.8, 120.8, 120.7, 111.6, 107.7, 92.0, 80.0, 65.6, 48.5, 39.9, 30.4, 27.9, 24.5, 14.7; HRMS (EI) *m/z* 526.22 [calculated for $C_{29}H_{30}F_3N_3O_3$ (M^+) 526.28].

Dimer 164. FTIR (thin film/NaCl) 3268 (s), 3060 (w), 2978 (m), 2929 (m), 1722 (s), 1643 (m), 1585 (w), 1547 (w), 1498 (m), 1455 (s), 1358 (w), 1279 (w), 1239 (m), 1189 (s), 1156 (s), 909 (m), 853 (w), 732 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.51 (bs, 1H), 9.83 (bs, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 7.54 (d, *J*=7.9 Hz, 1H), 7.38 (s, 1H), 7.35-7.19 (m, 11H), 7.13-7.08 (m, 1H), 7.06-7.01 (m, 3H), 6.97-6.93 (m, 2H), 6.37 (bs, 1H), 6.45 (s, 1H), 6.28 (d, *J*=13.1 Hz, 1H), 6.00 (d, *J*=13.0 Hz, 1H), 5.95 (bs, 1H), 5.36 (d, *J*=13.1 Hz, 1H), 5.12 (d, *J*=13.0 Hz, 1H), 5.00 (s, 2H), 4.88 (s, 2H), 3.99 (bd, *J*=10.5 Hz, 1H), 3.76 (q, *J*=7.1 Hz, 2H), 3.65 (bd, *J*=10.5 Hz, 1H), 3.62 (q, *J*=7.1, 2H), 3.31 (dd, *J*=1.4 Hz, 15.5 Hz, 1H), 2.77 (dd, *J*=10.5 Hz, 15.5 Hz, 1H), 2.57 (bd, *J*=13.1 Hz, 1H), 2.29 (dd, *J*=11.3 Hz, 13.1 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H),

1.21 (t, J=7.1 Hz, 3H), 1.11 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7 (q, J=37.2), 152.9, 152.6, 145.9, 145.4, 139.7, 136.7, 136.6, 136.3, 135.1, 134.8, 134.7, 133.1, 132.4, 130.6, 128.9, 128.8, 127.9, 127.8, 127.7, 127.2, 126.9, 126.8, 126.7, 126.5, 125.9, 123.5, 122.9, 121.9, 120.7, 119.1, 119.0, 118.8, 113.4, 110.6, 92.6, 92.3, 80.9, 76.7, 65.3, 65.2, 48.4, 48.3, 39.9, 39.5, 34.3, 28.5, 27.6, 25.2, 24.3, 23.1, 14.6; HRMS (EI) *m/z* 955.47 [calculated for $C_{56}H_{61}F_3N_6O_5$ (M^+) 955.58].

Preparation of Amide 165:

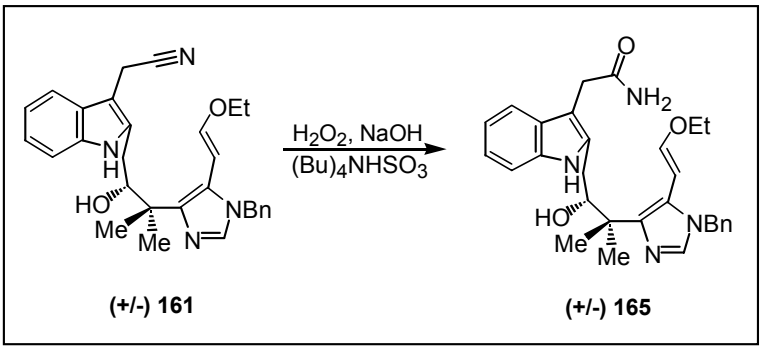


Amide 165. To a stirred solution of **159** (30 mg, 0.058 mmol) in THF (1 mL) was added NH_4OH (0.5 mL) and the mixture was refluxed for 4 hours. H_2O (3 mL) was added and the mixture was extracted with EtOAc (3 x 2 mL). The organic layers were combined and dried with $MgSO_4$ and the solvent was removed in vacuo. The resulting oil was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to afford **165** (25 mg, 91% yield) as a white solid.

Amide 165. m.p. 111-112°C; FTIR (thin film/NaCl) 3280 (s), 2977 (m), 2929 (w), 1665 (s), 1497 (m), 1462 (m), 1384 (w), 1239 (w), 1184 (m), 1061 (w), 909 (w), 852 (w), 733 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (bs, 1H), 7.50 (d, J=7.7 Hz, 1H),

7.37 (s, 1H), 7.37-7.27 (m, 4H), 7.15-7.01 (m, 4H), 6.30 (d, *J*=12.9 Hz, 1H), 6.11 (bd, *J*=2.5 Hz, 1H), 5.70 (bd, *J*=2.5 Hz, 1Hz), 5.36 (d, *J*=12.9 Hz, 1H), 4.97 (s, 2H), 3.95 (dd, *J*=1.5 Hz, 10.5 Hz, 1H), 3.80 (q, *J*=7.0 Hz, 2H), 3.62 (s, 2H), 2.95 (dd, *J*=1.5 Hz, 15.1 Hz, 1H), 2.62 (dd, *J*=10.5 Hz, 15.1 Hz, 1H), 1.43 (s, 2H), 1.37 (s, 3H), 1.30 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 152.9, 144.9, 136.7, 136.6, 135.4, 135.1, 128.8, 127.8, 127.6, 126.6, 122.8, 121.3, 119.3, 117.7, 110.7, 104.9, 92.2, 80.2, 65.4, 48.3, 40.0, 32.0, 28.1, 26.8, 24.5, 14.6; HRMS (EI) *m/z* 487.2711 [calculated for $C_{29}H_{34}N_4O_3$ (M^+) 487.2709].

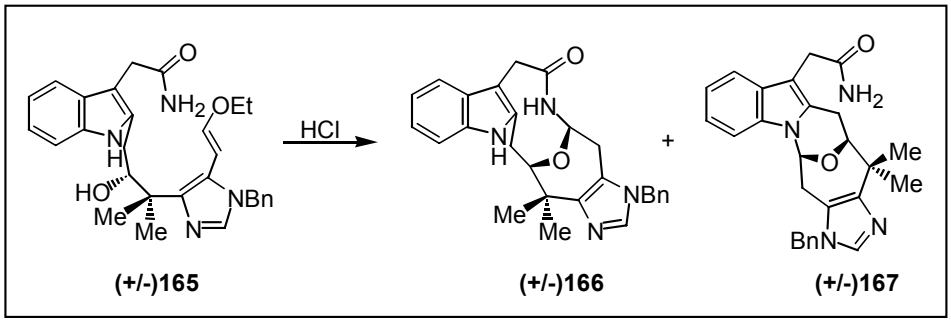
Preparation of Amide 165:



Amide 165. To a solution of **161** (500 mg, 1.07 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added H_2O_2 (aq., 30%) (2 mL), NaOH (aq., 20%) (2 mL) and $(Bu)_4NHSO_3$ (36 mg, 0.11 mmol, 0.1 equiv.). The reaction was stirred vigorously for 2 hours and then poured into H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL) and the organic layers were combined and dried with $MgSO_4$. After removal of the solvent *in*

vacuo, the mixture was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to afford **165** (445 mg, 85% yield) as a white solid.

Preparation of Aminals 166 and 167:



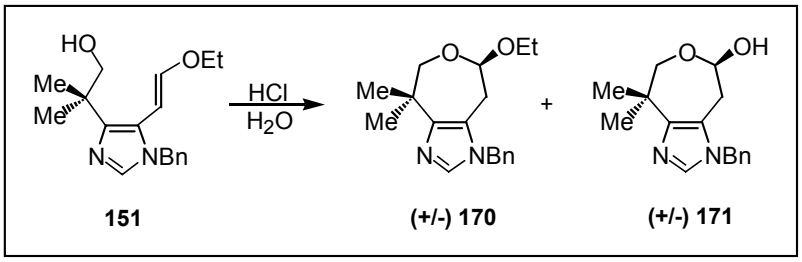
Aminals 166 and 167. To amide **165** (15 mg, 0.031 mmol) was added concentrated HCl (0.5 mL) and the reaction was stirred at room temperature for 24 hours. $NaHCO_3$ (sat., aq.) was added until the mixture was neutral, at which point it was extracted with EtOAc (5 x 2 mL). The organics were combined and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel to afford **166** (2 mg 16% yield) and **167** (2 mg 16% yield) as waxy solids.

Aminal 166. FTIR (thin film/NaCl) 3181 (m), 2970 (m), 2927 (m), 1667 (s), 1609 (w), 1461 (m), 1362 (m), 1243 (w), 1117 (w), 1102 (w), 1052 (m), 910 (m), 730 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.71 (s, 1H), 7.19 (m, 3H), 7.08 dt, (*J*=1.3 Hz, 7.8 Hz, 1H), 7.01 (m, 1H), 6.91 (m, 2H), 6.76 (dt, *J*=1.0 Hz, 7.6 Hz, 1H), 6.52 (d, *J*=7.7 Hz, 1H), 4.96 (d, *J*=6.2 Hz), 4.45 (dd, *J*=7.5 Hz, 9.8 Hz, 1H), 3.75 (dd, *J*=6.3 Hz, 11.9 Hz, 1H), 3.04 (d, *J*=17.7 Hz, 1H), 2.86 (dd, *J*=9.7 Hz, 17.2 Hz, 1H), 2.67 (d, *J*=17.5 Hz, 1H),

2.42 (dd, *J*=6.6 Hz, 14.9 Hz, 1H), 2.08 (dd, *J*=7.5 Hz, 17.5 Hz, 1H), 2.01 (dd, *J*=11.9 Hz, 14.8 Hz, 1H), 1.41 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.9, 149.6, 142.6, 137.1, 136.7, 131.3, 129.1, 128.8, 127.8, 127.0, 123.7, 121.2, 119.4, 110.0, 80.8, 76.5, 74.5, 55.1, 44.4, 42.0, 33.2, 29.8, 28.4, 23.1; HRMS (EI) *m/z* 441.22 [calculated for $C_{27}H_{28}N_4O_2$ (M^+) 441.17].

Aminal 167. FTIR (thin film/NaCl) 3336 (s), 2927 (m), 2244 (w), 1669 (s), 1497 (m), 1458 (s), 1362 (m), 1243 (w), 1177 (m), 1102 (m), 1052 (m), 968 (w), 910 (m), 730 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J*=7.6 Hz, 1H), 7.25-7.17 (m, 6H), 6.97 (s, 1H), 6.62 (d, *J*=7.3 Hz, 2H), 6.26 (t, *J*=2.5 Hz, 1H), 5.24 (bs, 2H), 4.26 (d, *J*=15.5 Hz, 1H), 4.19 (d, *J*=8.1 Hz, 1H), 3.98-3.91 (m, 1H), 3.84 (d, *J*=15.5 Hz, 1H), 3.66 (dd, *J*=3.2 Hz, 11.1 Hz, 1H), 3.43 (dd, *J*=7.9 Hz, 11.1 Hz, 1H), 3.35-3.17 (m, 4H), 3.07 (d, *J*=16.7 Hz, 1H), 1.53 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 135.5, 135.2, 133.9, 131.7, 129.3, 128.6, 127.1, 122.3, 121.7, 121.0, 119.0, 109.8, 104.3, 79.2, 68.7, 68.5, 48.5, 40.7, 31.5, 30.6, 26.1, 24.5, 21.7, 19.3; HRMS (EI) *m/z* 441.22 [calculated for $C_{27}H_{28}N_4O_2$ (M^+) 441.29].

Preparation of Acetal 170 and Hemiacetal 171:

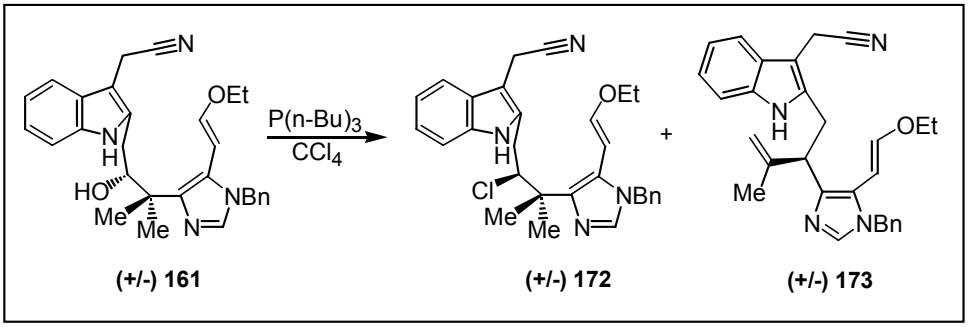


Acetal 170 and Hemiacetal 171. To a solution of **151** (100 mg, 0.33 mmol) in THF (5 mL) at room temperature was added HCl (aq., 1N) (200 μL). The reaction was stirred for 2 hours and then quenched by the slow addition of $NaHCO_3$ until the reaction was basic. H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* and the reaction was chromatographed on silica gel (50% EtOAc/Hexanes) to afford **170** (61 mg, 61% yield) and **171** (23 mg, 26% yield) as colorless oils.

Acetal 170. FTIR (thin film/NaCl) 2972 (m), 2927 (m), 2867 (m), 1752 (w), 1688 (w), 1498 (m), 1454 (m), 1373 (m), 1357 (m), 1230 (m), 1124 (m), 1070 (s), 862 (w), 835 (w), 731 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.36-7.26 (m, 3H), 7.01 (d, *J*=7.4 Hz, 2H), 5.03 (s, 2H), 4.59 (dd, *J*=3.4 Hz, 8.3 Hz, 1H), 3.91 (d, *J*=12.3 Hz, 1H), 3.86 (m, 1H), 3.5 (d, *J*=12.3 Hz, 1H), 3.43 (m, 1H), 2.80 (m, 2H), 1.34 (s, 3H), 1.25 (s, 3H), 1.19 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 136.3, 135.9, 128.9, 127.9, 126.2, 120.0, 102.7, 76.1, 63.3, 48.6, 37.9, 31.2, 26.6, 24.2, 15.0; HRMS (EI) *m/z* 301.1916 [calculated for $C_{18}H_{24}N_2O_2$ (M^+) 301.1916].

Hemiacetal 171. FTIR (thin film/NaCl) 3397 (s), 2958 (m), 2924 (m), 2863 (w), 1567 (w), 1499 (s), 1453 (m), 1357 (m), 1326 (w), 1283 (w), 1231 (m), 1083 (s), 1056 (m), 863 (w), 832 (w), 720 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37-7.27 (m, 3H), 7.01 (d, *J*=7.3 Hz, 2H), 5.03 (s, 2H), 4.97 (dd, *J*=3.2 Hz, 8.2 Hz, 1H), 3.86 (d, *J*=12.3 Hz, 1H), 3.66 (bs, 1H), 3.55 (d, *J*=12.3 Hz, 1H), 2.87-2.86 (m, 2H), 1.32 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 136.2, 136.0, 129.0, 128.0, 126.3, 119.8, 97.7, 76.5, 48.7, 37.8, 32.1, 26.5, 24.0; HRMS (EI) *m/z* 273.1602 [calculated for $C_{16}H_{20}N_2O_2$ (M^+) 273.1603].

Preparation of Chloride 172 and Olefin 173:

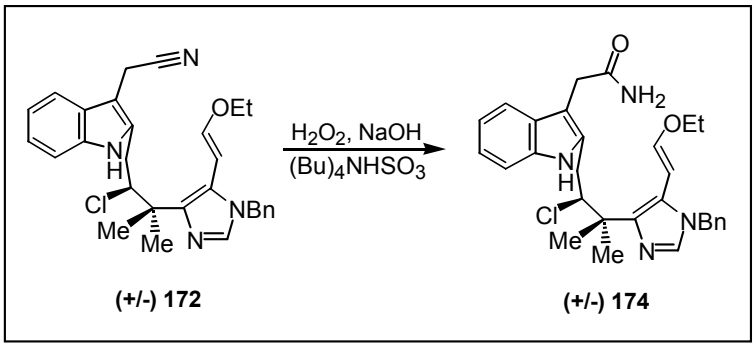


Chloride 172 and Olefin 173. To a stirred solution of **161** (200 mg, 0.43 mmol, 1.0 equiv.) in CCl_4 (4 mL) and CH_3CN (1 mL) at 75°C was added P(*n*-Bu)$_3$ (213 μL, 0.85 mmol, 2.0 equiv.). The reaction was refluxed for 10 minutes and then cooled to room temperature. The solvent was removed *in vacuo*, and the mixture chromatographed on silica gel (15-20% Acetone/Hexanes) to afford **172** (145 mg, 69% yield) and **173** (14 mg, 7% yield) as colorless oils.

Chloride 172. FTIR (thin film/NaCl) 2978 (m), 2931 (w), 2247 (w), 1659 (s), 1496 (m), 1455 (s), 1370 (w), 1183 (s), 1106 (m), 1029 (w), 934 (w), 806 (w), 740 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 7.56 (m, 2H), 7.29-7.10 (m, 6H), 6.91-6.86 (m, 2H), 5.16 (d, *J*=12.7 Hz, 1H), 4.98 (d, *J*=16.0 Hz, 1H), 4.96 (d, *J*=12.7 Hz, 1H), 4.90 (d, *J*=16.0 Hz, 1H), 3.63-3.09 (m, 7H), 1.90 (s, 3H), 1.48 (s, 3H), 0.97 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 136.3, 136.2, 136.1, 135.9, 135.0, 128.9, 127.9, 126.9, 126.4, 122.0, 120.0, 118.0, 117.8, 110.7, 100.9, 90.6, 77.2, 75.2, 66.4, 51.1, 48.7, 32.2, 28.3, 27.5, 14.5, 12.8; HRMS (EI) *m/z* 487.2263 [calculated for $C_{29}H_{31}ClN_4O$ (M^+) 487.2265].

Olefin 173. FTIR (thin film/NaCl) 2977 (m), 2932 (m), 2241 (w), 1659)s), 1496 (m), 1455 (s), 1373 (w), 1300 (w), 1226 (w), 1185 (s), 1110 (m), 1015 (w), 898 (w), 729 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 7.62 (s, 1H), 7.54 (d, *J*=7.2 Hz, 1H), 7.29-7.22 (m, 4H), 7.18-7.09 (m, 2H), 6.96-6.90 (m, 2H), 6.11 (d, *J*=12.9 Hz, 1H), 5.11 (d, *J*=12.9 Hz, 1H), 5.02 (d, *J*=15.7 Hz, 1H), 4.97 (d, *J*=15.7 Hz, 1H), 4.91 (s, 2H), 3.80-3.56 (m, 6H), 3.22 (dd, *J*=2.1 Hz, 13.0 Hz, 1H), 1.78 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 147.2, 135.8, 135.2, 134.9, 129.1, 128.3, 128.2, 127.0, 126.7, 126.4, 121.6, 119.6, 118.3, 117.4, 112.0, 111.0, 100.1, 90.6, 77.2, 66.0, 49.0, 45.2, 29.3, 21.0, 14.6, 13.0; HRMS (EI) *m/z* 451.2499 [calculated for $C_{29}H_{30}N_4O$ (M^+) 451.2498].

Preparation of Amide 174:

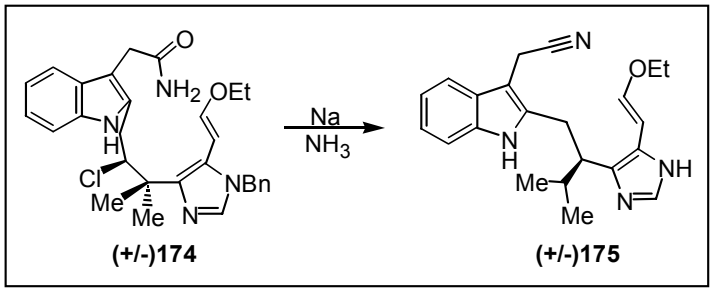


Amide 174. To a solution of **172** (500 mg, 1.03 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added H_2O_2 (aq., 30%) (2 mL), NaOH (aq., 20%) (2 mL) and $(Bu)_4NHSO_3$ (35 mg, 0.10 mmol, 0.1 equiv.). The reaction was stirred vigorously for 2 hours and then poured into H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (2 x 10 mL) and the organic layers were combined and dried with $MgSO_4$. After removal of the solvent *in vacuo*, the mixture was chromatographed on silica gel (5% MeOH/CH_2Cl_2) to afford **174** (385 mg, 74% yield) as a colorless oil.

Amide 174. FTIR (thin film/NaCl) 3454 (m), 3187 (m), 2978 (m), 2930 (w), 1665 (s), 1496 (m), 1454 (m), 1370 (m), 1314 (w), 1227 (w), 1184 (m), 1107 (m), 910 (m), 732 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.51 (s, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 7.26-7.06 (m, 6H), 6.81 (d, *J*=7.2 Hz, 2H), 5.55 (bs, 1H), 5.47 (bs, 1H), 5.34 (d, *J*=12.7 Hz, 1H), 4.99 (d, *J*=12.7 Hz, 1H), 4.96 (d, *J*=16.1 Hz, 1H), 4.91 (d, *J*=16.1 Hz, 1H), 3.62-3.43 (m, 4H), 3.38-3.23 (m, 3H), 1.85 (s, 3H), 1.49 (s, 3H), 1.00 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 152.4, 137.1, 136.6, 136.5, 136.4, 135.1, 128.9, 127.8, 127.7, 127.3, 126.1, 121.6, 119.7, 118.2, 110.5, 105.5, 90.9, 75.0,

66.3, 51.0, 48.5, 32.0, 31.7, 28.6, 27.4, 14.5; HRMS (EI) *m/z* 505.2368 [calculated for $C_{29}H_{33}ClN_4O_2$ (M^+) 505.2370].

Preparation of Imidazole 175:

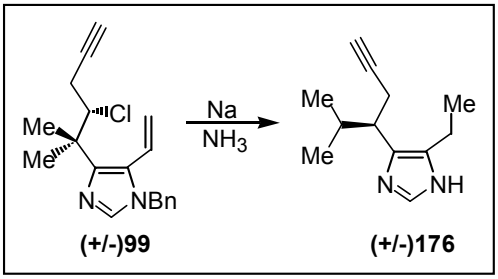


Imidazole 175. To a stirred solution of **174** (6 mg, 0.012 mmol, 1.0 equiv.) in THF (0.5 mL) and NH_3 (0.5 mL) at -78°C was added Na (~0.5 mg, 2.0 equiv.). The reaction was stirred at -78°C and monitored by TLC. Upon consumption of starting material (as indicated by TLC), NH_4Cl (sat., aq.) (0.5 mL) was added to quench the reaction. The mixture was allowed to warm to room temperature and stirred for another hour. H_2O (2 mL) was added the mixture was extracted with EtOAc (3 x 2 mL). The organic layers were combined, dried with $MgSO_4$, and the solvent was removed *in vacuo*. Silica gel chromatography of the resulting oil afforded **175** (3 mg, 65% yield) as a colorless oil.

Imidazole 175. FTIR (thin film/NaCl) 3280 (m), 2977 (m), 2242 (w), 1665 (s), 1497 (m), 1462 (s), 1384 (m), 1184 (m), 1061 (w), 909 (w), 733 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.31 (bs, 1H), 7.47 (bs, 1H), 7.45 (d, *J*=7.6 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 1H), 7.14-7.05 (m, 2H), 6.68 (d, *J*=12.8 Hz, 1H), 5.68 (bs, 1H), 5.58 (d, *J*=12.8 Hz, 1H),

5.41 (bs, 1H), 3.80-3.73 (m, 2H), 3.66 (q, *J*=17.5 Hz, 2H), 3.27 (dd, *J*=10.4 Hz, 14.8 Hz, 1H), 3.11 (dd, *J*=3.6 Hz, 14.8 Hz, 1H), 2.76-2.83 (m, 1H), 2.06-1.97 (m, 1H), 1.28 (t, *J*=7.1 Hz, 3H), 1.03 (d, *J*=6.7 Hz, 3H), 0.83 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 147.7, 136.9, 135.8, 133.6, 128.1, 121.8, 119.9, 118.0, 111.2, 105.3, 95.1, 66.5, 43.9, 33.0, 32.2, 28.5, 21.3, 21.1, 15.1; HRMS (EI) *m/z* 363.21 [calculated for $C_{22}H_{26}N_4O$ (M^+) 363.21].

Preparation of Imidazole 176:



Imidazole 164. To a stirred solution of **99** (31 mg, 0.10 mmol, 1.0 equiv.) in THF (1 mL) and NH_3 (1 mL) at -78°C was added Na (~2.5 mg, 1.1 equiv). The reaction was stirred at -78°C and monitored by TLC. Upon consumption of starting material (as indicated by TLC), NH_4Cl (sat., aq.) (1 mL) was added to quench the reaction. The mixture was allowed to warm to room temperature and stirred for another hour. H_2O (2 mL) was added the mixture was extracted with EtOAc (3 x 3 mL). The organic layers were combined, dried with $MgSO_4$, and the solvent was removed *in vacuo*. Silica gel chromatography of the resulting oil afforded **176** (13 mg, 71% yield) as a colorless oil.

Imidazole 176. FTIR (thin film/NaCl) 3295 (s), 2977 (s), 2118 (w), 1631 (m), 1542 (m), 1463 (s), 1347 (m), 1280 (m), 1069 (s), 1048 (s), 985 (m), 907 (s), 733 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 2.72-2.59 (m, 5H), 2.14-2.05 (m, 1H), 2.01 (t, *J*=2.3 Hz, 1H), 1.27 (t, *J*=7.6 Hz, 3H), 1.04 (d, *J*=6.7 Hz, 3H), 0.81 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.05, 83.6, 70.67, 41.99, 32.0, 22.9, 21.6, 21.2, 19.1, 15.1; HRMS (EI) *m/z* 191.15 [calculated for $C_{12}H_{18}N_2$ (M^+) 191.15].

3.8 Notes and References

(1) Several aldehydes were present in the crude reaction mixture. While it was likely that one of them was the desired product, the reaction was obviously low yielding, and preliminary attempts to separate the products were unsuccessful.

(2) "The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles", Stille, J. K., *Angewandte Chemie-International Edition in English* **1986**, *25*, 508-523.

(3) "Regioselective Addition of Stannylcyanocuprates to Acetylenic Ethers - A Chemical and Spectroscopic Study", Cabezas, J. A.; Oehlschlager, A. C., *Synthesis-Stuttgart* **1994**, 432-442.

(4) While Cabezas and Oehlschlager report an impressive 4:96 ratio of stannanes in favor of the desired 1,2-addition product, in the hands of this lab the ratios of products were typically between 1:3 and 1:1.

(5) Distillation of the vinyl stannanes afforded lower boiling fractions slightly enriched in the desired 1,2-addition product. In no case, however, was clean separation achieved.

(6) "Recent Developments and New Perspectives in the Heck Reaction", Cabri, W.; Candiani, I., *Accounts of Chemical Research* **1995**, *28*, 2-7.

(7) "Palladium-Catalyzed Vinylation of Organic Halides", Heck, R. F., *Organic Reactions* **1982**, *27*, 345-390.

(8) While the oxygen might be imagined to play a role in some sort of chelation effect, it was suspected that the effect might again be simply due to sterics.

(9) "Convenient Synthesis of 1-Alkynyl Ketones and 2-Alkynamides", Tohda, Y.; Sonogashira, K.; Hagihara, N., *Synthesis-Stuttgart* **1977**, 777-778.

(10) "Substitution of Aryl Iodides with Cuprous Acetylides - a Synthesis of Tolanes and Heterocyclics", Stephens, R. D.; Castro, C. E., *Journal of Organic Chemistry* **1963**, *28*, 3313.

(11) "Stereoselective Synthesis of Exocyclic Allylsilanes by Intramolecular Reductive Heck Cyclization of Propargylsilanes", Tietze, L. F.; Schimpf, R., *Chemische Berichte* **1994**, *127*, 2235-2240.

(12) A partial list of reaction conditions employed includes combinations of the following: catalysts ($Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, $PdCl_2$) ligands (PPh_3, $P(o\text{-}tol)_3$, ttmpp) bases (K_2CO_3, $NaHCO_3$, Et_3N, Et_2NH) solvents (DMF, THF, CH_3CN) at various temperatures.

(13) HPLC provided no separation of the alkylated and unalkylated indoles. Careful silica gel chromatography would yield early and late fractions enriched in the separate components, but in no case were pure fractions obtained.

(14) "Efficient asymmetric synthesis of important tryptophan analogs for biological research via the Schollkopf chiral auxiliary", Ma, C. R.; Yu, S.; He, X. H.; Liu, X. X.; Cook, J. M., *Tetrahedron Letters* **2000**, *41*, 2781-2785.

(15) Several other products were visible in the crude reaction mixture. Although their isolation and purification were unsuccessful, it was suspected that they were other diastereomers of the aminals.

(16) "Synthesis of enamides related to the salicylate antitumor macrolides using copper-mediated vinylic substitution", Shen, R. C.; Porco, J. A., *Organic Letters* **2000**, *2*, 1333-1336.

Appendix Three: Spectra Relevant to Chapter Three

Appendix 4

Notebook Cross Reference

The following notebook cross reference has been included to facilitate access to the original spectroscopic data obtained for the compounds presented in this work. For each compound a folder name is given (e.g., SCCC.079.H) which corresponds to an archived characterization folder hard copy and folders stored on a compact disk. For each folder a characterization notebook page number (e.g., 099) is given and for each spectrum a code (i.e.: H for ^{1}H NMR, C for ^{13}C NMR and I for FTIR) and a number (e.g., 099) are given. The characterization notebook, spectral data and disks are stored in the Wood Group archives.

Table A.4.1 Compounds Appearing in Chapter 2.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
79	SCCC.079	SCCC.079.H	SCCC.079.C	SCCC.079.I
86	SCCC.086	SCCC.086.H	SCCC.086.C	SCCC.086.I
87	SCCC.087	SCCC.087.H	SCCC.087.C	SCCC.087.I
88	SCCC.088	SCCC.088.H	SCCC.088.C	SCCC.088.I
89&90	SCCC.089	SCCC.089.H	SCCC.089.C	SCCC.089.I
91&92	SCCC.091	SCCC.091.H	SCCC.091.C	SCCC.091.I
93	SCCC.093	SCCC.093.H	SCCC.093.C	SCCC.093.I
94	SCCC.094	SCCC.094.H	SCCC.094.C	SCCC.094.I
95	SCCC.095	SCCC.095.H	SCCC.095.C	SCCC.095.I
96	SCCC.096	SCCC.096.H	SCCC.096.C	SCCC.096.I

Table A.4.1 Compounds Appearing in Chapter 2 (Continued)

97	SCCC.097	SCCC.097.H	SCCC.097.C	SCCC.097.I
98	SCCC.098	SCCC.098.H	SCCC.098.C	SCCC.098.I
99	SCCC.099	SCCC.099.H	SCCC.099.C	SCCC.099.I
100	SCCC.100	SCCC.100.H	SCCC.100.C	SCCC.100.I
108	SCCC.108	SCCC.108.H	SCCC.108.C	SCCC.108.I
109	SCCC.109	SCCC.109.H	SCCC.109.C	SCCC.109.I
110	SCCC.110	SCCC.110.H	SCCC.110.C	SCCC.110.I
112	SCCC.112	SCCC.112.H	SCCC.112.C	SCCC.112.I
113	SCCC.113	SCCC.113.H	SCCC.113.C	SCCC.113.I
114	SCCC.114	SCCC.114.H	SCCC.114.C	SCCC.114.I
115	SCCC.115	SCCC.115.H	SCCC.115.C	SCCC.115.I
120	SCCC.120	SCCC.120.H	SCCC.120.C	SCCC.120.I
126	SCCC.126	SCCC.126.H	SCCC.126.C	SCCC.126.I
127	SCCC.127	SCCC.127.H	SCCC.127.C	SCCC.127.I
137	SCCC.137	SCCC.137.H	SCCC.137.C	SCCC.137.I
139	SCCC.139	SCCC.139.H	SCCC.139.C	SCCC.139.I

Table A.4.2 Compounds Appearing in Chapter 3.

Compound	Folder	^{1}H NMR	^{13}C NMR	FTIR
144	SCC.144	SCC.144.H	SCC.144.C	SCC.144.I
148	SCC.148	SCC.148.H	SCC.148.C	SCC.148.I
149	SCC.149	SCC.149.H	SCC.149.C	SCC.149.I
150	SCC.150	SCC.150.H	SCC.150.C	SCC.150.I
151	SCC.151	SCC.151.H	SCC.151.C	SCC.151.I
152	SCC.152	SCC.152.H	SCC.152.C	SCC.152.I
153	SCC.153	SCC.153.H	SCC.153.C	SCC.153.I
154	SCC.154	SCC.154.H	SCC.154.C	SCC.154.I
155	SCC.155	SCC.155.H	SCC.155.C	SCC.155.I
156	SCC.156	SCC.156.H	SCC.156.C	SCC.156.I
157	SCC.157	SCC.157.H	SCC.157.C	SCC.157.I
159&160	SCC.159	SCC.159.H	SCC.159.C	SCC.159.I
160	SCC.160	SCC.160.H	SCC.160.C	SCC.160.I
161	SCC.161	SCC.161.H	SCC.161.C	SCC.161.I
162	SCC.162	SCC.162.H	SCC.162.C	SCC.162.I
163	SCC.163	SCC.163.H	SCC.163.C	SCC.163.I
164	SCC.164	SCC.164.H	SCC.164.C	SCC.164.I
165	SCC.165	SCC.165.H	SCC.165.C	SCC.165.I
166	SCC.166	SCC.166.H	SCC.166.C	SCC.166.I
167	SCC.167	SCC.167.H	SCC.167.C	SCC.167.I
170	SCC.170	SCC.170.H	SCC.170.C	SCC.170.I
171	SCC.171	SCC.171.H	SCC.171.C	SCC.171.I
172	SCC.172	SCC.172.H	SCC.172.C	SCC.172.I
173	SCC.173	SCC.173.H	SCC.173.C	SCC.173.I
174	SCC.174	SCC.174.H	SCC.174.C	SCC.174.I

175	SCC.175	SCC.175.H	SCC.175.C	SCC.175.I
176	SCC.176	SCC.176.H	SCC.176.C	SCC.176.I

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About the Author

The son of Clarence and Judith Chaffee, Stuart was born September 14, 1973 in Rockland Maine. After spending the first four years of his life in coastal Maine, Stuart's family moved to the northern Virginia suburbs of Washington, D.C.

The third of what would eventually be seven children, Stuart attended grade school at Fairhill Elementary, followed by seven and eighth grades at Luther Jackson Intermediate. After moving across town, Stuart attended James Madison High School in Vienna where his interest in science and nature found a foothold in biology class.

In the fall of 1991, Stuart began his undergraduate studies at the College of William and Mary in Williamsburg, VA as a biology major. Discouraged by the bland memorization of botany and zoology classes in his junior year, Stuart found the concrete scientific relevance he was looking for in chemistry class and switched majors. His decision to pursue chemistry was quickly solidified in the labs of Professor Robert Pike, where he became fascinated with the coordination complexes of manganese. The encouraging words of Professor Pike convinced Stuart to undertake honors studies, and in 1996 he graduated *summa cum laude* from William and Mary.

In the fall of 1996 Stuart began graduate studies at Yale University as an inorganic chemist. Several months later Stuart would change the direction of his education again when he found the allure of synthetic chemistry irresistible and asked to work in the organic labs of Professor John Wood. Handed an isolation paper in his first year, Stuart would spend the next five years in pursuit of a natural product called Securamine A.

In the spring of 2001, Stuart accepted a position as a medicinal chemist with Amgen in Boston, MA.