The Pennsylvania State University

The Graduate School

Eberly College of Science

STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF SECURINE A AND SECURAMINE A

A Thesis in

Chemistry

by

Pooja Aggarwal

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ABSTRACT

The aim of this research project was to synthesize securamine A (**6**) and to make use of the facile equilibrium between securamine A (**6**) and securine A (**13**) in the strategic design. The original synthetic strategy was to prepare these alkaloids based on the construction of the neopentyl alcohol **86** by coupling lithiated indole **58** with simple epoxide **85**. However, we were not able to obtain any of the desired product in this model study.

An alternative strategy was then employed for a total synthesis of these alkaloids based on the coupling of the indole ester **146** with the aldehyde functionality of advanced imidazole intermediate **120**, which proceeded in good yield to give ester alcohol **147**. A benzyl group was found to be the most compatible nitrogen protecting group for the indole **110** in the synthetic sequence. A key intermediate, protected oxime **169**, was then formed by condensation of aldehyde **153** and BOM-protected hydroxylamine **168**. Many attempts to chlorinate various neopentyl alcohols were tried; however, it seems that it will be necessary to remove the protecting group on the indole nitrogen in order for this step to be successful.

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I would especially like to thank my family and friends for their love, support, and understanding. Finally, above all others, I wish to thank my mother; it is to her that I dedicate this thesis and the work within it.

Studies Directed Towards Total Syntheses of Securine A and Securamine A

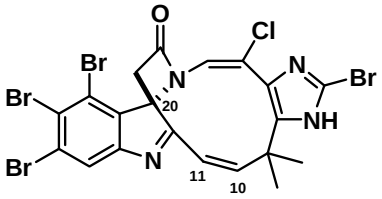
PART ONE

Introduction and Background

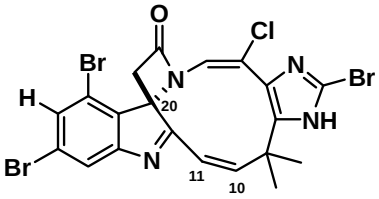
1.1 Isolation and Structural Identification of the Chartellines, Securamines, and Related Alkaloids

Chartellines A (**1**), B (**2**), and C (**3**) were isolated by Christophersen and coworkers from the marine bryozoan *Chartella papyracea* collected near the west coast of Denmark in the 1980's. These molecules have fascinating structures containing an unusual highly halogenated indolenine-imidazole system and a spiro-β-lactam ring. The structure and stereochemistry of chartelline A (**1**) was determined by X-ray crystallography. The absolute configuration of chartelline A (**1**) was established as *S* at the *C*-20 position at a better than 99.5% significance level according to Hamilton's *R*-factor test.[1] A biogenetically related pair of alkaloids containing a similar spiro-β-lactam ring, chartellamides A (**4**) and B (**5**), was isolated from the same organism.[2] The relative stereochemistry of these alkaloids has been determined by NOE experiments.

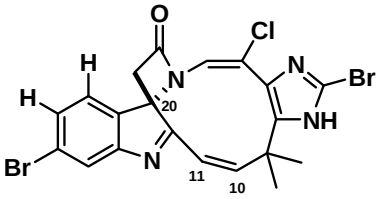
Comparison of the CD spectra of **4** and **5** indicates that these alkaloids have the same absolute configuration. Based on the assumption that the absolute configuration at *C*-20 of the chartellines is the same as the chartellamides, it was proposed that the chartellamides have the 9(*S*), 11(*R*), 12(*R*), and 20(*S*) configuration.[2]



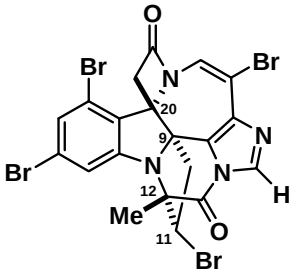
1 chartelline A



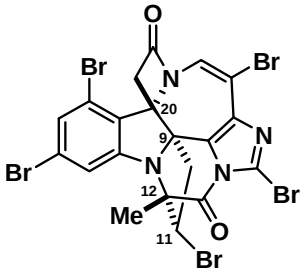
2 chartelline B



3 chartelline C



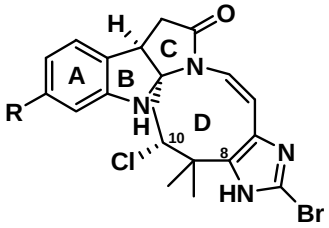
4 chartellamide A



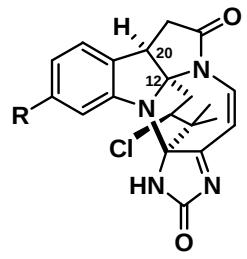
5 chartellamide B

In 1994, seven new halogenated indole-imidazole alkaloids, securamines A (**6**), B (**7**), C (**8**), D (**9**), E (**10**), F (**11**), and G (**12**), were isolated by Christophersen and coworkers from the marine bryozoans *Securiflustra securifrons*, also found in the North Sea.[3] The securamines contain a γ-lactam moiety as opposed to the β-lactam moiety found in the chartellines and chartellamides. The structures of these alkaloids were determined by NMR analysis and mass spectrometry. The relative configuration of all of

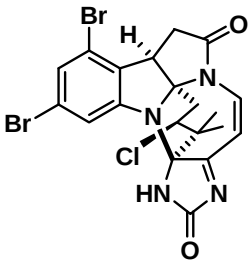
these alkaloids, except for securamines A (**6**) and B (**7**), was confirmed by NOE experiments, but the absolute configurations are yet to be determined.



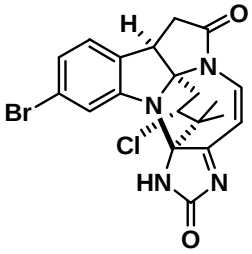
6 R = H (securamine A)
7 R = Br (securamine B)



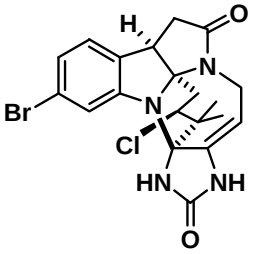
8 R = Br (securamine C)
9 R = H (securamine D)



10 securamine E



11 securamine F



12 securamine G

Interestingly, during the NMR structure elucidation studies, it was observed that securamines A (**6**) and B (**7**) existed as an equilibrium mixture with the macrocyclic indoles securine A (**13**) and B (**14**), respectively, when dissolved in DMSO-d_6 solution (Figure 1). Furthermore, upon concentration of the solution and then redissolving the residue in $CDCl_3$, the securines converted back to the securamines. The structures of securines have been inferred by HMBC and NOESY experiments as well as by comparison to the data of the securamines.[3a] However, it is difficult to assess whether

the securines are actual natural products since they were not isolated from the natural source.

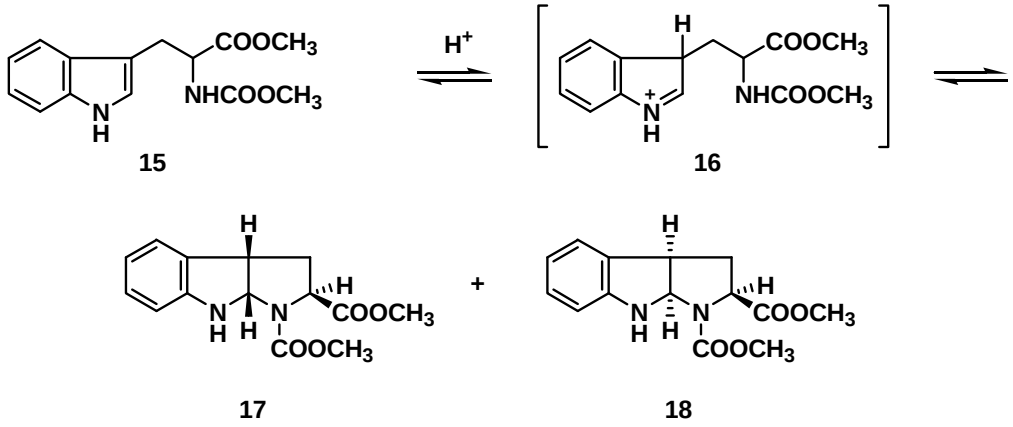
Figure 1. Securamines and Securines Equilibrium

6 R = H (securamine A)
7 R = Br (securamine B)

13 R = H (securine A)
14 R = Br (securine B)

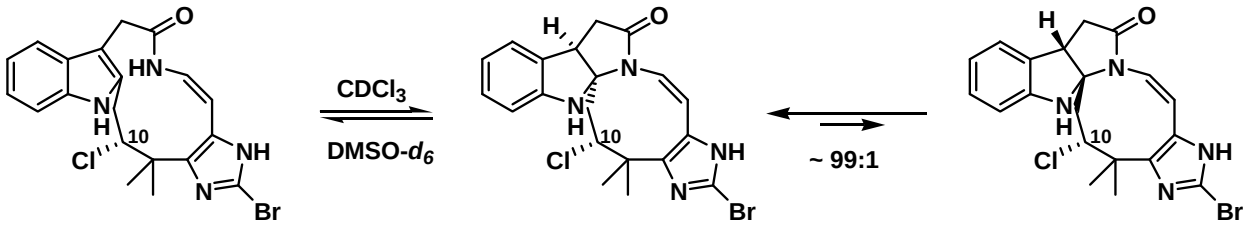
Precedent for the facile interconversion between the securamines and securines comes from acid promoted cyclization experiments performed on simple tryptophan systems such as **15** (Scheme 1).[4] Thus, in the presence of acid, the *C*-3 position of indole **15** is protonated to generate the iminium ion **16**, which cyclizes rapidly to afford a mixture of tricyclic diastereomers **17** and **18**.[5]

Scheme 1



The presence of only one diastereoisomer for securamines A (**6**) and B (**7**) in $CDCl_3$ solution according to NMR analysis indicates that the stereogenicity found at the *C*-10 chlorine-containing center in securamine isomer a (**6a**) and securamine isomer b (**6b**) is specifically relayed in forming the two new stereogenic centers during the conversion of the securines to the securamines. In order to probe which of the two diastereomers of securamine A (**13**) is more stable, an *ab initio* calculation was performed[6] with the Gaussian 03 package (Figure 2).[7] These calculations show that isomer **6a** is ~2.68 kcal/mol more stable than isomer **6b**, which corresponds to a ~99:1[8] thermodynamic ratio. It should be noted that the chlorine configuration at *C*-10 is chosen arbitrarily here, as the absolute stereochemistry of these compounds is presently unknown.

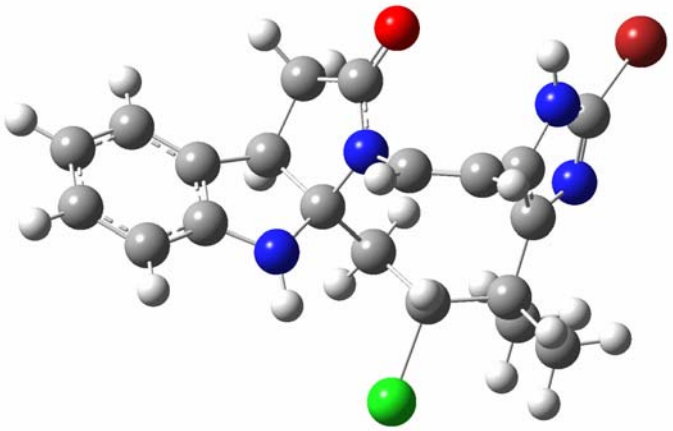
Figure 2. Securamine A Isomers (Ab Initio Calculation)

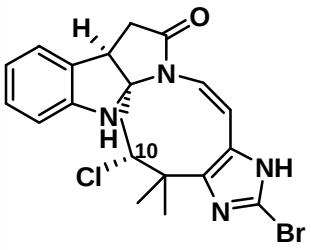


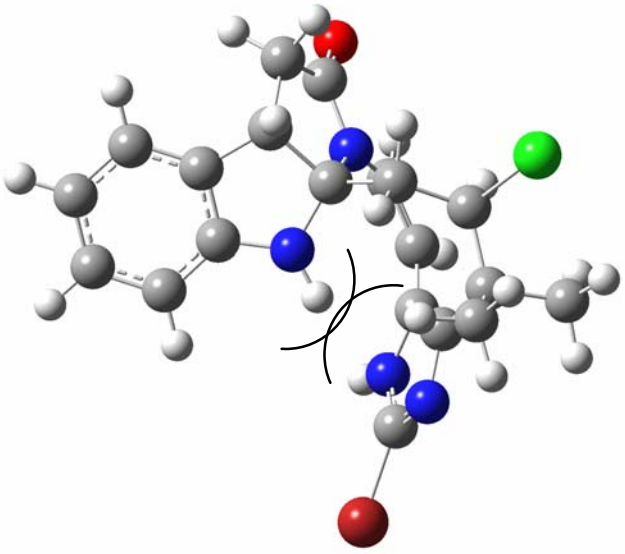
13 securine A **6a securamine isomer a** **6b securamine isomer b**

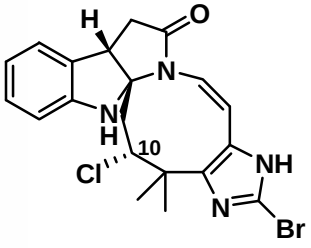
In order to better understand why isomer **6a** is more stable than isomer **6b**, three-dimensional minimized structural representations were analyzed and are shown below (Figure 3). In the top structure, which represents securamine isomer a (**6a**), the indole and imidazole ring systems are far away from each other. However, in securamine isomer b (**6b**), the indole is in close proximity to the imidazole ring, causing unfavorable steric interactions between the two aromatic ring systems.

Figure 3. 3D Representations of Securamine Isomers a (6a) and b (6b)





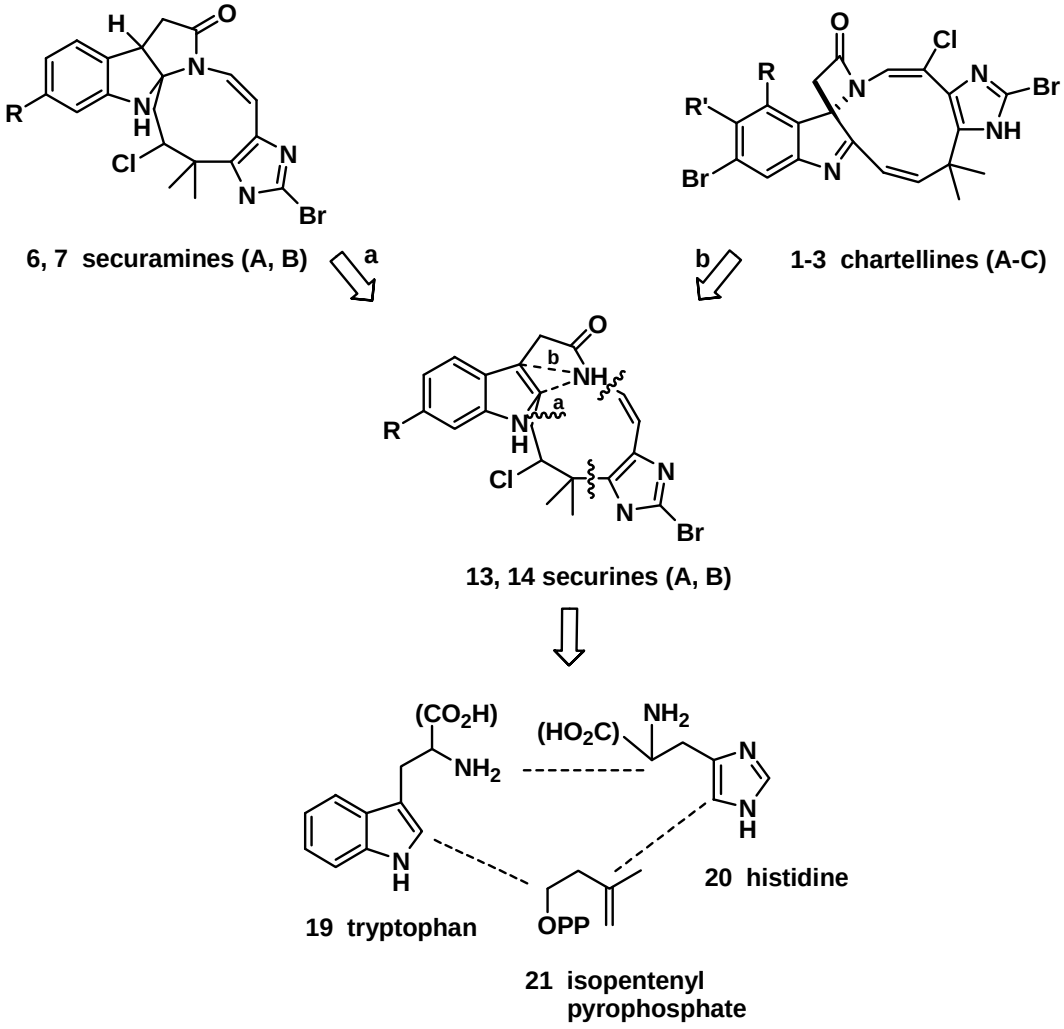




1.2 Proposed Biosynthesis of the Securamine, Securine, and Chartelline Alkaloids

Christophersen and coworkers have proposed a biosynthesis of securamine A (**6**) and chartelline A (**1**), which is outlined in Figure 4.[1a] It was proposed that the securines are precursors for both the securamines, containing a γ-lactam ring, and the chartellines, containing a spiro-β-lactam ring.

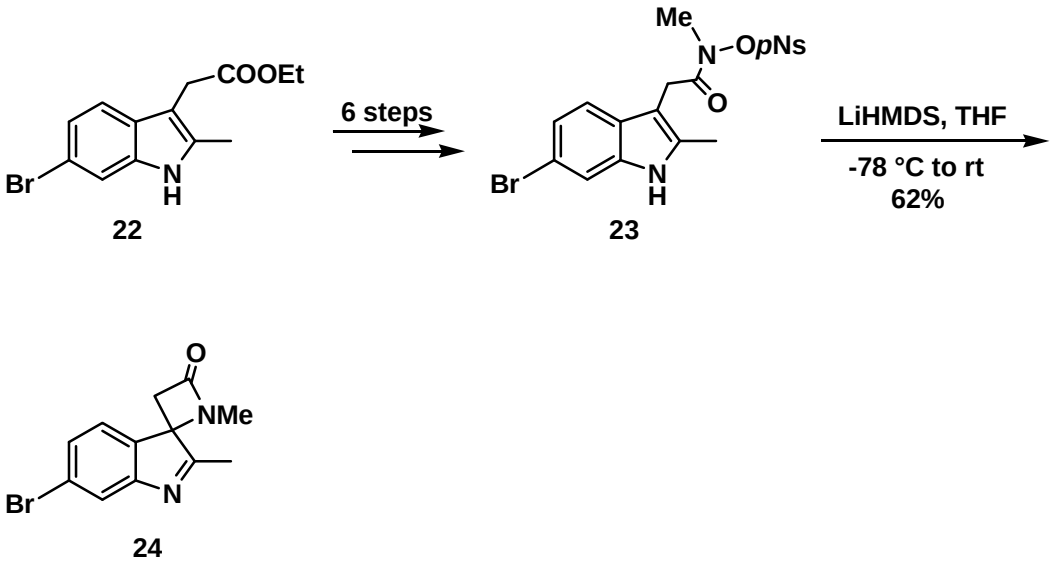
Figure 4. Proposed Biogenesis for Securamine, Securine, Chartelline Alkaloids



Protonation at the *C*-3 position of the indole moiety of the securines, followed by attack of the amide nitrogen onto the indole *C*-2 would generate the securamines framework (path a). Oxidative cyclization of the amide nitrogen of the securines onto the indole at *C*-3 would in turn generate the chartellines framework (path b). Most likely, the securines are composed of modified tryptophan (**19**) and histidine (**20**) units, which are joined by an isopentenyl pyrophosphate-derived unit (**21**), to form the macrocyclic ring system. However, the biosynthesis of these compounds has not been investigated experimentally.[1a]

Isobe and Nishikawa[9a] have recently synthesized the spiro-β-lactam moiety of the chartellines using a biogenetically-patterned strategy that incorporates a nucleophilic substitution at the nitrogen atom of an *O*-*p*Ns hydroxamic acid **23**, which was prepared from 2-methylindole-3-acetic acid ester **22** (Scheme 2).

Scheme 2



Indole ester **22** was converted to precursor **23** for β-lactam formation in six steps. Treatment of **23** with lithium hexamethyldisilazide at -78 ˚C and warming to rt provided the desired spiro-β-lactam **24** in good yield. The approach mimics the biogenetic pathway in that the bond between the *C*-3 of the indole and the nitrogen of the amide is formed to generate the spiro-β-lactam ring (*vide supra*).

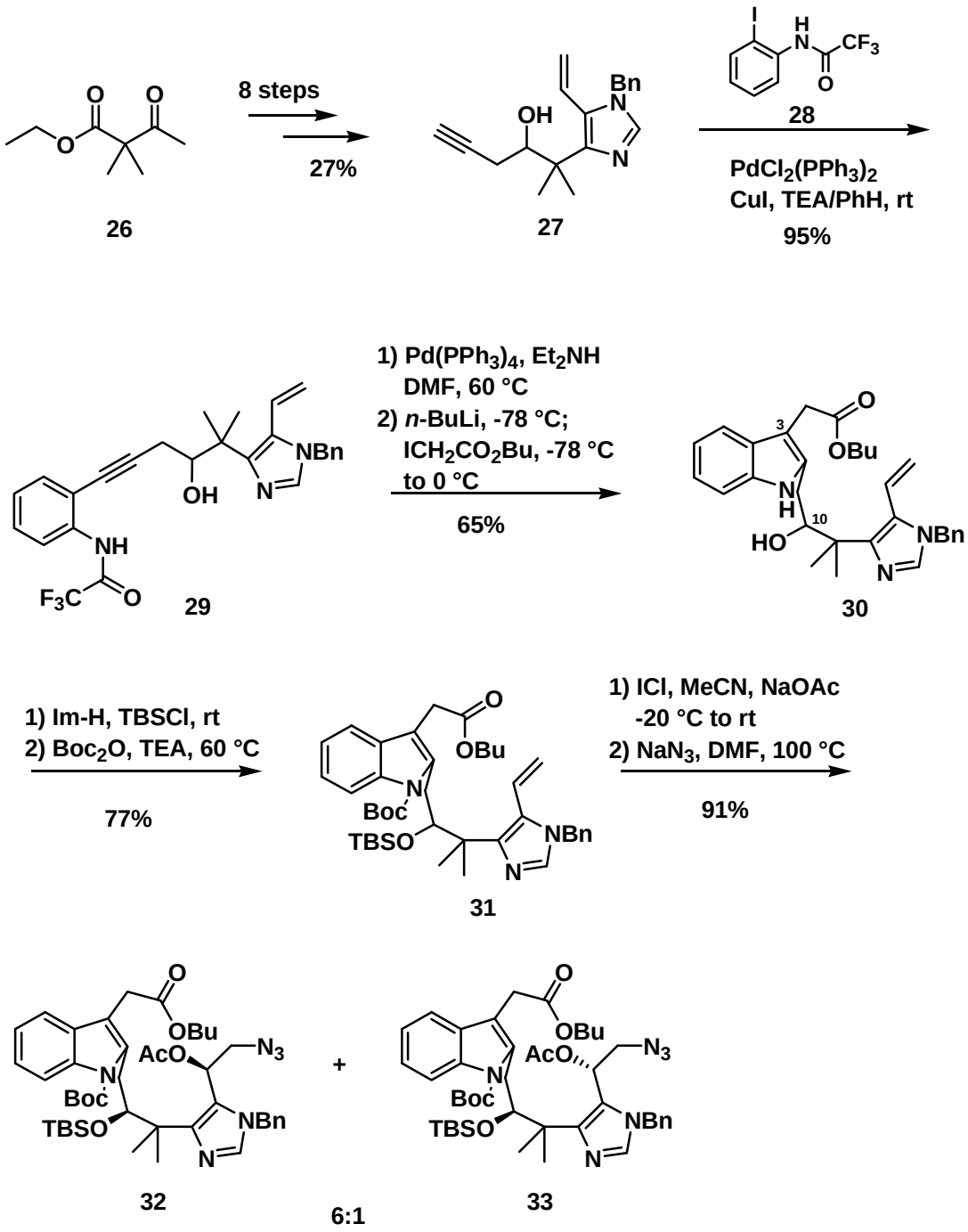
1.3 Synthetic Approaches to the Securines

The securamines, chartellines, and chartellamides provide challenging synthetic targets in that they incorporate several unusual structural features. However, there are only a few reports of synthetic work on these alkaloids to date.[10] Our group has reported the first synthetic studies on the chartellines[11] and chartellamides.[12] The Isobe group has reported two strategies for synthesis of the spiro β-lactam moiety of the chartellines.[9] Thus far, only the Baran group has reported a completed total synthesis of (±)-chartelline C.[13]

Wood's Synthetic Approach to the Securine Macrocycle[14]

The Wood group has reported a strategy for construction of the macrocyclic system of securine A (**13**). β-Ketoester **26** was elaborated in 8 steps to afford the functionalized imidazole **27** (Scheme 3).

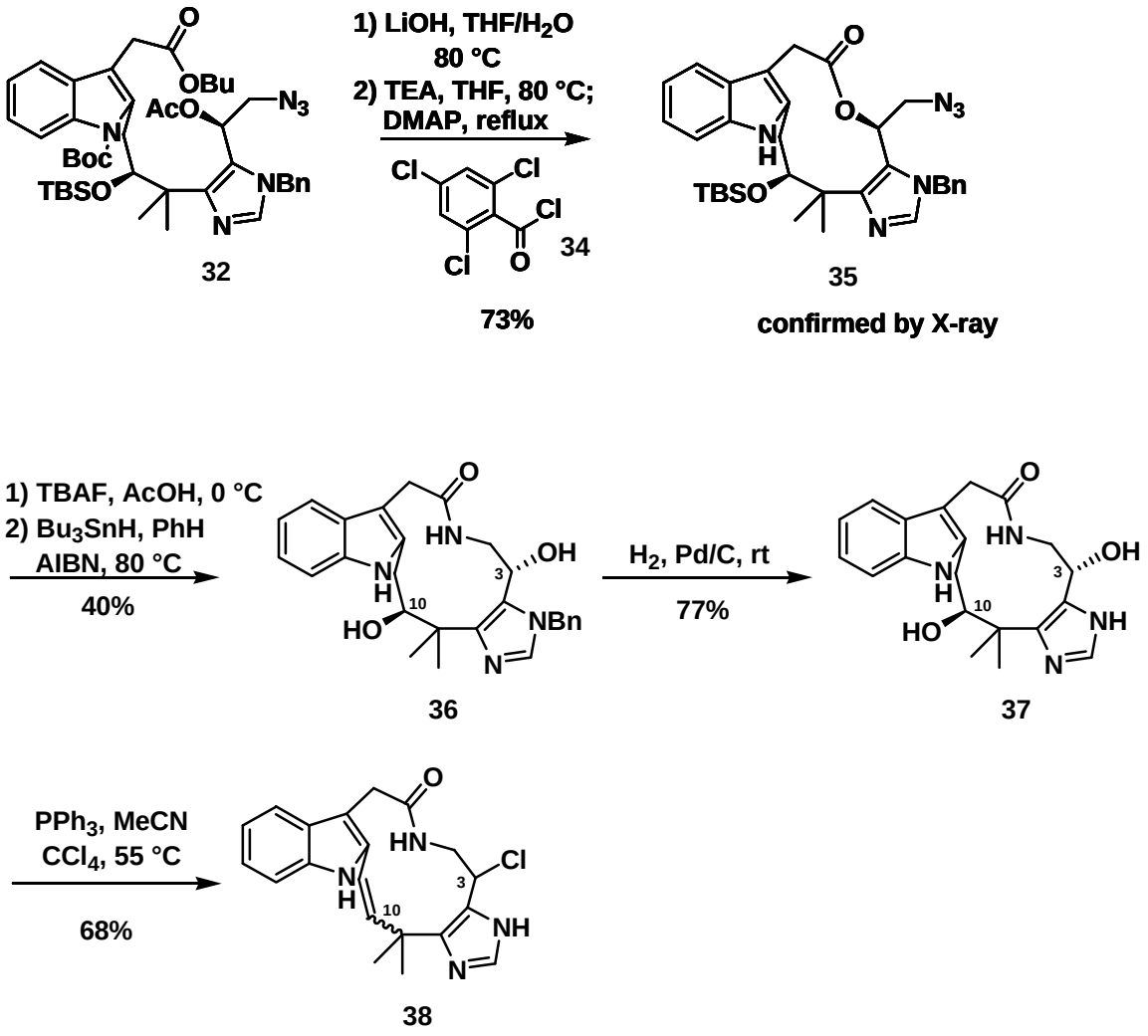
Scheme 3


8 steps
27%
26
27
28
PdCl2(PPh3)2
CuI, TEA/PhH, rt
95%
29
1) Pd(PPh3)4, Et2NH
DMF, 60 °C
2) n-BuLi, -78 °C;
ICH2CO2Bu, -78 °C
to 0 °C
65%
30
1) Im-H, TBSCl, rt
2) Boc2O, TEA, 60 °C
77%
31
1) ICl, MeCN, NaOAc
-20 °C to rt
2) NaN3, DMF, 100 °C
91%
32
+
33
6:1

The terminal alkyne of the imidazole **27** was coupled with iodoaniline derivative **28** under Sonagashira conditions to form internal alkyne **29**. Prolonged exposure of alkyne **29** to tetrakis(triphenylphosphine) palladium formed the indole, which was then metallated and alkylated at *C*-3 using *n*-butyllithium and *n*-butyl α-iodoacetate to afford alkylated indole **30**. The *C*-10 hydroxyl moiety of alkylated indole **30** was then protected as a silyl ether with TBSCl and the indole nitrogen was protected as a carbamate with BOC_2O to afford indole **31**. Treatment of the olefin moeity of **31** with iodine monochloride/sodium acetate followed by sodium azide gave diastereomeric azido acetates **32** and **33** as a separable 6:1 mixture.

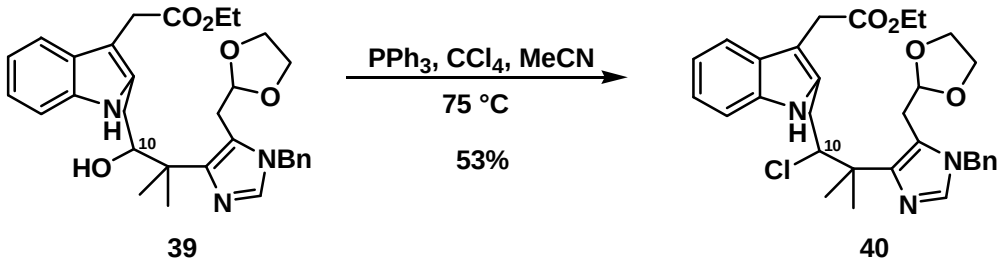
The major diastereomer, azido acetate **32**, was then treated with lithium hydroxide to hydrolyze the ester moieties and to cleave the *N*-Boc protecting group to afford the corresponding hydroxy acid. Upon treatment with Yamaguchi's reagent (2,4,6-trichlorobenzoyl chloride, **34**) the acid underwent macrocylization to afford lactone **35** as a single diastereomer (Scheme 4). The structure of lactone **35** was confirmed by X-ray crystallography. Removal of the TBS group, followed by a tandem azide reduction-ring expansion of lactone **35** gave the macrocyclic lactam **36**. Hydrogenolysis of the lactam **36** with hydrogen and palladium/carbon removed the benzyl protecting group to afford the debenzylated derivative **37**. Problems ensued when efforts were made to convert the alcohol at *C*-10 to the chloride and to simultaneously generate the *Z*-enamide. Thus, when lactam **37** was treated with carbon tetrachloride and triphenylphosphine, the alcohol at *C*-10 underwent elimination instead of chlorination, and the alcohol at the *C*-3 position underwent chlorination instead of elimination to give **38**.

Scheme 4



Model studies involving the installation of a neopentyl chloride at *C*-10 on an acyclic substrate were also conducted by the Wood group (Scheme 5).[14] For example, neopentyl alcohol **39** was treated with triphenylphosphine and carbon tetrachloride to afford neopentyl chloride **40** in moderate yield. It is therefore possible to convert a hindered alcohol like **39** into the corresponding chloride.

Scheme 5



39 **40**

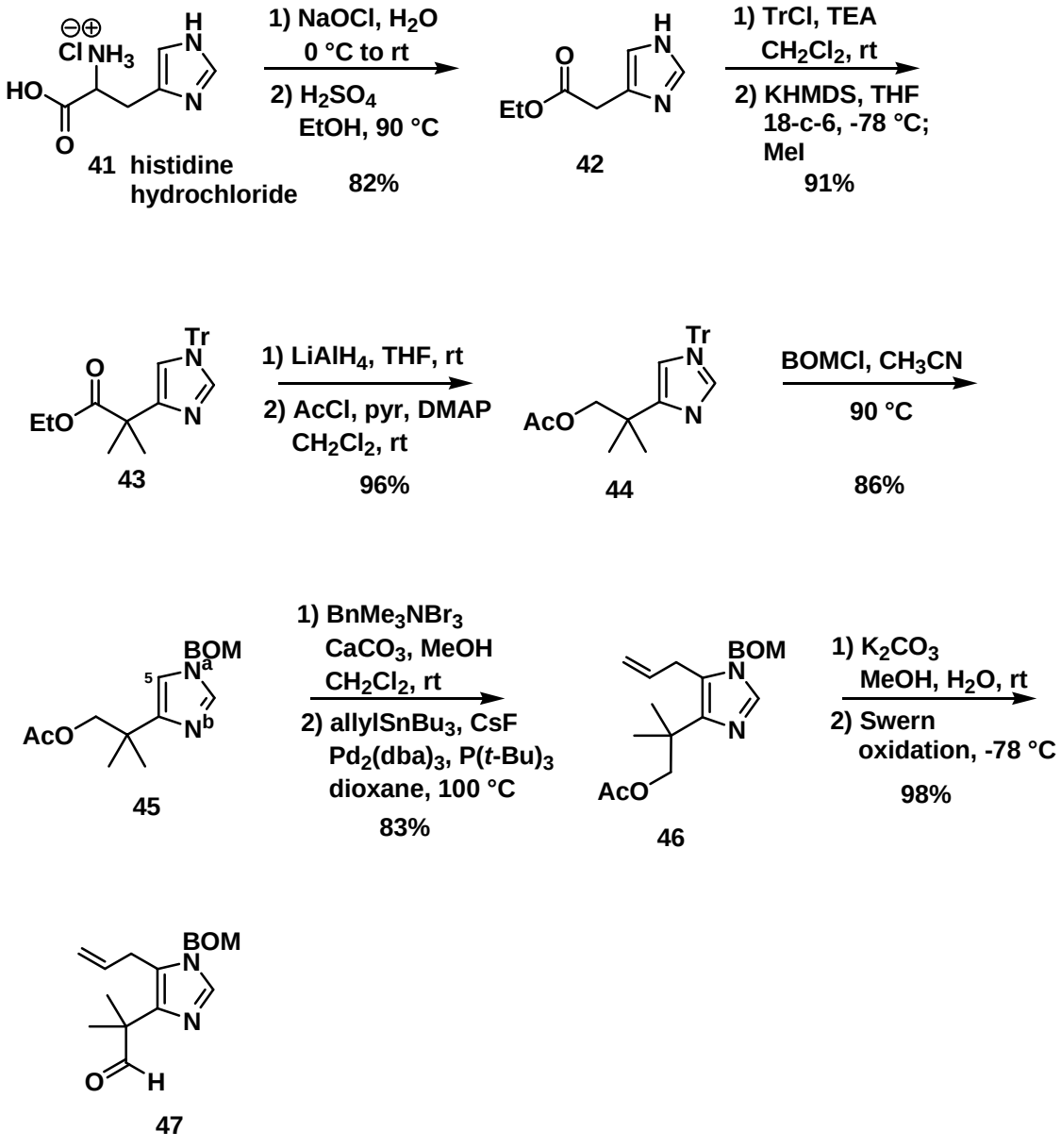
1.4 Previous Synthetic Studies on the Imidazole Fragment of the Chartellines in the Weinreb Group[15, 16]

The approach to the formation of the imidazole fragment **47** developed by Xichen Lin[15] and Cuixiang Sun[16] started with the oxidation of histidine hydrochloride (**41**) to the known 4-cyanomethylimidazole,[17] which was hydrolyzed to the known imidazole ester **42**[18] with concentrated sulfuric acid in refluxing ethanol (Scheme 6). The imidazole ester **42** was regioselectively *N*-protected with TrCl and subsequently alkylated with potassium hexamethyldisilazide and iodomethane to afford the dimethylated ester **43**. Treatment of the dimethylated ester **43** with $LiAlH_4$ afforded the corresponding alcohol, which was protected with acetyl chloride to form imidazole acetate **44**.

Attempts to brominate the imidazole acetate **44** were unsuccessful due to cleavage of the trityl protecting group under the reaction conditions. Hence, it became necessary to use a more stable protecting group. Thus, treatment of imidazole acetate **44** with BOMCl in refluxing acetonitrile provided *N*-BOM imidazole **45** as a single regioisomer.

It was initially assumed that the BOM group occupied the N^b position in *N*-BOM imidazole **45**. However, it was later shown that the *N*-BOM protected imidazole **45** is in fact the N^a-BOM regioisomer and not the N^b-BOM isomer (*vide infra*).

Scheme 6

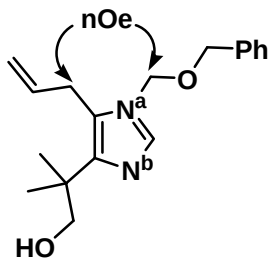


Regioselective bromination at the *C*-5 position of the *N*-BOM imidazole **45** with benzyltrimethylammonium tribromide followed by a Stille coupling with allyltributylstannane gave the allyl imidazole **46** in moderate yield along with the debrominated imidazole **45**. Ester hydrolysis of allyl imidazole **46** under basic conditions gave the corresponding primary alcohol, which was subjected to Swern oxidation conditions to give aldehyde **47**.

1.4.1 Protection of the Imidazole Fragment

N-BOM imidazole **48** was previously thought to be the N^b-BOM regioisomer (*vide supra*). However, an NOE experiment showed that imidazole **48** is actually the N^a-BOM regioisomer (Figure 5).[16] The allylic methylene protons could be seen on irradiation at the frequency of the BOM methylene protons and vice versa, which strongly indicates that the BOM group is in fact at the N^a position.

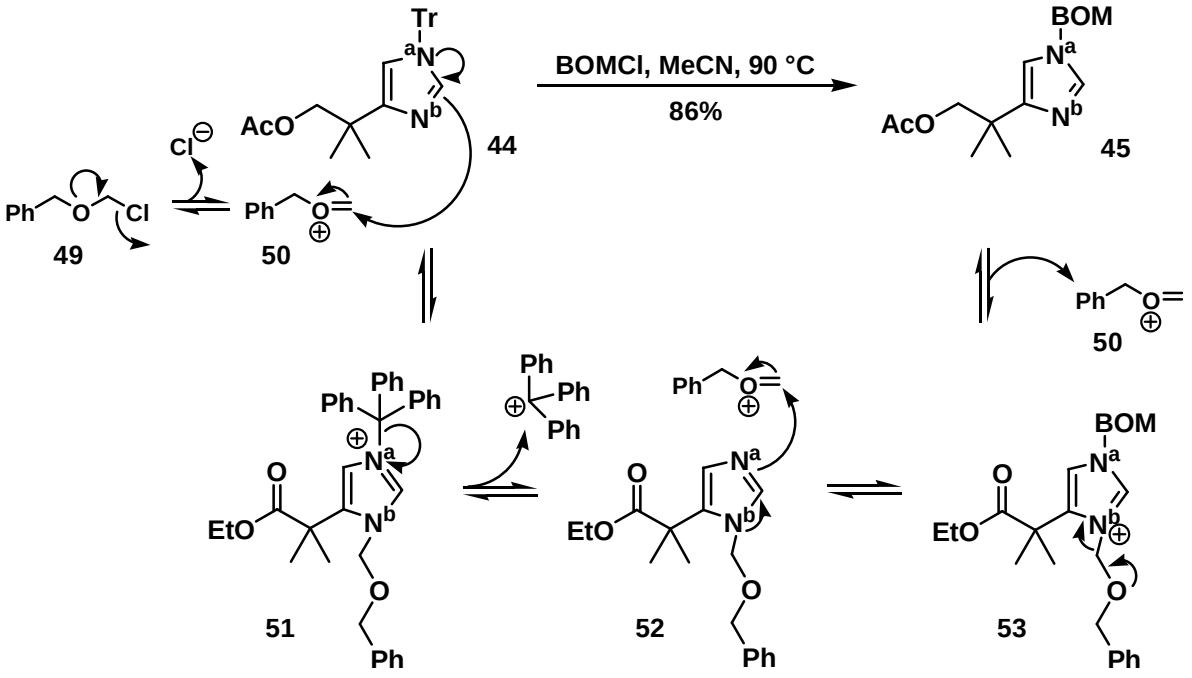
Figure 5. NOE Study of Allyl Imidazole **48**



48

Our group has proposed a mechanism for the conversion of N^a-Tr-imidazole **44** to N^a-BOM imidazole **45** (Scheme 7). Attack of N^b of the N^a-Tr-imidazole **43** on the BOM-derived oxonium ion **50** will form the N^b-BOM regioisomer **51**, followed by the loss of the trityl group. Because of the presence of the bulky dimethyl ester on the adjacent carbon of the imidazole, the N^b-BOM regioisomer **52** is unstable and therefore rearranges to form the thermodynamically more stable N^a-BOM regioisomer **54** through intermediate **53**. During the synthetic efforts by Sun towards chartelline A (**1**), it was observed that the BOM group has the propensity to shift from one nitrogen of the imidazole ring to the other under various reaction conditions, presumably via a similar mechanism. However, this rearrangement does not pose a problem for the synthesis of securine A (**13**) and securamine A (**6**) because the BOM protecting group will eventually be removed.

Scheme 7



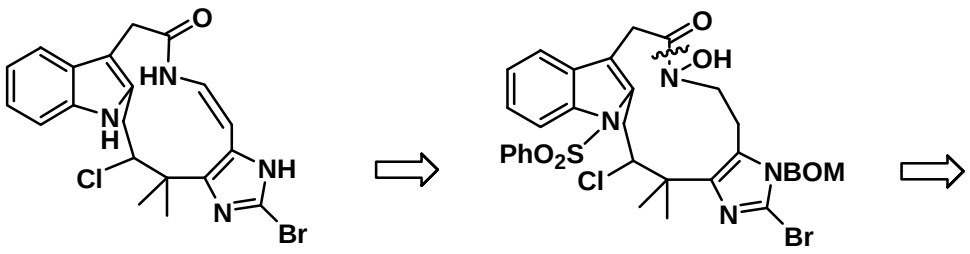
PART TWO

Results and Discussion

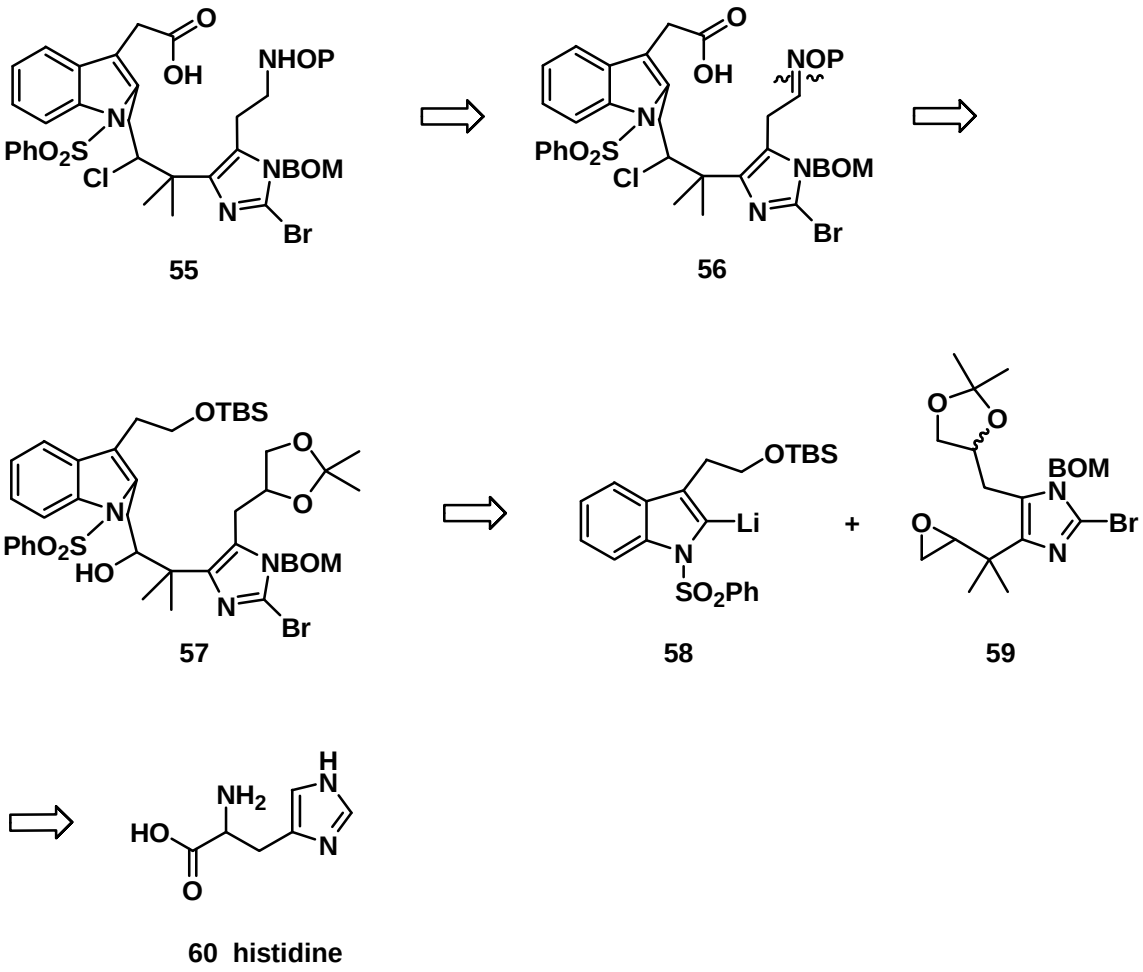
2.1 Approaches Towards a Total Synthesis of Securine A and Securamine A

Our original retrosynthetic analysis for the synthesis of (±)-securine A (**13**) is outlined in Scheme 8. Securine A would be obtained by the dehydration of hydroxamic acid **54** to form the less strained *Z*-enamide functionality. By analogy, treatment of hydroxamic acid **61** with 2,6-lutidine and triflic anhydride in methylene chloride gives triflate **62** (Scheme 9).[19] The triflate group then eliminates, giving acyliminium ion **63**, which is then trapped with either allyltrimethyl silane or *i*-PrOH to give amides **64** or **65**, respectively.

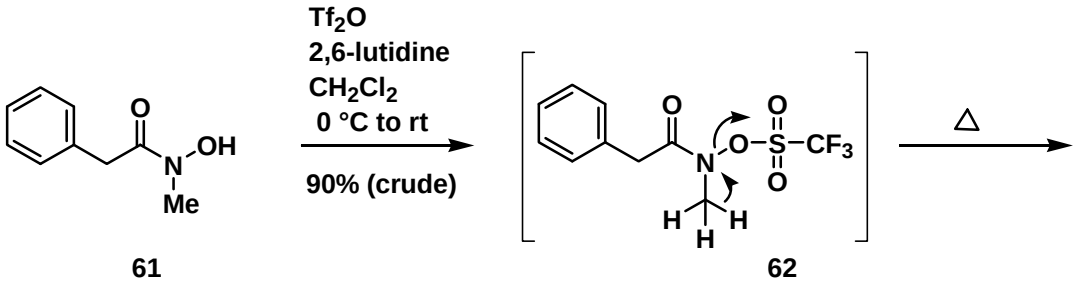
Scheme 8

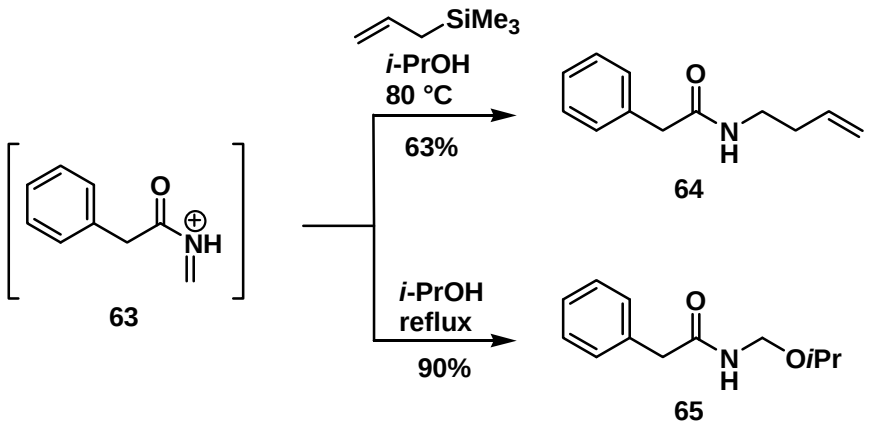


13 (±)-securine A **54**


O
OH
NHOP
N
PhO2S
Cl
NBOM
N
Br
55
NOP
56
OTBS
O
HO
57
Li
SO2Ph
58
+
BOM
59
NH2
HO
60 histidine

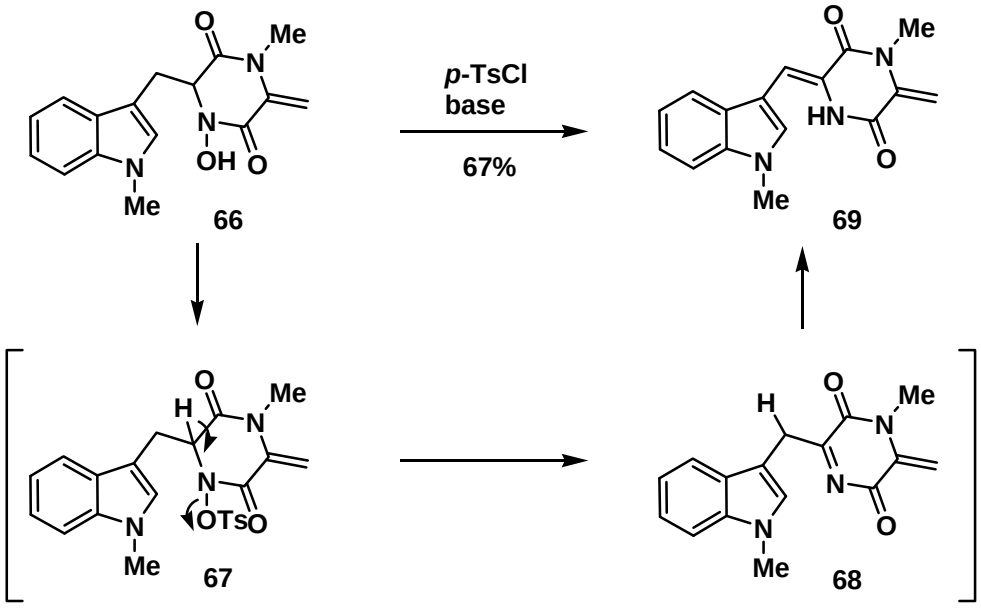
Scheme 9


Tf2O
2,6-lutidine
CH2Cl2
0 °C to rt
90% (crude)
OH
N
Me
61
O
O
O
O
S
CF3
H
H
H
62
△



In addition, treatment of hydroxy piperazine dione **66** with tosyl chloride and triethylamine gives *O*-tosyl derivative **67**, which eliminates to give acylimine **68**. This intermediate then tautomerizes to give enamide **69** in good yield (Scheme 10).[20]

Scheme 10



Hydroxamic acid derivative **54** would be made by reduction of the protected oxime **56** to hydroxylamine **55**, which would undergo subsequent macrocyclization to form the twelve-membered ring.[21] Similar cyclizations for the formation of medium-sized hydroxamic acid rings have been reported, but no examples of large ring systems exist.[22] However, macrolactamizations of simple ω-amino acids abound.[23] Conversion of the neopentyl alcohol functionality in acetonide **57** to the chloride **56** would be effected prior to macrolactamization, similar to that done by Wood (Cf. Scheme 5).

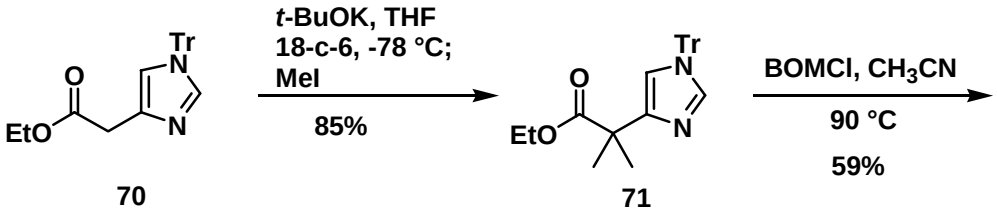
The protected oxime moiety in **56** would be prepared from intermediate **57** via a series of functional group transformations, involving hydrolysis of the acetonide, oxidative cleavage of the diol to the aldehyde, and finally condensation with the appropriate hydroxylamine derivative. The neopentyl alcohol **57** could be disconnected to give two advanced intermediates, the functionalized epoxide-imidazole fragment **59** and metallated tryptophol derivative **58**.[24] The epoxide-imidazole fragment **59** would be made from histidine (**60**) using methodology similar to that previously devised for the chartelline project (*vide supra*).

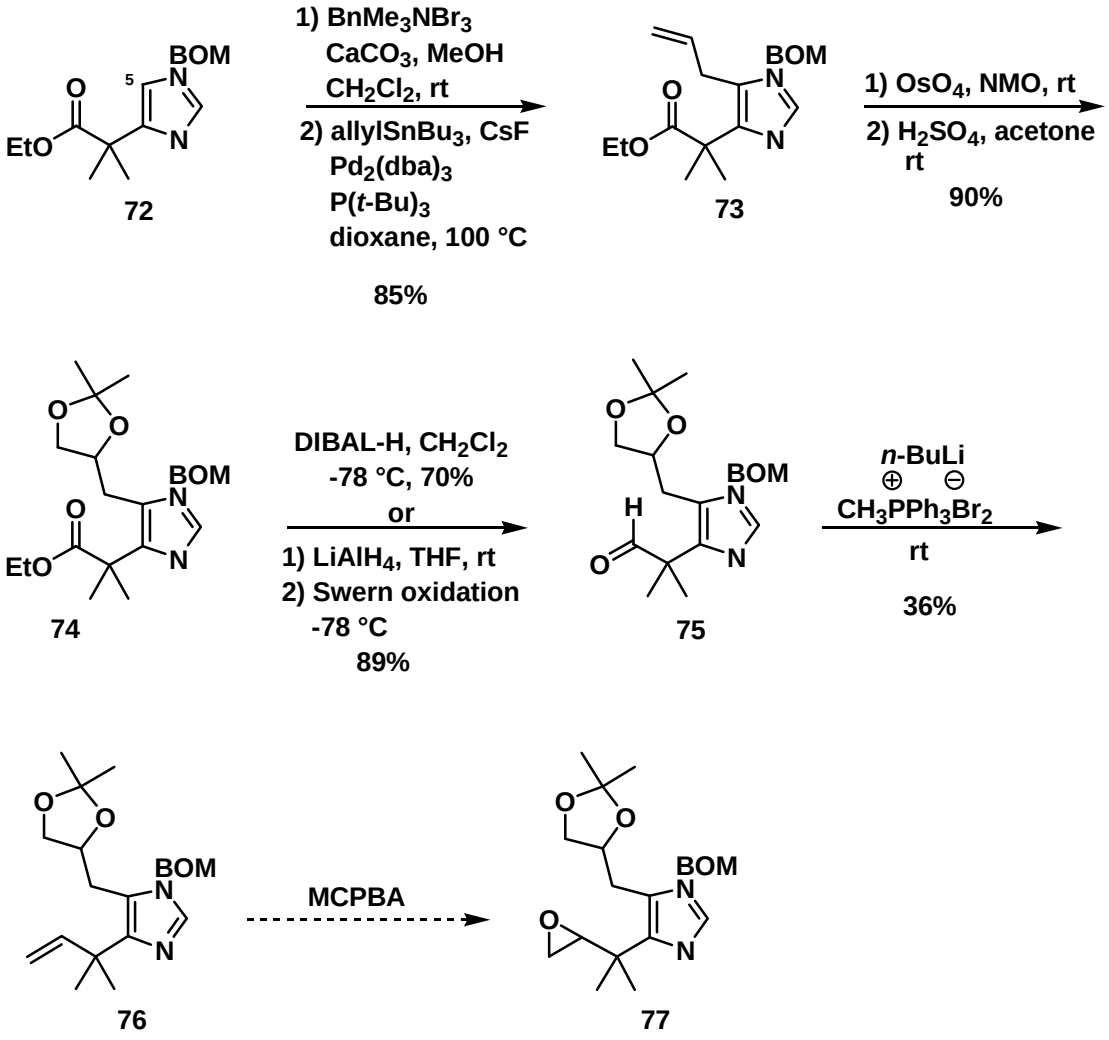
2.1.1 Construction of the Imidazole Fragment

We first modified the strategy for the preparation of the advanced imidazole intermediate **73** used in the chartelline sequence (Cf. Scheme 6). By using this approach, we were able to circumvent formation of acetate **44**, which shortened the synthetic route

by two steps. Thus, treatment of imidazole **70** with *t*-BuOK and MeI gave dimethylated ester **71** in good yield (Scheme 11). The trityl protecting group of ester **71** was replaced with the less bulky and more stable BOM group to afford *N*-BOM imidazole **72** (see Section 1.4.1). Bromination at the *C*-5 position of the imidazole ring of *N*-BOM imidazole **72** with benzyltrimethylammonium tribromide, followed by Stille coupling with allyltributylstannane gave allyl imidazole **73**. Treatment of the allyl imidazole with OsO_4 and NMO gave the corresponding diol, which was then converted to acetonide **74** with acetone and sulfuric acid. Partial reduction of the ester moiety of acetonide **74** with DIBAL-H subsequently gave the corresponding aldehyde **75**. Alternatively, the ester **74** could be converted to the aldehyde **75** in two steps: reduction to the corresponding primary alcohol with $LiAlH_4$ followed by Swern oxidation.[25] Wittig reaction of aldehyde **75** gave the terminal olefin **76** in 36% unoptimized yield. Finally, oxidation with MCPBA of the terminal olefin should lead to the desired epoxide **77**, although this step was never conducted (*vide infra*).

Scheme 11

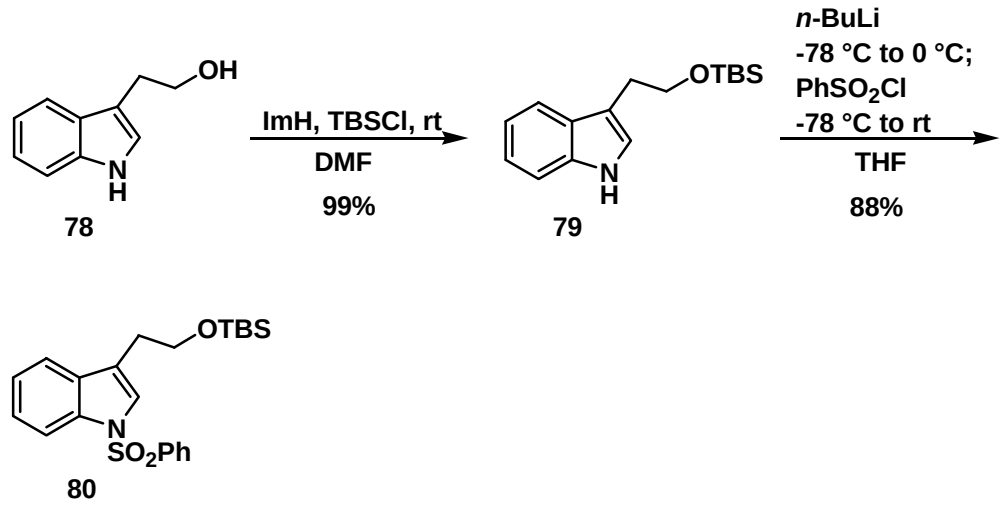




2.1.2 Preparation of the Indole Fragment

The indole derivative **80** was obtained by protecting the hydroxyl group of commercially available tryptophol (**78**) with TBSCl, followed by protection of the indole nitrogen with benzenesulfonyl chloride (Scheme 12).[26]

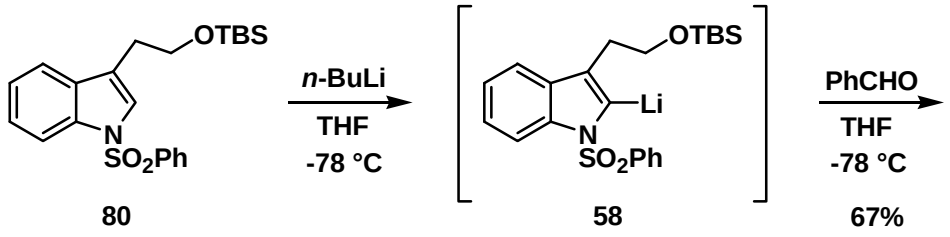
Scheme 12

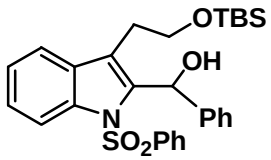


2.2 Model Studies for the Coupling of the Indole and Imidazole Epoxide Fragments

To test the reactivity of the indole **80**, we decided to conduct some model studies for its coupling to the imidazole epoxide fragment. Coupling of the *C*-2 lithiated indole moiety **58** with benzaldehyde gave alcohol **81** in good yield, indicating that the indole could indeed be metallated as desired (Scheme 13).

Scheme 13

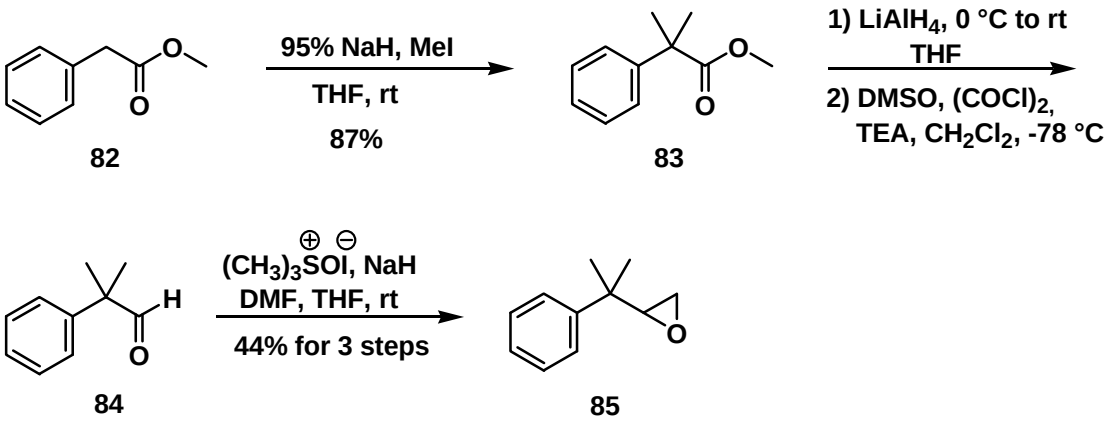




81

A model epoxide **85** was then prepared to test the key coupling reaction with lithio indole **58** (Scheme 14).[27] Commercially available phenylacetic acid methyl ester (**82**) was treated with sodium hydride and methyl iodide to afford known dimethylated ester **83**.[28] The ester **83** was then converted to the aldehyde **84** via a $LiAlH_4$ reduction/Swern oxidation sequence. A direct DIBAL-H reduction of ester **82** to aldehyde **84** proved to be problematic in this case. The aldehyde **84** was then treated with the ylide derived from trimethylsulfoxonium iodide to afford the model epoxide **85**.[29]

Scheme 14



Unfortunately, all attempted couplings of the lithiated indole moiety **58** with the model epoxide **85** failed (Scheme 15). A summary of the attempted reactions is outlined in Table 1. Since the lithiated derivative **58** itself did not show any promise, it was converted into the corresponding cuprate using different copper (I) salts, but this also did not lead to the desired coupling product **86** (entries 2-9).[30] In addition, catalysis of the coupling with Lewis acids was investigated (entries 9-14).[31] Unfortunately, the Lewis acids did not appear to activate epoxide **85** towards nucleophilic attack.

Scheme 15

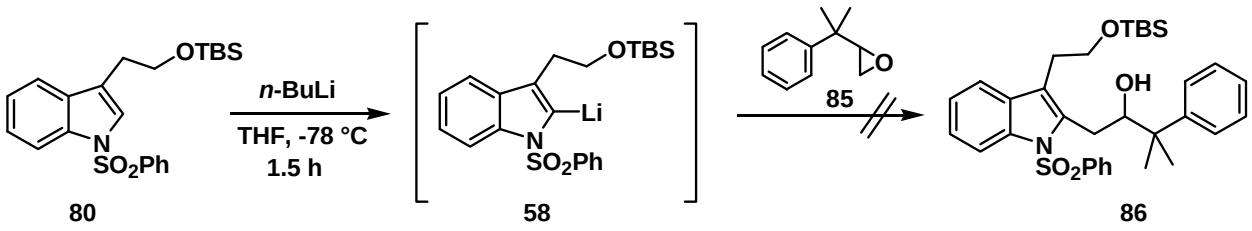
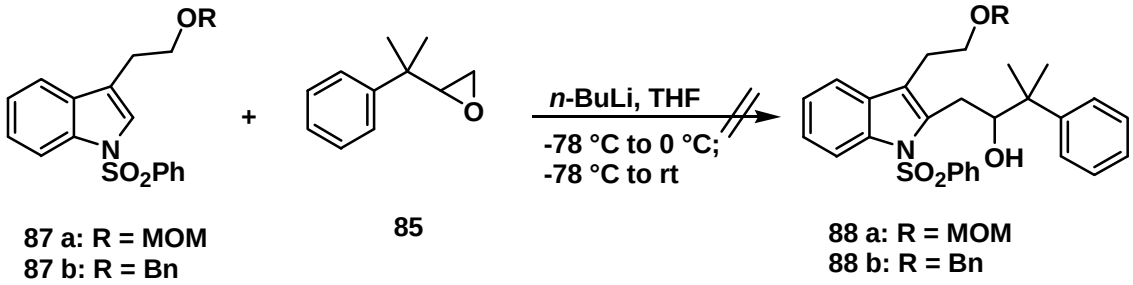


Table 1 Attempted Couplings of the Indole and Imidazole Fragments

Entry	Equiv M/LA	Temp (°C) of addition for M/LA	M and/or LA	Time	Temp (°C)	Yield of starting material(s)
1	---	---	---	overnight	-78	72% (**80**)
2	1.0	-20	$CuBr•S(CH_3)_2$	overnight	-20 to rt	---
3	1.0	-20	CuCl	overnight	-20 to rt	39% (**80**)
4	0.2	0	CuI	2 d	-78 to -20 to 70	---
5	0.2	-20	CuI	overnight	-78 to -20 to rt	---
6	1.0	-20	CuCN	overnight	-20 to rt	40% (**80**)
7	1.0	-20	CuCN	3 d	-20 to rt to 70	20% (**80**)
8	1.0	-20	CuCN	overnight	-20 to rt	23% (**80**)
9	1.0; 2.0	-78	CuCN; $BF_3•Et_2O$	4 h	-78	---
10	1.5	-78	$BF_3•Et_2O$	2 h	-78	41% (**80**)
11	1.1	-78	$BF_3•Et_2O$	7 h	-78 to rt	---
12	1.1	-78	$ZnCl_2$	4.75 h	-78 to 0	---
13	1.1	rt	$MgBr_2$	overnight	rt	unidentifiable products
14	1.1	-78	$MgBr_2$	overnight	-78	---

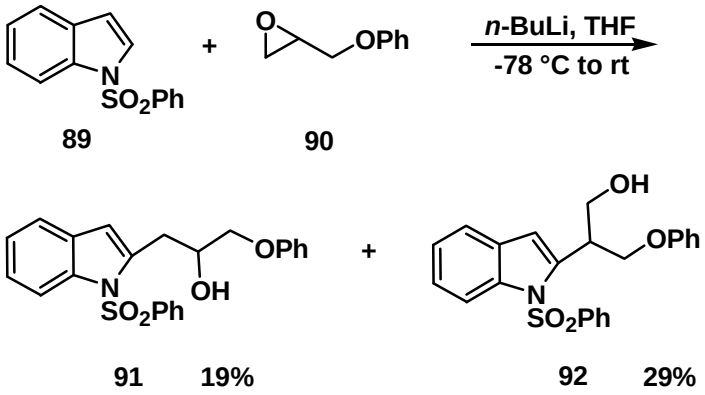
We believed that the failure of the lithio indole **58** to add to the model epoxide **85** might be due to the bulky *O*-TBS protecting group. Hence, the TBS group was replaced by smaller *O*-MOM (**87**) and *O*-Bn (**87b**) protecting groups. However, these compounds did not afford the desired coupling products **88a** or **88b**, respectively, using conditions similar to those in Table 1 (Scheme 16).

Scheme 16



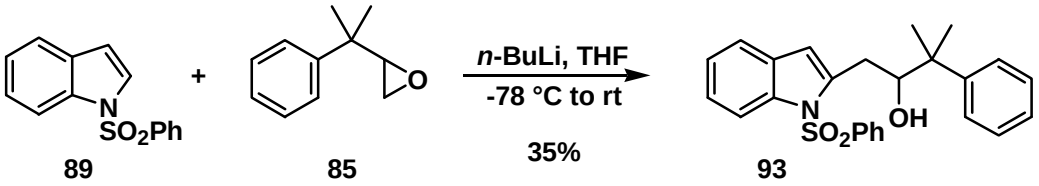
Because none of the coupling of the 3-substituted indoles with the model epoxide **85** gave the desired products, the reaction of an unsubstituted indole **89** with the simple epoxide phenyl glycidol (**90**) was tested (Scheme 17). This reaction, which was conducted in order to determine whether or not the problem was due to steric issues, afforded a chromatographically separable mixture of regioisomeric adducts **91** and **92** in moderate total yield. Thus, it was established that alkylation with a less substituted epoxide and unsubstituted indole was possible, and that steric interactions probably do contribute to the failure of the coupling reactions with indole **80**.

Scheme 17



Since the reaction of the lithio derivative of simple indole **89** with phenyl glycidol (**90**) was successful, we attempted the coupling with the model epoxide **85** in the hope that we could obtain the neopentyl alcohol **93**, and then subsequently alkylate the *C*-3 position of the indole (Scheme 18). However, when *N*-sulfonyl indole **89** was metallated with *n*-BuLi and the model epoxide **85** was added, the desired product **93** was obtained only in low yield. Attempts to improve the yield by using LDA as the base or by preparing a cuprate derivative of the lithiated indole proved futile.

Scheme 18

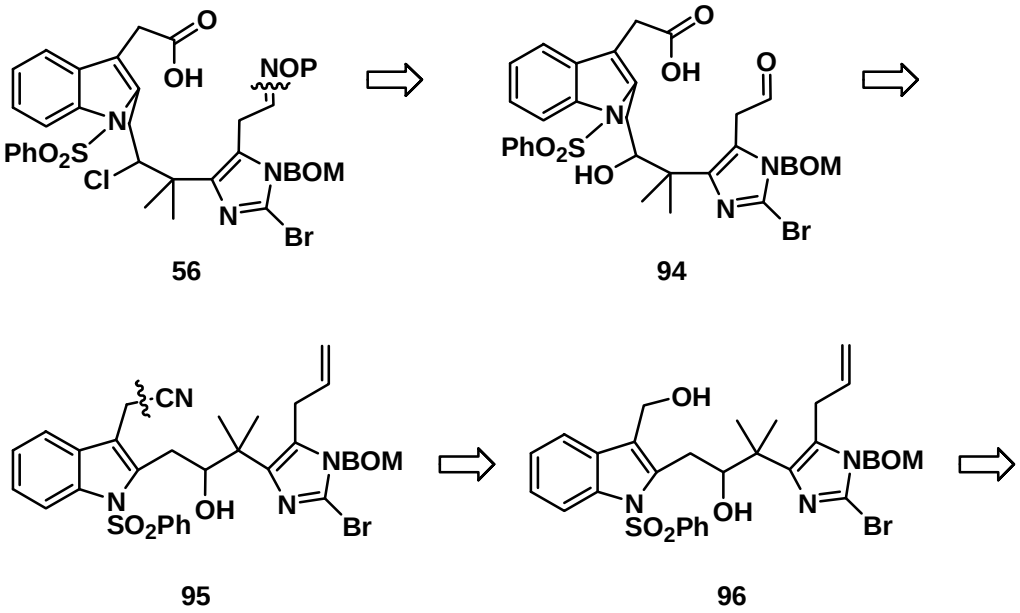


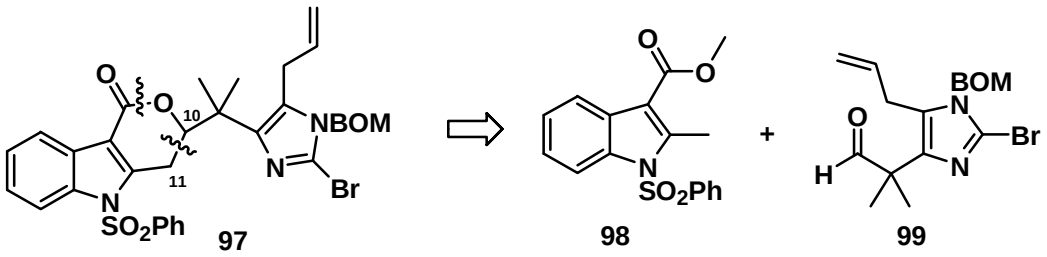
In view of these disappointing results, an alternative strategy was investigated for the total synthesis of securine A (**13**) and securamine A (**6**).

2.3 Revised Approach Towards a Total Synthesis of Securine A and Securamine A

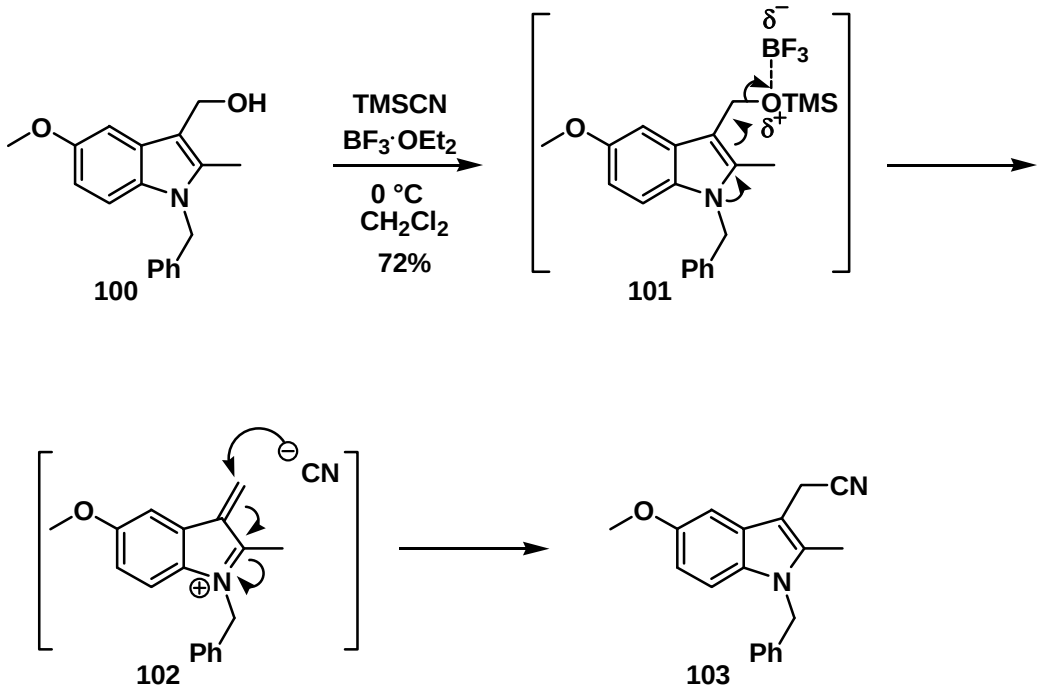
The revised retrosynthesis diverges from the original at oxime **56**, which would be prepared from the aldehyde **94** (Scheme 19). The acid functionality in acid aldehyde **94** would come from the hydrolysis of nitrile **95**, which could be formed by a one-carbon homologation of the primary alcohol of diol **96**. Maguire and coworkers have reported a similar homologation of a hydroxylmethyl group at *C*-3 of indole **100** using TMSCN and BF_3•OEt_2, which affords nitrile **103** (Scheme 20).[32] This reaction is proposed to proceed via the formation of the TMS ether of indole alcohol **100**, which then complexes with BF_3•OEt_2 to give intermediate **101**. Intermediate **101** subsequently undergoes elimination to give the α,β-unsaturated iminium ion **102**. 1,4-Addition of cyanide ion to the iminium ion **102** then gives the homologated product **103**.

Scheme 19





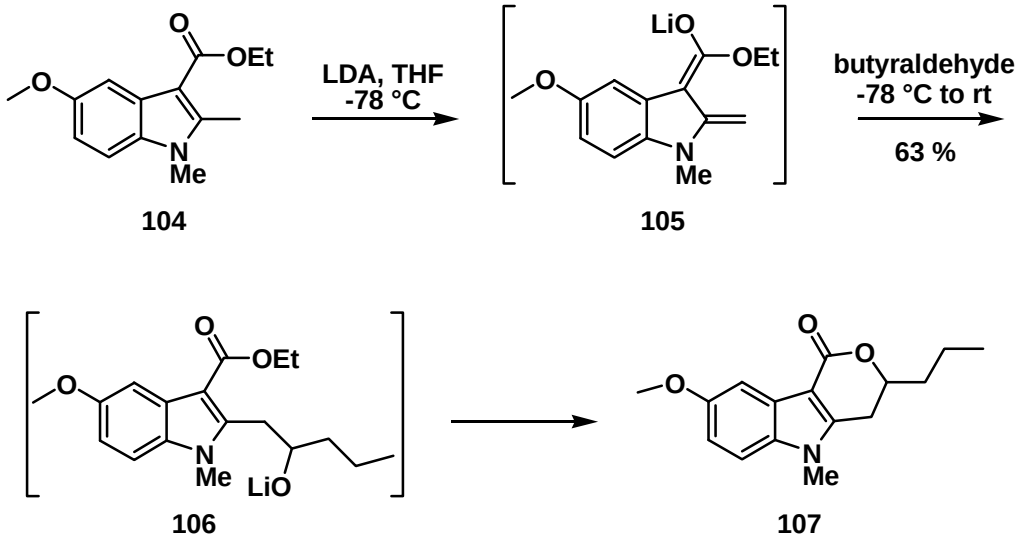
Scheme 20



Oxidative cleavage of alkene **95** should provide the aldehyde moiety of acid aldehyde **94**. Diol **96** will be formed by reduction of lactone **97**, which would be

constructed from the indole ester **98** and the imidazole aldehyde **99** using methodology developed by Macor and coworkers.[33] For example, treatment of indole **104** with LDA and butyraldehyde was shown to give lactone **107** in moderate yield (Scheme 21). In this transformation, the methyl substituent at the *C*-2 position of indole **104** is deprotonated to form the dienolate **105**. Alkylation of the dienolate with butyraldehyde gives the vinylogous aldol product **106**, which subsequently cyclizes to form lactone **107**. Thus, in the revised strategy, the indole ester moiety **98** will be coupled with the imidazole aldehyde fragment **99** by formation of the *C*-11/*C*-10 bond to afford lactone **97**.

Scheme 21

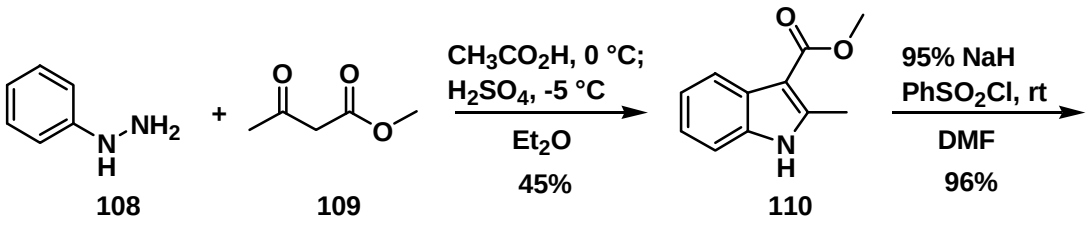


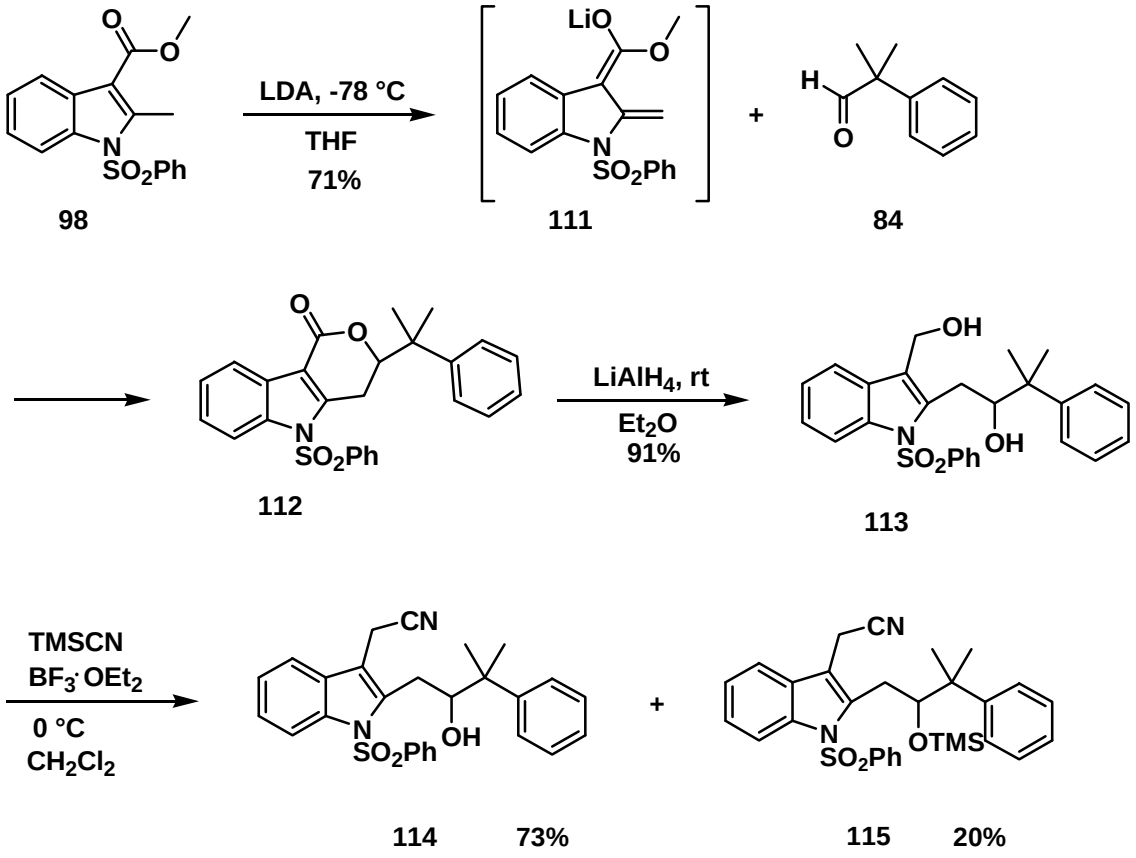
104 **105** **106** **107**

2.3.1 Model Studies for the Coupling of Indole Ester **98** with Aldehyde **84**

To test the new strategy for the coupling of the *C*-2 methyl indole ester **98** with neopentyl aldehyde **99**, a model study was first carried out (Scheme 22). Phenylhydrazine (**108**) was combined with methyl acetoacetate (**109**) in a Fischer indole synthesis to construct known indole **110**,[34] which was then N-protected with benzenesulfonyl chloride to form the *N*-sulfonyl indole **98**. Treatment of indole **98** with lithium diisopropylamide generated the lithio derivative **111**, which was successfully coupled with the model aldehyde **84** to form lactone **112**. The lactone **112** was subsequently reduced to diol **113** with $LiAlH_4$. Treatment of the hydroxylmethyl indole **113** with TMSCN and BF_3•OEt_2, using the conditions of Maguire,[32] gave the requisite nitrile **114** along with the *O*-TMS protected alcohol **115** in high total yield. Although the homologation step proceeded in good yield on a small (milligram) scale, effecting this reaction on a larger (gram) scale was problematic, as the yields fell precipitously.

Scheme 22



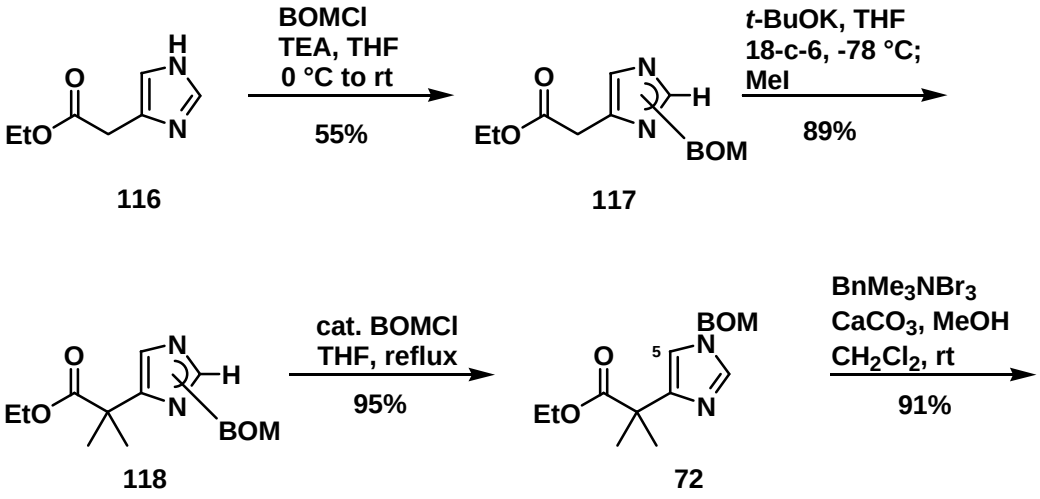


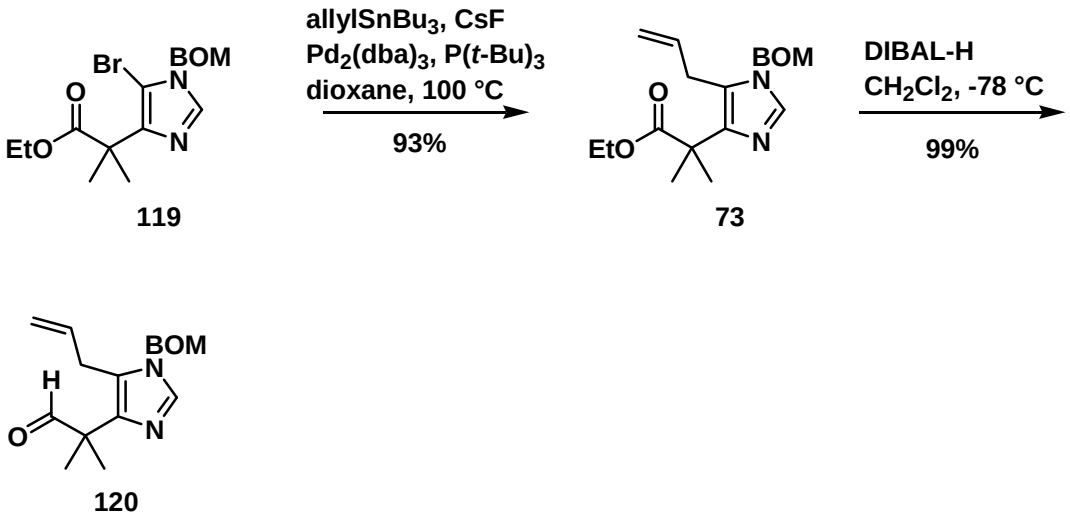
2.3.2 Construction of the Imidazole Aldehyde Fragment

Encouraged by the success of this model study, we investigated applying these reaction conditions to the actual imidazole subunit, aldehyde **120**, which was prepared from ester imidazole **116** in six steps (Scheme 23). This sequence proved to be more efficient than the route previously employed by our group (Cf. Section 1.4), as the imidazole is directly protected with a BOM group, rather than using an intermediate trityl

protecting group. Thus, *N*-BOM protection of ester imidazole **116** gave an inseparable regioisomeric mixture of esters **117**, which was then treated with *t*-BuOK and MeI to afford an *N*-BOM regioisomeric mixture of dimethylated esters **118**. In order to avoid complicated spectral data of mixtures later in the synthesis, we investigated the equilibration of dimethylated esters **118** to one regioisomer. Towards this end, it was found that the mixture of BOM isomers could be easily converted to the more stable regioisomer **72** upon treatment with a catalytic amount of BOMCl in refluxing THF (Cf. Scheme 7).[35] The dimethylated ester **72** was then regioselectively brominated at the *C*-5 position of the imidazole to give brominated imidazole **119**, which was next subjected to a Stille reaction with allyltributylstannane to form the allyl imidazole **73**. The ester moiety of allyl imidazole **73** was then partially reduced with DIBAL-H to afford the desired aldehyde **120** in good yield.

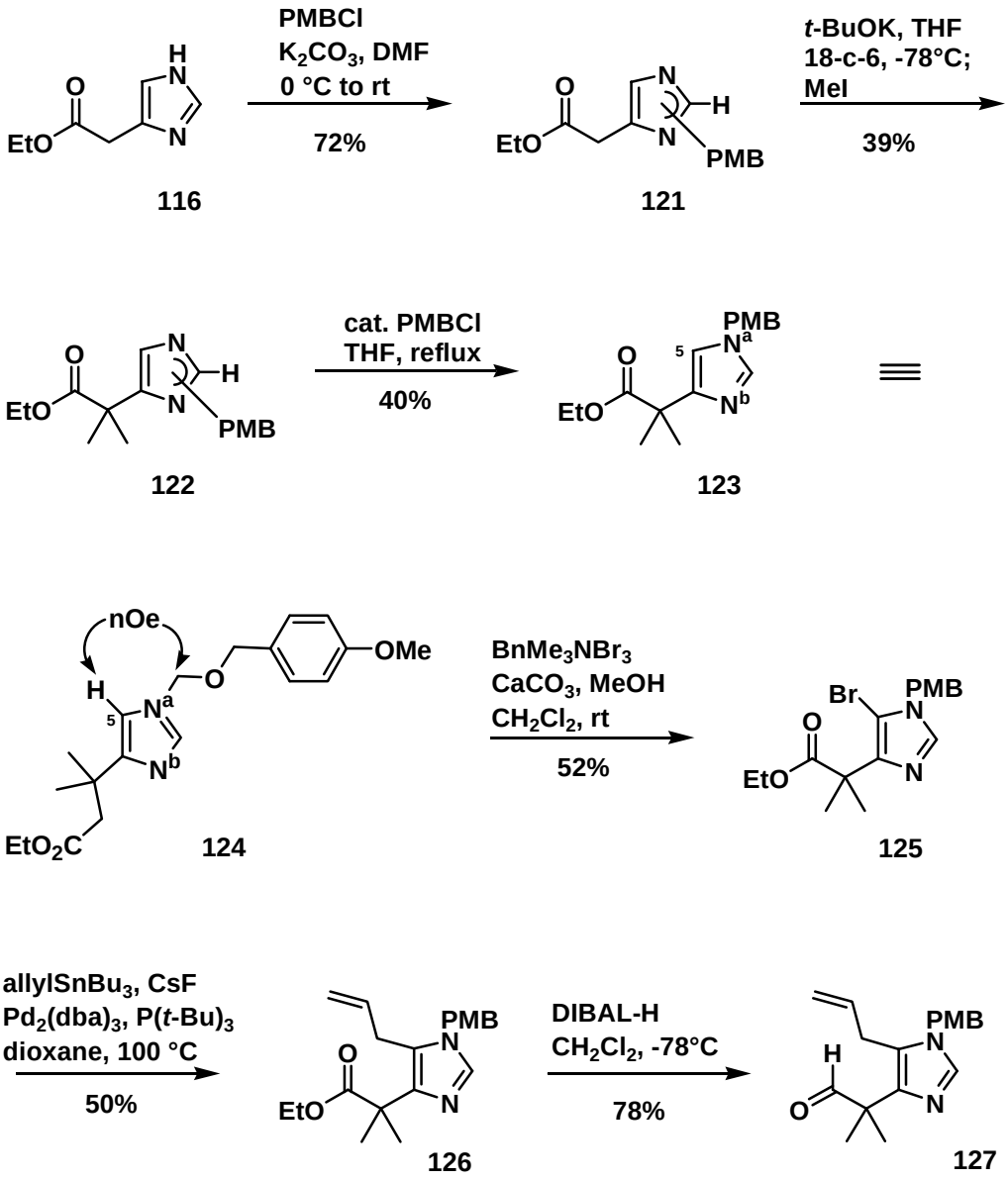
Scheme 23





Along with the BOM series, we prepared a backup series of PMB-protected imidazoles (Scheme 24). This was done because at times *N*-BOM protection of imidazole **116** gave inconsistent yields. PMB protection of imidazole ester **116** proceeded in a higher yield than for the BOM protection, but an inseparable mixture of regioisomers **121** was again observed. After dimethylation of this mixture, thermodynamic isomerization of the regioisomers **122** was accomplished with a catalytic amount of PMBCl in refluxing THF, analogous to the strategy used for the BOM-protected imidazoles. The regiochemistry of the major PMB-protected product **123** was then confirmed by a NOESY study (see Section 1.4.1). PMB-protected imidazole **123** was then brominated at the *C*-5 position to give **125**, followed by a Stille reaction of the bromide to produce **126**. Finally, partial reduction of ester **126** with DIBAL-H gave aldehyde **127** in good yield.

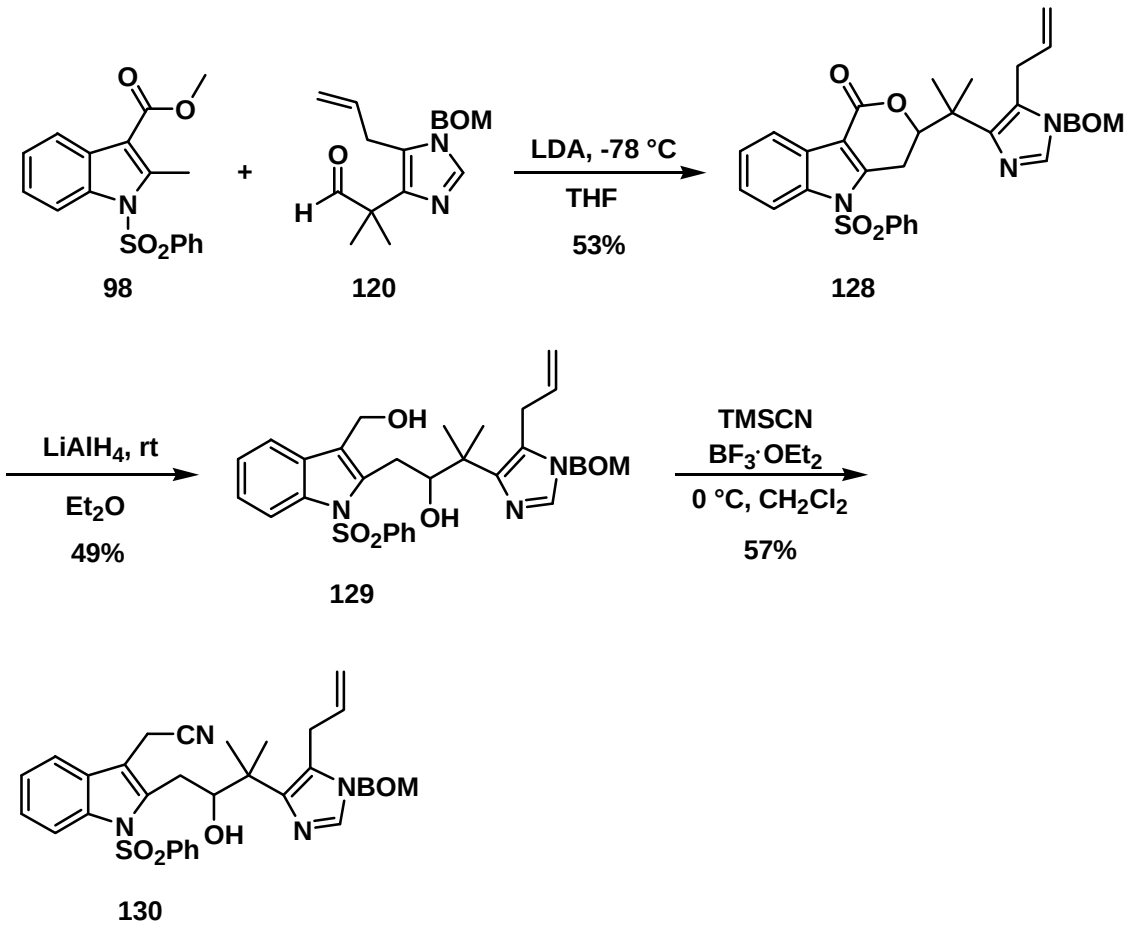
Scheme 24


PMBCl
K2CO3, DMF
0 °C to rt
72%
t-BuOK, THF
18-c-6, -78°C;
MeI
39%
116
121
cat. PMBCl
THF, reflux
40%
122
123
nOe
OMe
BnMe3NBr3
CaCO3, MeOH
CH2Cl2, rt
52%
124
125
allylSnBu3, CsF
Pd2(dba)3, P(t-Bu)3
dioxane, 100 °C
50%
DIBAL-H
CH2Cl2, -78°C
78%
126
127

2.3.3 Coupling of the Indole Ester **98** and Imidazole Aldehyde **120** Fragments

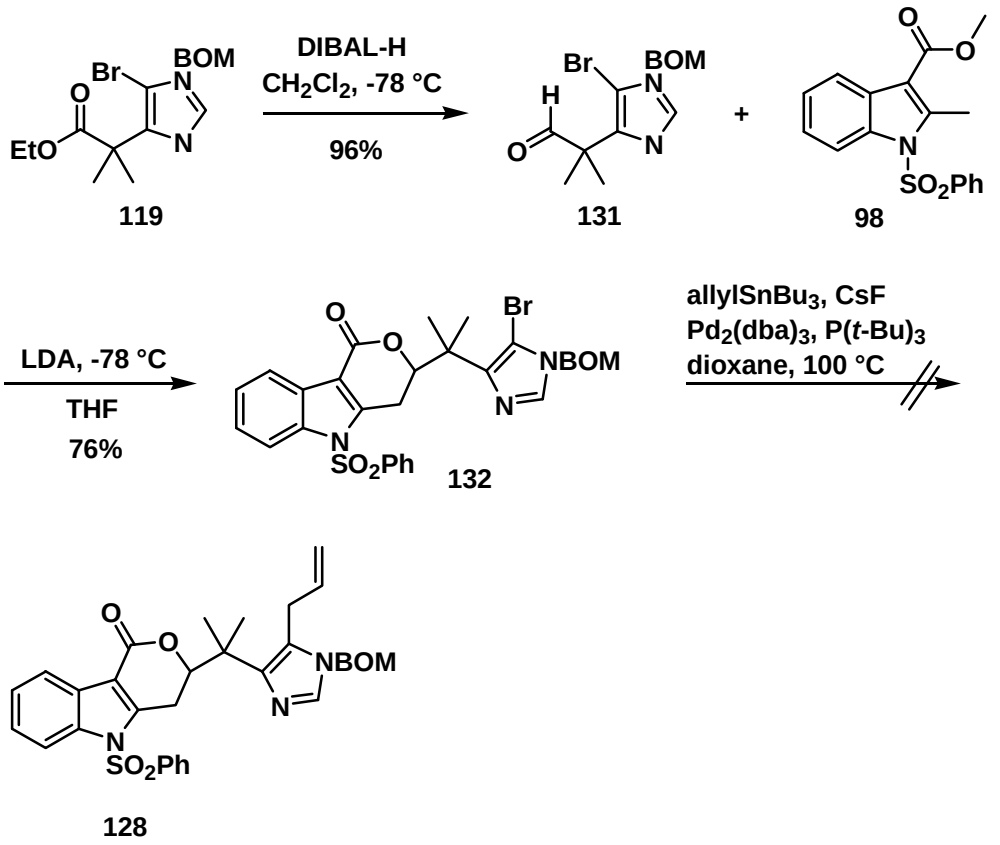
We then proceeded to couple the lithio anion of protected indole ester **98**, formed by treatment with LDA, with imidazole aldehyde intermediate **120** to give lactone **128** in moderate yield (Scheme 25). The lactone **128** was then reduced to the corresponding diol **129** with $LiAlH_4$ in 49% unoptimized yield. Treatment of 3-hydroxylmethyl indole **129** with TMSCN and BF_3•OEt_2 gave the corresponding nitrile **130** in 57% yield.

Scheme 25



In an attempt to improve the overall yield of this sequence, coupling the indole sulfonamide **98** with the aldehyde moiety of bromo imidazole **131** to form bromo lactone **132**, followed by a Stille reaction with allyltributylstannane to prepare allyl lactone **128** was also tested. Thus, reduction of bromo ester **119** with DIBAL-H gave bromoimidazole aldehyde **131**, which was coupled with metallated indole **98** to afford lactone **132** in good yield (Scheme 26). However, when bromide **132** was subjected to the standard Stille reaction conditions with allyltributylstannane, it decomposed, and the desired allylimidazole **128** was not obtained.

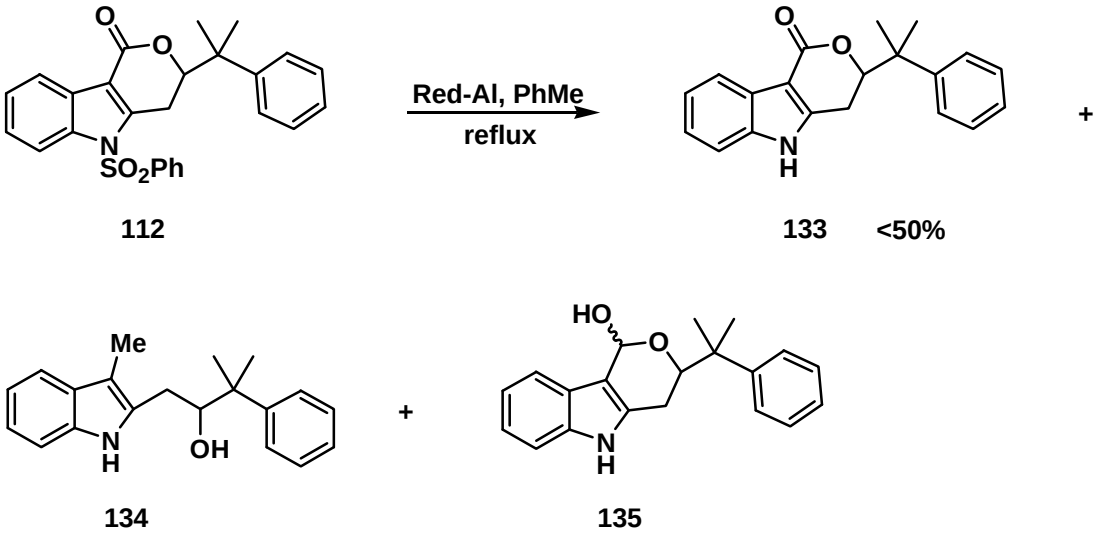
Scheme 26



2.3.4 Investigation of Nitrogen Protecting Groups on the Indole Fragment

In an attempt to improve the cyanide homologation step, we decided to test whether or not removal of the electron withdrawing protecting group from indole **112** would be helpful. Removal of the *N*-sulfonyl group was first tried on lactone **112**. Thus, treatment of lactone **112** with Red-Al in refluxing toluene[36] gave indole **133** along with reduced[37] product **134** and lactol[38] **135** (Scheme 27). In spite of efforts to optimize this reaction, the best yield of the desired unprotected indole lactone **133** was less than 50%.

Scheme 27

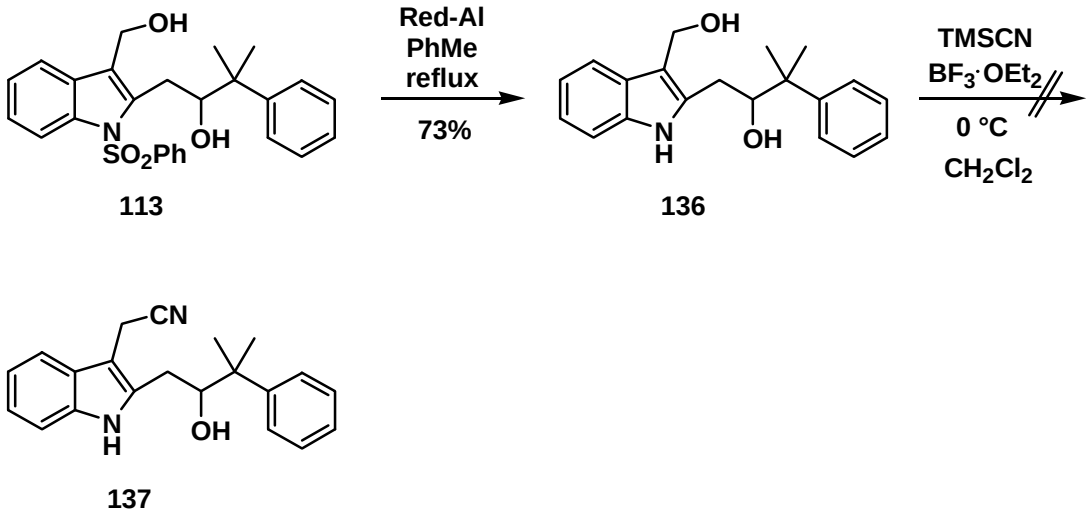


112 **133** **<50%** **134** **135**

In order to avoid the undesired reduced byproducts observed in the reaction above, removal of the sulfonyl group from a later intermediate **113**, which already

contained a primary alcohol, was tried (Scheme 28). It was possible to remove the sulfonyl group of indole **113** with Red-Al in refluxing toluene to give indole **136** in good yield. Unfortunately, the attempted homologation of diol **136** did not give the desired nitrile **137**.

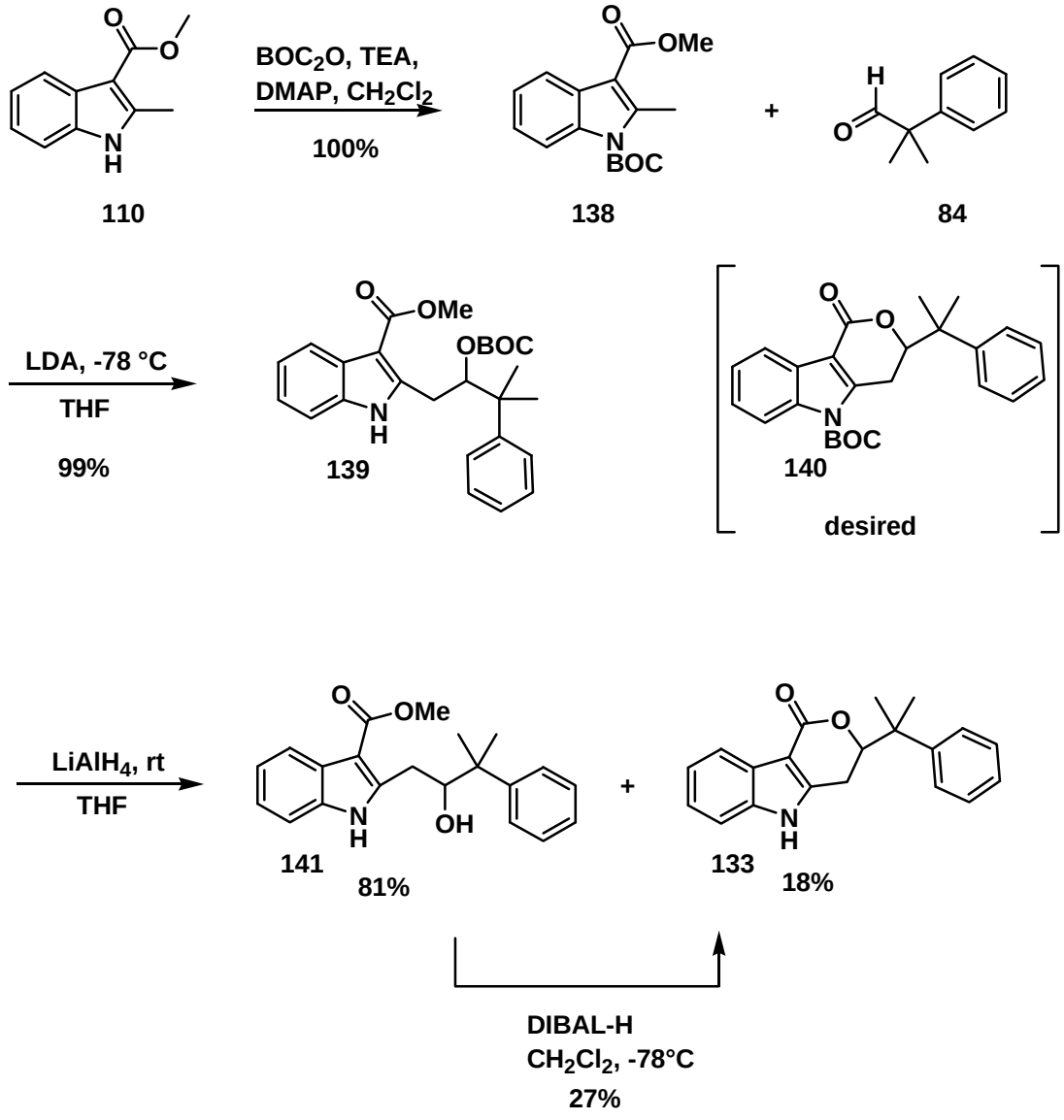
Scheme 28



We next decided to examine *N*-BOC protection for the indole since we could not optimize the homologation step with an *N*-sulfonyl group. Indole **110** was treated with BOC_2O and TEA to give *N*-BOC indole **138** (Scheme 29). However, when protected indole **138** was treated with LDA in THF at -78 °C, followed by addition of model aldehyde **84**, *O*-BOC protected alcohol **139** was obtained in high yield instead of the desired lactone **140**.[33] Reduction of ester **140** to the corresponding alcohol was attempted with $LiAlH_4$ in THF.[39] However, the major product formed here was the deprotected

neopentyl alcohol ester **141**. A small amount of lactone **133** was also formed in the process. Attempts to reduce the alcohol ester **141** with DIBAL-H in methylene chloride were not successful, and only the lactone **133** was formed.

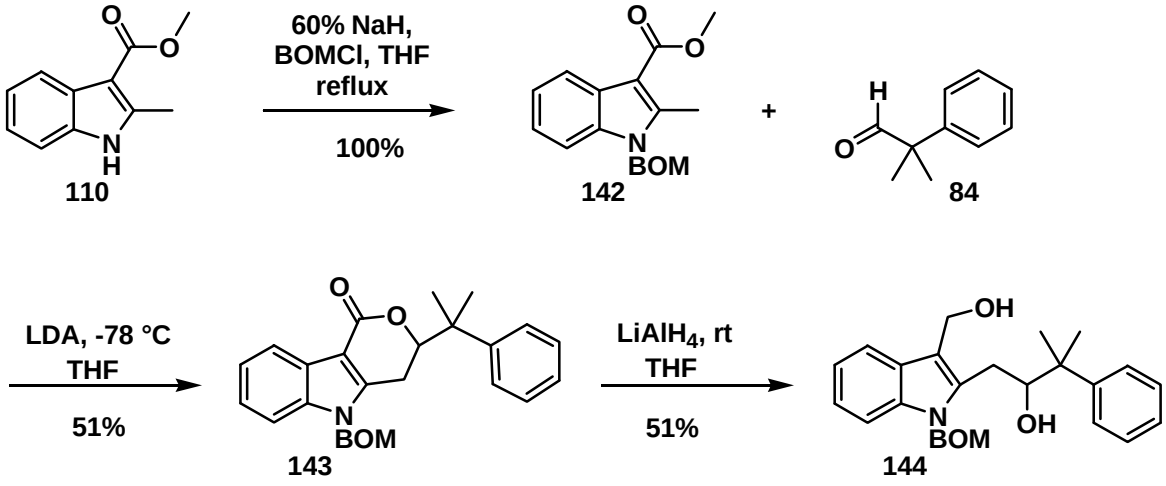
Scheme 29

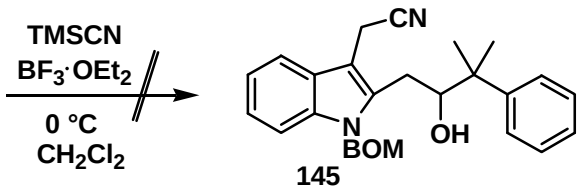


Reduction of lactone **133** to form diol **136** was tried under a variety of conditions, including: $LiAlH_4$/THF/rt, Red-Al/Tol/reflux, $LiBH_4$/THF/0 °C to 50 °C,[39] and DIBAL-H/CH_2Cl_2/-78 °C to -40 °C. However, only starting material was recovered in all of these attempts.

In view of these results, it was evident that we should explore protecting the indole with a group other than BOC. Thus, indole **110** was treated with 60% NaH and BOMCl in refluxing THF to give the *N*-BOM protected indole **142** (Scheme 30). The indole **142** was then treated with LDA in THF at -78 °C, followed by the addition of model aldehyde **84**, to give lactone **143**. The lactone **143** was reduced with $LiAlH_4$ in THF at -78 °C to give diol **144** in moderate yield. Unfortunately, the attempted homologation reaction of diol **144** to nitrile **145** with TMSCN and BF_3•OEt_2 did not proceed as desired, and only diol decomposition was observed.

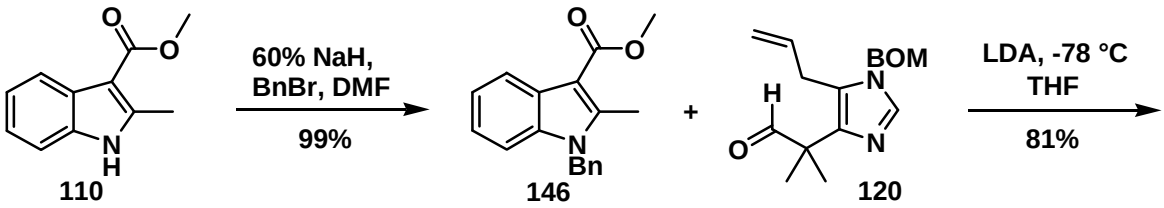
Scheme 30

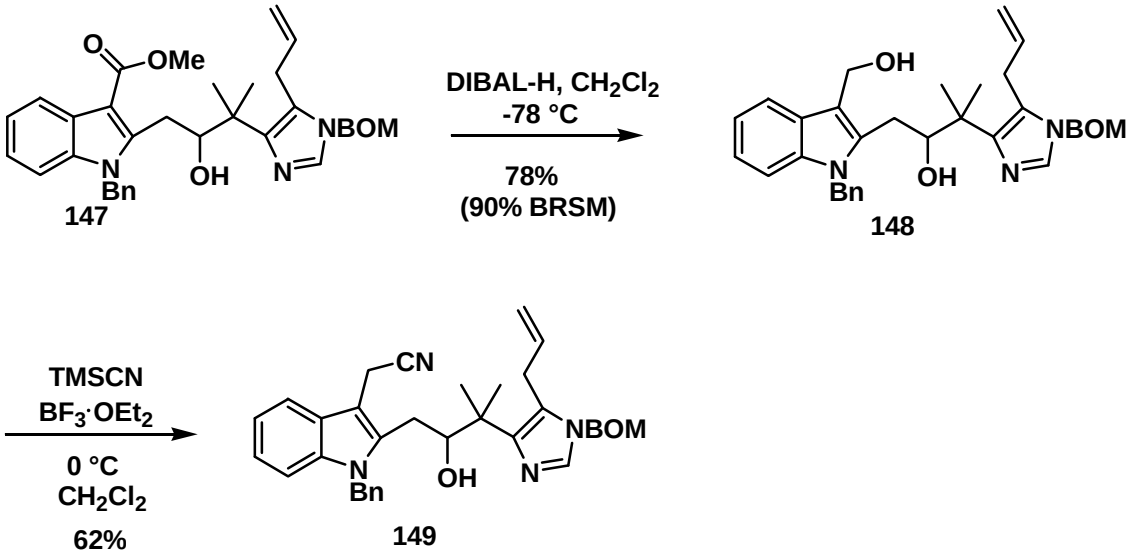




Because the homologation reaction did not proceed as desired in the *N*-BOM series, an *N*-benzyl protecting group was investigated. Thus, indole **110** was treated with 60% NaH and BnBr in DMF to give the *N*-Bn protected indole **146**. Indole **146** was then treated with LDA in THF at -78 °C, followed by the addition of aldehyde **120** at -78 °C and subsequent quenching of the reaction at this temperature, to give ester-alcohol **147** rather than the desired lactone (Scheme 31). Fortunately, the formation of **147** did not pose a major problem since the ester moiety could be reduced with DIBAL-H in methylene chloride at -78 °C to give the requisite diol **148**. Reduction of **147** also proceeded equally well with $LiAlH_4$ in THF at 0 °C to rt. The homologation reaction of diol **148** with TMSCN and BF_3•OEt_2 to nitrile **149** then proceeded in acceptable yield.

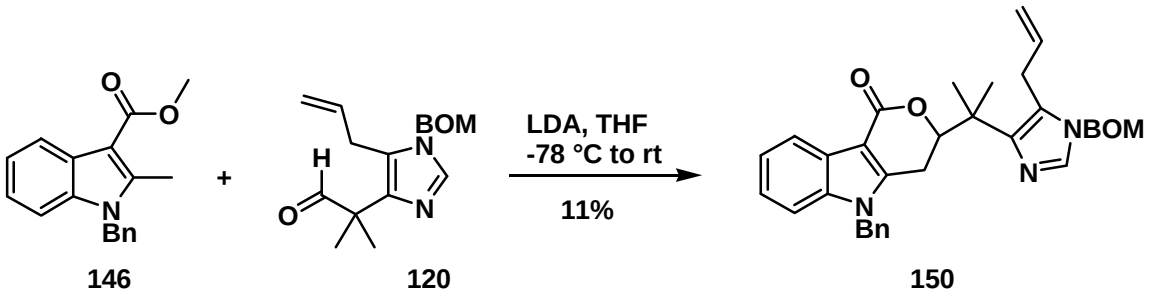
Scheme 31





It should be noted that it is also possible to form lactone **150** via condensation of **146** and **120**, albeit in very low yield. Thus, the coupling of indole **146** with aldehyde **149** proceeds to afford lactone **150** in only 11% yield when the reaction mixture is warmed from -78 °C to rt, rather than quenching the reaction mixture at -78 °C (Scheme 32).[33]

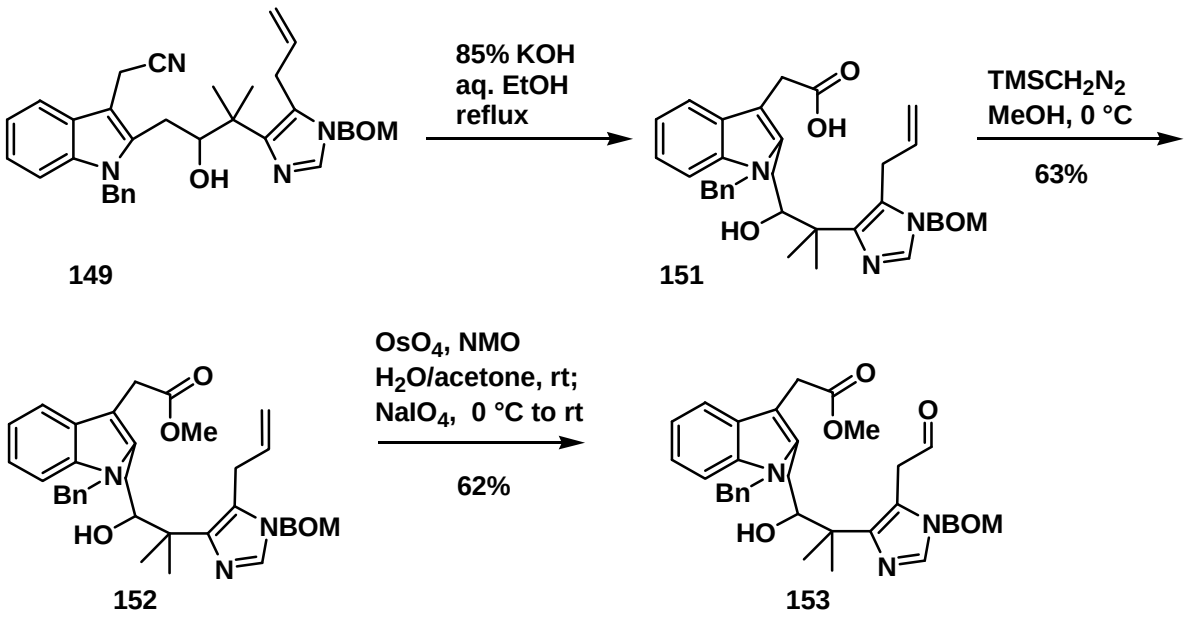
Scheme 32



2.3.5 Approaches Towards the Macrocyclic Ring of Securine A and Securamine A

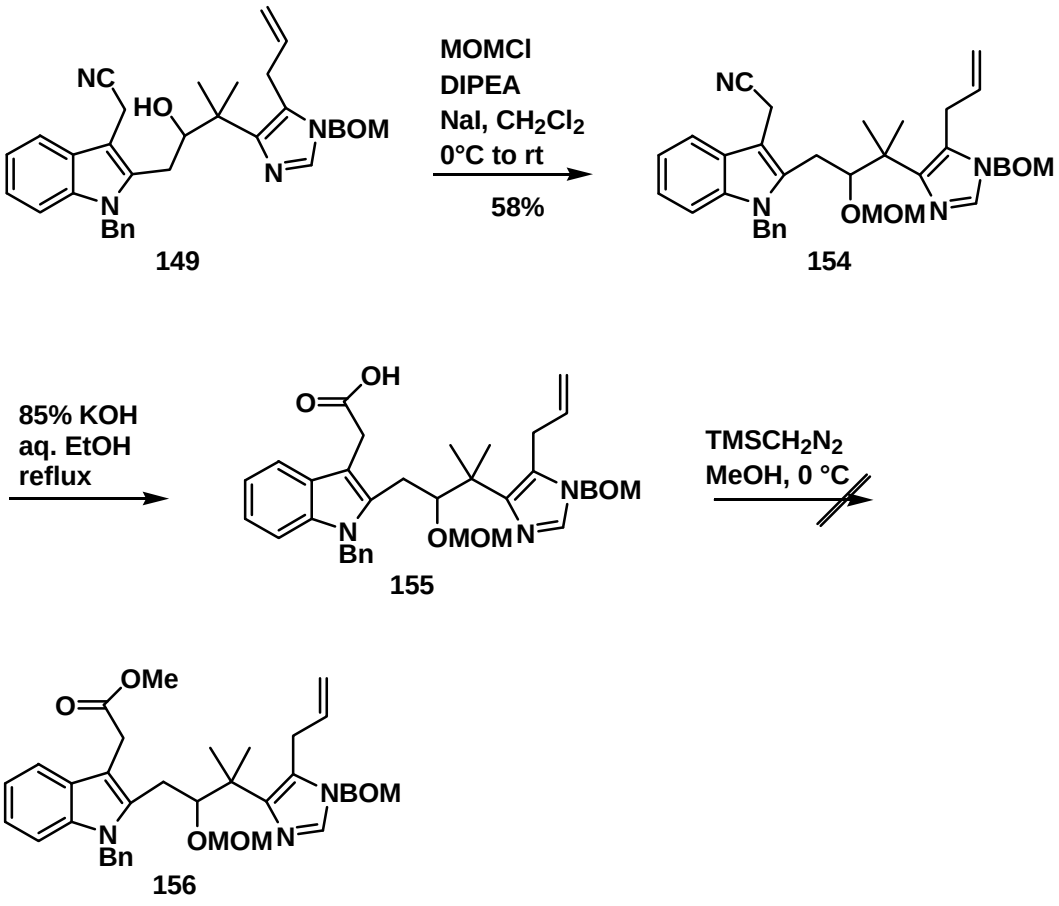
Continuing the synthesis, conversion of nitrile **149** to ester **152** was achieved in two steps in moderate overall yield (Scheme 33): basic hydrolysis of nitrile **149** with 85% KOH in refluxing aqueous EtOH gave acid **151**,[40] which was then esterified with $TMSCH_2N_2$ in methanol at 0 °C to give ester **152**.[41] Oxidative cleavage of the alkene moiety of **152** was then achieved by treating the alkene with OsO_4 and NMO and subsequent addition of $NaIO_4$ to give aldehyde **153** in moderate yield.

Scheme 33



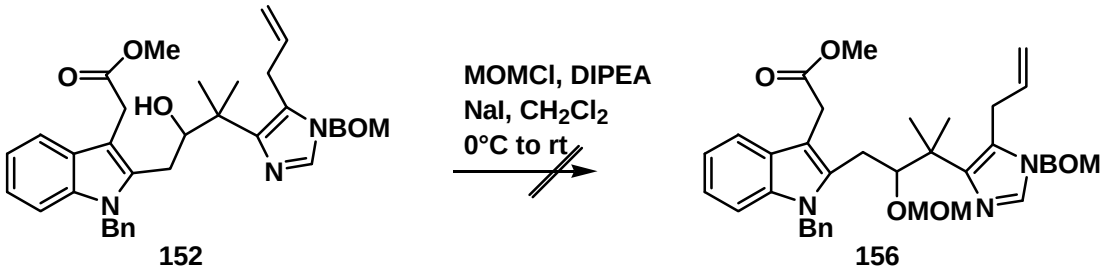
It was decided to *O*-protect neopentyl alcohol **149** at this stage as a precautionary measure to avoid the possibility that the free alcohol would cause problems later in the synthesis. Thus, alcohol **149** was treated with MOMCl, DIPEA, and NaI in methylene chloride to give MOM-protected alcohol **154** (Scheme 34). Basic hydrolysis of nitrile **154** gave acid **155**, which inexplicably could not be converted to ester **156**, as was done with acid **151**.

Scheme 34



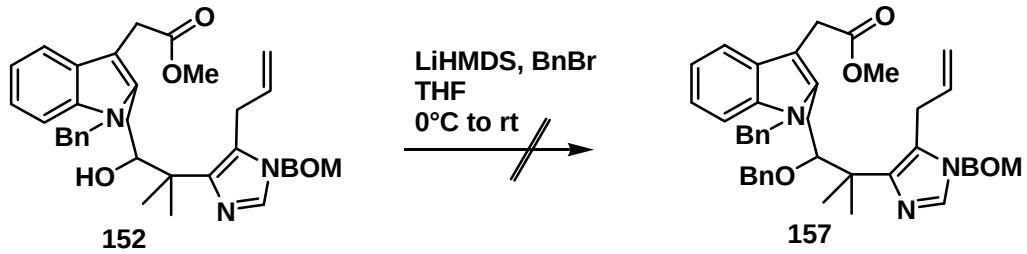
Because this esterification was problematic, we decided to switch the order of steps. However, when the neopentyl alcohol ester **152** was treated with MOMCl, DIPEA, and NaI in methylene chloride, only starting material was recovered (Scheme 35).

Scheme 35



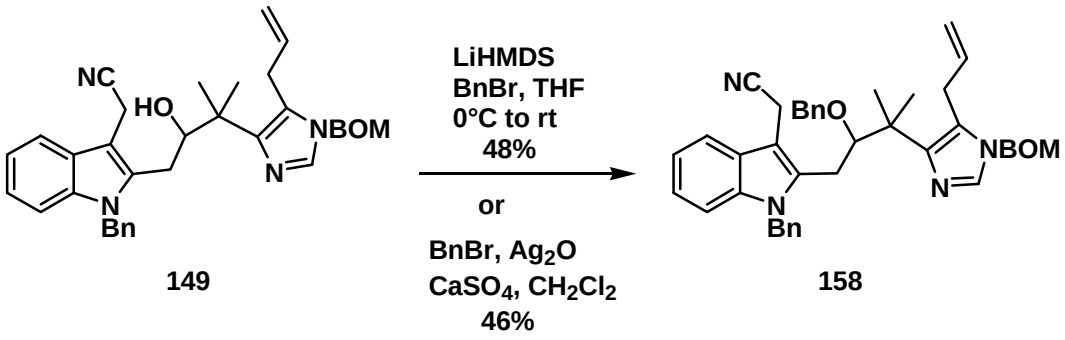
Because we could not continue the synthesis utilizing a MOM protecting group on the neopentyl alcohol, a benzyl protecting group was investigated. However, treatment of the alcohol ester **152** with LiHMDS and BnBr in THF did not give the desired protected alcohol **157** (Scheme 36).

Scheme 36



The *O*-benzylation reaction was also attempted on an earlier intermediate in order to determine whether sterics could be a factor in the failed benzylation of alcohol **152** (Scheme 37). Therefore, nitrile **149** was treated with LiHMDS and BnBr in THF, which did indeed give protected alcohol **158** in 48% unoptimized yield. Treatment of nitrile alcohol **149** with BnBr, Ag_2O, and $CaSO_4$ in methylene chloride at room temperature also gave the *O*-benzyl protected alcohol **158** in similar yield.[42]

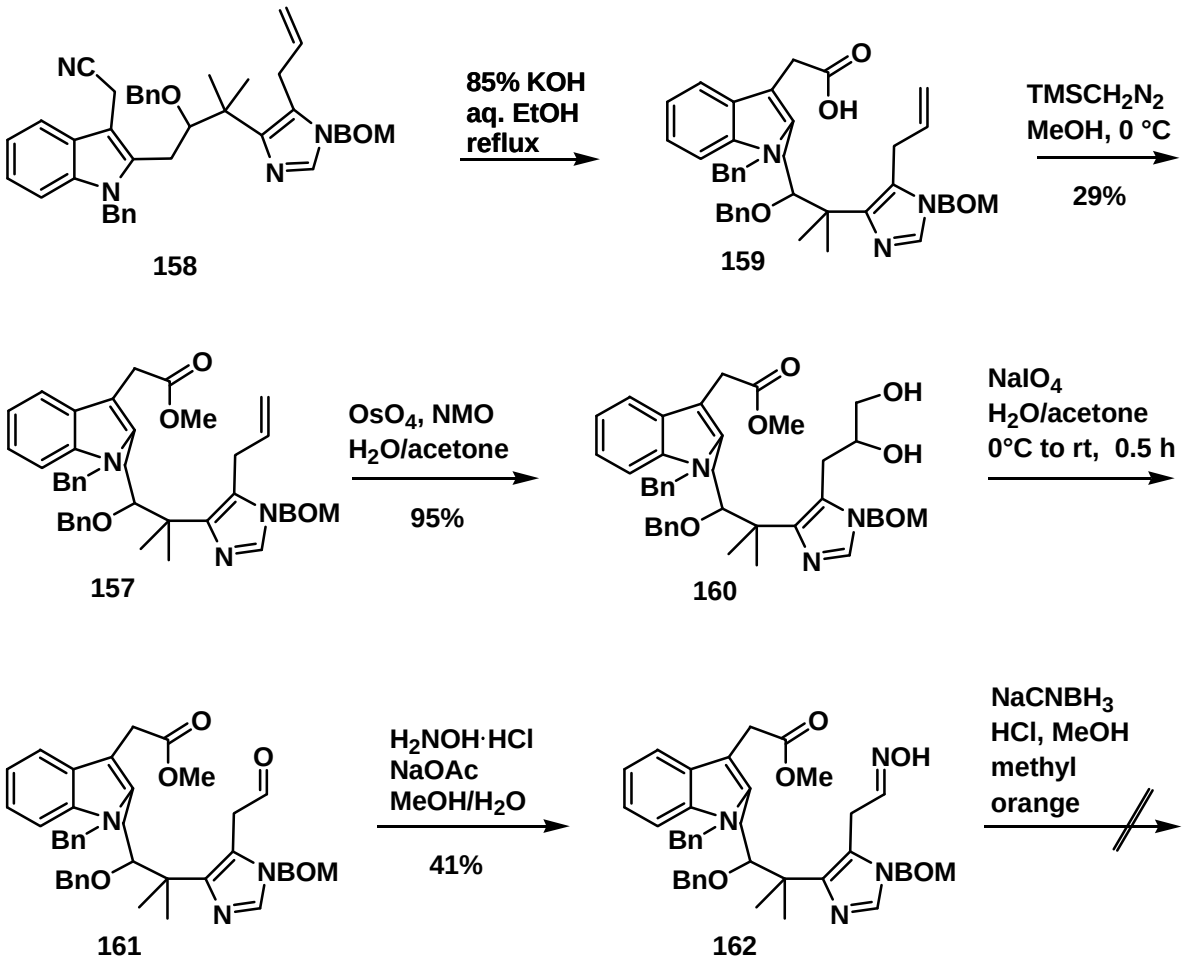
Scheme 37

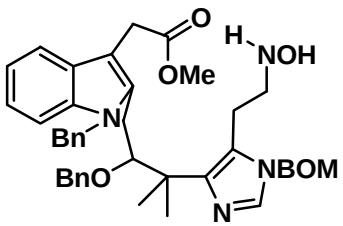


Since benzyl protection of the neopentyl alcohol functionality could be accomplished to afford **158**, the synthetic scheme was pursued with this intermediate (Scheme 38). Nitrile **158** was then hydrolyzed to acid **159** under basic conditions, followed by esterification to form methyl ester **157**. Alkene **157** was then oxidized with osmium tetraoxide and NMO in acetone/water to give diol **160**. This diol was subsequently cleaved with sodium periodate to produce aldehyde **161**, which was condensed with hydroxylamine hydrochloride to afford oxime **162**. However, reduction of oxime **162** to hydroxylamine **163** with sodium cyanoborohydride under acidic

conditions did not proceed as desired, and only starting material decomposition was observed.[43] In an attempt to solve this problem, we decided to explore the use of an *O*-protected oxime.

Scheme 38

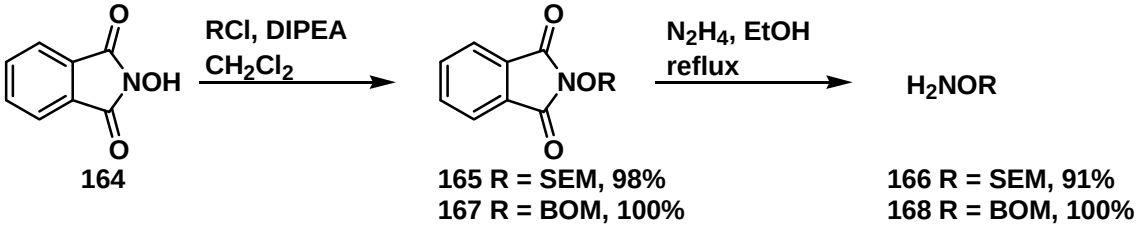




163

Only reduction of *O*-Bn[43a] and *O*-Me[44] protected oximes to protected hydroxylamines have been previously reported. We hoped that the use of a SEM or BOM group on our oxime would provide us with greater flexibility in late stage protecting group removal. We therefore decided to prepare two new hydroxylamines for use in these studies (Scheme 39). *N*-Hydroxyphthalimide (**164**) was treated with DIPEA and either SEMCl or BOMCl in methylene chloride to give *O*-protected phthalimides **165** and **167**, respectively, in good yields. The phthalimides were then cleaved using hydrazine in refluxing ethanol to give the desired hydroxylamines **166** and **168**.[45]

Scheme 39



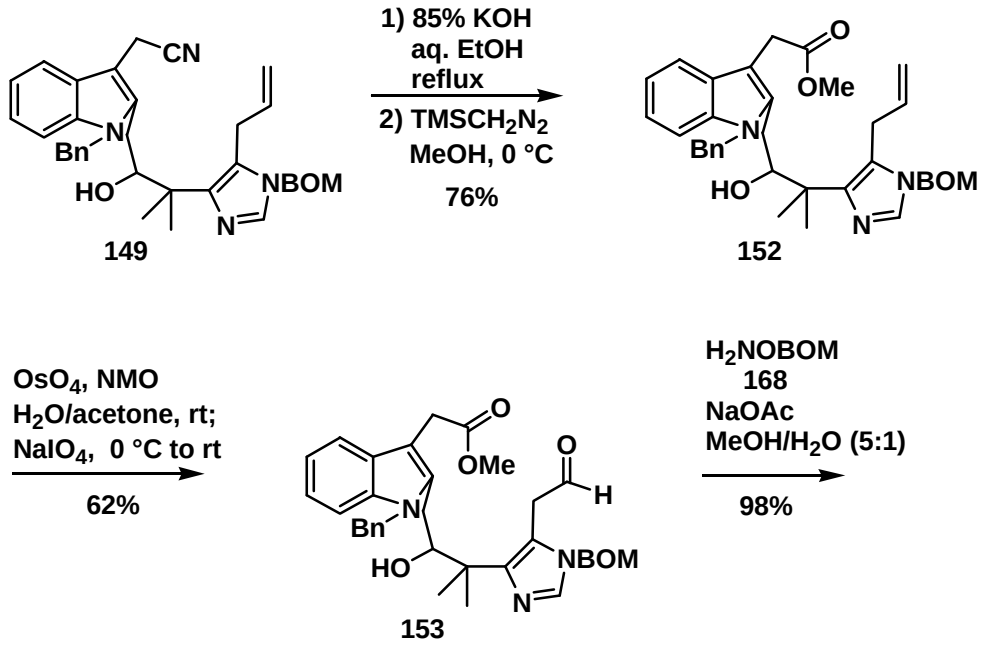
164

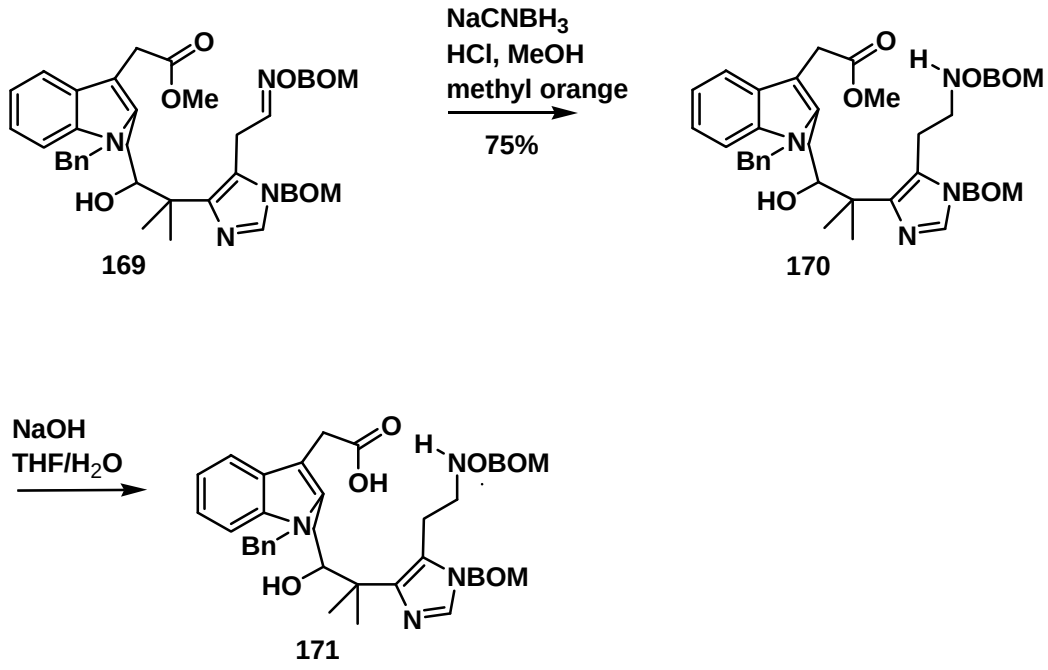
165 R = SEM, 98%
167 R = BOM, 100%

166 R = SEM, 91%
168 R = BOM, 100%

Along with the synthetic route utilizing a benzyl-protected neopentyl alcohol, we explored a route employing the free neopentyl alcohol. Thus, nitrile **149** was hydrolyzed to the corresponding acid under basic conditions, followed by esterification of the acid to give methyl ester **152** (Scheme 40). Johnson-Lemieux oxidation of alkene **152** gave aldehyde **153** in moderate yield, which was then condensed with BOM-protected hydroxylamine **168** to give oxime derivative **169** in good yield. We were pleased to find that the reduction of BOM-protected oxime **169** with sodium cyanoborohydride under acidic conditions proceeded smoothly to give hydroxylamine **170**. Unfortunately, hydrolysis of ester **170** with NaOH in THF/H_2O gave acid **171** in only poor yield. Other conditions for hydrolysis of the ester to the acid, such as LiOH in THF or NaOH in methanol,[46] resulted in decomposition of the starting material.

Scheme 40





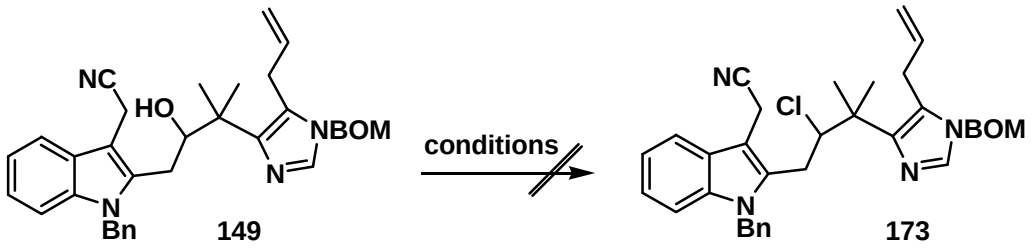
In view of this problem, and also to reduce the number of synthetic steps, a direct macrocyclization of hydroxylamine ester **171** was tried. However, treatment of **171** with NaOMe in methanol at rt gave only recovered starting material and none of the desired lactam **172** (Scheme 41).[47]

Scheme 41

2.3.6 Efforts Towards the Chlorination of Various Neopentyl Alcohols

Conversion of a neopentyl alcohol to the corresponding chloride is a required step in our synthesis of the securines. Following the precedent of Wood in conversion of neopentyl alcohol systems related to securine chlorides (Cf. Scheme 5), we attempted to chlorinate acyclic alcohol **149**. However, using a wide variety of conditions[48] shown in Scheme 42, in all of these reactions either the starting material was recovered or decomposed (Scheme 42).

Scheme 42

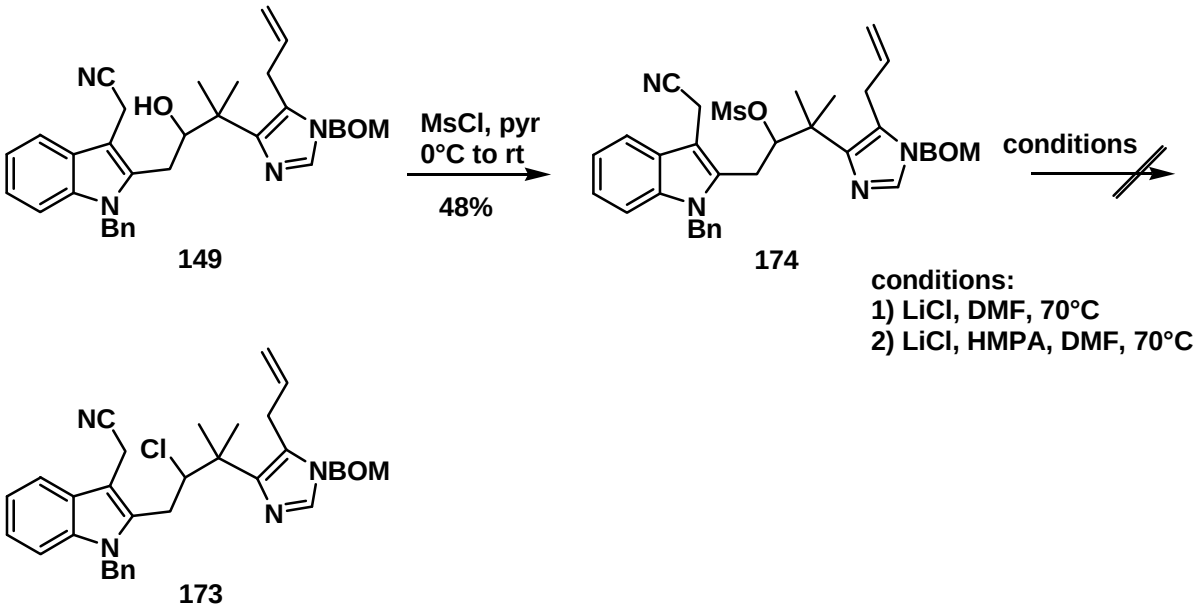


conditions:	
1) P(*n*-Bu)$_3$, CCl_4, reflux	decomposition
2) P(*n*-Bu)$_3$, CCl_4/CH_3CN (5:1), reflux	decomposition
3) $SOCl_2$, pyr, 0-40°C	----
4) $SOCl_2$, Et_2O, 0-40°C	SM only
5) $SOCl_2$, pyr/Et_2O (1:1), 0-40°C	----
6) NCS, PPh_3, THF	SM only
7) NCS, P(*n*-Bu)$_3$, THF	----

Because we could not directly convert the alcohol **149** to the corresponding chloride, we next prepared a mesylate that might be displaced with chloride ion. Thus,

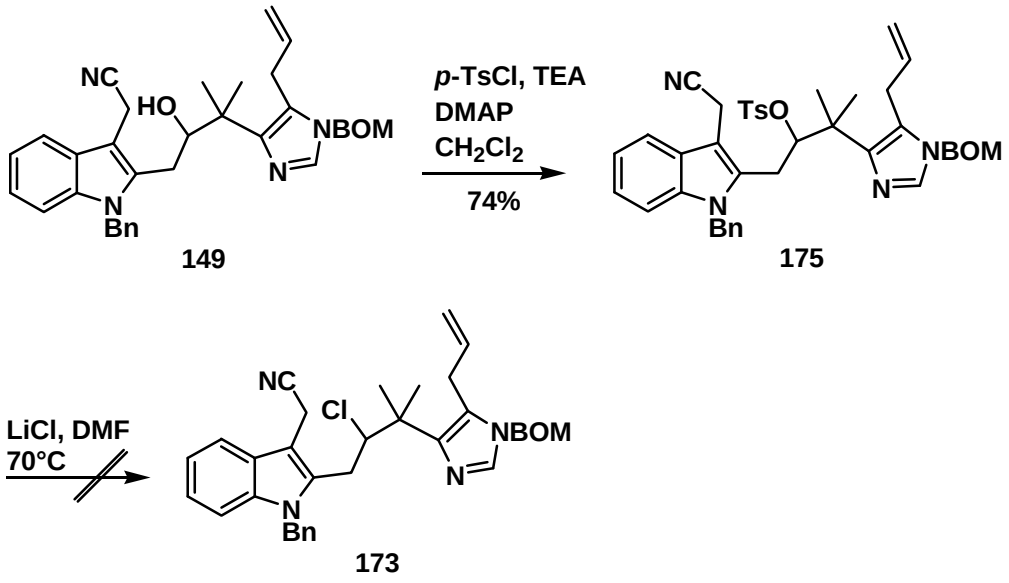
treatment of alcohol **149** with MsCl in pyridine gave mesylate **174** in moderate yield (Scheme 43).[49] However, when mesylate **174** was treated with LiCl in DMF at 70 °C or with LiCl/HMPA in DMF at 70 °C,[50] the desired chloride **173** was not obtained.

Scheme 43



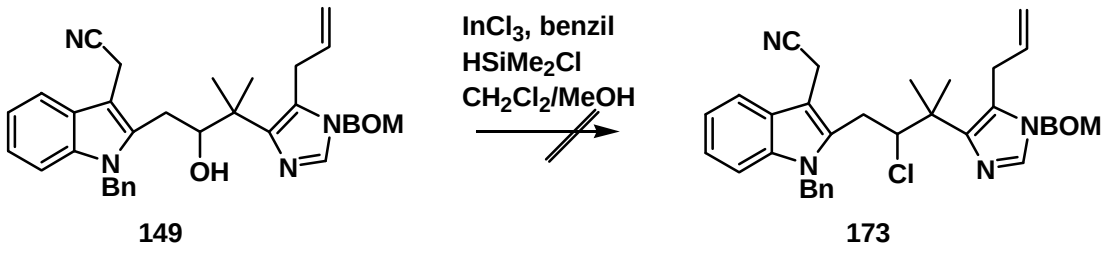
In addition, the tosylate derivative **175** of alcohol **149** was prepared with *p*-TsCl, TEA, and DMAP in methylene chloride (Scheme 44). Attempted subsequent displacement of the tosyl group with LiCl in DMF did not proceed as desired and only starting material decomposition occurred.[50b]

Scheme 44



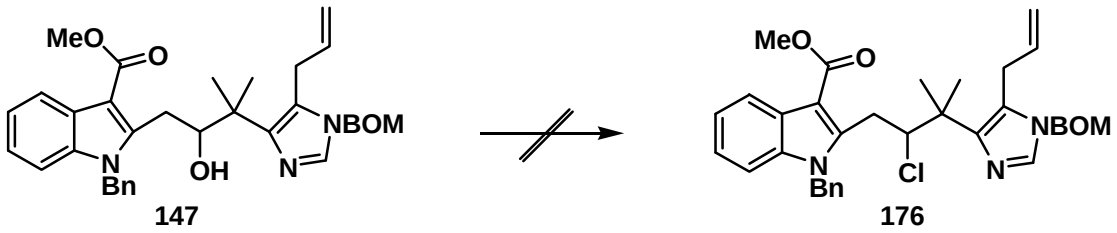
We also attempted to apply a new strategy for chlorination of sterically hindered alcohols that was recently published by Yasuda and coworkers.[51] Thus, alcohol **149** was treated with dimethylchlorosilane and benzil in the presence of indium trichloride as a catalyst (Scheme 45). However, the desired chloride **173** was not obtained and decomposition of the starting material was observed.

Scheme 45



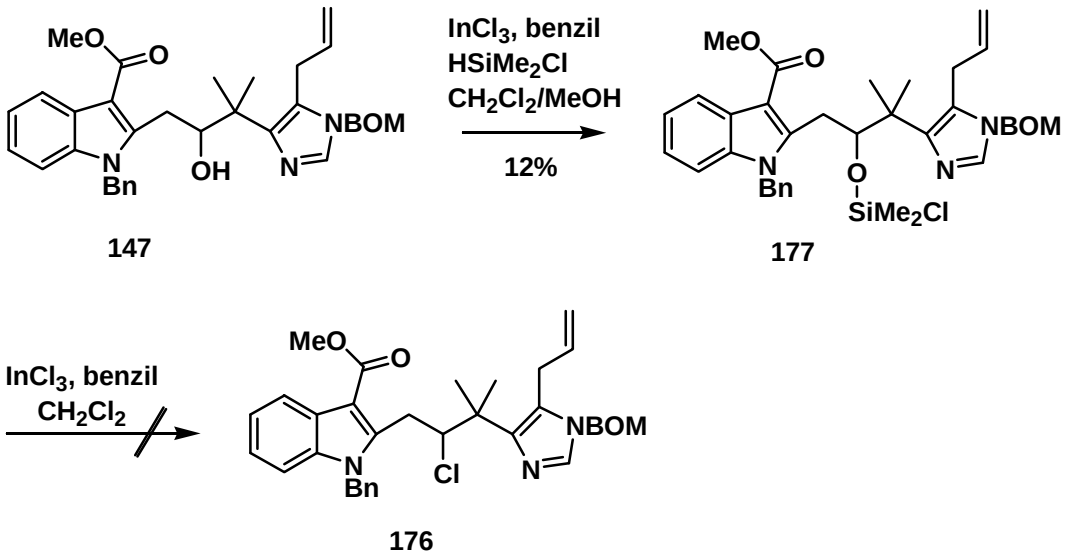
Because the chlorination of nitrile alcohol **149** was problematic, we also tested the chlorination of ester alcohol **147** (Scheme 46). However, none of the conditions attempted for nitrile alcohol **149** led to chloride **176**. In addition, treatment of alcohol **147** with MsCl in pyridine or with *p*-TsCl with TEA and DMAP did not give the desired mesylate or tosylate.

Scheme 46



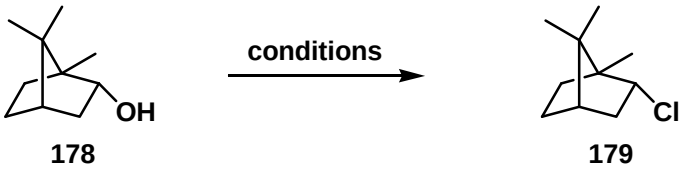
Ester alcohol **147** was also subjected to dimethylchlorosilane and benzil in the presence of indium trichloride as a catalyst (Scheme 54).[51] Although the desired neopentyl chloride was not obtained, the *O*-dimethylsilyl chloride intermediate **177** was isolated in low yield. Yasuda and coworkers have reported that resubjecting such an *O*-dimethylsilyl chloride intermediate to indium trichloride and benzil in methylene chloride could provide the desired chloride. However, when intermediate **177** was resubjected to indium tichloride and benzil, the desired chloride **176** was not obtained.

Scheme 47



Recent reports have shown that the neopentyl alcohol group of norbornene **178** can be converted to the corresponding chloride **179** via several different protocols.[52] Thus, treatment of alcohol **178** with either 2,4,6-trichloro[1,3,5]triazine (TCT) and DMF, manganese dioxide and silicon tetrachloride, or potassium carbonate and silicon tetrachloride in methylene chloride furnished neopentyl chloride **179** in excellent yields (Scheme 48). Encouraged by these precedents, we tried to chlorinate neopentyl alcohol **147** using the various conditions listed above, but none gave the desired chloride **176**.

Scheme 48



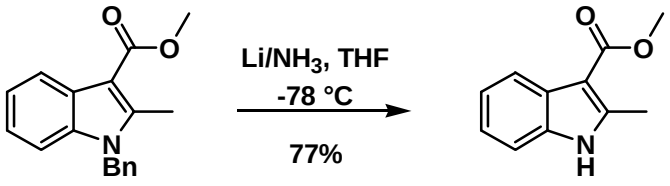
178 **179**

conditions:
1) TCT, DMF, CH_2Cl_2, rt, 12h 98%
2) MnO_2, $SiCl_4$, CH_2Cl_2, rt, 1 h 94%
3) K_2CO_3, $SiCl_4$, CH_2Cl_2, rt, 50 min 95%

The neopentyl alcohol substrates successfully used by Wood in the chlorination did not have a protecting group on the indole nitrogen, and we felt that this could be the reason why our chlorinations did not go as desired. We therefore decided to remove the protecting group from the indole in order to test this assumption.

Before exploring the deprotection of an advanced intermediate, we first tested the transformation on a simple indole **146** (Scheme 49). Thus, *N*-benzyl indole **146** was treated with Li/NH_3 in THF at -78 °C to afford deprotected indole **110** in good yield.[53]

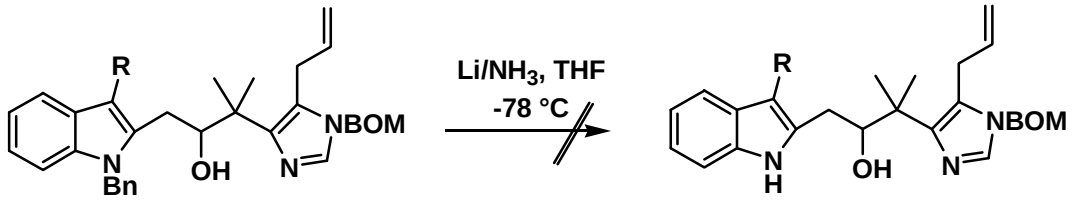
Scheme 49



146 **110**

Encouraged by these preliminary results, we attempted to remove the benzyl group from the advanced intermediates **147**, **148**, and **152**. However, when indoles **147**, **148**, and **152** were subjected to Birch conditions, the starting materials decomposed, and we were unable to obtain any of the free *N*-H indoles **180-182**, respectively (Scheme 50).

Scheme 50

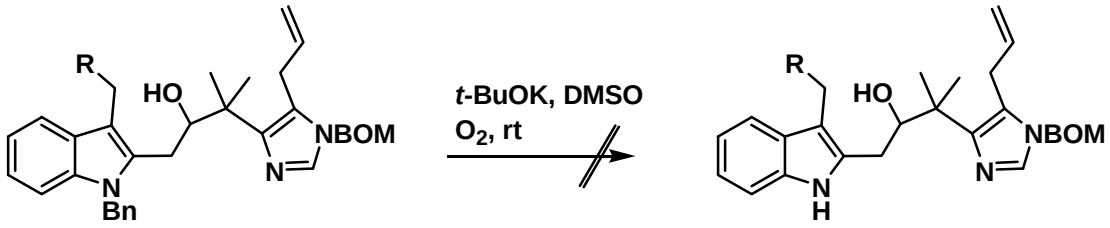


147 R = CO_2Me
148 R = CH_2OH
152 R = CH_2CO_2Me

180 R = CO_2Me
181 R = CH_2OH
182 R = CH_2CO_2Me

In addition, it has been shown that benzyl group removal from an indole can be accomplished with *t*-BuOK, DMSO, and O_2 at rt.[54] However, when indoles **149** and **152** were subjected to these conditions, the protecting group could not be removed (Scheme 51).

Scheme 51

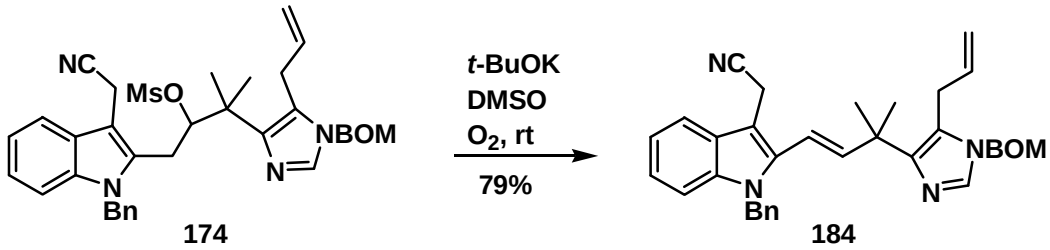


149 R = CN
152 R = CO_2Me

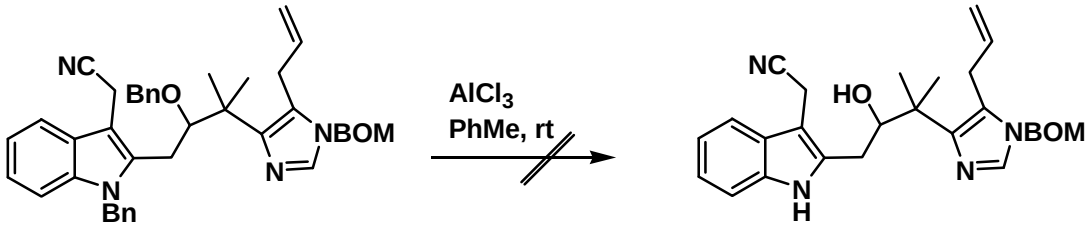
183 R = CN
182 R = CO_2Me

Removal of the benzyl group was also tried on an intermediate mesylate **174**. However, when indole **174** was treated with *t*-BuOK, DMSO, and O_2 at rt, only the elimination product **184** was obtained in good yield (Scheme 52). In addition, treatment of indole **158** with aluminum trichloride in toluene at rt did not cleave the benzyl group (Scheme 53).[55]

Scheme 52



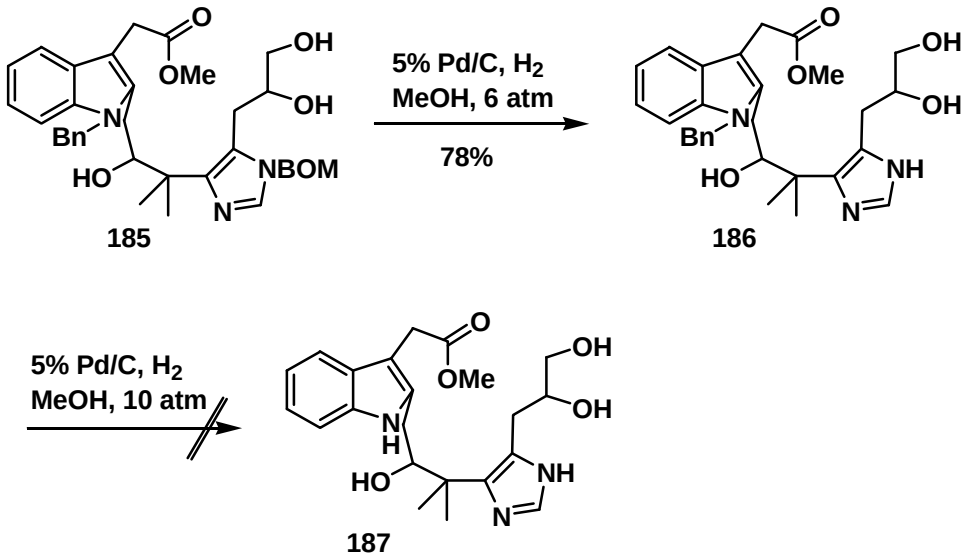
Scheme 53



158 **183**

We have also attempted high pressure hydrogenolysis of the advanced intermediate **185**.[56] Indole imidazole **185** was treated with 5% Pd/C and hydrogen in methanol at 6 atmospheres to give BOM-deprotected imidazole **186** in good yield (Scheme 54). However, resubjecting this compound to hydrogenolysis at a higher pressure (10 atm) did not lead to benzyl group removal.

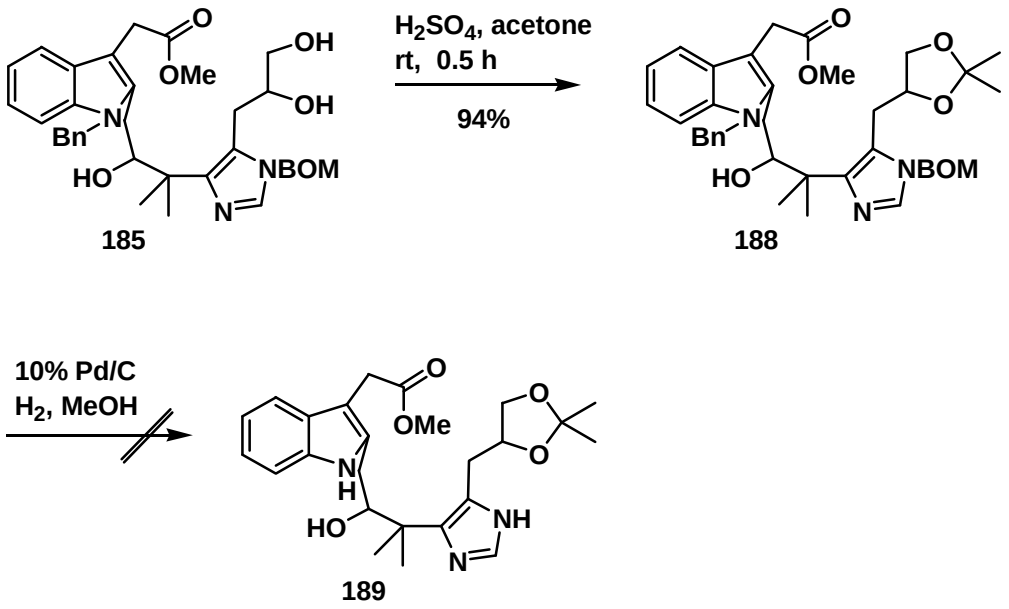
Scheme 54



185 **186** **187**

To ensure that the diol moiety of **185** was not interfering with the hydrogenolysis, the diol **185** was protected as an acetonide **188** with sulfuric acid and acetone at rt (Scheme 55). Indole **188** was then subjected 10% Pd/C in methanol, but neither of the protecting groups were removed and only starting material was recovered. In addition, treatment of indole **188** with Adam's catalyst and H_2 in methanol gave only the diol **185** and not the desired product **189**.

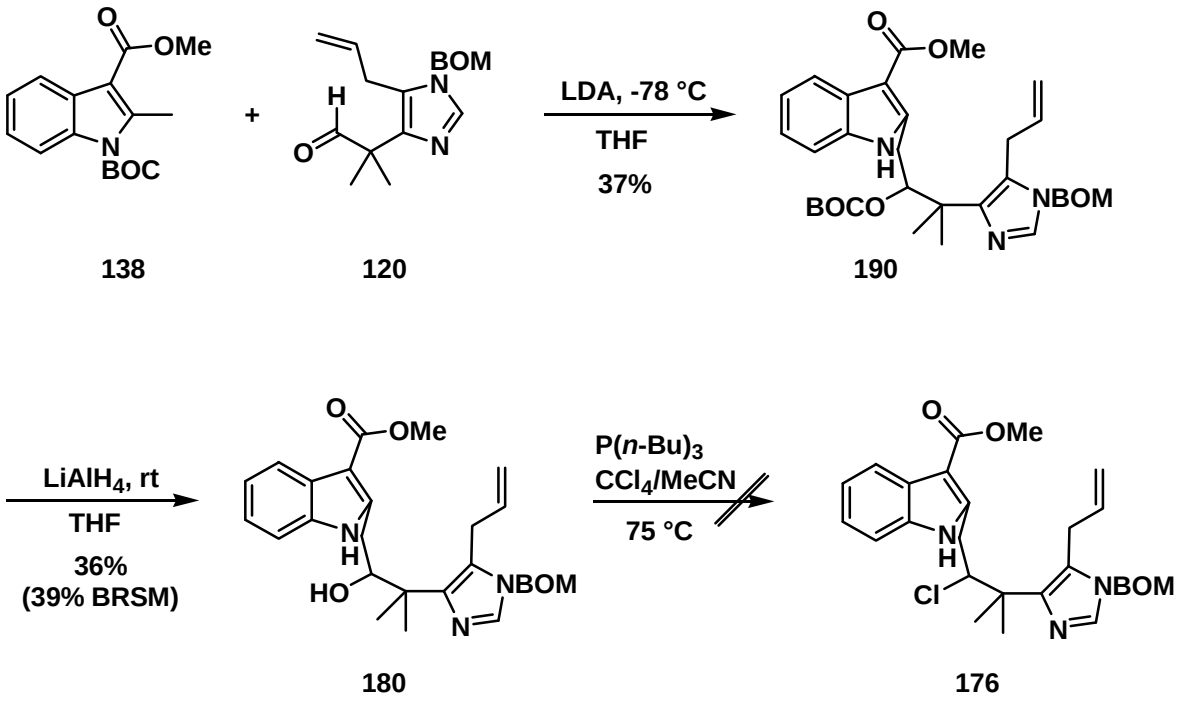
Scheme 55



Finally, we reconsidered using the product **139** of the coupling reaction of BOC-protected indole **138** with imidazole aldehyde **84** (Cf. Scheme 29). Thus, BOC-protected indole **138** was treated with LDA in THF at -78 °C, followed by the addition of aldehyde

120, to give the BOC-transfer coupled product **190**, having a free indole *N*-H. The BOC group was removed with $LiAlH_4$, and the alcohol moiety of **180** was then exposed to Wood's chlorination conditions. However, only a mixture of starting material **180** and an unidentifiable chlorinated product was obtained (Scheme 56).

Scheme 56

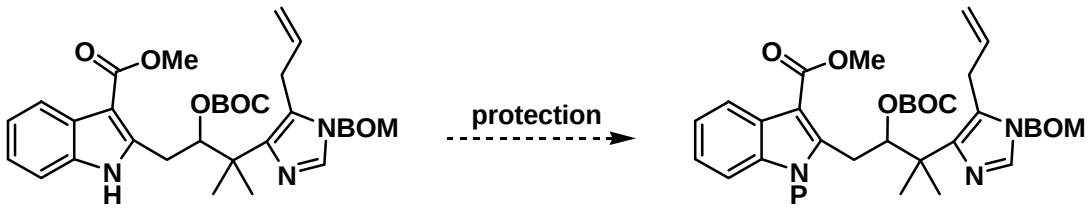


2.4 Conclusion and Future Work

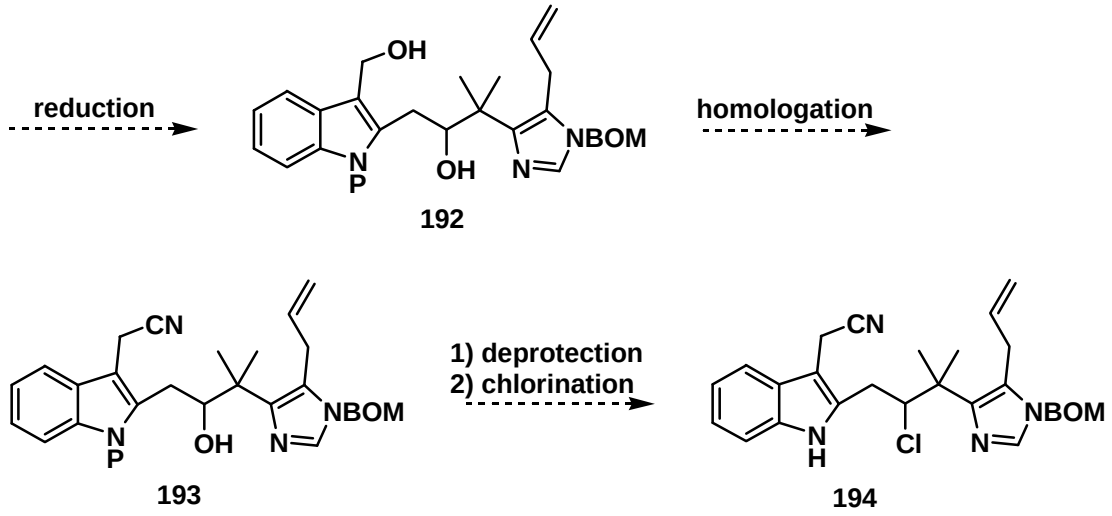
Synthetic efforts towards a total synthesis of securine A (**13**) and securamine A (**6**) have been described. The key features of the synthesis involve the successful coupling of the lithio derivative of indole ester **146** with the aldehyde moiety of the advanced imidazole intermediate **120** to afford ester alcohol **147**. Subsequent one-carbon homologation of the hydroxylmethyl indole **148** to the requisite nitrile **149**, and the condensation of aldehyde **153** with BOM-protected hydroxylamine **168** gave oxime **169**.

It should be possible to overcome the difficulties associated with the introduction of chlorine into an appropriate neopentyl alcohol by utilizing the BOC-transferred coupling product **190**. Thus, indole **190** could be *N*-protected with MOMCl, followed by simultaneous reduction of ester **191** and BOC-removal with $LiAlH_4$ (Scheme 57). Homologation of the resulting diol **192** would then occur, followed by deprotection of the nitrogen of indole **193**. Chlorination of corresponding alcohol using Wood's conditions should give **194**.

Scheme 57



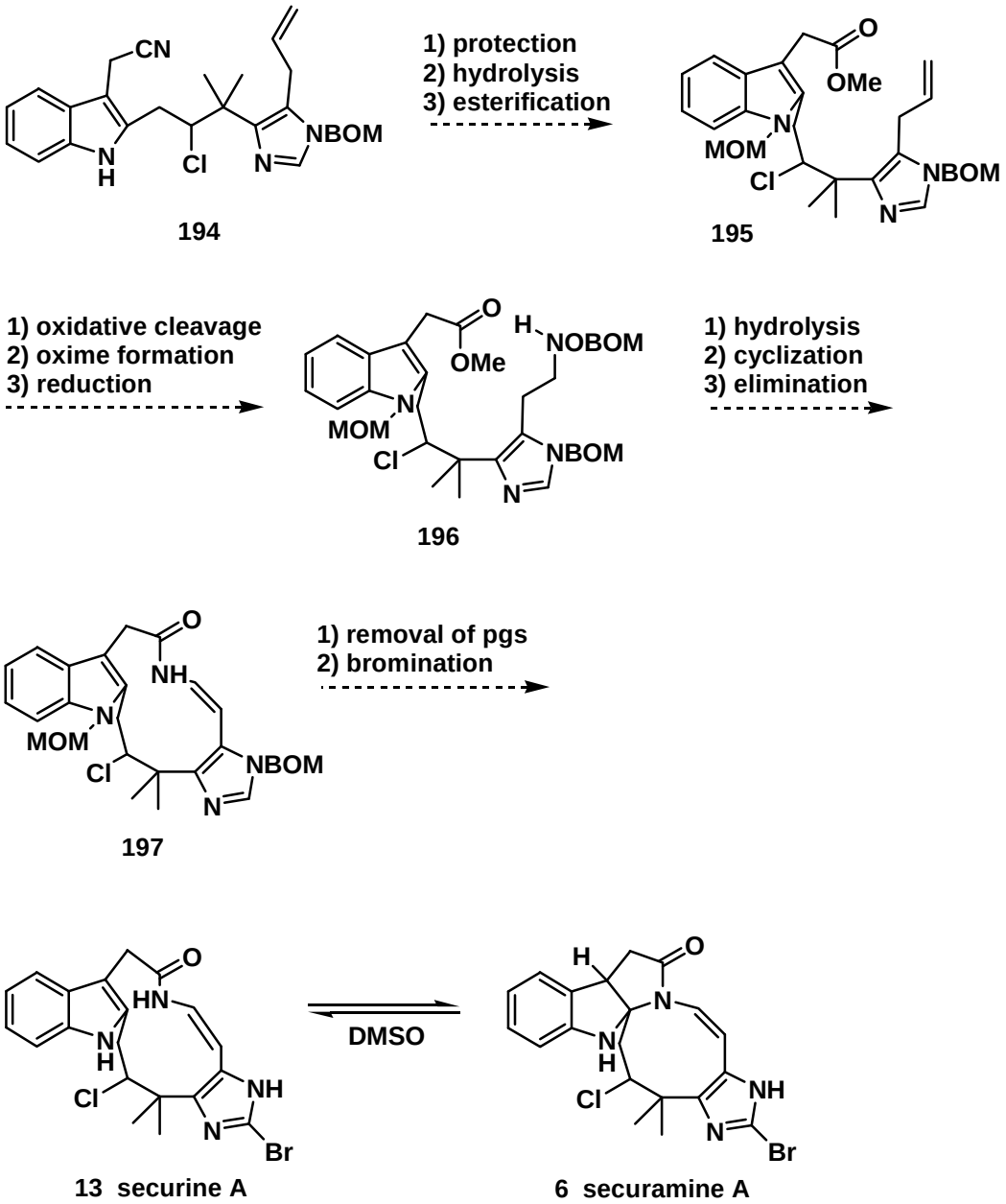
190 **191**



The indole **194** could then be reprotected, and the nitrile functionality of **194** would be hydrolyzed to the corresponding acid, followed by conversion to ester **195** (Scheme 58). The olefin moiety of **195** would be oxidatively cleaved to the corresponding aldehyde, which could then be condensed with BOM-protected hydroxylamine to form an oxime derivative. The *O*-BOM oxime would then be reduced to give *O*-BOM hydroxylamine **196**. At this point, hydrolysis of the ester moiety of **196** to the corresponding acid and subsequent lactamization should give key macrocyclic intermediate hydroxamic acid **197**. Dehydration of hydroxamic acid **197**, followed by removal of the protecting groups and bromination of the *C*-2 position of the imidazole, should give racemic securine A (**13**). Securamine A (**6**) can then be accessed by making

use of the fact that securine A (**13**) and securamine A (**6**) are in equilibrium in DMSO solution.[3a]

Scheme 58

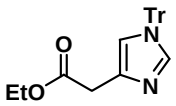


PART THREE

Experimental Section

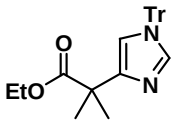
General Methods. All non-aqueous reactions were carried out under an inert atmosphere of argon in flame-dried glassware. Air and moisture sensitive liquid reagents were added via a dry syringe or canula. THF, benzene, and ether were either dried over and distilled from sodium/benzophenone ketyl or were obtained from a solvent dispensing system. Methylene chloride, toluene, MeOH, and DMF were either distilled from CaH_2 or were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (230-400 mesh). Analytical and preparative thin layer chromatography (TLC) was performed on EM Science silica gel 60 PF_{254} plates. ^{1}H and ^{13}C NMR spectral data were recorded on Bruker DPX-300, CDPX-300, AMX-360, or DRX-400 MHz spectrometers. Infrared spectral data were obtained using a Perkin-Elmer 1600 FTIR. Low-resolution mass spectral data (MS) were obtained at 50-70 eV by electron impact (EI).

(1-Trityl-1*H*-imidazol-4-yl)-acetic Acid Ethyl Ester (70).



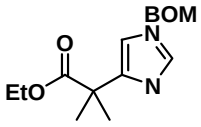
To a solution of imidazole **116** (2.21 g, 14.34 mmol) in 230 mL of CH_2Cl_2 at rt was added trityl chloride (4.80 g, 17.21 mmol) and triethylamine (2.40 mL, 17.21 mmol). The solution was stirred overnight at rt and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50-100% EtOAc/hexanes gradient) to give the protected imidazole **70** as a white solid (4.57 g, 80%); mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.3 Hz, 1H), 7.29-7.26 (m, 9H), 7.14-7.11 (m, 6H), 6.77 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.58 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.8, 142.1, 138.0, 133.8, 129.4, 127.8, 127.7, 119.4, 74.9, 60.3, 34.4, 13.8; HRMS (APCI+) calcd for $C_{26}H_{24}N_2O_2$ (MH^+) 397.1917, found 397.1936.

2-Methyl-2-(1-trityl-1*H*-imidazol-4-yl)-propionic Acid Ethyl Ester (71).

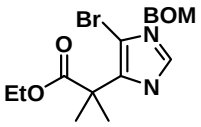


To a solution of imidazole **70** (4.57 g, 11.52 mmol) in 270 mL of THF at -78 °C was added *t*-BuOK (7.76 g, 69.13 mmol) and 18-crown-6 (1.0 g, 2.9 mmol). After the solution was stirred for 30 min at -78 °C, MeI (3.6 mL, 57.6 mmol) was added, and the resulting solution was stirred for 2 h at -78 °C. The reaction mixture was diluted with water and then was warmed to rt. The aqueous layer was extracted with ether, the extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50-100% EtOAc/hexanes gradient) to afford dimethylated imidazole **71** as a light yellow solid (4.14 g, 85%); mp 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 10H), 7.14-

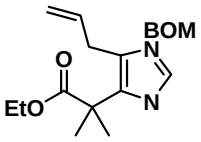
7.11 (m, 6H), 6.64 (d, J = 1.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.52 (s, 6H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.3, 145.3, 142.5, 138.0, 129.8, 128.0, 127.9, 117.5, 75.2, 60.6, 43.1, 25.4, 14.1; HRMS (APCI+) calcd for $C_{28}H_{28}N_2O_2$ (MH^+) 425.2230, found 425.2223.

2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (72). 

To a solution o f protected imidazole **71** (1.50 g, 3.53 mmol) in 118 mL of CH_3CN was added BOMCl (94% purity, 1.0 mL, 7.07 mmol). The solution was refluxed in an oil bath at 90 °C for 1.2 h and subsequently cooled to rt. Saturated $NaHCO_3$ was added, and the mixture was stirred for 10 min. The aqueous layer was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to yield protected imidazole **72** as a clear yellow oil (0.60 g, 56%). IR (film) 2980, 2935, 1727, 1500, 1455, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.51-7.26 (m, 5H), 6.92 (s, 1H), 5.27 (s, 2H), 4.49 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.58 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.1, 124.3, 114.7, 75.5, 70.7, 32.7, 27.7, 25.7, 14.3; HRMS (APCI+) calcd for $C_{17}H_{23}N_2O_3$ (MH^+) 303.1709, found 303.1717.

2-[3-(Benzyloxy)methyl-5-bromo-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (119). 

To a solution of protected imidazole **72** (100 mg, 0.33 mmol) in 7 mL of CH_2Cl_2-MeOH (5:2) at rt was added benzyltrimethylammonium tribromide (155 mg, 0.40 mmol) and $CaCO_3$ powder (50 mg, 0.50 mmol). The solution was stirred for 4 h, and the solid $CaCO_3$ was filtered off. The filtrate was then concentrated, water was added to the residue, and the aqueous layer was extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to yield bromoimidazole **119** as a clear oil (115 mg, 91%). IR (film) 2978, 2919, 2355, 1725, 1455, 1378, 1249, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.38-7.31 (m, 5H), 5.31 (s, 2H), 4.51 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 1.62 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.3, 128.8, 128.5, 128.0, 74.5, 70.6, 61.2, 43.6, 25.5, 14.3, 1.2; HRMS (APCI+) calcd for $C_{17}H_{22}BrN_2O_3$ (MH^+) 381.0815, found 381.0794.

2-[5-Allyl-3-(benzyloxy)methyl-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (73). 

A solution of protected imidazole **119** (1.93 g, 5.07 mmol) in 10 mL of dioxane, a solution of P(*t*-Bu)$_3$ (1.23 mL, 0.41 mmol, 0.1 M in hexane), and allyltributylstannane (1.80 mL, 5.58 mmol) were added sequentially at rt to a Schlenk tube containing $Pd_2(dba)_3$ (0.093 g, 0.10 mmol) and CsF (1.70 g, 11.15 mmol). The tube was then sealed under argon and the mixture was stirred overnight at 100 °C in an oil bath. After the mixture was cooled to rt,

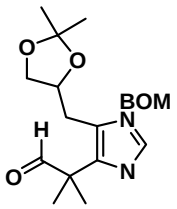
ether was added, and the resulting mixture was filtered through a pad of silica gel. The silica gel was washed with ether and the total filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to give imidazole **73** as a clear oil (1.62 g, 93%). IR (film) 2980, 1726, 1639, 1498, 1455, 1383, 1364, 1257, 1142, 1091, 1028, 909, 747, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.36-7.26 (m, 5H), 5.91-5.78 (m, 1H), 5.21 (s, 2H), 5.03 (dq, *J* = 1.8, 1.8 Hz, 1H), 4.90 (dq, *J* = 1.9, 1.9 Hz, 1H), 4.41 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.42 (d, *J* = 5.4 Hz, 2H), 1.59 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 142.3, 136.2, 135.6, 134.6, 128.4, 127.9, 127.7, 123.3, 115.9, 73.3, 69.4, 60.4, 43.2, 27.2, 26.0, 13.9; HRMS (ESCI+) calcd for $C_{20}H_{27}N_2O_3$ 343.2022 (MH^+), found 343.2022.

2-[3-(Benzyloxy)methyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethy)-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (73a). To a solution of alkene **73** (0.25 g, 0.74 mmol) in 4.7 mL of H_2O and 9.5 mL of acetone was added *N*-methylmorpholine-*N*-oxide (0.43 g, 3.7 mmol) and OsO_4 (4% weight in H_2O, 0.23 mL, 0.04 mmol) at rt. The solution was kept at rt in a water bath and was stirred overnight. The solution was concentrated, and the aqueous layer was extracted with EtOAc. The extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50-100% EtOAc/hexanes gradient) to yield a diol **73a** as a colorless oil (0.27 g, 95%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.37-7.26 (m, 5H), 5.40 (d, *J* = 5.6 Hz, 2H), 5.25 (d, *J*

= 5.6 Hz, 2H), 4.15 (dq, *J* = 2.3, 7.1 Hz, 2H), 3.89-3.85 (m, 1H), 3.65 (dd, *J* = 1.8, 1.8 Hz, 1H), 3.48 (dd, *J* = 3.0, 3.1 Hz, 1H), 2.83 (d, *J* = 3.0 Hz, 2H), 1.63 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 141.9, 136.1, 128.4, 128.0, 127.7, 123.9, 73.8, 71.6, 69.7, 65.9, 60.8, 43.6, 27.1, 26.1, 26.0, 13.8; HRMS (ESCI+) calcd for $C_{20}H_{29}N_2O_5$ 377.2077 (MH^+), found 377.2076.

2-[3-(Benzyloxy)methyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (74). To a solution of diol **73a** (9 mg, 0.024 mmol) in 2.3 mL of dry acetone was added concentrated H_2SO_4 (9 μL). The mixture was stirred for 1.5 h at rt and saturated $NaHCO_3$ (20 mL) was added. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (10% MeOH/EtOAc) to give acetonide **74** as a colorless oil (14 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.38-7.25 (m, 5H), 5.68 (d, *J* = 11 Hz, 2H), 5.20 (d, *J* = 11 Hz, 2H), 4.40 (q, *J* = 11.8 Hz, 2H), 4.21-4.03 (m, 4H), 3.56 (t, *J* = 7.7 Hz, 1H), 2.95-2.89 (m, 2H), 1.61 (d, *J* = 1.6 Hz, 6H), 1.40 (s, 3H), 1.28 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 142.2, 136.3, 136.2, 128.5, 128.0, 127.7, 123.3, 109.2, 75.8, 74.0, 69.5, 69.0, 60.6, 43.5, 27.3, 26.6, 26.4, 26.0, 25.4, 14.0; HRMS (APCI+) calcd for $C_{23}H_{33}N_2O_5$ (MH^+) 417.2390, found 417.2364.

2-[3-Benzyloxymethyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3*H*-imidazol-4-yl]-2-methylpropionaldehyde (75).

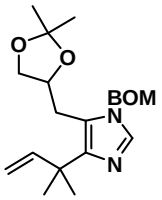


Method 1. To a solution of ester **74** (30 mg, 0.07 mmol) in 3.5 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.0 M solution in CH_2Cl_2, 0.13 mL, 1.08 mmol) dropwise at -78 °C. The reaction mixture was stirred overnight at -78 °C under argon and was quenched with ethyl acetate (7.5 mL) and saturated NH_4Cl (0.13 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield aldehyde **75** as a colorless oil (19 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.52 (s, 1H), 7.38-7.26 (m, 5H), 5.66 (d, *J* = 11 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 4.43 (q, *J* = 11.9 Hz, 2H), 4.15-4.04 (m, 2H), 3.53 (t, *J* = 7.6 Hz, 1H), 2.86-2.83 (m, 2H), 1.48 (d, *J* = 2.7 Hz, 6H), 1.40 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 139.0, 137.2, 136.2, 128.5, 128.1, 127.7, 125.3, 109.4, 76.0, 74.1, 69.8, 69.0, 47.8, 27.3, 26.5, 25.4, 22.2, 21.9; HRMS (APCI+) calcd for $C_{21}H_{29}N_2O_4$ (MH^+) 373.2128, found 373.2127.

Method 2. To a solution of ester **74** (0.16 g, 0.38 mmol) in 19.0 mL of THF was slowly added $LiAlH_4$ (95%, pellets, 18 mg, 0.46 mmol) at 0 °C. The mixture was warmed to rt and stirred for 3 h. The reaction was quenched with 1.2 mL of 15% potassium hydroxide solution. The resulting mixture was stirred overnight, filtered, dried over $MgSO_4$, and concentrated to afford alcohol **74a** as a cloudy, white oil, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39-7.29 (m, 5H), 5.64 (d, *J* = 11.0 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 4.46 (q, *J* = 12.0 Hz, 2H),

4.31-4.25 (m, 1H), 4.11 (t, *J* = 6.0 Hz, 1H), 3.68 (s, 2H), 3.62 (t, *J* = 7.8 Hz, 1H), 3.06-3.03 (m, 2H), 1.44 (s, 3H), 1.32 (d, *J* = 4.1 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 136.3, 136.0, 128.5, 128.0, 127.7, 123.0, 109.3, 76.2, 73.9, 73.2, 69.7, 68.9, 37.4, 27.6, 26.5, 25.7, 25.3, 25.3; HRMS (APCI+) calcd for $C_{21}H_{31}N_2O_4$ (MH^+) 375.2285, found 375.2284.

To a solution of DMSO (75 μL, 0.70 mmol) in 7.0 mL of CH_2Cl_2 was added oxalyl chloride (54 μL, 0.62 mmol) at -78 °C. After stirring this solution for 10 min at -78 °C, a solution of the above alcohol **74a** (166 mg, 0.44 mmol) in 7.0 mL of CH_2Cl_2 was added. The resulting mixture was then stirred for 20 min at -78 °C and triethylamine (0.31 mL, 2.20 mmol) was added. The mixture was warmed to 0 °C and stirred for 15 min. The reaction was diluted with saturated NH_4Cl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (EtOAc) to yield aldehyde **75** as a colorless oil (127 mg, 89% for two steps).

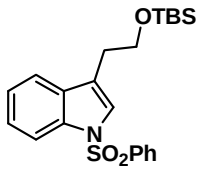
1-Benzyloxymethyl-5-(1,1-dimethylallyl)-4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)1*H*-imidazole (76). 

To a solution of methyltriphenylphosphonium bromide (25 mg, 0.07 mmol) in 1.5 mL of THF was added *n*-BuLi (1.8 M solution in hexanes, 40 μL, 0.07 mmol) at 0 °C. The mixture immediately turned bright red, was allowed to stir for 1 h at rt, and was then recooled to 0 °C. Aldehyde **75** (11 mg, 0.03 mmol) was added and the solution turned yellow-orange. The resulting mixture was stirred overnight and was diluted with water

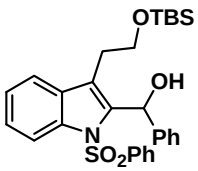
(1.0 mL) and ether (1.5 mL). The aqueous layer was extracted twice with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield alkene **76** as a colorless oil (4 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.47-7.33 (m, 5H), 6.13 (dd, *J* = 17.5, 10.54 Hz, 1H), 5.65 (d, *J* = 11.0 Hz, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 5.08 (dt, *J* = 17.5 Hz, 1H), 5.04 (dt, *J* = 10.5 Hz, 1H), 4.43 (q, *J* = 11.9 Hz, 2H), 4.24-4.20 (m, 1H), 4.02 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.56 (t, *J* = 7.9 Hz, 1H), 3.1 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.92 (dd, *J* = 15.5, 8.5 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H); LRMS-APCI *m/z* 371 (MH^+).

3-[2-(*t*-Butyldimethylsilanyloxy)-ethyl]-1*H*-indole (79). To a solution of 2-(1*H*-Indol-3-yl)-ethanol (**78**) (1.0 g, 6.20 mmol) in 10 mL of DMF, was added imidazole (0.93 g, 13.64 mmol) and TBDMSCl (1.12 g, 7.44 mmol) at rt. The resulting solution was then stirred overnight at rt. Ether (10 mL) and water (20 mL) were added and the aqueous layer was extracted with ether (2 x 10 mL). The combined ethereal extracts were then washed with water (3 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield *O*-protected indole **79** as an orange-yellow oil (1.70 g, 99%). IR (film) 3413, 3060, 2931, 28489, 1455, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9 (s, NH), 7.59-7.06 (m, 4H), 7.01 (s, 1H), 3.85 (t, *J* = 7.5 Hz, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 127.7, 122.4, 121.8, 119.2, 118.9, 112.6, 111.3, 64.1,

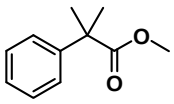
53.4, 29.2, 26.2, 18.6, 18.5, -5.1; HRMS (APCI+) calcd for $C_{16}H_{26}NOSi$ (MH^+) 276.1784, found 276.1788.

1-Benzenesulfonyl-3-[2-(*t*-Butyldimethylsilanyloxy)-ethyl]-1*H*-indole (80). 

To a solution of indole **79** (1.39 g, 5.03 mmol) in 40 mL of THF was added dropwise *n*-BuLi (2.5 M solution in hexanes, 2.6 mL, 6.54 mmol) at -78 °C. The orange mixture was stirred at -78 °C for 15 min and then at 0 °C for 1h. The solution was then recooled to -78 °C, and benzenesulfonyl chloride (0.83 mL, 6.54 mmol) was added. The solution was then slowly warmed to rt and stirred overnight. Saturated NH_4Cl was then added, followed by saturated $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to yield *N*-protected indole **80** as a dark yellow-brown oil (1.84 g, 88%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-7.87 (m, 5H), 7.54-7.42 (m, 4H), 7.28 (s, 1H), 3.89 (t, J = 6.8 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H), 0.89 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.3, 133.8, 131.4, 129.3, 126.9, 124.8, 123.6, 123.5, 120.5, 119.8, 113.8, 62.7, 28.7, 26.1, 18.4; HRMS (APCI+) calcd for $C_{22}H_{33}N_2O_3SSi$ $[M+NH_4]^+$ 433.2022, found 433.1941.

{1-Benzenesulfonyl-3-[2-(*t*-butyldimethylsilanyloxy)-ethyl]-1*H*-indol-2-yl}-phenylmethanol (81). 

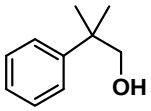
To a solution of protected indole **80** (0.20 g, 0.48 mmol) in 13 mL of THF was added dropwise *n*-BuLi (2.5 M solution in hexanes, 0.19 mL, 0.48 mmol) at -78 °C. To this solution was added benzaldehyde (0.10 mL, 0.96 mmol). The resulting mixture was then stirred overnight at -78 °C under argon and was quenched with saturated $NaHCO_3$ (3 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (20-50% EtOAc/hexanes) to yield alcohol **81** as a yellow-green oil (0.17 g, 69%). IR (film) 3057, 2936, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.74-7.71 (m, 2H), 7.66-7.36 (m, 12H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.71 (d, *J* = 8.5 Hz, 1H), 3.89-3.83 (m, 1H), 3.74 (dt, *J* = 4.3, 11.8 Hz, 1H), 2.99-2.90 (m, 1H), 2.78 (dt, *J* = 4.3, 11.8 Hz, 1H), 0.80 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 140.6, 136.9, 133.9, 129.5, 128.5, 127.4, 127.1, 126.5, 125.6, 123.9, 120.5, 119.3, 115.7, 68.0, 62.7, 53.9, 27.8, 26.3, 18.8, -5.2, -5.3; LRMS-APCI *m/z* 504 $[MH^+-H_2O]^+$.

2-Methyl-2-phenylpropionic Acid Methyl Ester (83). 

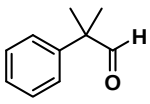
To a solution of NaH (95%, 3.16 g, 125.13 mmol) in 60 mL of THF was added phenylacetic acid methyl ester (**82**, 6.00 mL, 41.71 mmol) dropwise at rt. The solution was stirred for 0.5 h and then CH_3I (26.0 mL, 417.1 mmol) was added. The resulting solution was stirred overnight at rt. Ethyl acetate and water were added, and the aqueous

layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2) to yield the dimethylated ester **83** as a yellow oil (5.41 g, 87%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-6.94 (m, 5H), 3.54 (s, 3H), 1.48 (s, 6H); HRMS (ESCI+) calcd for $C_{11}H_{15}O_2$ 179.1073 (MH^+), found 179.1072.

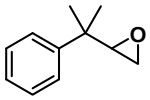
2-Methyl-2-phenylpropan-1-ol (83a). To a solution of dimethylated ester **83** (5.40 g, 30.3 mmol) in 200 mL of THF was slowly added $LiAlH_4$ (95%, pellets, 1.45 g, 36.4 mmol) at 0 °C. The mixture was warmed to rt and stirred for 3 h. The reaction was quenched with 90 mL of 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated to afford an alcohol **83a** as a cloudy, white oil which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-6.78 (m, 5H), 3.39 (s, 2H), 2.72 (bs, 1H), 1.17 (s, 6H).



2-Methyl-2-phenylpropionaldehyde (84). To a solution of DMSO (4.75 mL, 66.9 mmol) in 50 mL of CH_2Cl_2 was added dropwise oxalyl chloride (3.20 mL, 36.5 mmol) at -78 °C. After stirring this solution for 10 min at -78 °C, a solution of the above alcohol **83a** (4.57 g, 30.42 mmol) in 50 mL of CH_2Cl_2 was added. The resulting mixture was then stirred for 20 min at -78 °C and triethylamine (20.40 mL, 146.0 mmol) was added. The mixture was warmed to 0 °C and stirred for 15



min. The reaction mixture was diluted with saturated NH_4Cl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to afford aldehyde **84** as a colorless oil, which was used immediately without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.70-8.56 (m, 5H), 2.71 (s, 6H).

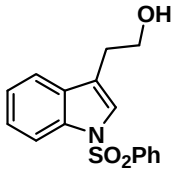
2-(1-Methyl-1-phenylethyl)-oxirane (85).  To a solution of trimethylsulfoxonium iodide (11.35 g, 51.60 mmol) in 70.5 mL of DMSO was added NaH (95%, 1.30 g, 51.60 mmol) at rt. The mixture was stirred for 0.5 h at rt, and then a solution of aldehyde **84** (6.37 g, 43.00 mmol) in 37.0 mL of DMSO/THF (1:1) was added by canula at 0 °C. The resulting mixture was stirred for 25 min at rt. The reaction mixture was diluted with water, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to yield epoxide **85** as a yellow oil (2.16 g, 44% for 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.01 (m, 5H), 3.08 (dd, J = 4.0, 2.8 Hz, 1H), 2.76 (t, 1H), 2.68 (dd, J = 4.8, 2.9 Hz, 1H), 1.35 (d, J = 24.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 128.8, 126.9, 126.7, 60.0, 44.8, 38.4, 25.2, 24.6.

3-(2-Methoxymethoxy-ethyl)-1*H*-indole (86a). To a stirred solution of tryptophol (**78**, 100 mg, 0.62 mmol) in 15 mL of methylene chloride was added dropwise DIPEA (0.22 mL, 1.24 mmol) and NaI (189 mg, 1.24 mmol) at rt. The mixture was then cooled to 0 °C, and MOMCl (71 μL, 0.93 mmol) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C and then warmed to rt and stirred overnight. Methylene chloride (70 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford *O*-protected indole **86a** as a clear yellow oil (110 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.71-7.67 (m, 1H), 7.38-7.05 (m, 4H), 4.7 (s, 2H), 3.92 (t, *J* = 7.2 Hz, 2H), 3.42 (s, 3H), 3.14 (dt, *J* = 0.8, 12.9 Hz, 2H).

1-Benzenesulfonyl-3-(2-methoxymethoxy-ethyl)-1*H*-indole (87a). To a solution of protected indole **86a** (110 mg, 0.54 mmol) in 16.3 mL of THF was added dropwise *n*-BuLi (2.5 M solution in hexanes, 0.28 mL, 0.71 mmol) at -78 °C. The mixture was stirred at -78 °C for 15 min and then at 0 °C for 1h. The solution was recooled to -78 °C, and benzenesulfonyl chloride (91 μL, 0.71 mmol) was added. The solution was slowly warmed to rt and stirred overnight. Saturated NH_4Cl was then added, followed by saturated $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield *N*-protected indole **87a** as a

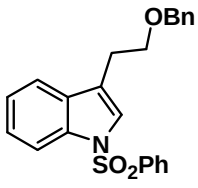
yellow oil (155 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.89-7.86 (m, 1H), 7.55-7.18 (m, 8H), 4.63 (s, 2H), 3.82 (t, *J* = 6.8 Hz, 2H), 3.30 (s, 3H), 2.98 (dt, *J* = 0.9, 7.2 Hz, 2H).

1-Benzenesulfonyl-3-(2-benzyloxy-ethyl)-1H-indole (86b).



To a solution of tryptophol (**78**, 200 mg, 0.54 mmol) in 38 mL of THF was added dropwise *n*-BuLi (2.2 M solution in hexanes, 0.84 mL, 1.86 mmol) at -78 °C. The mixture was stirred at -78 °C for 15 min and then at 0 °C for 1h. The solution was recooled to -78 °C, and benzenesulfonyl chloride (0.24 mL, 1.86 mmol) was added. The solution was slowly warmed to rt and stirred overnight. Saturated NH_4Cl was then added, followed by saturated $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to yield *N*-protected indole **86b** as a yellow oil (364 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.56-7.19 (m, 10H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.06 (t, *J* = 6.4 Hz, 2H);

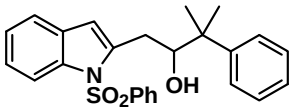
1-Benzenesulfonyl-3-(2-benzyloxyethyl)-1*H*-indole (87b).



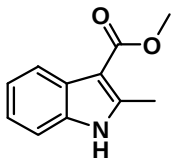
To a stirred solution of *N*-protected tryptophol **86b** (138 mg, 0.46 mmol) in 1.4 mL of DMF was added NaH (60% dispersion in mineral oil, 26 mg, 0.64 mmol) and benzyl bromide (80 μL, 0.64 mmol) at rt. The resulting

mixture was stirred for 1.5 h and methanol was added. The mixture was diluted with toluene and the organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford protected tryptophol **87b** as a clear yellow oil (35 mg, 25%).

1-(1-Benzenesulfonyl-1*H*-indol-2-yl)-2-phenoxyethanol (91) and 2-(1-Benzenesulfonyl-1*H*-indol-2-yl-3-phenoxypropan-1-ol (92). To a solution of indole **89** (0.1 g, 0.39 mmol) in 0.94 mL of THF was added dropwise *n*-BuLi (2.4 M solution in hexanes, 0.2 mL, 0.47 mmol) at -78 °C. The red solution was stirred for 1.5 h at -78 °C and was then warmed to 5°C over 1 h. The solution was recooled to -78 °C, upon which the epoxide **90** (53 μL, 0.39 mmol) in 0.16 mL of THF was added by canula. The mixture was warmed slowly to rt overnight. Saturated NH_4Cl was added, and the aqueous layer was extracted with ethyl acetate. The organic extract was washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford an inseparable mixture of regioisomeric alcohols **91** and **92** as a red-orange oil (0.65:1; 76 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.41-6.96 (m, 25H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 5.57 (m, 1H), 5.11 (q, *J* = 6.4 Hz, 1H), 4.54 (m, 1H), 4.41 (dd, *J* = 15.1, 1.1 Hz, 2H), 4.19 (dd, *J* = 7.2, 0.95 Hz, 2H), 4.13 (dd, *J* = 9.5, 3.8 Hz, 1H), 4.04 (dd, *J* = 9.4, 6.1 Hz, 1H), 3.46 (dd, *J* = 15.3, 4.45 Hz, 1H), 3.31 (dd, *J* = 15.3, 7.7 Hz, 1H), 1.72 (s, 2H).

1-(1-Benzenesulfonyl-1*H*-indol-2-yl)-3-methyl-3-phenylbutan-2-ol (93). 

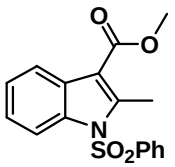
To a solution of indole **89** (100 mg, 0.39 mmol) in 0.90 mL of THF was added *n*-BuLi (2.5 M solution in hexanes, 0.23 mL, 0.59 mmol) dropwise at -78 °C. The resulting red solution was stirred for 1.5 h at -78 °C and was then warmed to 5°C over 1 h. The solution was recooled to -78 °C, and was added by canula to the epoxide **85** (147 mg, 0.91 mmol) in 0.20 mL of THF. The mixture was then warmed slowly to rt overnight. Saturated NH_4Cl was added, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated NH_4Cl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford alcohol **93** as a clear yellow oil (65 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 (d, *J* = 8.2 Hz, 1H), 7.58-7.00 (m, 15H), 6.48 (d, *J* = 0.7 Hz, 1H), 4.20-4.12 (m, 1H), 3.19 (dq, *J* = 2.9, 1.0, 0.9 Hz, 1H), 2.77 (ddd, *J* = 10.9, 10.4, 0.5 Hz, 1H), 1.90 (bs, 1H), 1.51 (s, 6H); LRMS-APCI *m/z* 402 $[MH^+-H_2O]^+$.

2-Methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (110). 

Method 1. To a stirred solution of methyl acetoacetate (**109**) (0.97 g, 7.93 mmol) in 6.2 mL of ether was added phenylhydrazine (**108**) (1 mL, 10.16 mmol) and 1 drop of acetic acid at 0 °C. The mixture was then stirred for 1 h at 0 °C and evaporated under reduced pressure at rt. The residue was added

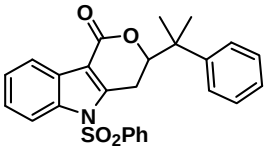
dropwise to concentrated sulfuric acid (4.3 mL) at -5°C over 10 min. The resulting mixture was stirred for 30 min at -5°C and poured onto ice. The precipitate was collected and washed with cold water. The compound was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford indole **110** as a white solid (0.69 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.53 (bs, 1H), 8.06-8.01 (m, 1H), 7.33-7.28 (m, 1H), 7.16-7.07 (m, 2H), 3.88 (s, 3H), 2.71 (s, 3H); HRMS (ESCI+) calcd for $C_{11}H_{12}NO_2$ 190.0869 (MH^+), found 190.0868.

Method 2. See page 133.

1-Benzenesulfonyl-2-methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (98). 

To a solution of NaH (95%, 153 mg, 6.06 mmol) in 11 mL of DMF was added a solution of indole **110** (955 mg, 5.05 mmol) in 11 mL of DMF dropwise at 0 °C. The mixture was warmed to rt, stirred for 30 min and then recooled to 0 °C. Benzenesulfonyl chloride (0.77 mL, 6.06 mmol) was added dropwise and the resulting solution was stirred overnight at rt. Saturated NH_4Cl was added and the aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford protected indole **98** as a light yellow solid (1.59 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.27 (m, 1H), 8.10-8.08 (m, 1H), 7.85-7.83 (m, 2H), 7.53-7.49 (m, 1H), 7.42-7.28 (m, 4H), 3.91 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6,

145.5, 139.1, 136.3, 134.7, 130.0, 127.6, 126.9, 125.3, 124.8, 122.2, 114.6, 112.1, 51.8, 14.3; HRMS (ESCI+) calcd for $C_{17}H_{16}NO_4S$ 330.0801 (MH^+), found 330.0800.

5-Benzenesulfonyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (112). 

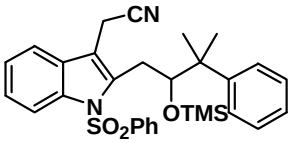
To a solution of methyl indole **98** (300 mg, 0.91 mmol) in 3.1 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.91 mL, 1.82 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, to which a solution of aldehyde **84** (196 mg, 1.32 mmol) in 3.1 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 50 min and diluted at -60 °C with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford lactone **112** as a bright yellow oil (290 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.09 (m, 2H), 7.64-7.61 (m, 3H), 7.48-7.37 (m, 9H), 4.57 (dd, *J* = 3.9, 12.4, Hz, 1H), 3.10 (dd, *J* = 3.9, 17.9 Hz, 1H), 2.97 (dd, *J* = 12.4, 18.3 Hz, 1H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 146.3, 145.1, 138.3, 136.6, 135.1, 130.2, 129.1, 127.3, 127.1, 125.5, 121.6, 114.3, 109.6, 38.8, 21.5, 14.7; HRMS (ESCI+) calcd for $C_{26}H_{24}NO_4S$ 446.1427 (MH^+), found 446.1426.

1-(1-Benzenesulfonyl-3-hydroxymethyl-1*H*-indol-2-yl)-3-methyl-3-phenylbutan-2-ol (113). To a solution of lactone **112** (275 mg, 0.62 mmol) in 30 mL of anhydrous ether was added $LiAlH_4$ (95%, pellets, 50 mg, 1.23 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated to afford diol **113** as a clear oil (253 mg, 91%), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 1.4, 6.8 Hz, 1H), 7.59-7.26 (m, 14H), 4.52 (dd, *J* = 12.5, 32.9 Hz, 2H), 4.23 (dd, *J* = 1.7, 10.7 Hz, 1H), 3.33 (dd, *J* = 1.8, 14.4 Hz, 1H), 2.82 (dd, *J* = 10.9, 14.4 Hz, 1H), 1.53 (d, *J* = 6.7 Hz, 1H); LRMS-ESCI+ *m/z* 450.3 (MH^+).

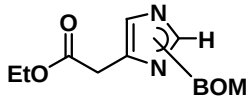
[1-Benzenesulfonyl-2-(2-hydroxy-3-methyl-3-phenylbutyl)-1*H*-indol-3-yl]-acetonitrile (114). To a stirred solution of boron trifluoride diethyl etherate (19 μL, 0.15 mmol) and TMSCN (27 μL, 0.20 mmol) in 1.3 mL of CH_2Cl_2 was added by canula a solution of crude diol **113** (23 mg, 0.05 mmol) in 0.32 mL of CH_2Cl_2 dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Saturated $NaHCO_3$ was added and the solution was stirred for 45 min at rt. The organic layer was washed with 1.0 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to afford nitrile **114** (15 mg, 46% for two steps from lactone **xx** as a

yellow oil. IR (film) 3554, 3059, 2968, 2250, 1723, 1601, 1448, 1367, 1247, 1488, 1172, 1128, 1089, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, *J* = 1.4, 6.8 Hz, 1H), 7.61-7.26 (m, 14H), 4.15 (dd, *J* = 1.8, 10.6 Hz, 1H), 3.65 (q, *J* = 17.9, 35.8 Hz, 2H), 3.22 (dd, *J* = 2.0, 14.5 Hz, 1H), 2.78 (dd, *J* = 10.7, 14.7 Hz, 1H), 1.53 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 139.1, 136.8, 136.7, 134.4, 129.8, 128.9, 127.2, 126.9, 126.5, 125.6, 124.5, 118.6, 117.6, 115.5, 112.8, 79.3, 43.4, 28.9, 24.5, 23.9, 13.9; HRMS (ESCI+) calcd for $C_{27}H_{26}N_2O_3SNa$ 481.1562 (MNa^+), found 481.1562.

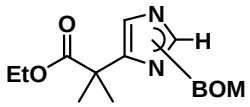
[1-Benzenesulfonyl-2-(3-methyl-3-phenyl-2-trimethylsilanyloxy-butyl)-1*H*-indol-3-yl]-acetonitrile (115).



To a stirred solution of boron trifluoride diethyl etherate (19 μL, 0.15 mmol) and TMSCN (27 μL, 0.20 mmol) in 1.3 mL of CH_2Cl_2 was added by canula a solution of crude diol **113** (23 mg, 0.05 mmol) in 0.32 mL of CH_2Cl_2 dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Saturated $NaHCO_3$ was added and the solution was stirred for 45 min at rt. The organic layer was washed with 1.0 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to afford nitrile **115** (15 mg, 46% for two steps from lactone **xx**). ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 1.3, 6.9 Hz, 1H), 7.58-7.30 (m, 14H), 4.56 (dd, *J* = 2.8, 10.6 Hz, 1H), 3.56 (ABq, *J* = 62.8, 18.0 Hz, 2H), 2.90 (dd, *J* = 2.7, 14.7 Hz, 1H), 2.66 (dd, *J* = 10.7, 14.7 Hz, 1H), 1.49 (d, *J* = 4.0 Hz, 6H), -0.33 (s, 9H); LRMS-ESCI+ *m/z* 553.3 $[M+Na]^+$.

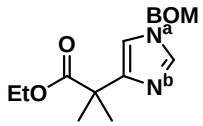
(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-acetic Acid Ethyl Ester and (3-Benzyloxymethyl-3*H*-imidazol-4-yl)-acetic Acid Ethyl Ester (117). 

To a solution of imidazole **116** (3.0 g, 19.5 mmol) in 24 mL of THF was added triethylamine (9.2 mL, 66.2 mmol) and BOMCl (94% purity, 4.9 mL, 33.1 mmol) at 0 °C. The resulting solution was then warmed to rt and stirred for 1.5 h. The mixture was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc-20% MeOH/EtOAc gradient) to yield a mixture (~2:1) of protected imidazole regioisomers **117** as a clear yellow-brown oil (2.9 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of regioisomers) δ 7.5 (s, 1H, *major and minor*), 7.43-7.19 (m, 5H, *major and minor*), 7.02 (s, 1H, *minor*), 6.98 (s, 1H, *major*), 5.33 (s, 2H, *major*), 5.25-5.24 (m, 2H, *minor*), 4.41 (s, 2H, *minor*), 4.37 (s, 2H, *major*), 4.20-4.06 (m, 2H, *major and minor*), 3.69 (s, 2H, *major*), 3.64 (s, 2H, *minor*), 1.29-1.13 (m, 3H, *major and minor*).

2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester and 2-[3-(Benzyloxy)methyl-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (118). 

To a solution of protected imidazole regioisomers **117** (5.14 g, 18.74 mmol) in 150 mL of THF at -78 °C, was added *t*-BuOK (8.41 g, 74.96 mmol) and 18-crown-6 (1.63 g, 4.68 mmol). After the

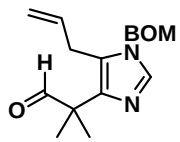
solution was stirred for 30 min at -78 °C, MeI (5.8 mL, 93.7 mmol) was added, and the resulting solution was stirred for 1 h at -78 °C. The reaction mixture was diluted with water, warmed to rt, and the aqueous layer was extracted with ether. The extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc-20% MeOH/EtOAc gradient) to afford a mixture of dimethylated imidazole regioisomers **118** as a clear light yellow oil (5.03 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of regioisomers) δ 7.52 (s, 1H, *major*), 7.51-7.26 (m, 5H, *major*), 6.92 (s, 1H, *major*), 5.27 (s, 2H, *major*), 4.49 (s, 2H, *major*), 4.14 (q, *J* = 7.1 Hz, 2H, *major*), 1.58 (s, 6H, *major*), 1.22 (t, *J* = 7.1 Hz, 3H, *major*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.1, 124.3, 114.7, 75.5, 70.7, 32.7, 27.7, 25.7, 14.3; HRMS (APCI+) calcd for $C_{17}H_{23}N_2O_3$ (MH^+) 303.1709, found 303.1717.

2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (73). 

To a solution of dimethylated imidazole regioisomers **118** (5.03 g, 16.64 mmol) in 60 mL of THF, was added a catalytic amount of BOMCl (90% purity, 0.13 mL, 0.83 mmol) at rt. The resulting solution was then warmed and stirred at 70 °C for 3 h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc) to yield dimethylated imidazole **73** as a clear light yellow oil (4.76 g, 95%). IR (film) 2980, 2935, 1727, 1500, 1455, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.51-7.26 (m, 5H), 6.92 (s, 1H), 5.27 (s, 2H), 4.49 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 1.58 (s,

6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.1, 124.3, 114.7, 75.5, 70.7, 32.7, 27.7, 25.7, 14.3; HRMS (APCI+) calcd for $C_{17}H_{23}N_2O_3$ (MH^+) 303.1709, found 303.1717.

2-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionaldehyde (120).



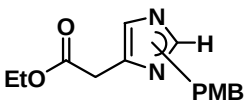
Method 1. To a solution of ester **73** (150 mg, 0.44 mmol) in 21.6 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.0 M solution in toluene, 2.60 mL, 2.60 mmol) dropwise at -78 °C. The reaction mixture was stirred overnight at -78 °C under argon and was quenched with ethyl acetate and saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield aldehyde **120** as a colorless oil (130 mg, 99%).

Method 2. To a solution of ester **73** (19 mg, 0.06 mmol) in 3 mL of THF was slowly added $LiAlH_4$ (95%, pellets, 10 mg, 0.13 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford an alcohol as a clear oil (15 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 6H), 5.95-5.82 (m, 1H), 5.20 (s, 2H), 5.07 (dq, J = 1.7, 3.3, 10.1 Hz, 1H), 4.86 (dq, J = 1.9, 3.5, 17.1 Hz, 1H), 4.44 (s, 2H), 3.64 (s, 2H), 3.56-3.53 (m, 2H), 1.29 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.4, 136.8, 135.8, 129.1, 128.6, 128.3,

116.6, 73.8, 73.7, 70.2, 37.6, 28.2, 25.7; HRMS (APCI+) calcd for $C_{18}H_{25}N_2O_2$ (MH^+) 301.1917, found 301.1911.

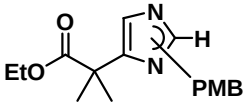
To a solution of DMSO (30 μL, 0.42 mmol) in 3.3 mL of CH_2Cl_2 was added oxalyl chloride (2.0 M solution in hexanes, 0.12 mL, 0.23 mmol) at -78 °C. After stirring this solution for 10 min at -78 °C, a solution of the above alcohol (57 mg, 0.19 mmol) in 3.3 mL of CH_2Cl_2 was added. The resulting mixture was then stirred for 20 min at -78 °C and triethylamine (0.13 mL, 4.8 mmol) was added. The mixture was warmed to 0 °C and stirred for 15 min. The reaction mixture was diluted with saturated NH_4Cl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc) to yield aldehyde **120** as a colorless oil (49 mg, 88 % for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.55 (s, 1H), 7.42-7.32 (m, 5H), 5.41-5.32 (m, 1H), 5.27 (s, 2H), 5.11 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.89 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.49 (s, 2H), 3.42 (d, *J* = 5.3 Hz, 2H), 1.51 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.9, 139.2, 136.9, 136.2, 134.8, 128.6, 128.2, 127.9, 125.4, 116.4, 73.5, 69.9, 47.7, 27.2, 21.9; HRMS (APCI+) calcd for $C_{18}H_{23}N_2O_2$ (MH^+) 299.1760, found 299.1758.

[(4-Methoxybenzyl)-1*H*-imidazol-4-yl]-acetic Acid Ethyl Esters (121). To a solution of imidazole **116** (90 mg, 0.58 mmol) in



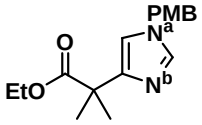
5.3 mL of DMF was added potassium carbonate (89 mg, 0.64 mmol) and the mixture was stirred for 10 min. To this mixture was added PMBCl (94 μL, 0.70 mmol) at rt. The

resulting mixture was then warmed to 55˚C and stirred overnight. After cooling the mixture to rt, H_2O and ethyl acetate were added. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc) to yield a mixture (~7:3) of protected imidazole regioisomers **121** as a bright yellow oil (155 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.33 (m, 1H, *major and minor*), 7.04 (dt, *J* = 2.9, 8.8 Hz, 1H, *major and minor*), 6.94 (dd, *J* = 2.1, 6.6 Hz, 1H, *major and minor*), 6.81-6.71 (m, 3H, *major and minor*), 4.99 (s, 2H, *minor*), 4.91 (s, 2H, *major*), 4.10-3.98 (m, 2H, *major and minor*), 3.70 (s, 3H, *major and minor*), 3.52 (s, 2H, *major*), 3.39 (s, 2H, *minor*), 1.19-1.13 (m, 3H, *major and minor*).

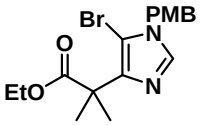
2-[(4-Methoxybenzyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Esters (122). 

To a solution of protected imidazole regioisomers **121** (1.37 g, 4.99 mmol) in 42 mL of THF at -78 °C, was added *t*-BuOK (3.36 g, 29.97 mmol) and 18-crown-6 (0.44 g, 1.25 mmol). After the solution was stirred for 30 min at -78 °C, MeI (1.6 mL, 24.95 mmol) was added, and the resulting solution was stirred for 2 h at -78 °C. The reaction mixture was diluted with water, warmed to rt, and the aqueous layer was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford a mixture (~7:3) of dimethylated imidazole regioisomers **122** (0.59 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of regioisomers) δ 7.43 (d, *J* = 1.3 Hz, 1H, *major*), 7.32 (s, 1H, *minor*), 7.12-7.05 (m, 2H,

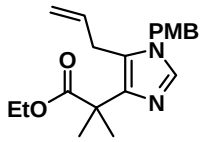
major and minor), 7.00-6.97 (m, 1H, *major and minor*), 6.91-6.71 (m, 3H, *major and minor*), 6.65 (d, *J* = 1.4 Hz, 1H, *major and minor*), 4.97 (s, 2H, *major*), 4.93 (s, 2H, *minor*), 4.11 (qd, *J* = 1.0, 7.1, 14.3 Hz, 2H, *major*), 3.95 (qd, *J* = 1.2, 7.1, 14.3 Hz, 2H, *minor*), 3.79-3.76 (m, 3H, *major and minor*), 1.54 (d, *J* = 11.3 Hz, 6H, *major and minor*), 1.22-1.13 (m, 3H, *major and minor*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 176.0, 159.9, 147.2, 136.8, 129.4, 128.9, 128.4, 115.2, 114.7, 61.7, 61.2, 55.8, 50.8, 49.0, 43.5, 41.7, 26.6, 26.0, 14.5.

2-[(4-Methoxybenzyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (123). 

To a solution of dimethylated imidazole regioisomers **122** (62 mg, 0.21 mmol) in 0.7 mL of THF, was added a catalytic amount of PMBCl (1.4 μL, 0.01 mmol) at rt. The resulting solution was then stirred at 70 °C overnight. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc) to yield dimethylated imidazole **123** as a clear light yellow oil (25 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.1 Hz, 1H), 7.11 (dt, *J* = 1.8, 2.8, 8.6 Hz, 1H), 6.88 (dt, *J* = 2.0, 2.8, 8.7 Hz, 2H), 6.74 (d, *J* = 1.3 Hz, 1H), 4.13 (q, *J* = 7.1, 14.2 Hz, 2H), 3.80 (s, 3H), 1.54 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 159.9, 147.2, 136.8, 129.3, 128.4, 115.2, 114.7, 61.1, 55.7, 50.8, 43.5, 26.0, 14.5, 1.5; HRMS (ESCI+) calcd for $C_{17}H_{23}N_2O_3$ (MH^+) 303.1709, found 303.1709.

2-[5-Bromo-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (125). 

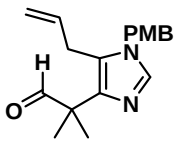
To a solution of protected imidazole **123** (137 mg, 0.45 mmol) in 5.6 mL of CH_2Cl_2-MeOH (5:2) at rt was added benzyltrimethylammonium tribromide (212 mg, 0.54 mmol) and $CaCO_3$ powder (68 mg, 0.68 mmol). The solution was stirred for 5 h, and the solid $CaCO_3$ was filtered off. The filtrate was then concentrated, water was added to the residue, and the aqueous layer was extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to yield bromoimidazole **125** as a pale yellow oil (89 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.11 (dt, *J* = 2.1, 2.9, 8.8 Hz, 1H), 7.05 (dt, *J* = 2.1, 3.0, 8.7 Hz, 2H), 4.99 (s, 2H), 4.13 (q, *J* = 7.1, 14.3 Hz, 2H), 3.76 (s, 3H), 1.58 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 159.9, 143.2, 136.2, 129.1, 127.6, 114.7, 99.9, 61.3, 55.7, 49.7, 43.8, 32.0, 25.7, 23.1, 14.6.

2-[5-Allyl-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (126). 

A solution of bromoimidazole **125** (89 mg, 0.23 mmol) in 1.2 mL of dioxane and a solution of P(*t*-Bu)$_3$ (56 μL, 0.018 mmol, 0.1 M solution in hexane) were added sequentially at rt to a Schlenk tube containing $Pd_2(dba)_3$ (4 mg, 0.005 mmol), CsF (77 mg, 0.506 mmol), and allyltributylstannane (81 μL, 0.250 mmol). The tube was then sealed under argon and the solution was stirred overnight at 100 °C in an oil bath. After

the mixture was cooled to rt, ethyl acetate was added, and the resulting mixture was filtered through a pad of silica gel. The silica gel was washed with ethyl acetate and the total filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to give imidazole **126** (28 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.94 (dt, *J* = 2.2, 2.7, 8.9 Hz, 1H), 6.83 (dt, *J* = 2.3, 2.7, 8.7 Hz, 2H), 5.81-5.69 (m, 1H), 5.04 (dq, *J* = 1.7, 3.4, 10.2 Hz, 1H), 4.91 (s, 2H), 4.86 (dq, *J* = 1.8, 3.5, 17.1 Hz, 1H), 4.08 (q, *J* = 7.1, 14.3 Hz, 2H), 3.78 (s, 3H), 3.20-3.17 (m, 2H), 1.57 (s, 6H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 159.7, 142.3, 135.7, 135.2, 128.6, 128.5, 123.9, 116.6, 114.7, 61.1, 55.7, 48.4, 43.8, 28.1, 26.7, 14.5.

2-[5-Allyl-1-(4-methoxybenzyl)-1*H*-imidazol-4-yl]-2-methylpropionaldehyde (127). To a solution of ester **126** (28 mg, 0.08

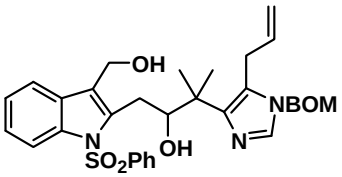


mmol) in 4.0 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.0 M solution in toluene, 0.49 mL, 0.49 mmol) dropwise at -78 °C. The reaction mixture was stirred for 1 h at -78 °C under nitrogen and was quenched with ethyl acetate and saturated NH_4Cl. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield aldehyde **127** (19 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.46 (s, 1H), 7.01 (m, 2H), 6.89 (dt, *J* = 2.2, 2.8, 9.4 Hz, 2H), 5.85-5.72 (m, 1H), 5.10 (dq, *J* = 1.7, 3.2, 10.2 Hz, 1H), 4.95 (s, 2H), 4.87 (dq, *J* = 1.9, 3.4, 17.3 Hz, 1H), 3.82 (s, 3H), 3.20-3.17 (m, 2H), 1.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 159.8, 138.7, 137.0, 135.1, 128.7, 128.2, 125.8,

116.9, 114.8, 77.7, 55.7, 48.6, 48.1, 27.9, 22.3; HRMS (ESCI+) calcd for $C_{18}H_{23}N_2O_2$ (MH^+) 299.1760, found 299.1760.

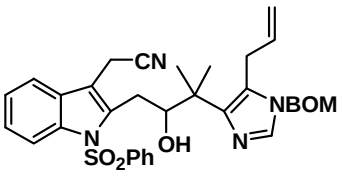
5-Benzenesulfonyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (128). To a solution of methyl indole **98** (114 mg, 0.35 mmol) in 1.2 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.35 mL, 0.70 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, upon which a solution of aldehyde **120** (155 mg, 0.52 mmol) in 1.2 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 20 min and diluted at -78 °C with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (100% EtOAc) to afford lactone **128** as a clear oil (110 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.09 (m, 2H), 7.82 (d, *J* = 7.6 Hz, 2H), 7.61-7.27 (m, 13H), 6.01-5.92 (m, 1H), 5.25 (d, *J* = 2.5 Hz, 2H), 5.10 (d, *J* = 10.2 Hz, 1H), 4.90 (m, 2H), 4.46 (s, 2H), 4.17-4.07 (m, 1H), 3.75-3.63 (m, 2H), 3.48 (dd, *J* = 3.7, 18.4 Hz, 1H), 3.10 (dd, *J* = 12.7, 18.2 Hz, 1H), 1.59 (d, *J* = 7.8 Hz, 6H); HRMS (ESCI+) calcd for $C_{34}H_{34}N_3O_5S$ (MH^+) 596.2220, found 596.2219.

1-(1-Benzenesulfonyl-3-hydroxymethyl-1*H*-indol-2-yl)-3-methyl-3-phenylbutan-2-ol (129). To a



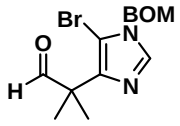
solution of lactone **128** (133 mg, 0.22 mmol) in 11 mL of anhydrous ether was added $LiAlH_4$ (95%, pellets, 20 mg, 2.28 mmol) at 0 °C. The mixture was warmed to rt and stirred for 2.3 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (100% EtOAc) to afford diol **129** as a clear oil (40 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.14 (m, 1H), 7.69-7.66 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.23 (m, 13H), 6.02-5.89 (m, 1H), 5.24 (s, 2H), 5.12 (dd, *J* = 1.48, 10.2 Hz, 1H), 4.89 (dd, *J* = 1.5, 17.2 Hz, 1H), 4.62 (dd, *J* = 12.4, 23.3 Hz, 1H), 4.48 (s, 2H), 4.18-4.07 (m, 1H), 3.67-3.65 (m, 2H), 3.58 (dd, *J* = 1.6, 14.2 Hz, 1H), 2.87 (dd, *J* = 10.7, 14.1 Hz, 1H), 1.53 (d, *J* = 11.1 Hz, 6H); HRMS (ESCI+) calcd for $C_{34}H_{38}N_3O_5S$ (MH^+) 600.2533, found 600.2532.

[1-Benzenesulfonyl-2-(2-hydroxy-3-methyl-3-phenylbutyl)-1*H*-indol-3-yl]-acetonitrile (130). To a



stirred solution of boron trifluoride diethyl etherate (3.6 μL, 0.029 mmol) and TMSCN (12.7 μL, 0.095 mmol) in 0.05 mL of CH_2Cl_2 was added by canula a solution of diol **129** (5.7 mg, 0.010 mmol) in 0.05 mL of CH_2Cl_2 dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 22 min. Saturated $NaHCO_3$ was added and the solution was stirred for 11 min at rt. The organic layer was washed with 1.0 M

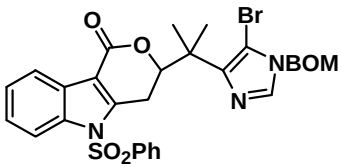
HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to afford nitrile **130** (3.3 mg, 57%) as a light yellow-brown oil. IR (film) 2971, 2242, 1499, 1454, 1366, 1174, 1090, 990, 910, 732, 574, 496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19-8.12 (m, 1H), 7.71-7.67 (m, 2H), 7.57-7.28 (m, 14H), 6.01-5.89 (m, 1H), 5.26 (d, *J* = 3.5 Hz, 2H), 5.12 (dd, *J* = 1.5, 10.2 Hz, 1H), 4.90 (dd, *J* = 1.5, 17.2 Hz, 1H), 4.51 (d, *J* = 1.1 Hz, 2H), 4.02 (dd, *J* = 2.1, 10.8 Hz, 1H), 3.81 (q, J = 13.0, 54.0 Hz, 2H), 3.66-3.64 (m, 1H), 3.48 (dd, *J* = 2.1, 14.2 Hz, 1H), 2.76 (dd, *J* = 10.7, 14.5 Hz, 1H), 1.52 (d, *J* = 13.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 137.7, 136.8, 136.6, 136.1, 135.8, 134.2, 129.8, 129.3, 129.1, 128.7, 128.3, 126.5, 125.2, 125.0, 124.3, 118.5, 118.0, 116.8, 115.5, 112.9, 80.5, 79.3, 74.1, 70.5, 40.9, 30.0, 28.2, 27.7, 24.2, 14.1; HRMS (APCI+) calcd for $C_{35}H_{37}N_4O_4S$ (MH^+) 609.2536, found 609.2536.

2-(1-Benzyloxymethyl-5-bromo-1*H*-imidazol-4-yl)-2-methylpropionaldehyde (131). 

To a solution of ester **119** (378 mg, 0.57 mmol) in 3.4 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.0 M solution in toluene, 3.4 mL, 3.4 mmol) dropwise at -78 °C. The reaction mixture was stirred for 1 h at -78 °C under nitrogen and was quenched with ethyl acetate and saturated NH_4Cl. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50-100% EtOAc/hexanes gradient) to afford aldehyde **131** as a colorless oil (322 mg, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.64 (s, 1H), 7.36-7.24 (m, 5H), 5.29 (s, 2H),

4.49 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 140.0, 138.2, 136.5, 129.0, 128.7, 128.72, 100.5, 74.6, 71.0, 53.9, 47.9, 21.6, 19.5; HRMS (ESCI+) calcd for $C_{15}H_{18}N_2O_2Br$ (MH^+) 337.0552, found 337.0552.

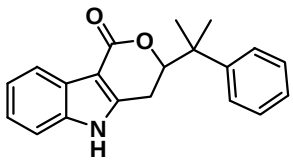
5-Benzenesulfonyl-3-[1-(1-benzyloxymethyl-5-bromo-1*H*-imidazol-4-yl)-1-methylethyl]-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (132).



Method 1. To a solution of methyl indole **98** (75 mg, 0.15 mmol) in 0.5 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.15 mL, 0.30 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, upon which a solution of aldehyde **131** (69 mg, 0.20 mmol) in 0.5 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 20 min and diluted at -78 °C with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc) to afford lactone **132** as a yellow oil (74 mg, 51%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.14-8.10 (m, 2H), 7.83-7.79 (m, 2H), 7.68 (s, 1H), 7.61-7.55 (m, 1H), 7.53-7.46 (m, 2H), 7.41-7.27 (m, 8H), 5.45-5.31 (m, 2H), 5.02 (dd, *J* = 3.6, 12.6 Hz, 1H), 4.56 (s, 2H), 3.48 (dd, *J* = 3.7, 18.3 Hz, 1H), 3.17 (dd, *J* = 12.6, 18.3 Hz, 1H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 146.6, 143.7, 138.3, 137.7, 136.5, 135.1, 130.1, 129.8, 129.1, 128.7, 128.4, 127.0, 126.5, 126.0, 125.5, 121.7, 114.3, 109.8, 99.8, 83.5, 74.5, 70.9, 40.2, 25.7, 25.5, 21.7, 21.6; HRMS (ESCI+) calcd for $C_{31}H_{29}BrN_3O_5S$ (MH^+) 634.1012, found 634.1011.

Method 2. To a solution of lactone **132a** (30 mg, 0.05 mmol) in 0.7 mL of CH_2Cl_2-MeOH (5:2) at rt was added benzyltrimethylammonium tribromide (25 mg, 0.07 mmol) and $CaCO_3$ powder (8 mg, 0.08 mmol). The solution was stirred for 4 h, and the solid $CaCO_3$ was filtered off. The filtrate was then concentrated *in vacuo*. Water was added to the residue, and the aqueous layer was extracted with ethyl acetate. The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to yield brominated lactone **132** as a clear oil (12 mg, 35%).

3-(1-Methyl-1-phenylethyl)-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (133).



Method 1. To a solution of ester **112** (8.4 mg, 0.018 mmol) in 90 μL of anhydrous toluene was added Red-Al (65% weight in toluene, 28 μL, 0.140 mmol) at rt. The reaction mixture was refluxed overnight. After cooling to rt, NaOH (15%) and EtOAc was added. The organic layer was washed with 15% NaOH, water, and brine, and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (20% EtOAc/hexanes) to yield lactone **133** as a yellow oil (2.8 mg, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (bs, 1H), 7.51-6.59 (m, 9H), 3.96 (dd, *J* = 1.7, 10.3 Hz, 1H), 2.95 (dd, *J* = 1.6, 15.0 Hz, 1H), 2.60 (dd, *J* = 10.3, 15.0 Hz, 1H), 1.62 (d, *J* = 17.8 Hz, 6H).

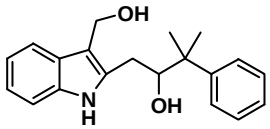
Method 2. See Page 108.

3-Methyl-1-(3-methyl-1*H*-indol-2-yl)-3-phenyl-butan-2-ol (134). To a stirred solution of lactone **112** (8 mg, 0.018 mmol) in 90 μL of anhydrous toluene was added Red-Al (65% weight in toluene, 28 μL, 0.14 mmol) at rt. The reaction mixture was refluxed overnight. After cooling to rt, 15% NaOH and EtOAc was added. The organic layer was was washed with 15% NaOH, water, and brine, and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to yield alcohol **134** (3 mg, 55%). IR (film) 3413, 3060, 2966, 2908, 2849, 1455, 1437, 1308, 1237, 1055, 1002, 908, 732, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (bs, 1H), 7.63-7.24 (m, 7H), 7.13-7.09 (m, 2H), 3.95 (dd, *J* = 1.6, 10.2 Hz, 1H), 2.94 (dd, *J* = 1.7, 15.0 Hz, 1H), 2.59 (dd, *J* = 10.2, 15.0 Hz, 1H), 2.17 (s, 3H), 1.47 (d, *J* = 2.1 Hz, 6H); LRMS-APCI+ *m/z* 294.2 $[M+H]^+$.

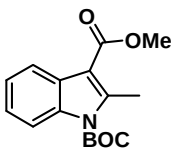
3-(1-Methyl-1-phenyl-ethyl)-1,3,4,5-tetrahydro-pyrano[4,3-b]indol-1-ol (135). To a stirred solution of lactone **112** (23 mg, 0.052 mmol) in 0.52 mL of anhydrous toluene was added Red-Al (65% weight in toluene, 0.1 mL, 0.52 mmol) at rt. The reaction mixture was refluxed overnight. After cooling to rt, 15% NaOH and EtOAc was added. The organic layer was was washed with 15% NaOH, water, and brine, and then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to yield lactol **135** (3.5 mg, 22%). ^1H NMR (300

MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.51-7.06 (m, 9H), 3.97 (dd, *J* = 1.6, 10.4 Hz, 1H), 2.94 (d, *J* = 14.5 Hz, 1H), 2.68 (dd, *J* = 10.6, 14.8 Hz, 1H), 1.27 (s, 6H).

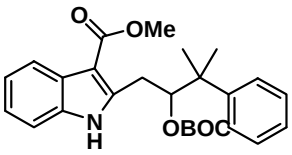
1-(3-Hydroxymethyl-1*H*-indol-2-yl)-3-methyl-3-phenyl-butan-2-ol (136). To a solution of diol **113** (5 mg, 0.01 mmol) in 50 μL of toluene at rt, was added Red-Al (65% weight in toluene, 13 μL, 0.06 mmol). The solution was warmed to 115 °C and refluxed overnight. After cooling the mixture to rt, 15% NaOH and EtOAc was added. The organic layer was washed with 15% NaOH, water, and brine, was then dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes) to yield **136** as a clear oil (6 mg, 73%).



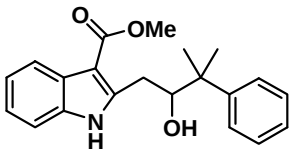
2-Methylindole-1,3-dicarboxylic Acid 1-*tert*-Butyl Ester 3-methyl ester (138). To a solution of indole **110** (1.06 g, 5.6 mmol) in 180 mL of CH_2Cl_2 was added DMAP (684 mg, 5.6 mmol), TEA (0.78 mL, 5.6 mmol), and BOC_2O (1.9 mL, 8.4 mmol) dropwise at rt. The mixture was stirred for 25 min at rt and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford protected indole **138** as a light yellow solid (1.62 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 3.3, 9.4 Hz, 2H), 7.32 (dd, *J* = 3.3, 9.4 Hz, 2H), 3.99 (s, 3H), 3.01 (s, 3H), 1.74 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 150.4, 146.4, 135.9, 127.5, 124.6, 124.0, 121.7, 115.3,



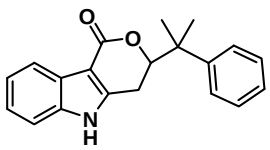
110.6, 85.5, 51.6, 28.6, 15.5; HRMS (ESCI+) calcd for $C_{16}H_{20}NO_4$ (MH^+) 290.1393, found 290.1392.



2-(2-*tert*-Butoxycarbonyloxy-3-methyl-3-phenyl-butyl)-1*H*-indole-3-carboxylic Acid Methyl Ester (139). To a stirred solution of methyl indole **138** in (300 mg, 0.91 mmol) in 3.1 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.91 mL, 1.82 mmol) at -78 °C. The mixture was stirred for 20 min and then a solution of aldehyde **84** (196 mg, 1.32 mmol) in 3.1 mL of in THF was added by canula at -78 °C. The resulting mixture was stirred at -78 °C for 10 min and diluted with saturated $NaHCO_3$. The solution was stirred for 10 min and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The dark orange-brown residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes to 20% EtOAc/hexanes gradient) to afford the *O*-Boc protected indole **139** (170 mg, 99%) as a light brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (bs, 1H), 8.19-8.09 (m, 1H), 7.56-7.19 (m, 10H), 5.30 (dd, *J* = 2.6, 10.1 Hz, 1H), 3.88 (s, 3H), 3.65 (dd, *J* = 2.5, 15.4 Hz, 1H), 2.99 (dd, *J* = 10.1, 15.4 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 6H), 1.25 (s, 9H).

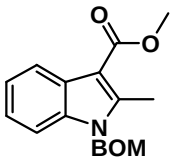


2-(2-Hydroxy-3-methyl-3-phenylbutyl)-1*H*-indole-3-carboxylic Acid Methyl Ester (141). To a solution of *O*-Boc protected indole **139** (117 mg, 0.27 mmol) in 10 mL of anhydrous THF was added $LiAlH_4$ (95%, pellets, 50 mg, 1.25 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the deprotected alcohol **141** as a white solid (73 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (bs, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.47-7.20 (m, 9H), 4.0 (d, *J* = 8.6 Hz, 1H), 3.92 (s, 3H), 3.78 (dd, *J* = 1.6, 15.1 Hz, 1H), 2.82 (dd, *J* = 10.3, 15.1 Hz, 1H), 2.38 (bs, 1H), 1.48 (d, *J* = 5.3 Hz, 6H).

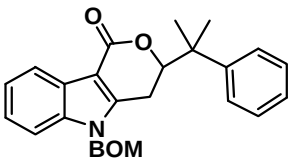


3-(1-Methyl-1-phenylethyl)-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (133).

Method 2. To a solution of ester **141** (73 mg, 0.22 mmol) in 11 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.0 M solution in toluene, 2.60 mL, 2.60 mmol) dropwise at -78 °C. The reaction mixture was warmed to rt overnight under argon and was quenched with ethyl acetate and saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/hexanes) to yield lactone **133** as a yellow oil (18 mg, 27%).



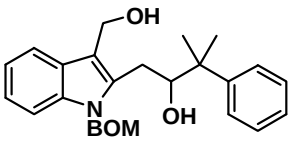
1-Benzyloxymethyl-2-methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (142). To a stirred solution of indole **110** (118 mg, 0.62 mmol) in 12 mL of THF was added NaH (60%, 27 mg, 0.69 mmol) at 0 °C. The mixture was warmed to rt, stirred for 1h and then recooled to 0 °C. BOMCl (90% purity, 0.11 mL, 0.69 mmol) was added, and the resulting mixture was refluxed for 45 min. After cooling the mixture to rt, sat. $NaHCO_3$ was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield **142** as a yellow oil (192 mg, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 1H), 7.42-7.28 (m, 9H), 5.57 (s, 2H), 4.48 (s, 2H), 3.99 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.8, 137.2, 137.0, 129.0, 128.5, 128.1, 127.0, 123.0, 122.6, 122.0, 109.9, 106.1, 72.1, 70.4, 53.9, 51.3, 12.1.



5-Benzyloxymethyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3*H*-pyrano[4,3-b]indol-1-one (143). To a solution of methyl indole **142** (114 mg, 0.35 mmol) in 1.2 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.35 mL, 0.70 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, upon which a solution of aldehyde **84** (155 mg, 0.52 mmol) in 1.2 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 20 min and diluted at -78 °C with saturated $NaHCO_3$.

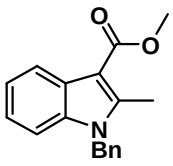
The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (100% EtOAc) to afford lactone **143** as a clear oil (110 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21-8.10 (m, 1H), 7.51-7.28 (m, 13H), 7.16-7.13 (m, 2H), 5.37 (q, *J* = 11.2, 16.8 Hz, 2H), 4.69 (dd, *J* = 3.8, 12.7 Hz, 1H), 4.38 (d, *J* = 1.7 Hz, 2H), 2.73 (dd, *J* = 12.3, 17.0 Hz, 1H), 2.52 (dd, *J* = 3.8, 17.0 Hz, 1H), 1.60 (d, *J* = 2.0 Hz, 6H).

1-(1-Benzyloxymethyl-3-hydroxymethyl-1H-indol-2-yl)-3-methyl-3-phenylbutan-2-ol (144). To a solution of

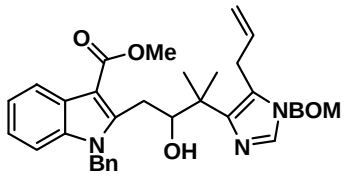


lactone **143** (43 mg, 0.10 mmol) in 5 mL of anhydrous ether was added $LiAlH_4$ (95%, pellets, 8 mg, 0.21 mmol) at 0 °C. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (100% EtOAc) to afford diol **144** as a clear oil (22 mg, 51%); LRMS-ESCI+ *m/z* 448 $[M+H_2O]^+$.

1-Benzyl-2-methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (146). To a stirred solution of indole **110** (2.67 g, 14.11 mmol) in 60 mL of DMF was added NaH (60 % dispersion in mineral oil, 621 mg, 15.52 mmol) at 0 °C. The mixture was warmed to rt, stirred for 1 h and then recooled to 0 °C. BnBr (98% purity, 1.9 mL, 15.52 mmol) was added, and the resulting mixture was



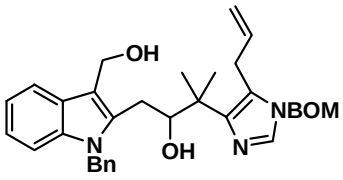
warmed to rt and stirred overnight. H_2O was added and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed w/H_2O (2x), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield **146** as a yellow solid (3.93 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21-8.18 (m, 1H), 7.34-7.22 (m, 7H), 7.03-7.00 (m, 2H), 5.40 (s, 2H), 4.00 (s, 3H), 2.77 (s, 3H); HRMS (ESCI+) calcd for $C_{18}H_{18}NO_2$ (MH^+) 280.1338, found 280.1338.

2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1*H*-indole-3-carboxylic Acid Methyl Ester (147). 

To a solution of methyl indole **146** (403 mg, 1.44 mmol) in 4.9 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 1.44 mL, 2.88 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, upon which a solution of aldehyde **120** (646 mg, 2.17 mmol) in 5.0 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 20 min and diluted at -78 °C with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes to 100% EtOAc gradient) to afford ester alcohol **147** as a yellow gum (679 mg, 81%). IR (film) 3300, 3031, 2948, 1692, 1606, 1532, 1498, 1464, 1454, 1365, 1281, 1216, 1137, 1114, 1076, 909, 735, 697, 497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 7.5 Hz, 1H), 7.43-7.13 (m, 11H), 6.92-6.89 (m, 2H), 5.92-

5.80 (m, 1H), 5.67 (d, J = 17.3 Hz, 1H), 5.45 (d, J = 17.3 Hz, 1H), 5.18 (s, 2H), 5.02 (dd, J = 1.4, 10.2 Hz, 1H), 4.74 (dd, J = 1.5, 17.2 Hz, 1H), 4.37 (s, 2H), 4.21-4.09 (m, 1H), 3.97 (s, 3H), 3.60 (d, J = 4.9 Hz, 2H), 3.50 (dd, J = 2.1, 13.8 Hz, 1H), 2.95 (dd, J = 11.1, 13.7 Hz, 1H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 149.0, 145.5, 137.6, 137.0, 136.7, 136.3, 135.9, 129.1, 128.7, 128.4, 127.7, 126.2, 124.6, 122.7, 122.2, 121.9, 116.5, 110.4, 104.9, 80.8, 73.8, 70.2, 51.3, 47.2, 41.3, 29.4, 28.1, 25.7, 25.0; LRMS-APCI *m/z* 578 (MH^+).

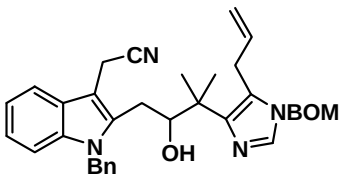
3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-1-(1-benzyl-3-hydroxymethyl-1*H*-indol-2-yl)-3-methyl-butan-2-ol (148).



Method 1. To a solution of ester **147** (236 mg, 0.409 mmol) in 20 mL of anhydrous CH_2Cl_2 was added DIBAL-H (1.5 M in toluene, 0.9 mL, 1.35 mmol) dropwise at -78 °C. The resulting solution was stirred for 45 min at -78 °C under nitrogen, was quenched with ethyl acetate at -78 °C, and then saturated NH_4Cl was added. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (75% EtOAc/hexanes) to afford diol **148** as a yellow oil (176 mg, 78%). IR (film) 3318, 3060, 3031, 2976, 2932, 2873, 1732, 1638, 1605, 1562, 1496, 1468, 1363, 1265, 1216, 1151, 1076, 992, 909, 738, 698 cm^{-1}; HRMS (ESCI+) calcd for $C_{35}H_{40}N_3O_3$ (MH^+) 550.3070, found 550.3070.

Method 2. To a solution of ester **147** (145 mg, 0.25 mmol) in 12 mL of anhydrous CH_2Cl_2 was added DIBAL-H (20% weight in toluene, 0.62 mL, 0.75 mmol) dropwise at -78 °C. The resulting solution was stirred for 45 min at -78 °C under nitrogen, and then an additional amount of DIBAL-H (20% weight in toluene, 0.62 mL, 0.75 mmol) was added and the mixture was stirred for 1.25 h at -78 °C . The reaction mixture was quenched with ethyl acetate at -78 °C and then saturated NH_4Cl was added. The resulting mixture was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (75% EtOAc/hexanes) to afford diol **148** as a yellow oil (99 mg, 72%).

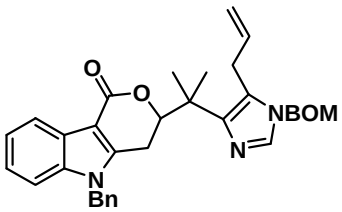
Method 3. To a solution of ester **147** (73 mg, 0.13 mmol) in 6 mL of anhydrous ether was added $LiAlH_4$ (95%, pellets, 17 mg, 0.43 mmol) at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction was quenched with H_2O/15% NaOH/H_2O (1:1:3; 17 μL, 17 μL, 51 μL). The resulting mixture was stirred for 10 min, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc) to afford diol **148** as a yellow oil (39 mg, 69%).



{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetonitrile (149). To a stirred solution of boron trifluoride diethyl etherate (0.11 mL, 0.79 mmol) and TMSCN (0.15 mL, 1.52 mmol) in 1.4 mL of CH_2Cl_2 was added by canula a solution of diol **148** (111 mg, 0.20 mmol) in 1.5 mL of

CH_2Cl_2 dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Saturated $NaHCO_3$ was added and the solution was stirred for 10 min at rt. The organic layer was washed with 1.0 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (50% EtOAc/hexanes to 75% EtOAc/hexanes gradient) to afford nitrile **149** (70 mg, 62%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67-7.65 (m, 1H), 7.51 (s, 1H), 7.42-7.16 (m, 14H), 6.93 (d, *J* = 6.4 Hz, 2H), 5.93-5.81 (m, 1H), 5.54 (d, *J* = 17.3 Hz, 1H), 5.35 (d, *J* = 17.3 Hz, 1H), 5.21 (s, 2H), 5.05 (dd, *J* = 1.4, 10.2 Hz, 1H), 4.80 (dd, *J* = 1.4, 17.2 Hz, 1H), 4.45 (s, 2H), 3.92 (q, *J* = 18.0, 33.1 Hz, 2H), 3.80 (d, *J* = 1.9 Hz, 1H), 2.87 (dd, *J* = 2.1, 15.1 Hz, 1H), 2.71 (dd, *J* = 10.6, 14.9 Hz, 1H), 1.41 (d, *J* = 3.3 Hz, 6H). LRMS ($C_{36}H_{38}N_4O_2$) calcd 558.7 (MH^+), found 559.3.

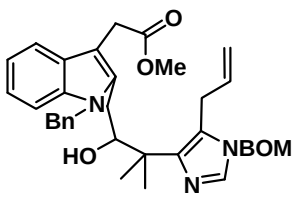
3-[1-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-1-methylethyl]-5-benzyl-4,5-dihydro-3H-pyrano[4,3-b]indol-1-one (150). To a solution of methyl indole **146**



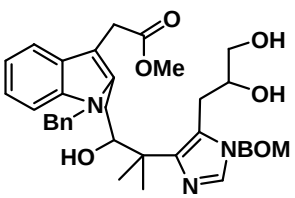
(227 mg, 0.81 mmol) in 3.5 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 0.81 mL, 1.62 mmol) at -78 °C. The resulting dark red solution was stirred for 20 min, upon which a solution of aldehyde **120** (364 mg, 1.22 mmol) in 3.5 mL of THF was added by canula at -78 °C. The resulting mixture was warmed to rt and stirred overnight. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and

concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes to 100% EtOAc gradient) to afford ester alcohol **150** (50 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.39-7.20 (m, 12H), 6.99-6.97 (m, 2H), 5.97-5.84 (m, 1H), 5.22 (d, *J* = 11.0 Hz, 4H), 5.02 (dd, *J* = 1.4, 10.2 Hz, 1H), 4.85-4.79 (m, 2H), 4.42 (s, 2H), 3.78 (dd, *J* = 5.3, 17.9 Hz, 1H), 3.61 (dd, *J* = 5.3, 17.8 Hz, 1H), 2.98-2.75 (m, 2H), 1.59 (s, 6H); LRMS-ESCI+ *m/z* 546.3 (MH^+).

{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetic Acid (151). To a solution of nitrile **149** (24 mg, 0.043 mmol) in 0.74 mL of EtOH-H_2O (4:1) was added aqueous KOH (85%, 28 μL, 0.43 mmol). The mixture was refluxed overnight. After cooling the mixture to rt, 15% NaOH (0.59 mL) was added, and the aqueous layer was extracted with Et_2O. The aqueous layer was acidified under ice cooling and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford acid **151**, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 1H), 7.48 (s, 1H), 7.41-7.14 (m, 13H), 6.90-6.87 (m, 2H), 5.89-5.79 (m, 1H), 5.40 (d, *J* = 17.5 Hz, 1H), 5.21 (d, *J* = 17.8 Hz, 1H), 5.04 (dd, *J* = 1.4, 10.1 Hz, 1H), 4.78 (dd, *J* = 1.4, 17.2 Hz, 1H), 3.90-3.68 (m, 2H), 3.54 (d, *J* = 5.1 Hz, 2H), 2.82 (d, *J* = 14.0 Hz, 1H), 2.69 (dd, *J* = 10.4, 15.0 Hz, 1H), 1.39 (d, *J* = 2.9 Hz, 6H).

{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetic Acid Methyl Ester (152). 

To a solution of crude acid **151** (25 mg, 0.043 mmol) in 0.88 mL of MeOH was added aqueous $TMSCHN_2$ (2.0 M solution in ether, 0.43 mL, 0.86 mmol) dropwise at 0 °C. The mixture was stirred for 15 min and then concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (75% EtOAc/hexanes) to yield ester **152** (16 mg, 63% for 2 steps) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.57 (m, 1H), 7.45 (s, 1H), 7.42-7.09 (m, 12H), 6.91-6.85 (m, 2H), 5.95-5.79 (m, 1H), 5.52 (d, *J* = 17.4 Hz, 1H), 5.35 (d, *J* = 17.4 Hz, 1H), 5.18 (s, 2H), 5.03 (dd, *J* = 1.3, 10.1 Hz, 1H), 4.79 (dd, *J* = 1.6, 17.1 Hz, 1H), 4.39 (s, 2H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.81 (q, *J* = 15.5, 26.0 Hz, 2H), 3.70 (s, 3H), 3.57 (d, *J* = 5.2 Hz, 2H), 2.91 (dd, *J* = 2.0, 14.9 Hz, 1H), 2.70 (dd, *J* = 10.7, 15.1 Hz, 1H), 1.45 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 145.2, 138.7, 137.3, 137.0, 136.7, 136.5, 136.0, 129.1, 129.0, 128.7, 128.4, 128.3, 127.4, 126.3, 124.6, 121.7, 119.8, 118.6, 116.5, 110.0, 106.2, 106.2, 79.7, 73.8, 70.2, 52.5, 47.1, 41.2, 31.2, 28.6, 28.2, 25.5, 24.7; HRMS (ESCI+) calcd for $C_{37}H_{42}N_3O_4$ 592.3176 (MH^+), found 592.3175.

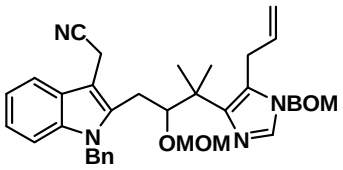
(1-Benzyl-2-{3-[1-benzyloxymethyl-5-(2,3-dihydroxy-propyl)-1*H*-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (185). 

To a solution of alkene **152** (3.5 mg, 0.0059 mmol) in 0.1 mL of H_2O and 0.2 mL of

acetone was added *N*-methylmorpholine-*N*-oxide (3.5 mg, 0.0296 mmol) and OsO_4 (4% weight in H_2O, 2 μL, 0.2957 μmol) at rt. The solution was stirred overnight at rt and then the solution was cooled to concentrated, and the aqueous layer was extracted with EtOAc. The extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (100% EtOAc) to yield an inseparable mixture of diastereomers of diol **185** as a colorless oil (5.0 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.48 (m, 1H), 7.45-7.42 (m, 2H), 7.39-7.32 (m, 5H), 7.27-7.11 (m, 10H), 6.89 (d, *J* = 7.1 Hz, 2H), 5.53 (d, *J* = 17.1 Hz, 1H), 5.35 (d, *J* = 17.3 Hz, 2H), 5.23-5.12 (m, 3H), 4.67 (d, *J* = 6.4 Hz, 1H), 4.40 (s, 2H), 4.30 (d, *J* = 20.1 Hz, 1H), 3.97 (d, *J* = 16.0 Hz, 1H), 3.86-3.78 (m, 5H), 3.77-3.66 (m, 2H), 3.05-2.79 (m, 4H), 1.26 (d, *J* = 2.4 Hz, 6H); LRMS-ESCI+ *m/z* 626.3 (MH^+).

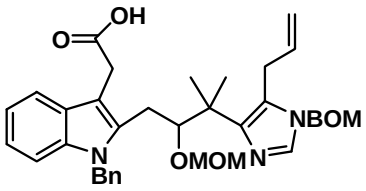
(1-Benzyl-2-{3-[1-benzyloxymethyl-5-(2-oxoethyl)-1*H*-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1H-indol-3-yl)-acetic Acid Methyl Ester (153). To a solution of alkene **152** (8 mg, 14 μmol) in 0.23 mL of H_2O and 0.45 mL of acetone was added *N*-methylmorpholine-*N*-oxide (16 mg, 68 μmol) and OsO_4 (4% weight in H_2O, 9 μL, 0.68 μmol) at rt. The solution was stirred overnight at rt and then cooled to 0 °C, upon which $NaIO_4$ (7.2 mg, 34 μmol) was added. The resulting mixture was warmed to rt and was stirred for 1 h. Saturated sodium sulfite was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to afford aldehyde **153** (5 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m,

15H), 5.50 (d, *J* = 17.3 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 5.19-5.10 (m, 2H), 4.42-4.37 (m, 2H), 4.32 (d, *J* = 2.4 Hz, 1H), 4.18-4.08 (m, 1H), 3.97-3.77 (m, 5H), 3.0-2.83 (m, 2H), 2.60 (dd, *J* = 8.2, 15.8 Hz, 1H), 1.40 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 146.3, 138.0, 137.4, 136.8, 136.6, 136.4, 136.1, 129.2, 129.0, 128.6, 128.2, 127.9, 127.7, 126.6, 126.1, 122.0, 120.0, 118.6, 118.4, 110.1, 106.7, 99.1, 95.0, 74.4, 73.7, 70.1, 52.8, 47.2, 41.9, 41.8, 30.8, 30.1, 28.2, 26.9, 26.1, 21.4; HRMS (ESCI+) calcd for $C_{36}H_{40}N_3O_5$ 594.2969 (MH^+), found 594.2968.

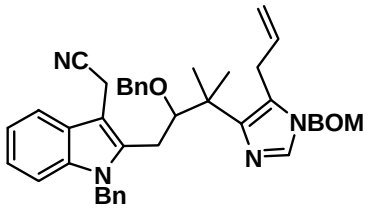
{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-methoxymethoxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetonitrile (154). 

To a stirred solution of neopentyl alcohol **149** (8 mg, 0.014 mmol) in 0.7 mL of methylene chloride was added dropwise DIPEA (5 μL, 0.028 mmol) and NaI (4 mg, 0.028 mmol) at rt. The mixture was then cooled to 0 °C, and MOMCl (2 μL, 0.021 mmol) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C, warmed to rt and stirred overnight. Saturated $NaHCO_3$ and methylene chloride were added. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (75% EtOAc/hexanes) to afford protected neopentyl alcohol **154** as a yellow oil (5 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (t, *J* = 7.6 Hz, 1H), 7.54-6.84 (m, 25H), 6.70 (d, *J* = 3.9 Hz, 2H), 5.86-5.68 (m, 1H), 5.41-4.96 (m, 5H), 4.74 (t, *J* = 17.7 Hz, 1H), 4.49-4.04 (m, 6H), 3.84 (d, *J*

= 10.9 Hz, 1H), 3.56-3.29 (m, 4H), 2.27-2.07 (m, 2H), 1.42-1.34 (m, 6H). LRMS-APCI *m/z* 603 (MH^+).

{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-methoxymethoxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetic Acid (155). 

To a solution of nitrile **154** (27 mg, 0.045 mmol) in 0.76 mL of EtOH-H_2O (4:1) was added aqueous KOH (85%, 30 μL, 0.45 mmol). The mixture was refluxed overnight. After cooling the mixture to rt, 15% NaOH (0.61 mL) was added, and the aqueous layer was extracted with Et_2O. The aqueous layer was acidified under ice cooling and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford acid **155**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 1H), 7.54 (s, 1H), 7.40-7.13 (m, 13H), 6.84 (d, *J* = 7.9 Hz, 2H), 5.91-5.79 (m, 1H), 5.43 (d, *J* = 3.8 Hz, 2H), 5.17 (s, 2H), 5.02 (dd, *J* = 1.3, 8.9 Hz, 1H), 4.77 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.44-4.05 (m, 6H), 3.87 (d, *J* = 1.1 Hz, 2H), 3.58-3.55 (m, 2H), 3.09 (s, 2H), 2.88-2.79 (m, 1H), 2.73-2.68 (m, 1H), 1.47-1.38 (m, 6H).

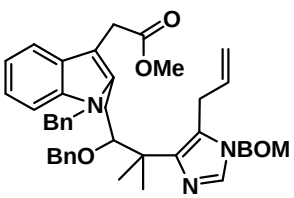
{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-benzyloxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetonitrile (158). 

To a stirred solution of neopentyl alcohol **149** (9 mg, 0.016 mmol) in 0.8 mL of THF was added LiHMDS (1.0 M

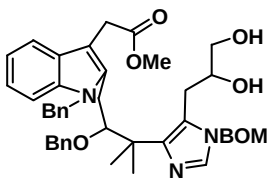
solution in THF, 19 μL, 0.019 mmol) and benzyl bromide (98% purity, 2 μL, 0.019 mmol) at -78 °C. The resulting mixture was stirred for 45 min at rt and H_2O was added. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexanes) to afford protected neopentyl alcohol **158** as a cream-colored solid (5 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1H), 7.44-7.18 (m, 19H), 6.87 (d, *J* = 7.3 Hz, 2H), 5.88-5.80 (m, 1H), 5.53 (d, *J* = 17.4 Hz, 1H), 5.34-5.15 (m, 4H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.77 (d, *J* = 17.2 Hz, 1H), 4.42 (d, *J* = 9.18 Hz, 2H), 4.22-4.08 (m, 2H), 3.76 (d, *J* = 8.6 Hz, 1H), 3.54-3.46 (m, 3H), 3.37-3.32 (m, 1H), 2.56-2.42 (m, 2H), 1.37 (d, *J* = 14.5 Hz, 6H). LRMS-APCI *m/z* 649 (MH^+).

{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-benzyloxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetic Acid (159). To a solution of nitrile **158** (36 mg, 0.055 mmol) in 1.0 mL of EtOH-H_2O (4:1) was added aqueous KOH (85%, 37 μL, 0.55 mmol) and the mixture was refluxed overnight. After cooling the mixture to rt, 15% NaOH (0.8 mL) was added, and the aqueous layer was extracted with Et_2O. The aqueous layer was acidified under ice cooling and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford acid **159**, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 1H), 7.48-7.68 (m, 15H), 5.77-5.73 (m, 1H), 5.38-5.08 (m, 6H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 17.2 Hz, 1H), 4.46 (s, 2H), 3.98 (dd, *J* = 3.7, 11.0 Hz, 1H),

3.59-3.57 (m, 4H), 3.31-3.24 (m, 1H), 2.20 (d, *J* = 14.5 Hz, 1H), 1.98 (dd, *J* = 11.1, 15.1 Hz, 1H), 1.34-1.25 (m, 6H).

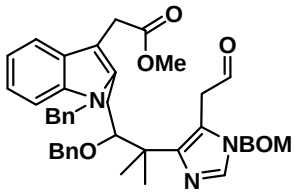


{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-benzyloxy-3-methylbutyl]-1-benzyl-1*H*-indol-3-yl}-acetic Acid Methyl Ester (157). To a solution of crude acid **159** (30 mg, 0.045 mmol) in 2.2 mL of MeOH was added aqueous $TMSCHN_2$ (2.0 M solution in ether, 90 μL, 0.18 mmol) dropwise at 0 °C. The mixture was stirred for 15 min and then concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (75% EtOAc/hexanes) to yield ester **157** (11 mg, 29% for 2 steps).

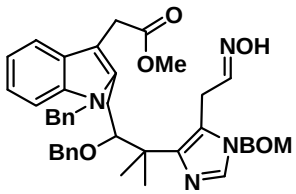


(1-Benzyl-2-{2-benzyloxy-3-[1-benzyloxymethyl-5-(2,3-dihydroxy-propyl)-1*H*-imidazol-4-yl]-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (160). To a solution of alkene **157** (6 mg, 9 μmol) in 0.15 mL of H_2O and 0.30 mL of acetone was added *N*-methylmorpholine-*N*-oxide (5 mg, 44 μmol) and OsO_4 (4% weight in H_2O, 3 μL, 0.44 μmol) at rt. The solution was stirred overnight at rt and was concentrated. The remaining aqueous layer was extracted with EtOAc. The organic extract was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (100% EtOAc) to yield an inseparable mixture of

diastereomers of diol **160** as a colorless oil (6 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.72 (m, 1H), 7.60-7.51 (m, 2H), 7.37-7.02 (m, 26H), 6.94-6.86 (m, 4H), 6.78 (d, *J* = 7.1 Hz, 1H), 5.41-5.11 (m, 6H), 4.46-4.19 (m, 7H), 3.96 (d, *J* = 10.8 Hz, 1H), 3.88 (d, *J* = 14.2 Hz, 3H), 3.63-3.38 (m, 2H), 3.19-2.79 (m, 3H), 1.14 (d, *J* = 34.3 Hz, 6H).



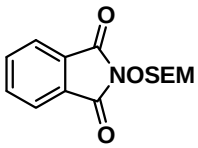
(1-Benzyl-2-{2-benzyloxy-3-[1-benzyloxymethyl-5-(2-oxo-ethyl)-1*H*-imidazol-4-yl]-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (161). To a solution of diol **160** (5 mg, 7 μmol) in 0.12 mL of H_2O and 0.20 mL of acetone was added sodium periodate (4 mg, 17 μmol) at 0 °C. The solution was warmed to rt and stirred for 30 min. Saturated $NaHCO_3$ and EtOAc were added, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford aldehyde **161**, which was used without further purification.



(1-Benzyl-2-{2-benzyloxy-3-[1-benzyloxymethyl-5-(2-hydroxyiminoethyl)-1*H*-imidazol-4-yl]-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (162). To a solution of crude aldehyde **161** (5 mg, 7 μmol) in 1.0 mL of methanol and 0.2 mL of H_2O was added sodium acetate (1 mg, 15 μmol) and hydroxylamine hydrochloride (0.1 mg, 14 μmol) at rt. The resulting solution was stirred overnight, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel

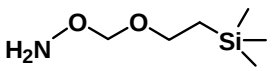
(100% EtOAc) to yield oxime **162** as a clear oil (2 mg, 41% for 2 steps). IR (film) 3412, 3054, 2986, 2928, 2854, 2304, 1731, 1455, 1422, 1265, 1056, 1028, 896, 738, 704, 515 cm^{-1}; LRMS-APCI *m/z* 699 (MH^+).

2-(2-Trimethylsilanylethoxymethoxy)-isoindole-1,3-dione



(165). To a solution of *N*-hydroxyphthalimide (**164**, 200 mg, 1.23 mmol) in 12 mL of methylene chloride was added DIPEA (0.86 mL, 4.92 mmol) and SEMCl (0.65 mL, 3.68 mmol) at rt. The resulting solution was stirred overnight and H_2O was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield protected phthalimide **165** as a white solid (359 mg, 100%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.86-7.80 (m, 2H), 7.77-7.71 (m, 2H), 5.16 (s, 2H), 4.06-4.00 (m, 2H), 1.01-0.96 (m, 2H), 0.06 (s, 9H).

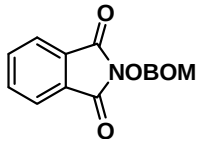
***O*-(2-Trimethylsilanylethoxymethyl)-hydroxylamine**



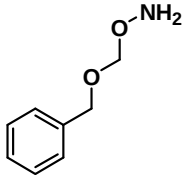
(166). To a solution of protected phthalimide **165** (50 mg, 0.17 mmol) in 5 mL of EtOH was added hydrazine (6 μL, 0.19 mmol) at rt. The resulting solution was warmed to 40 °C and stirred for 1 h. After cooling the mixture to rt, the solution was acidified to pH 1-2 with 1.0 M HCl solution and CH_2Cl_2 and H_2O were added. The aqueous layer was basified with saturated $NaHCO_3$ and extracted with Et_2O.

The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield protected hydroxylamine **166** (22 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (bs, 2H), 4.77 (d, J = 0.7 Hz, 2H), 3.71-3.65 (m, 2H), 1.02-0.97 (m, 2H), 0.04 (d, J = 0.7 Hz, 9H).

2-Benzyloxymethoxyisoindole-1,3-dione (167). To a solution of *N*-hydroxyphthalimide (**164**, 200 mg, 1.23 mmol) in 12 mL of methylene chloride was added DIPEA (0.86 mL, 4.92 mmol) and SEMCl (0.65, 3.68 mmol) at rt. The resulting solution was stirred overnight and H_2O was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield protected phthalimide **167** as a white solid (359 mg, 100%). HRMS (ESCI+) calcd for $C_{16}H_{14}NO_4$ 284.0924 (MH^+), found 284.0923.

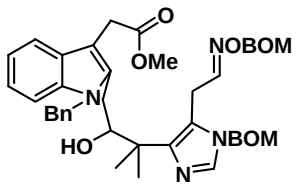


***O*-Benzyloxymethylhydroxylamine (168).** To a solution of protected phthalimide **167** (50 mg, 0.17 mmol) in 5 mL of EtOH was added hydrazine (6 μL, 0.19 mmol) at rt. The resulting solution was warmed to 40 °C and stirred for 1 h. After cooling the mixture to rt, the solution was acidified to pH 1-2 with 1.0 M HCl solution, and CH_2Cl_2 and H_2O were added. The



aqueous layer was basified with saturated $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to yield *O*-protected hydroxylamine phthalimide **168** (22 mg, 79%) as a clear colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 5.55 (s, 2H), 4.86 (d, J= 0.4 Hz, 2H), 4.68 (s, 2H).

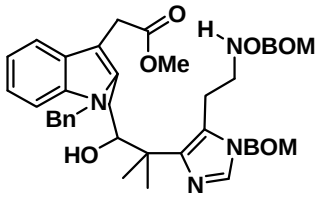
(1-Benzyl-2-{3-[5-(2-benzyloxymethoxyimino-ethyl)-1-benzyloxymethyl-1*H*-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (169).



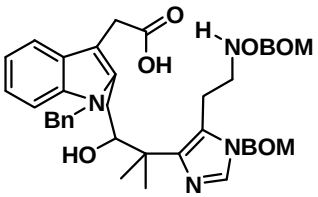
To a solution of aldehyde **153** (5 mg, 0.008 mmol) in 1.20 mL of MeOH and 0.23 mL of H_2O was added sodium acetate (1.5 mg, 0.018 mmol) and hydroxylamine **xx** (2.6 mg, 0.017 mmol) at rt. The resulting solution was stirred overnight, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (100% EtOAc) to afford oxime ether **169** (6 mg, 98%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.54 (m, 1H), 7.46-7.04 (m, 18H), 6.88 (d, *J* = 6.1 Hz, 2H), 5.46 (d, *J* = 17.3 Hz, 1H), 5.33-5.28 (m, 2H), 5.21 (s, 2H), 5.11 (s, 2H), 4.62 (s, 2H), 4.38 (s, 2H), 3.97-3.72 (m, 4H), 3.69 (s, 3H), 2.92 (d, *J* = 13.1 Hz, 1H), 2.68 (dd, *J* = 10.9, 15.1 Hz, 1H), 1.46 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 150.4, 145.8, 138.6, 138.1, 137.1, 136.9, 136.6, 129.1, 128.8, 128.4, 128.2, 127.5, 126.3, 122.7, 121.8, 121.7, 119.9, 118.6, 110.0, 106.4, 96.8, 79.2, 73.9, 71.0, 70.6,

70.2, 53.9, 52.6, 47.1, 41.3, 31.1, 30.1, 28.5, 25.6, 25.4, 25.1, 23.1, 14.6; HRMS (ESCI+) calcd for $C_{44}H_{49}N_4O_6$ 729.3653 (MH^+), found 729.3652.

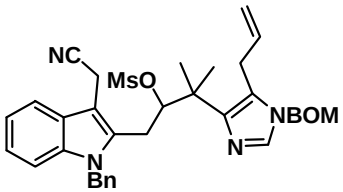
(1-Benzyl-2-{3-[5-(2-benzyloxymethoxyaminoethyl)-1-benzyloxymethyl-1*H*-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (170).



To a stirred solution of oxime ether **169** (2 mg, 0.003 mmol) in 0.21 mL of MeOH was added $Na(CN)BH_3$ (1.6 mg, 0.025 mmol) and methyl orange at rt. HCl (conc.) was added dropwise over 0.5 h, until the pink color persisted. The resulting mixture was stirred at rt overnight and was then concentrated *in vacuo*. H_2O was added and the pH was adjusted to 9 with 15% KOH solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford *O*-benzylhydroxylamine **170**, which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.56 (m, 1H), 7.46 (s, 1H), 7.44-7.10 (m, 21H), 6.89-6.87 (m, 2H), 5.48 (d, *J* = 17.2 Hz, 1H), 5.33 (s, 1H), 5.23 (s, 2H), 5.15 (s, 1H), 4.88 (s, 2H), 4.67 (s, 2H), 4.40 (s, 2H), 3.96-3.92 (m, 1H), 3.80 (q, *J* = 15.5 Hz, 1H), 3.70 (s, 3H), 3.19-2.95 (m, 4H), 2.90 (dd, *J* = 1.6, 14.6 Hz, 1H), 2.70 (dd, *J* = 10.9, 14.8 Hz, 1H), 1.46 (s, 6H); HRMS (ESCI+) calcd for $C_{44}H_{51}N_4O_6$ 731.3809 (MH^+), found 731.3809.

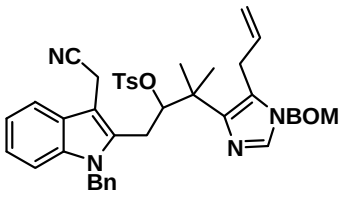


(1-Benzyl-2-{3-[5-(2-benzyloxymethoxyamino-ethyl)-1-benzyloxymethyl-1*H*-imidazol-4-yl]-2-hydroxy-3-methyl-butyl}-1*H*-indol-3-yl)-acetic Acid (171). To a stirred solution of ester **170** (5 mg, 0.007 mmol) in 1.2 mL of THF and 0.6 mL of $H_2O$was added NaOH (0.3 mg, 0.008 mmol) at rt. The resulting mixture was stirred at rt overnight and made acidic with 1.0 M HCl. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (75% EtOAc/hexanes) to afford acid **171** (6 mg, 98%). HRMS (ESCI+) calcd for $C_{43}H_{49}N_4O_6$ 717.3653 (MH^+), found 717.3652.

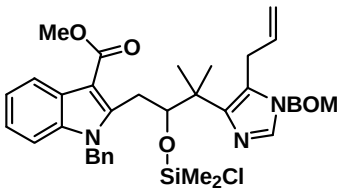


Methanesulfonic Acid 2-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-1-(1-benzyl-3-cyanomethyl-1*H*-indol-2-ylmethyl)-2-methylpropyl Ester (174). To a solution of neopentyl alcohol **149**(11 mg, 0.02 mmol) in 1.0 mL of anhydrous pyridine was added MsCl (9.0 μL, 0.12 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred overnight under nitrogen. H_2O was added, and the aqueous layer was extracted with Et_2O. The combined ethereal layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (75% EtOAc/hexanes) to yield mesylate **174** (6 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 1H), 7.48 (s, 1H), 7.43-7.12 (m, 14H), 6.87 (d, *J* = 6.7 Hz, 2H), 5.91-5.81 (m, 1H), 5.53-5.32 (m, 3H), 5.17 (s, 2H), 5.05 (dd, *J* = 1.3, 10.3 Hz, 1H), 4.79

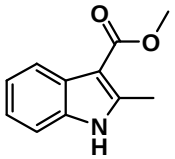
(dd, *J* = 1.3, 17.3 Hz, 1H), 3.89 (q, *J* = 18.0, 32.9 Hz, 2H), 3.58 (d, *J* = 5.1 Hz, 2H), 3.08 (dd, *J* = 11.4, 15.7 Hz, 1H), 2.92 (dd, *J* = 2.4, 15.6 Hz, 1H), 2.14 (s, 3H), 1.51 (d, *J* = 10.3 Hz, 6H). LRMS-APCI *m/z* 637 (MH^+).

Toluene-4-sulfonic Acid 2-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-1-(1-benzyl-3-cyanomethyl-1*H*-indol-2-ylmethyl)-2-methylpropyl Ester (175). 

To a solution of neopentyl alcohol **149** (5.0 mg, 0.008 mmol) in 80 μL of anhydrous CH_2Cl_2 was added *p*-TsCl (2.0 mg, 0.009 mmol), DMAP (0.2 mg, 0.002 mmol), and TEA (4.0 μL, 0.025 mmol) at rt. The reaction mixture stirred for 1 h and $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to yield tosylate **175** (4.5 mg, 74%) as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.44 (m, 2H), 7.38-7.14 (m, 14H), 7.04-6.92 (m, 1H), 6.78-6.69 (m, 3H), 5.90-5.80 (m, 1H), 5.63 (d, *J* = 8.7 Hz, 1H), 5.37-5.02 (m, 5H), 4.82 (d, *J* = 18.1 Hz, 1H), 4.39 (q, *J* = 13.6, 21.4 Hz, 2H), 3.61-3.50 (m, 4H), 2.97-2.75 (m, 2H), 2.22 (s, 3H), 1.53 (d, *J* = 2.1 Hz, 6H).

2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-chloro-3-methylbutyl]-1-benzyl-1*H*-indole-3-carboxylic Acid Methyl Ester (177). 

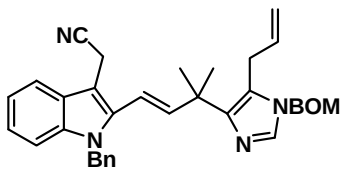
To a solution of $InCl_3$ (0.1 mg, 0.660 μmol) and benzil (3.0 mg, 0.120 mmol) in 0.030 mL of methanol and 0.55 mL of CH_2Cl_2 was added $HSiMe_2Cl$ (1.5 μL, 0.013 mmol). The mixture was stirred at rt for 1 h. A solution of neopentyl alcohol **147** (7.0 mg, 0.012 mmol) in 0.025 mL CH_2Cl_2 was added, and the resulting mixture was stirred at rt for 15 min. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (75% EtOAc/hexanes) to yield the (dimethyl)chlorosilyl ether intermediate **177** (1.0 mg, 12%) as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87-7.84 (m, 1H), 7.76-7.71 (m, 1H), 7.58-7.53 (m, 1H), 7.40-7.35 (m, 4H), 7.23-7.20 (m, 4H), 7.14-7.09 (m, 2H), 6.89-6.83 (m, 2H), 5.93-5.77 (m, 1H), 5.66 (d, *J* = 16.7 Hz, 2H), 5.41 (d, *J* = 18.1 Hz, 1H), 5.22 (s, 2H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 6.1 Hz, 1H), 4.43 (s, 2H), 4.25 (dd, *J* = 3.4, 5.6 Hz, 2H), 3.60 (d, *J* = 9.5 Hz, 2H), 3.44 (s, 3H), 3.03 (d, *J* = 15.2 Hz, 1H), 2.65-2.57 (m, 1H), 1.46 (d, *J* = 7.1 Hz, 6H). LRMS-APCI *m/z* 670 (MH^+).

2-Methyl-1*H*-indole-3-carboxylic Acid Methyl Ester (110). 

Method 2. To a 3-neck round bottom flask fitted with a coldfinger condenser at -78 °C, was condensed ammonia. A solution of benzylated indole **146** (50 mg, 0.18 mmol) in 6 mL of THF was added to the ammonia *via* a gas-tight

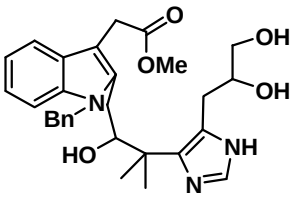
syringe, followed by Li wire (13 mg, 1.8 mmol). After approximately 5-10 min., the color of the solution changed from pale yellow to blue and the mixture was stirred for 35 min. at -78 °C. Saturated NH_4Cl was added slowly and the solution was allowed to warm to rt slowly over 5-6 h. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to afford the free indole **110** as a white solid (26 mg, 77%).

{2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-3-methyl-but-1-enyl]-1-benzyl-1*H*-indol-3-yl}-acetonitrile (184). To a stirred solution of benzylated

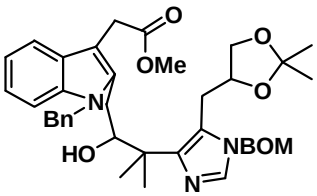


imidazole **174** (6 mg, 0.009 mmol) in 0.26 mL of DMSO was added *t*-BuOK (1.0 M solution in THF, 90 μL, 0.09 mmol) at rt. The resulting yellow solution was stirred for 5 min and then O_2 was bubbled through the mixture at rt for 30 min. The reaction mixture was quenched with saturated NH_4Cl and the aqueous layer was extracted with Et_2OAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel to afford alkene **184** (4 mg, 79%) as a yellow oil. IR (film) 3419, 2956, 2944, 2861, 2351, 1724, 1451, 1368, 1238, 1166, 1095, 1024, 1095, 1024, 988, 846, 739, 697, 662 cm^{-1}.

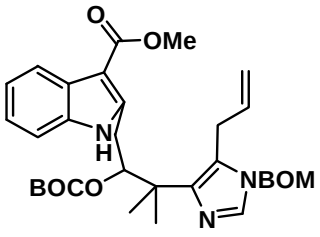
(1-Benzyl-2-{3-[5-(2,3-dihydroxy-propyl)-1H-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1H-indol-3-yl)-acetic Acid Methyl Ester (186). To an ampule containing benzylated imidazole **185** (3 mg, 0.0045 mmol) in 1 mL of MeOH was added a catalytic amount of 5% Pd/C at rt. The ampule was then placed in a high pressure reactor (6 atm) andwas stirred overnight under H_2 gas. The reaction mixture was filtered through a pad of celite, washed with CH_2Cl_2, and concentrated *in vacuo* to afford deprotected imidazole **186** (2 mg, 78%). LRMS-ESCI+ *m/z* 506.3 (MH^+).



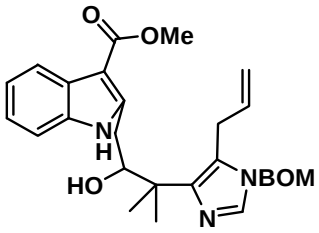
(1-Benzyl-2-{3-[1-benzyloxymethyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1*H*-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1*H*-indol-3-yl)-acetic Acid Methyl Ester (188). To a solution of diol **185** (3 mg, 0.0048 mmol) in 0.24 mL of dry acetone was added concentrated H_2SO_4 (1 μL). The mixture was stirred for 0.5 h at rt and a few drops of saturated $NaHCO_3$ (20 mL) were added. The mixture was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (100% EtOAc) to give acetonide **188** as a colorless oil (3 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.55 (m, 1H), 7.45 (d, *J*= 5.2 Hz, 1H), 7.38-7.09 (m, 11H), 6.89 (d, *J*= 6.9 Hz, 2H), 5.62 (dd, *J* = 3.0, 3.1 Hz, 1H), 5.51 (dd, *J* = 9.1, 9.4 Hz, 1H), 5.33 (dd, *J* = 3.7, 3.8 Hz, 1H), 5.18 (dd, *J* = 1.6, 1.7 Hz, 1H), 4.43-4.22 (m, 3H), 4.10-4.04 (m, 1H), 3.96 (q, *J* = 4.5, 8.6 Hz, 1H), 3.84 (d, *J* = 15.5 Hz, 1H), 3.78 (d, *J* = 4.7 Hz, 1H), 3.70 (s, 3H), 3.58 (q, *J* = 7.7, 13.9 Hz, 1H), 3.17-2.86 (m, 3H), 2.69



(dd, *J* = 10.2, 12.5 Hz, 1H), 1.45 (d, *J* = 3.3 Hz, 5H), 1.40 (d, *J* = 7.9 Hz, 4H), 1.28 (d, *J* = 3.1 Hz, 6H); LRMS-APCI *m/z* 666 (MH^+).



2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-*tert*-butoxycarbonyloxy-3-methyl-butyl]-1*H*-indole-3-carboxylic acid methyl ester (190). To a solution of methyl BOC-protected indole **138** (9.3 mg, 0.031 mmol) in 0.75 mL of THF was added LDA (2.0 M solution in heptane/THF/ethylbenzene, 31 μL, 0.062 mmol) at -78 °C. The resulting dark red solution was stirred for 25 min, upon which a solution of aldehyde **120** (14 mg, 0.047 mmol) in 0.75 mL of THF was added by canula at -78 °C. The resulting solution was stirred for 30 min and diluted at -78 °C with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10% EtOAc/hexanes to 100% EtOAc gradient) and preparative thin layer chromatography (100% EtOAc) to afford ester alcohol **190** (7 mg, 37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (bs, 1H), 8.17-8.06 (m, 1H), 7.47 (s, 1H), 7.41-7.25 (m, 8H), 7.20-7.13 (m, 2H), 5.99-5.90 (m, 1H), 5.55 (dd, *J* = 3.2, 8.9 Hz, 1H), 5.19 (s, 2H), 5.09 (dd, *J* = 1.5, 10.3 Hz, 1H), 5.33 (dd, *J* = 1.6, 17.4 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.66-3.63 (m, 1H), 3.56 (dd, *J* = 3.1, 15.8 Hz, 1H), 3.38 (dd, *J* = 8.9, 15.7 Hz, 1H), 1.54 (s, 3H), 1.44 (s, 3H).



2-[3-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-hydroxy-3-methyl-butyl]-1*H*-indole-3-carboxylic acid methyl ester (180). To a solution of ester **190** (7 mg, 0.012 mmol) in 0.6 mL of anhydrous THF was added $LiAlH_4$ (95%, pellets, 2 mg, 0.048 mmol) at 0 °C. The mixture was warmed to rt and stirred for 2 h. The reaction was quenched with 15% potassium hydroxide solution. The resulting mixture was stirred overnight, dried over $MgSO_4$, filtered, and concentrated to afford neopentyl alcohol **180** (2.1 mg, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (bs, 1H), 8.11-8.08 (m, 1H), 7.47-7.30 (m, 8H), 7.24-7.15 (m, 2H), 6.02-5.89 (m, 1H), 5.23 (d, *J* = 1.7 Hz, 2H), 5.14 (dd, *J* = 1.4, 10.0 Hz, 1H), 4.90 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.48 (s, 2H), 3.94 (s, 3H), 3.63-3.61 (m, 2H), 2.74 (dd, *J* = 10.5, 16.1 Hz, 1H), 1.48 (d, *J* = 4.3 Hz, 6H).

References and Notes

[1] (a) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, U.; Christophersen, C. *J. Am. Chem. Soc.* **1985**, *107*, 4542. (b) Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 4709.

[2] Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem.* **1987**, *52*, 5638.

[3] (a) Rahbaek, L.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Petersen, B. O. *J. Org. Chem.* **1996**, *61*, 887. (b) Rahbaek, L.; Christophersen, C. *J. Nat. Prod.* **1997**, *60*, 175.

[4] (a) Hino, T.; Uehara, H.; Takashima, M.; Kawate, T.; Seki, H.; Hara, R.; Kuramochi, T.; Nakagawa, M. *Chem. Pharm. Bull*. **1990**, *38*, 2632. (b) Hino, T.; Taniguchi, M. *J. Am. Chem. Soc.* **1978**, *100*, 5564.

[5] Antoni, U.; Christophersen, C.; Nielsen, P. H.; Pedersen, E. J. *Acta Chem. Scand*.

1994, *48*, 91.

[6] The calculation was performed by Malika Kumarasiri and Sharon Hammes-Schiffer with density functional theory (DFT) using the B3LYP functional and the 6-311++G(d,p) basis set with the Gaussian 03 package.

[7] Gaussian 03, Revision D.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

[8] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; Plenum Press: New York, 1990; p. 123.

[9] (a) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, *11*, 2025. (b) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett*. **2004**, *33*, 440.

[10] For synthetic studies towards the chartellines and securamines, see:

(a) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem*. **2006**, *71*, 3159. (b) Sun, C.; Camp, J. E. *Org. Lett*. **2006**, *8*, 1779. (c) Rohde, J. Ph.D. Thesis, The Scripps Research Institute, 2005. (d) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 3714. (e) Camp, J. E. Ph.D. Thesis, The Pennsylvania State University, 2007. (f) Chaffee, S. C. Ph.D. Thesis, Yale University, 2001. (g) Korakas, P. Ph.D. Thesis, Yale University, 2003.

[11] Lin, X.; Weinreb, S. M. *Tetrahedron Lett*. **2001**, *42*, 2631.

[12] Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett*. **2003**, *44*, 4141.

[13] Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc*. **2006**, *128*, 14028.

[14] Korakas, P.; Chaffee, S.; Shotwell, J. B.; Duque, P.; Wood, J. L. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 12054.

[15] Lin, X. Ph.D. Thesis, The Pennsylvania State University, 2002.

[16] Sun, C. Ph.D. Thesis, The Pennsylvania State University, 2005.

[17] Bauer, H.; Tabor, H. *Biochem. Prep*. **1957**, *5*, 97.

[18] Pellicciari, R.; Curini, M.; Spagnoli, N.; Ceccherelli, P. *Synthesis* **1981**, *8*, 629.

[19] For examples of this type of hydroxamic acid elimination, see: (a) Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, D. M. *J. Org. Chem.* **1982**, *47*, 2147. (b) Hoffman, R. V.; Nayyar, N. K. *J. Org. Chem.* **1994**, *59*, 3530. (c) Hoffman, R. V.; Nayyar, N. K.; Shankweiler, J. M.; Klinekole, B. W., III *Tetrahedron Lett.* **1994**, *35*, 3231. (d) Kolasa, T. *Synthesis* **1983**, 539.

[20] Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, D. M. *J. Org. Chem.* **1982**, *47*, 2147.

[21] (a) Roosenberg, J. M.; Miller, M. J. *J. Org. Chem.* **2000**, *65*, 4833. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

[22] Walz, A. J.; Miller, M. J. *Org. Lett*. **2002**, *4*, 2047.

[23] (a) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310. (b) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004. (c) Gonthier, E.; Breinbauer, R. *Mol. Div.* **2005**, *9*, 51.

[24] (a) Saulnier, M. G.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 5435. (b) Wang, J.-C.; Just, G. *J. Org. Chem.* **1999**, *64*, 8090. (c) Wang, J.-C.; Just, G. *Tetrahedron Lett.* **1997**, *38*, 3797.

[25] Fadel, A.; Canet, J. L.; Salaun, J. *Tetrahedron: Asymm*. **1993**, *4*, 27.

[26] (a) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P.G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 12550. (b) Iyer, R. S.; Kuo, G.-H.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 5900.

[27] (a) Gribble, G. W.; Keavy, D. J.; Davis, D. A.; Saulnier, M. G.; Pelcman, B.; Barden, T. C.; Sibi, M. P.; Olson, E. R.; BelBruno, J. J. *J. Org. Chem.* **1992**, *57*, 5878. (b) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *19*, 3324. (c) Sundberg, R. J.; Broome, R.; Walters, C. P.; Schnur, D. *J. Heterocycl. Chem.* **1981**, *18*, 807. (d)

Hlasta, D .J.; Bell, M. R. *Heterocycles* **1989**, *29*, 849.

[28] Ohmoto, K.; Yamamoto, T.; Okuma, M.; Horiuchi, T.; Imanishi, H.; Odagaki, Y.; Kawabata, K.; Sekioka, T.; Hirota, Y.; Matsuoka, S.; Nakai, H.; Toda, M.; Cheronis, J. C.; Spruce, L. W.; Gyorkos, A.; Wieczorek, M. *J. Med. Chem.*, **2001**, *44*, 1268.

[29] Smith, A. B.; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438.

[30] Palandoken, H.; Wyatt, J. K.; Hitchcock, S. R.; Olmstead, M. M.; Nantz, M. H. *J. Organomet. Chem.* **1999**, *579*, 338.

[31] Manabe, S.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 9754.

[32] Maguire, A. R.; Plunkett, S. J.; Papot, S.; Clynes, M.; O'Connor, R.; Touhey, S. *Bioorg. Med. Chem.* **2001**, *9*, 745.

[33] Macor, J. E.; Ryan, K.; Newman, M. E. *J. Org. Chem.* **1989**, *54*, 4785.

[34] Mills, K.; Al Khawaja, I. K.; Al-Saleh, F. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 636.

[35] For similar isomerization reactions to form 1,4-disubstitued imidazoles, see: He, Y.; Chen, Y. Z.; Du, H. W.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529.

[36] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.

[37] Pawlak, J. M.; Khau, V. V.; Hutchison, D. R.; Martinelli, M. J. *J. Org. Chem.* **1996**, *61*, 9055.

[38] Genicot, C.; Ley, S. V. *Synthesis* **1994**, 1275.

[39] Wahlström, N.; Stensland, B.; Bergman, J. *Synthesis* **2004**, 8, 1187.

[40] Toyota, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 547.

[41] Bérubé, M.; Poirier, D. *Org. Lett.* **2004**, *6*, 3127.

[42] Ohno, H.; Wakayama, R.; Maeda, S.-i.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909.

[43] a) Bashiardes, G.; Bodwell, G. J.; Davies, S. G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 459. b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

[44] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.

[45] Welch, J. T.; Seper, K. W. *J. Org. Chem.* **1988**, *53*, 2991.

[46] Kornreich-Leshem, H.; Ziv, C.; Gumienna-Kontecka, E.; Arad-Yellin, R.; Chen, Y.; Elhabiri, M.; Albrecht-Gary, A.-M.; Hadar, Y.; Shanzer, A. *J. Am. Chem. Soc.* **2005**, *127*, 1137.

[47] Leeson, P. D.; Williams, B. J.; Baker, R.; Ladduwahetty, T.; Moore, K. W.; Rowley, M. *J. Chem. Soc., Chem. Commun*. **1990**, *22*, 1578.

[48] a) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1970**, *35*, 3717. b) Iwamoto, M.; Miyano, M.; Utsugi, M.; Kawada, H.; Nakada, M. *Tetrahedron Lett*. **2004**, *45*, 8647. c) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.

[49] a) Mehta, G.; Karmakar, S.; Chattopadhyay, S. K. *Tetrahedron* **2004**, *60*, 5013. b) Xu, L.; Wang, F.-P. *Tetrahedron* **2005**, *61*, 4467.

[50] a) Lansbury, P. T.; Zhi, B.-x. *Tetrahedron Lett*. **1998**, *29*, 5735. b) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173. c) Duri, Z. J.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 603.

[51] Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186.

[52] a) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553. b) Ha, D. S.; Yoon, M. J. *J. Korean Chem. Soc.* **1997**, *41*, 541. c) Ha, D. S.; Kim, H. A. *J. Korean Chem. Soc.* **1997**, *41*, 535.

[53] a) Yokoyama, Y.; Okuyama, N.; Iwadate, S.; Momoi, T.; Murakami, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1319. b) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046. c) Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220.

[54] a) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. *Tetrahedron Lett*. **2002**, *43*, 399. b) Rawat, M.; Wulff, W. D. *Org. Lett.* **2004**, *6*, 329.

[55] Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron* **1998**, *54*, 11079.

[56] Elhalem, E.; Bailey, B. N.; Docampo, R.; Ujváry, I.; Szajnman, S. H.; Rodriguez, J. B. *J. Med. Chem*. **2002**, *45*, 3984.

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