STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF SECURINE A AND SECURAMINE A

A Thesis in
Chemistry
by
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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.
TABLE OF CONTENTS

LIST OF FIGURES ............................................................................................................................vi

LIST OF TABLES .............................................................................................................................vii

ACKNOWLEDGEMENTS ..................................................................................................................viii

Part One  INTRODUCTION AND BACKGROUND .....................................................................1

1.1 Isolation and Structural Identification of the Chartellines, Securamines, and Related Alkaloids........................................................................................................................1

1.2 Proposed Biosynthesis of the Securamine, Securine, and Chartelline Alkaloids........................8

1.3 Synthetic Approaches to the Securines ...................................................................................10

1.4 Previous Synthetic Studies on the Imidazole Fragment of the Chartellines
   in the Weinreb group ..................................................................................................................14

   1.4.1 Protection of the Imidazole Fragment .........................................................................16

Part Two  RESULTS AND DISCUSSION ...............................................................................18

2.1 Approaches Towards a Total Synthesis of Securine A and Securamine A ..........18

   2.1.1 Construction of the Imidazole Fragment ..................................................................21

   2.1.2 Preparation of the Indole Fragment ........................................................................23

2.2 Model Studies for the Coupling of the Indole and Imidazole Epoxide Fragments .................................................................24
2.3 Revised Approach Towards a Total Synthesis of Securine A and Securamine A ..........................................................................................................................31

2.3.1 Model Studies for the Coupling of Indole Ester 98 with Aldehyde 84 ...............................................................................................................................34

2.3.2 Construction of the Imidazole Aldehyde Fragment ............................35

2.3.3 Coupling of the Indole Ester 98 and Imidazole Aldehyde 120 Fragments......................................................................................................................39

2.3.4 Investigation of Nitrogen protecting Groups on the Indole Fragment…41

2.3.5 Approaches Towards the Macrocyclic Ring of Securine A and Securamine A.................................................................................................................47

2.3.6 Efforts Towards the Chlorination of Various Neopentyl Alcohols.......55

2.4 Conclusion and Future Work......................................................................66

Part Three EXPERIMENTAL SECTION ........................................................................69

REFERENCES AND NOTES ......................................................................................132
LIST OF FIGURES

Figure 1: Securamines and Securines Equilibrium ......................................................4
Figure 2: Securamine A Isomers (Ab Initio Calculations)...........................................6
Figure 3: 3D Representations of Securamine Isomers a (6a) and b (6b)……………….7
Figure 4: Proposed Biogenesis for Securamine, Securine, Chartelline Alkaloids ......8
Figure 5: NOE study of Allyl Imidazole 48 .................................................................16
LIST OF TABLES

Table 1: Attempted Couplings of the Indole and Imidazole Fragments........................27
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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

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.

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

Precendent 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). 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.
The presence of only one diastereoisomer for securamines A (6) and B (7) in CDCl₃ 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 performed⁶ 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 ~99:1⁸ 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.
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. 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 Nishikawa9a 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-pNs hydroxamic acid 23, which was prepared from 2-methylindole-3-acetic acid ester 22 (Scheme 2).

**Scheme 2**

![Scheme 2 Diagram](image-url)
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. Our group has reported the first synthetic studies on the chartellines and chartellamides. The Isobe group has reported two strategies for synthesis of the spiro β-lactam moiety of the chartellines. Thus far, only the Baran group has reported a completed total synthesis of (±)-chartelline C.

*Wood’s Synthetic Approach to the Securine Macrocycle*  

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

1. 

2. 

3. 

4. 

5. 

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13. 

14. 

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23. 

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25. 

26. 

27. 

28. 

29. 

30. 

31. 

32. 

33. 

8 steps 27% PdCl$_2$(PPh$_3$)$_2$
CuI, TEA/PhH, rt 95%

1) Pd(PPh$_3$)$_4$, Et$_2$NH
DMF, 60 °C

2) n-BuLi, -78 °C;
ICH$_2$CO$_2$Bu, -78 °C
to 0 °C 65%

1) Im-H, TBSCl, rt
2) Boc$_2$O, TEA, 60 °C 77%

1) ICl, MeCN, NaOAc
-20 °C to rt
2) NaN$_3$, DMF, 100 °C 91%
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 BOC₂O to afford indole 31. Treatment of the olefin moiety 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 macrocyclization 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.
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). 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.
1.4 Previous Synthetic Studies on the Imidazole Fragment of the Chartellines in the Weinreb Group\textsuperscript{15, 16}

The approach to the formation of the imidazole fragment 47 developed by Xichen Lin\textsuperscript{15} and Cuixiang Sun\textsuperscript{16} started with the oxidation of histidine hydrochloride (41) to the known 4-cyanomethylimidazole,\textsuperscript{17} which was hydrolyzed to the known imidazole ester 42\textsuperscript{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\textsubscript{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 (\textit{vide supra}). However, an NOE experiment showed that imidazole 48 is actually the \( N^a \)-BOM regioisomer (Figure 5).\textsuperscript{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.

\textbf{Figure 5.} NOE Study of Allyl Imidazole 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). 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
Scheme 9

61

\[ \text{Tf}_2\text{O} \]
\[ 2,6\text{-lutidine} \]
\[ \text{CH}_2\text{Cl}_2 \]
\[ 0 \degree \text{C to rt} \]
\[ 90\% \text{ (crude)} \]

\[
\begin{align*}
\text{61} & \quad \rightarrow \\
& \quad \rightarrow \\
& \quad \rightarrow \\
\text{62}
\end{align*}
\]
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).
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. Similar cyclizations for the formation of medium-sized hydroxamic acid rings have been reported, but no examples of large ring systems exist. However, macrolactamizations of simple $\omega$-amino acids abound. 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. 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 (\textit{vide infra}).

\textbf{Scheme 11}

\[ \text{EtO} \begin{array}{c} \text{O} \\ \text{N} \end{array} \text{N} \text{Tr} \text{O} \begin{array}{c} \text{N} \\ \text{N} \end{array} \text{EtO} \]

\[ 70 \quad \text{t-BuOK, THF} \quad 18\text{-c-6, -78 °C; Mel} \quad 85\% \quad 71 \quad \text{BOMCl, CH\textsubscript{3}CN} \quad 90 \degree \text{C} \quad 59\% \]
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 TBSCI, followed by protection of the indole nitrogen with benzenesulfonfyl chloride (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).
A model epoxide 85 was then prepared to test the key coupling reaction with lithio indole 58 (Scheme 14).\textsuperscript{27} Commercially available phenylacetic acid methyl ester (82) was treated with sodium hydride and methyl iodide to afford known dimethylated ester 83.\textsuperscript{28} The ester 83 was then converted to the aldehyde 84 via a LiAlH\textsubscript{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.\textsuperscript{29}
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). In addition, catalysis of the coupling with Lewis acids was investigated (entries 9-14). 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv M/LA</th>
<th>Temp (°C) of addition for M/LA</th>
<th>M and/or LA</th>
<th>Time</th>
<th>Temp (°C)</th>
<th>Yield of starting material(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>overnight</td>
<td>-78</td>
<td>72% (80)</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>-20</td>
<td>CuBr•S(CH₃)₂</td>
<td>overnight</td>
<td>-20 to rt</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>-20</td>
<td>CuCl</td>
<td>overnight</td>
<td>-20 to rt</td>
<td>39% (80)</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0</td>
<td>CuI</td>
<td>2 d</td>
<td>-78 to -20 to 70</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
<td>-20</td>
<td>CuI</td>
<td>overnight</td>
<td>-78 to -20 to rt</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>-20</td>
<td>CuCN</td>
<td>overnight</td>
<td>-20 to rt</td>
<td>40% (80)</td>
</tr>
<tr>
<td>7</td>
<td>1.0</td>
<td>-20</td>
<td>CuCN</td>
<td>3 d</td>
<td>-20 to rt to 70</td>
<td>20% (80)</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>-20</td>
<td>CuCN</td>
<td>overnight</td>
<td>-20 to rt</td>
<td>23% (80)</td>
</tr>
<tr>
<td>9</td>
<td>1.0; 2.0</td>
<td>-78</td>
<td>CuCN; BF₃•Et₂O</td>
<td>4 h</td>
<td>-78</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>-78</td>
<td>BF₃•Et₂O</td>
<td>2 h</td>
<td>-78</td>
<td>41% (80)</td>
</tr>
<tr>
<td>11</td>
<td>1.1</td>
<td>-78</td>
<td>BF₃•Et₂O</td>
<td>7 h</td>
<td>-78 to rt</td>
<td>---</td>
</tr>
<tr>
<td>12</td>
<td>1.1</td>
<td>-78</td>
<td>ZnCl₂</td>
<td>4.75 h</td>
<td>-78 to 0</td>
<td>---</td>
</tr>
<tr>
<td>13</td>
<td>1.1</td>
<td>rt</td>
<td>MgBr₂</td>
<td>overnight</td>
<td>rt</td>
<td>unidentifiable products</td>
</tr>
<tr>
<td>14</td>
<td>1.1</td>
<td>-78</td>
<td>MgBr₂</td>
<td>overnight</td>
<td>-78</td>
<td>---</td>
</tr>
</tbody>
</table>
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.
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.
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). 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 $\alpha,\beta$-unsaturated iminium ion 102. 1,4-Addition of cyanide ion to the iminium ion 102 then gives the homologated product 103.

Scheme 19
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.\textsuperscript{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
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, 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 LiAlH₄. Treatment of the hydroxymethyl indole 113 with TMSCN and BF₃•OEt₂, using the conditions of Maguire, 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

\[ \text{EtO} \text{C} \begin{array}{c} \text{H} \\ \text{EtO} \end{array} \text{N} \text{Im} \] 116 \xrightarrow{\text{PMBCl, } K_2CO_3, \text{ DMF, } 0 \degree \text{C to rt}} \text{EtO} \begin{array}{c} \text{H} \\ \text{EtO} \end{array} \text{N} \text{Im} \text{PMB} \] 121 \xrightarrow{\text{t-BuOK, THF, } 18\text{-c-6, -78\degree C, MeI}} \] 39\%

\[ \text{EtO} \begin{array}{c} \text{H} \\ \text{EtO} \end{array} \text{N} \text{Im} \text{PMB} \] 122 \xrightarrow{\text{cat. PMBCl, THF, reflux}} \text{EtO} \begin{array}{c} \text{PMB} \\ \text{N}^{b} \end{array} \text{N}^{a} \text{Im} \text{PMB} \] 123 \xrightarrow{} = 

\[ \text{EtO}_2\text{C} \begin{array}{c} \text{H} \\ \text{EtO}_2\text{C} \end{array} \text{N}^{a} \text{N}^{b} \] 124 \xrightarrow{\text{BnMe}_3\text{NBr}_3, \text{ CaCO}_3, \text{ MeOH, CH}_2\text{Cl}_2, \text{ rt}} \text{EtO} \begin{array}{c} \text{N}^{a} \\ \text{PMB} \end{array} \text{N}^{b} \text{Im} \text{PMB} \] 125 \xrightarrow{52\%} 

\[ \text{EtO} \begin{array}{c} \text{H} \\ \text{EtO} \end{array} \text{N} \text{Im} \text{PMB} \] 126 \xrightarrow{\text{allylSnBu}_3, \text{ CsF, Pd}_2(\text{dba})_3, \text{ P(t-Bu)}_3, \text{ dioxane, 100 \degree C}} \text{EtO} \begin{array}{c} \text{PMB} \\ \text{Br} \end{array} \text{N}^{a} \text{N}^{b} \text{Im} \text{PMB} \] 127 \xrightarrow{78\%} 

\[ \text{EtO} \begin{array}{c} \text{H} \\ \text{EtO} \end{array} \text{N} \text{Im} \text{PMB} \] 128 \xrightarrow{50\%}
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 LiAlH₄ in 49% unoptimized yield. Treatment of 3-hydroxymethyl indole 129 with TMSCN and BF₃·OEt₂ 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](image)

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$_2$O 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. Reduction of ester 140 to the corresponding alcohol was attempted with LiAlH$_4$ in THF. 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: LiAlH₄/THF/rt, Red-Al/Tol/reflux, LiBH₄/THF/0 °C to 50 °C, and DIBAL-H/CH₂Cl₂/-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 LiAlH₄ 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 BF₃•OEt₂ 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 LiAlH₄ in THF at 0 °C to rt. The homologation reaction of diol 148 with TMSCN and BF₃•OEt₂ 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
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, which was then esterified with TMSCH$_2$N$_2$ in methanol at 0 °C to give ester 152. 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 \(\text{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**

\[
\begin{align*}
\text{MOMCl} & \quad \text{DIPEA} \\
& \quad \text{NaI, CH}_2\text{Cl}_2 \\
& \quad 0^\circ \text{C to rt} \quad 58\% \\
\end{align*}
\]
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 $O$-benzylolation reaction was also attempted on an earlier intermediate in order to determine whether steric 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$_2$O, 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 tetroxide 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. In an attempt to solve this problem, we decided to explore the use of an $O$-protected oxime.

**Scheme 38**
Only reduction of \(O\text{-}\text{Bn}\)\(^{43a}\) and \(O\text{-}\text{Me}\)\(^{44}\) 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
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/H₂O 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, 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 shown in Scheme 42, in all of these reactions either the starting material was recovered or decomposed (Scheme 42).

Scheme 42

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). However, when mesylate 174 was treated with LiCl in DMF at 70 °C or with LiCl/HMPA in DMF at 70 °C, 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.\(^{50b}\)
We also attempted to apply a new strategy for chlorination of sterically hindered alcohols that was recently published by Yasuda and coworkers.\textsuperscript{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.
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).\(^\text{51}\) 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.
Recent reports have shown that the neopentyl alcohol group of norbornene 178 can be converted to the corresponding chloride 179 via several different protocols.\textsuperscript{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.
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.$^{53}$
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

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).
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
We have also attempted high pressure hydrogenolysis of the advanced intermediate 185.\textsuperscript{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.
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 H₂ 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 hydroxymethyl 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 LiAlH₄ (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
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 CaH₂ 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 PF₃₅₄ plates. ¹H and ¹³C 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-1H-imidazol-4-yl)-acetic Acid Ethyl Ester (70).

To a solution of imidazole 116 (2.21 g, 14.34 mmol) in 230 mL of CH₂Cl₂ 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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 C₂₆H₂₄N₂O₂ (MH⁺) 397.1917, found 397.1936.

2-Methyl-2-(1-trityl-1H-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 MgSO₄, 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; ¹H NMR (400 MHz, CDCl₃) 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); 13C NMR (90 MHz, CDCl3) 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 C28H28N2O2 (MH+) 425.2230, found 425.2223.

2-(1-Benzylxoxymethyl-1H-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (72). To a solution of protected imidazole 71 (1.50 g, 3.53 mmol) in 118 mL of CH3CN 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 NaHCO3 was added, and the mixture was stirred for 10 min. The aqueous layer was extracted with ethyl acetate. The extract was dried over MgSO4, 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; 1H NMR (300 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 C17H23N2O3 (MH+) 303.1709, found 303.1717.
2-[3-(Benzyloxy)methyl-5-bromo-3H-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$_2$Cl$_2$-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$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_3$ (MH$^+$) 381.0815, found 381.0794.

2-[5-Allyl-3-(benzyloxy)methyl-3H-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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (ESI+) calcd for C₂₀H₂₇N₂O₃ 343.2022 (MH⁺), found 343.2022.

2-[3-(Benzyloxy)methyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3H-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 H₂O and 9.5 mL of acetone was added N-methylmorpholine-N-oxide (0.43 g, 3.7 mmol) and OsO₄ (4% weight in H₂O, 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 MgSO₄, 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, CDCl₃) 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); $^1$H 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 (ESCl+) calcd for C$_{20}$H$_{29}$N$_2$O$_5$ 377.2077 (MH$^+$), found 377.2076.

2-[3-(Benzyloxy)methyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3H-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$_2$SO$_4$ (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$_2$O$_5$ (MH$^+$) 417.2390, found 417.2364.
2-[3-Benzylxoymethyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-3H-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$_2$Cl$_2$ was added DIBAL-H (1.0 M solution in CH$_2$Cl$_2$, 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$_4$Cl (0.13 mL). The aqueous layer was extracted with CH$_2$Cl$_2$, 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_4$ (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$_3$) $\delta$ 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); δ 13C NMR (75 MHz, CDCl3) 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 C21H31N2O4 (MH+) 375.2285, found 375.2284.

To a solution of DMSO (75 μL, 0.70 mmol) in 7.0 mL of CH2Cl2 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 CH2Cl2 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 NH4Cl and the aqueous layer was extracted with CH2Cl2. The combined organic layers were dried over MgSO4 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-Benzylxymethyl-5-(1,1-dimethylallyl)-4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)1H-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 MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield alkene 76 as a colorless oil (4 mg, 36%). ¹H NMR (300 MHz, CDCl₃) 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-(*R*-Butyldimethylsilyloxy)-ethyl]-1H-indole (79). To a solution of 2-(1H-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 MgSO₄, 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; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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-Benzene sulfonyl-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\(_4\)Cl 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%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_2\)O\(_3\)SSi [M+NH\(_4\)]\(^+\) 433.2022, found 433.1941.
{1-Benzensulfonyl-3-[2-(t-butyldimethylsilanyloxy)-ethyl]-1H-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 NaHCO3 (3 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over MgSO4, 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺-H₂O]⁺.

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 CH₃I (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 MgSO₄ and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (CH₂Cl₂) to yield the dimethylated ester 83 as a yellow oil (5.41 g, 87%). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta \) 7.25-6.94 (m, 5H), 3.54 (s, 3H), 1.48 (s, 6H); HRMS (ESCl+) calcd for C₁₁H₁₅O₂ 179.1073 (MH⁺), found 179.1072.

\begin{center}
\textbf{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 LiAlH₄ (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 MgSO₄, and concentrated to afford an alcohol 83a as a cloudy, white oil which was used without further purification. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta \) 7.25-6.78 (m, 5H), 3.39 (s, 2H), 2.72 (bs, 1H), 1.17 (s, 6H).
\end{center}

\begin{center}
\textbf{2-Methyl-2-phenylpropionaldehyde (84).} To a solution of DMSO (4.75 mL, 66.9 mmol) in 50 mL of CH₂Cl₂ 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 CH₂Cl₂ 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 NH₄Cl and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated to afford aldehyde 84 as a colorless oil, which was used immediately without further purification. \(^1\)H NMR (300 MHz, CDCl₃) 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 MgSO₄, 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, CDCl₃) 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, CDCl₃) δ 147.1, 128.8, 126.9, 126.7, 60.0, 44.8, 38.4, 25.2, 24.6.
3-(2-Methoxymethoxy-ethyl)-1H-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 NaHCO₃ (15 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to yield O-protected indole 86a as a clear yellow oil (110 mg, 86%). ^1H NMR (300 MHz, CDCl₃) 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-Benzensulfonyl-3-(2-methoxymethoxy-ethyl)-1H-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 NH₄Cl was then added, followed by saturated NaHCO₃. The aqueous layer was extracted with ether, and the combined organic layers were dried over MgSO₄, 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$_3$) $\delta$ 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-Benzene sulfonyl-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 1 h. 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$_4$Cl 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$_3$) $\delta$ 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-Benzene sulfonyl-3-(2-benzyloxyethyl)-1H-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\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford protected tryptophol \textbf{87b} as a clear yellow oil (35 mg, 25%).

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{fig1}
\end{figure}
\end{center}

\textbf{1-(1-Benzenesulfonyl-1H-indol-2-yl)-2-phenoxyethanol (91) and 2-(1-Benzenesulfonyl-1H-indol-2-yl-3-phenoxypropan-1-ol (92).} To a solution of indole \textbf{89} (0.1 g, 0.39 mmol) in 0.94 mL of THF was added dropwise \textit{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 \textbf{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\textsubscript{4}Cl was added, and the aqueous layer was extracted with ethyl acetate. The organic extract was washed with saturated NH\textsubscript{4}Cl, saturated NaHCO\textsubscript{3}, and brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford an inseparable mixture of regioisomeric alcohols \textbf{91} and \textbf{92} as a red-orange oil (0.65:1; 76 mg, 48%). \textit{\textsuperscript{1}H NMR} (300 MHz, CDCl\textsubscript{3}) δ 8.18 (d, \textit{J} = 8.0 Hz, 1H), 7.75 (d, \textit{J} = 8.0 Hz, 2H), 7.41-6.96 (m, 25H), 6.78 (d, \textit{J} = 8.0 Hz, 1H), 6.50 (d, \textit{J} = 8.0 Hz, 1H), 5.57 (m, 1H), 5.11 (q, \textit{J} = 6.4 Hz, 1H), 4.54 (m, 1H), 4.41 (dd, \textit{J} = 15.1, 1.1 Hz, 2H), 4.19 (dd, \textit{J} = 7.2, 0.95 Hz, 2H), 4.13 (dd, \textit{J} = 9.5, 3.8 Hz, 1H), 4.04 (dd, \textit{J} = 9.4, 6.1 Hz, 1H), 3.46 (dd, \textit{J} = 15.3, 4.45 Hz, 1H), 3.31 (dd, \textit{J} = 15.3, 7.7 Hz, 1H), 1.72 (s, 2H).
1-(1-Benzensulfonyl-1H-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 NH₄Cl was added, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated NH₄Cl, saturated NaHCO₃, and brine, dried over Na₂SO₄ 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%). ¹H NMR (300 MHz, CDCl₃) 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⁺-H₂O]⁺.

2-Methyl-1H-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$_3$) $\delta$ 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 (ESCl+) calcd for C$_{11}$H$_{12}$NO$_2$ 190.0869 (MH$^+$), found 190.0868.

Method 2. See page 133.

1-Benzensulfonyl-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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 165.6,
5-Benzensulfonyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3H-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 NaHCO₃. The aqueous layer was extracted with CH₂Cl₂, dried over MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 (ESCl+) calcd for C₂₆H₂₄NO₄S 446.1427 (MH⁺), found 446.1426.
1-(1-Benzenesulfonyl-3-hydroxymethyl-1H-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 LiAlH₄ (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 MgSO₄, and concentrated to afford diol 113 as a clear oil (253 mg, 91%), which was used without further purification. ¹H NMR (300 MHz, CDCl₃) 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-ESI⁺ m/z 450.3 (MH⁺).

[1-Benzenesulfonyl-2-(2-hydroxy-3-methyl-3-phenylbutyl)-1H-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 CH₂Cl₂ was added by canula a solution of crude diol 113 (23 mg, 0.05 mmol) in 0.32 mL of CH₂Cl₂ dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Saturated NaHCO₃ was added and the solution was stirred for 45 min at rt. The organic layer was washed with 1.0 M HCl, saturated NaHCO₃, and brine, dried over MgSO₄, 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, 1488, 1172, 1128, 1089, 749 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 146.9, 139.1, 136.8, 136.7, 134.4, 129.8, 128.9, 127.2, 126.9, 126.5, 124.5, 118.6, 117.6, 115.5, 112.8, 79.3, 43.4, 28.9, 24.5, 23.9, 13.9; HRMS (ESI+) calcd for C\(_{27}\)H\(_{26}\)N\(_2\)O\(_3\)SNa 481.1562 (MNa\(^+\)), found 481.1562.

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

To a stirred solution of boron trifluoride diethyl etherate (19 \(\mu\)L, 0.15 mmol) and TMSCN (27 \(\mu\)L, 0.20 mmol) in 1.3 mL of CH\(_2\)Cl\(_2\) was added by canula a solution of crude diol 113 (23 mg, 0.05 mmol) in 0.32 mL of CH\(_2\)Cl\(_2\) 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). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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-ESI+ m/z 553.3 [M+Na]\(^+\).
(1-Benzoyloxymethyl-1H-imidazol-4-yl)-acetic Acid Ethyl Ester and (3-Benzoyloxymethyl-3H-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 CH₂Cl₂. The organic layer was washed with water, dried over MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) (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-Benzoyloxymethyl-1H-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester and 2-[3-(Benzyloxy)methyl-3H-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 MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) (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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₇H₂₃N₂O₃ (MH⁺) 303.1709, found 303.1717.

2-(1-Benzoyloxymethyl-1H-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 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); 13C NMR (100 MHz, CDCl3) 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 C17H23N2O3 (MH+) 303.1709, found 303.1717.

2-(5-Allyl-1-benzyloxymethyl-1H-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 CH2Cl2 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 NH4Cl. The aqueous layer was extracted with CH2Cl2, and the combined organic layers were washed with brine, dried over MgSO4, 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 LiAlH4 (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 MgSO4, 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%). 1H NMR (300 MHz, CDCl3) 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); 13C NMR (90 MHz, CDCl3) δ 146.4, 136.8, 135.8, 129.1, 128.6, 128.3,
To a solution of DMSO (30 μL, 0.42 mmol) in 3.3 mL of CH₂Cl₂ 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 CH₂Cl₂ 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 NH₄Cl and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ 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). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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 C₁₈H₂₃N₂O₂ (MH⁺) 299.1760, found 299.1758.

[(4-Methoxybenzyl)-1H-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, H₂O and ethyl acetate were added. The organic layer was washed with saturated NaHCO₃ and brine, dried over MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) 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)-1H-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 MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) (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); 13C NMR (75 MHz, CDCl$_3$) $\delta$ 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)-1H-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 $\mu$L, 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$_3$) $\delta$ 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$_3$) $\delta$ 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 (ESCl+) calcd for C$_{17}$H$_{23}$N$_2$O$_3$ (MH$^+$) 303.1709, found 303.1709.
2-[5-Bromo-1-(4-methoxybenzyl)-1H-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 CH₂Cl₂-MeOH (5:2) at rt was added benzyltrimethylammonium tribromide (212 mg, 0.54 mmol) and CaCO₃ powder (68 mg, 0.68 mmol). The solution was stirred for 5 h, and the solid CaCO₃ 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 MgSO₄ 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%). 

\[ \text{1H NMR (300 MHz, CDCl}_3 \} \delta 7.46 (s, 1H), 7.11 (dt, J = 2.1, 2.9, 8.8 Hz, 1H), 7.05 (dt, J = 2.1, 3.0, 8.7 Hz, 2H), 4.99 (s, 2H), 4.13 (q, J = 7.1, 14.3 Hz, 2H), 3.76 (s, 3H), 1.58 (s, 6H), 1.17 (t, J = 7.1 Hz, 3H); \]

\[ \text{13C NMR (100 MHz, CDCl}_3 \} \delta 176.4, 159.9, 143.2, 136.2, 129.1, 127.6, 114.7, 99.9, 61.3, 55.7, 49.7, 43.8, 32.0, 25.7, 23.1, 14.6. \]

2-[5-Allyl-1-(4-methoxybenzyl)-1H-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 Pd₂(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%).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 7.34 (s, 1H), 6.94 (dt, J = 2.2, 2.7, 8.9 Hz, 1H), 6.83 (dt, J = 2.3, 2.7, 8.7 Hz, 2H), 5.81-5.69 (m, 1H), 5.04 (dq, J = 1.7, 3.4, 10.2 Hz, 1H), 4.91 (s, 2H), 4.86 (dq, J = 1.8, 3.5, 17.1 Hz, 1H), 4.08 (q, J = 7.1, 14.3 Hz, 2H), 3.78 (s, 3H), 3.20-3.17 (m, 2H), 1.57 (s, 6H), 1.15 (t, J = 7.1 Hz, 3H); \] 
\[ ^13C \text{NMR (100 MHz, CDCl}_3 \delta 177.5, 159.7, 142.3, 135.7, 135.2, 128.6, 128.5, 123.9, 116.6, 114.7, 61.1, 55.7, 48.4, 43.8, 28.1, 26.7, 14.5.} \]

2-[5-Allyl-1-(4-methoxybenzyl)-1H-imidazol-4-yl]-2-methylpropionaldehyde (127). To a solution of ester 126 (28 mg, 0.08 mmol) in 4.0 mL of anhydrous CH\(_2\)Cl\(_2\) 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\(_4\)Cl. 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%).

\[ ^1H \text{NMR (300 MHz, CDCl}_3 \delta 9.51 (s, 1H), 7.46 (s, 1H), 7.01 (m, 2H), 6.89 (dt, J = 2.2, 2.8, 9.4 Hz, 2H), 5.85-5.72 (m, 1H), 5.10 (dq, J = 1.7, 3.2, 10.2 Hz, 1H), 4.95 (s, 2H), 4.87 (dq, J = 1.9, 3.4, 17.3 Hz, 1H), 3.82 (s, 3H), 3.20-3.17 (m, 2H), 1.47 (s, 6H); \] 
\[ ^13C \text{NMR (100 MHz, CDCl}_3 \delta 202.4, 159.8, 138.7, 137.0, 135.1, 128.7, 128.2, 125.8,} \]
116.9, 114.8, 77.7, 55.7, 48.6, 48.1, 27.9, 22.3; HRMS (ESCl+) calcd for C_{18}H_{23}N_{2}O_{2} (MH^+) 299.1760, found 299.1760.

5-Benzencesulfonyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3H-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 NaHCO₃. The aqueous layer was extracted with CH₂Cl₂, dried over MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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 (ESCl+) calcd for C_{34}H_{34}N_{3}O_{5}S (MH^+) 596.2220, found 596.2219.
1-(1-Benznesulfonyl-3-hydroxymethyl-1H-indol-2-yl)-3-methyl-3-phenylbutan-2-ol (129). To a solution of lactone \( \text{128} \) (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 \( \text{129} \) as a clear oil (40 mg, 49%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.20-8.14 (m, 1H), 7.69-7.66 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.23 (m, 1H), 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 (ESCl+) calcd for C\(_{34}\)H\(_{38}\)N\(_3\)O\(_5\)S (MH\(^+\)) 600.2533, found 600.2532.

[1-Benznesulfonyl-2-(2-hydroxy-3-methyl-3-phenylbutyl)-1H-indol-3-yl]-acetonitrile (130). To a stirred solution of boron trifluoride diethyl etherate (3.6 \( \mu \)L, 0.029 mmol) and TMSCN (12.7 \( \mu \)L, 0.095 mmol) in 0.05 mL of CH\(_2\)Cl\(_2\) was added by canula a solution of diol \( \text{129} \) (5.7 mg, 0.010 mmol) in 0.05 mL of CH\(_2\)Cl\(_2\) 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 NaHCO₃, and brine, dried over MgSO₄, 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₃₅H₃₇N₄O₄S (MH⁺) 609.2536, found 609.2536.

2-(1-Benzylxoxymethyl-5-bromo-1H-imidazol-4-yl)-2-methylpropionaldehyde (131). To a solution of ester 119 (378 mg, 0.57 mmol) in 3.4 mL of anhydrous CH₂Cl₂ 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 NH₄Cl. The resulting mixture was stirred overnight, dried over MgSO₄, 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, CDCl₃) 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$_3$) $\delta$ 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 (ESCl+) calcd for C$_{15}$H$_{18}$N$_2$O$_2$Br (MH$^+$) 337.0552, found 337.0552.

5-Benzencesulfonyl-3-[1-(1-benzyloxymethyl-5-bromo-1H-imidazol-4-yl)-1-methylethyl]-4,5-dihydro-3H-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$_2$Cl$_2$, 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$_3$) $\delta$ 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$_3$) $\delta$ 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 (ESCl+) calcd for C$_{31}$H$_{29}$BrN$_3$O$_5$S (MH$^+$) 634.1012, found 634.1011.
Method 2. To a solution of lactone 132a (30 mg, 0.05 mmol) in 0.7 mL of CH₂Cl₂-MeOH (5:2) at rt was added benzyltrimethylammonium tribromide (25 mg, 0.07 mmol) and CaCO₃ powder (8 mg, 0.08 mmol). The solution was stirred for 4 h, and the solid CaCO₃ 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 MgSO₄ 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-3H-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 MgSO₄ 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%). ¹H NMR (300 MHz, CDCl₃) 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-1H-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 washed with 15% NaOH, water, and brine, and then dried over MgSO₄ 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, CDCl₃) 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 washed with 15% NaOH, water, and brine, and then dried over MgSO₄ 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
104 MHz, CDCl₃) 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-1H-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 MgSO₄, 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 CH₂Cl₂ was added DMAP (684 mg, 5.6 mmol), TEA (0.78 mL, 5.6 mmol), and BOC₂O (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%). ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 166.3, 150.4, 146.4, 135.9, 127.5, 124.6, 124.0, 121.7, 115.3,
105.6, 85.5, 51.6, 28.6, 15.5; HRMS (ESCl+) calcd for C_{16}H_{20}NO_{4} (MH^{+}) 290.1393, found 290.1392.

2-(2-tert-Butoxycarbonyloxy-3-methyl-3-phenyl-butyl)-1H-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 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_{2}Cl_{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}) \delta 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)-1H-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 LiAlH₄ (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 MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) δ 9.19 (bs, 1H), 8.09 (d, J = 5.5 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), 1.48 (acuo). ¹H NMR (300 MHz, CDCl₃) δ 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-3H-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 CH₂Cl₂ 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 NH₄Cl. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were washed with brine, dried over MgSO₄, 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-Benzoyloxymethyl-2-methyl-1H-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 recool ed 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. NaHCO₃ was added and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over MgSO₄ 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%). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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-Benzoyloxymethyl-3-(1-methyl-1-phenylethyl)-4,5-dihydro-3H-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 NaHCO₃.
The aqueous layer was extracted with CH$_2$Cl$_2$, 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-Benzylxoymethyl-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-ESCl$^+$ m/z 448 [M+H$_2$O]$^+$.

1-Benzyl-2-methyl-1H-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 NaN (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. H₂O was added and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed w/H₂O (2x), dried over MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) 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 (ESI+) calcd for C₁₉H₂₀NO₂ (MH⁺) 280.1338, found 280.1338.

2-[3-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1H-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 NaHCO₃. The aqueous layer was extracted with CH₂Cl₂, and the combined organic layers were dried over MgSO₄, 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; ¹H NMR (300 MHz, CDCl₃) 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); 13C NMR (100 MHz, CDCl3) 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-1H-imidazol-4-yl)-1-(1-benzyl-3-hydroxymethyl-1H-indol-2-yl)-3-methylbutan-2-ol (148).

Method 1. To a solution of ester 147 (236 mg, 0.409 mmol) in 20 mL of anhydrous CH2Cl2 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 NH4Cl was added. The resulting mixture was stirred overnight, dried over MgSO4, 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 C35H40N3O3 (MH⁺) 550.3070, found 550.3070.
**Method 2.** To a solution of ester 147 (145 mg, 0.25 mmol) in 12 mL of anhydrous CH₂Cl₂ 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 NH₄Cl was added. The resulting mixture was stirred overnight, dried over MgSO₄, 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 LiAlH₄ (95%, pellets, 17 mg, 0.43 mmol) at 0 °C. The mixture was warmed to rt and stirred overnight. The reaction was quenched with H₂O/15% NaOH/H₂O (1:1:3; 17 μL, 17 μL, 51 μL). The resulting mixture was stirred for 10 min, dried over MgSO₄, 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-1H-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1H-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 CH₂Cl₂ was added by canula a solution of diol 148 (111 mg, 0.20 mmol) in 1.5 mL of
CH₂Cl₂ dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 15 min. Saturated NaHCO₃ was added and the solution was stirred for 10 min at rt. The organic layer was washed with 1.0 M HCl, saturated NaHCO₃, and brine, dried over MgSO₄, 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. ¹H NMR (300 MHz, CDCl₃) 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 (C₃₆H₃₈N₄O₂) calcld 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 NaHCO₃ was added and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, 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$_3$) $\delta$ 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-ESCl$^+$ m/z 546.3 (MH$^+$).

{2-[3-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1H-indol-3-yl}-acetic Acid (151). To a solution of nitrile 149 (24 mg, 0.043 mmol) in 0.74 mL of EtOH-H$_2$O (4:1) was added aqueous KOH (85%, 28 $\mu$L, 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$_2$O. 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$_3$) $\delta$ 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-1H-imidazol-4-yl)-2-hydroxy-3-methylbutyl]-1-benzyl-1H-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 (ESCl+) calcd for C$_{37}$H$_{42}$N$_3$O$_4$ 592.3176 (MH$^+$), found 592.3175.

(1-Benzyl-2-{3-[1-benzyloxymethyl-5-(2,3-dihydroxy-propyl)-1H-imidazol-4-yl]-2-hydroxy-3-methylbutyl]-1H-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$_2$O and 0.2 mL of
acetone was added N-methylmorpholine-N-oxide (3.5 mg, 0.0296 mmol) and OsO₄ (4% weight in H₂O, 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 MgSO₄, 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%). ¹H NMR (300 MHz, CDCl₃) 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, 2H), 1.26 (d, J = 2.4 Hz, 6H); LRMS-ESI+ m/z 626.3 (MH⁺).

(1-Benzyl-2-[3-[1-benzyloxymethyl-5-(2-oxoethyl)-1H-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 H₂O and 0.45 mL of acetone was added N-methylmorpholine-N-oxide (16 mg, 68 μmol) and OsO₄ (4% weight in H₂O, 9 μL, 0.68 μmol) at rt. The solution was stirred overnight at rt and then cooled to 0 °C, upon which NaIO₄ (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 MgSO₄, and concentrated in vacuo to afford aldehyde 153 (5 mg, 62%). ¹H NMR (300 MHz, CDCl₃) δ 7.50-7.10 (m,
{2-[3-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-2-methoxymethoxy-3-methylbutyl]-1-benzyl-1H-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 NaHCO₃ and methylene chloride were added. The organic layer was washed with saturated NaHCO₃, dried over MgSO₄ 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%). ¹H NMR (400 MHz, CDCl₃) 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-1H-imidazol-4-yl)-2-methoxymethoxy-3-methylbutyl]-1-benzyl-1H-indol-3-yl\}-acetic Acid (155). To a solution of nitrile 154 (27 mg, 0.045 mmol) in 0.76 mL of EtOH-H₂O (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 Et₂O. The aqueous layer was acidified under ice cooling and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo to afford acid 155, which was used without further purification. ¹H NMR (400 MHz, CDCl₃) 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-1H-imidazol-4-yl)-2-benzyloxy-3-methylbutyl]-1-benzyl-1H-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 H₂O was added. The aqueous layer was extracted with EtOAc, the combined organic layers were dried over MgSO₄ 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%). ¹H NMR (400 MHz, CDCl₃) 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-1H-imidazol-4-yl)-2-benzyloxy-3-methylbutyl]-1-benzyl-1H-indol-3-yl}-acetic Acid (159). To a solution of nitrile 158 (36 mg, 0.055 mmol) in 1.0 mL of EtOH-H₂O (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 Et₂O. The aqueous layer was acidified under ice cooling and was then extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo to afford acid 159, which was used without further purification. ¹H NMR (400 MHz, CDCl₃) 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).

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\text{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 \( \mu L, 0.18 \) mmol) dropwise at 0 °C. The mixture was stirred for 15 min and then concentrated \textit{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).}
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\text{(1-Benzyl-2-{2-benzyloxy-3-[1-benzyloxymethyl-5-(2,3-dihydroxy-propyl)-1H-imidazol-4-yl]-3-methylbutyl}-1H-indol-3-yl)-acetic Acid Methyl Ester (160). To a solution of alkene 157 (6 mg, 9 \( \mu \)mol) in 0.15 mL of H}_2\text{O and 0.30 mL of acetone was added N-methylmorpholine-\( N \)-oxide (5 mg, 44 \( \mu \)mol) and OsO}_4 (4% weight in H}_2\text{O, 3 \( \mu L, 0.44 \) \( \mu \)mol) 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 \textit{in vacuo}. The residue was purified by preparative thin layer chromatography on silica gel (100% EtOAc) to yield an inseparable mixture of}
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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)-1H-imidazol-4-yl]-3-methylbutyl}-1H-indol-3-yl)-acetic Acid Methyl Ester (161). To a solution of diol 160 (5 mg, 7 μmol) in 0.12 mL of H$_2$O 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)-1H-imidazol-4-yl]-3-methylbutyl}-1H-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$_2$O 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-hydroxypthalimide (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\(_2\)O was added. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) and the combined organic layers were dried over MgSO\(_4\) and concentrated \textit{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%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 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).

\textit{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 \(\mu\)L, 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\(_2\)Cl\(_2\) and H\(_2\)O were added. The aqueous layer was basified with saturated NaHCO\(_3\) and extracted with Et\(_2\)O. 
The combined organic layers were dried over MgSO₄ 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%). ¹H NMR (300 MHz, CDCl₃) 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-Benzylxoxymethoxyisoindole-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 H₂O was added. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ 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 C₁₆H₁₄NO₄ found 284.0923.

O-Benzylxoxymethylhydroxylamine (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 CH₂Cl₂ and H₂O were added. The
aqueous layer was basified with saturated NaHCO$_3$ and extracted with Et$_2$O. 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$_3$) $\delta$ 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-1H-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1H-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$_2$O 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$_3$) $\delta$ 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$_3$) $\delta$ 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 (ESCl+) calcd for C\textsubscript{44}H\textsubscript{49}N\textsubscript{4}O\textsubscript{6} 729.3653 (MH\textsuperscript{+}), found 729.3652.

(1-Benzyl-2-{3-[5-(2-benzyloxymethoxyaminoethyl)-1-benzyl-1H-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1H-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\textsubscript{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\textsubscript{2}O was added and the pH was adjusted to 9 with 15% KOH solution. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}, and the combined organic layers were dried over MgSO\textsubscript{4} and concentrated in vacuo to afford O-benzylhydroxylamine 170, which was used without further purification. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 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 (ESCl+) calcd for C\textsubscript{44}H\textsubscript{51}N\textsubscript{4}O\textsubscript{6} 731.3809 (MH\textsuperscript{+}), found 731.3809.
(1-Benzyl-2-{3-[5-(2-benzyloxymethoxyamino-ethyl)-1-benzyloxymethyl-1H-imidazol-4-yl]-2-hydroxy-3-methyl-butyl}-1H-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 H2O 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 MgSO4 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 (ESI+) calcd for C43H49N4O6 717.3653 (MH+), found 717.3652.

Methanesulfonic Acid 2-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-1-(1-benzyl-3-cyanomethyl-1H-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. H2O was added, and the aqueous layer was extracted with Et2O. The combined ethereal layers were dried over MgSO4 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%). 1H NMR (400 MHz, CDCl3) 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-1H-imidazol-4-yl)-1-(1-benzyl-3-cyanomethyl-1H-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$_2$Cl$_2$ 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. $^1$H 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-1H-imidazol-4-yl)-2-chloro-3-methylbutyl]-1-benzyl-1H-indole-3-carboxylic Acid Methyl Ester (177). To a solution of \( \text{InCl}_3 \) (0.1 mg, 0.660 \( \mu \)mol) and benzil (3.0 mg, 0.120 mmol) in 0.030 mL of methanol and 0.55 mL of \( \text{CH}_2\text{Cl}_2 \) was added \( \text{HSiMe}_2\text{Cl} \) (1.5 \( \mu \)L, 0.013 mmol). The mixture was stirred at room temperature (rt) for 1 h. A solution of neopentyl alcohol 147 (7.0 mg, 0.012 mmol) in 0.025 mL \( \text{CH}_2\text{Cl}_2 \) was added, and the resulting mixture was stirred at rt for 15 min. Saturated \( \text{NaHCO}_3 \) was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed dried over \( \text{MgSO}_4 \) 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. \( ^1\text{H NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 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-1H-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 NH₄Cl 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 MgSO₄ 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%).

\[
\text{NC} \quad \text{Bn} \quad \text{NBOM} \quad \text{N} \quad \text{B} \quad \text{n} \\
\text{110}
\]

\{2-[3-(5-Allyl-1-benzyloxymethyl-1H-imidazol-4-yl)-3-methyl-but-1-enyl]-1-benzyl-1H-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 \text{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 O₂ was bubbled through the mixture at rt for 30 min. The reaction mixture
was quenched with saturated NH₄Cl and the aqueous layer was extracted with Et₂OAc.
The combined organic layers were dried over MgSO₄ 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) and was stirred overnight under H₂ gas. The reaction mixture was filtered through a pad of celite, washed with CH₂Cl₂, and concentrated in vacuo to afford deprotected imidazole 186 (2 mg, 78%). LRMS-ESCl+ m/z 506.3 (MH⁺).

(1-Benzyl-2-{3-[1-benzyloxymethyl-5-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-1H-imidazol-4-yl]-2-hydroxy-3-methylbutyl}-1H-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 H₂SO₄ (1 μL). The mixture was stirred for 0.5 h at rt and a few drops of saturated NaHCO₃ (20 mL) were added. The mixture was dried over MgSO₄ 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%). ¹H NMR (300 MHz, CDCl₃) 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$_2$Cl$_2$, 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$_3$) $\delta$ 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-1H-imidazol-4-yl)-2-hydroxy-3-methyl-butyl]-1H-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 LiAlH₄ (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 MgSO₄, filtered, and concentrated to afford neopentyl alcohol 180 (2.1 mg, 36%). ¹H NMR (300 MHz, CDCl₃) 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


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.


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


VITA

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Pooja Aggarwal was born on November 30, 1979 in Flushing, New York. She attended Villanova University in Villanova, Pennsylvania, and received a Bachelor of Science degree in chemistry and biochemistry in May 2001. She then enrolled at The Pennsylvania State University as a chemistry graduate student and worked in the area of synthetic organic chemistry under the supervision of Professor Steven M. Weinreb.