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Total synthesis of (−)-hapalindole G: A novel tin-mediated indole synthesis

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Rice University, 1994
RICE UNIVERSITY

TOTAL SYNTHESIS OF (-)-HAPALINDOLE G
A NOVEL TIN-MEDIATED INDOLE SYNTHESIS

by

XIAOQI CHEN

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

APPROVED, THESIS COMMITTEE:

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Houston, Texas
March, 1994
Abstract

Total Synthesis of (−)-Hapalindole G
A Novel Tin-Mediated Indole Synthesis

By
Xiaoqi Chen

The first total synthesis of (−)-hapalindole G, a member of novel chlorine- and isonitrile-containing hapalindoles from the cultured cyanophyte Hapalosiphon fontinalis, is accomplished. Our 21-step synthesis of (−)-hapalindole G from (−)-carveol features a stereospecific introduction of chlorine next to a quaternary center via cleavage of the cyclopropane intermediate and facile elaboration of the indole moiety through a conjugate addition of lithium methyl methylthiomethyl sulfoxide to an enone followed by hydrolysis of the resultant adduct. The absolute configuration of (−)-hapalindole G has therefore been confirmed on the basis of the specific rotation of our synthetic sample.

Also described herein is a novel tin-mediated radical indole synthesis by using o-isocyanostyrene derivatives as starting materials via 2-tri-n-butylstannyl-3-substituted indoles as intermediates. The 2-tri-n-butylstannylindoles were also subjected to the one-pot Stille coupling reaction and iodination. The iodoindoles were capable of further manipulation. Our efficient synthesis paves the way for a facile construction of a variety of 3- or 2,3-substituted indoles from readily accessible isonitriles.
To my parents and Lianhong
Acknowledgment

I wish to express my sincere gratitude to Professor Tohru Fukuyama for his guidance and unceasing encouragement throughout my graduate study. His dedication, perseverance, and enthusiasm for chemistry provided a constant inspiration to me. My experience in this laboratory has been memorable and rewarding.

I would like to express my special thanks to my family for their support throughout my education years. Most of all to my wife Lianhong, for her love, understanding, and support.

I would also like to thank my co-workers, both past and present, for their support and friendship. Thanks are due to Miss Ge Peng for her initial studies on the indole synthesis, and to Tangqing Li for his help in my early graduate research. Special thanks go to Miss Melissa Deaton for her invaluable assistance in the preparation of this manuscript.

Finally, I would like to thank the Department of Chemistry, Rice University, National Institutes of Health, and Welch Foundation for their financial support.
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PART ONE: TOTAL SYNTHESIS OF (∼)-HAPALINDOLE G

Chapter I

Introduction

The hapalindoles were isolated by Moore and co-workers at the University of Hawaii in 1984 from an edaphic form of *Hapalosiphon fontinalis* (Ag.) Bornet (Stigonemataceae), strain number V-3-1. The lipophilic extract of the cultured alga showed antialgal and antimycotic activities. Hapalindole A (1) was responsible for part of the antialgal and antimycotic activity of *H. fontinalis*.\(^1\) In addition to hapalindole A, eighteen other minor hapalindoles, hapalindole B-Q and T-V (2-20), were later identified from the same alga (Figure 1).\(^2\) By using more polar solvent to elute the column, two more polar new alkaloids, fontonamide (21) and anhydrohapaloxindole A (22), were isolated from the same extract of the alga by the same research group in 1987.\(^3\) Both compounds appear to be singlet oxygen oxidation products of hapalindole A.

![Molecular structures and formulas of hapalindoles and derivatives.](image-url)

<table>
<thead>
<tr>
<th></th>
<th>R₁</th>
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<tr>
<td>1: A</td>
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<tr>
<td>2: B</td>
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<td>Cl</td>
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<tr>
<td>9: J</td>
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<tr>
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<td>7: G</td>
<td>NC</td>
<td>Cl</td>
</tr>
<tr>
<td>8: U</td>
<td>NC</td>
<td>H</td>
</tr>
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Figure 1
Hapalonamide A (23), a possible precursor of fontonamide (21) and anhydrohapaloxindole A (22), is indeed formed along with 21, 22 when an oxygen-aerated solution of hapalindole A in aqueous methanol containing a trace of rose bengal is irradiated at room temperature. However, hapalonamide A (23) has not yet been detected as a constituent of *H. fontinalis*.

![Figure 2](image_url)

Figure 2

In 1987, Schwartz and co-workers reported two structurally unusual indolinones, hapalindolinone A (24) and B (25), from cultured cyano-bacterium belonging to the genus *Fischerella* (ATCC 53558). The structure elucidation by IR, NMR, and mass spectral analysis as well as single-crystal X-ray diffraction revealed a unique molecular architecture featured by an intriguing spiro-fused cyclopropane ring. Hapalindolinone A inhibits the binding of [³H] arginine vasopressin to kidney tissue (v₂ receptor) with an IC₅₀ of 37.5 ± 7.6 mM (n = 3). It also inhibits kidney (v₂) arginine vasopressin stimulated adenylate cyclase with an IC₅₀ of 44.6 mM (n = 2).

In 1992, Moore and co-workers isolated another new antifungal tetracyclic alkaloid, fischerindole L (26) from *Fischerella muscicola* (Thuret) Gomont (UTEX 1892) which has the same relative stereochemistry as hapalindole L and inhibits the growth of four test fungi, viz. *Aspergillus oryzae*, *A. terreus*, *Trichoderma viride*, *Fusarium solani*, and *Fusarium oxysporum*.
*Pencillium notatum, Saccaromyces cerevisiae*, and *Trichophyton mentagrophytes.*\(^5\) The researchers at the University of Hawaii also examined the other species of blue-green algae, viz. *F. ambigua* (Nageli) Gomont (UTEX 1903), *H. hibernicus* W. and G. S. Westiellopsis prolifica Janet (UH isolate EN-3-1), for fungicidal activity. The extracts of these three species disclosed hitherto unknown ambiguine isonitrile A-F (Figure 3).\(^6\) The new alkaloids are characterized by an additional isoprene unit attached to the 2-position of the indole moiety. In ambiguines D-F the isoprenyl substituent is further fused to the isonitrile-bearing carbon.

26: fischerindole L

\[
\begin{align*}
27: & \quad \text{A} \quad \text{H} \quad \text{Cl} \\
28: & \quad \text{B} \quad \text{OH} \quad \text{Cl} \\
29: & \quad \text{C} \quad \text{OH} \quad \text{H}
\end{align*}
\]

30: D

31: E

32: F

Figure 3
The structure elucidation of the hapalindoles was elegantly performed by Moore and his collaborators through extensive spectroscopic characterization (MS, NMR, UV) and was partially confirmed by X-ray crystallography of hapalindole A. Since hapalindole A can be converted to hapalindole K, whose absolute configuration has been determined by using the anomalous dispersion technique, the absolute stereochemistry of hapalindole A was thus established. The absolute configuration of other hapalindoles was deduced by comparing their specific optical rotation to the known hapalindole A and K. The structures of ambiguine isonitrile A-F were determined by applying similar methods and were confirmed for ambiguine isonitrile D by X-ray crystallography. Although the reported X-ray crystallographic studies did not lead to the absolute stereochemistry of ambiguine isonitrile D, the circular dichroism (CD) spectra of ambiguine isonitrile A, B, C, E, and F and hapalindole G are similar in shape, suggesting similarity of their absolute stereochemistry. Because the absolute stereochemistry of hapalindole G was determined as mentioned above, the ambiguines may therefore have the total structures formulated in Figure 3.

The biosynthesis of hapalindoles has not been thoroughly studied. Moore proposed tryptophan and a monoterpene unit as the possible biogenetic precursors to fischerindole L (26) and hapalindole L (15). Schwartz et al. have also reported the isolation of a new tricyclic hapalindole 33 from Fischerella sp. ATCC 53558 which could be considered as the biosynthetic precursor of fischerindole L and hapalindole L (Figure 4).

The novel structural features of the hapalindoles as well as their interesting biological activities have made them worthy targets for total synthesis. The first synthetic work in the hapalindole area was reported by Natsume shortly after the isolation of the natural products. Readily available
methyl 1-toluenesulfonyl-4-indolylcarboxylate was used as starting material for their racemic synthesis of hapalindole J, M, H, and U. The methyl ester was converted to the tertiary alcohol 34 with methylmagnesium bromide. The alcohol 34 was further treated with a 5:2 mixture of silyl enol ethers 35 in the presence of SnCl₄ to give a mixture of two compounds, 36 and 37, which were treated with boron trifluoride etherate to give the expected tetracyclic compound 38 in 57% yield after chromatographic separation. The tetracyclic compound 38 was oxidized with N-bromosuccinimide to introduce bromide to the C₁₁ position. Upon treatment with sodium azide, the crude mixture of epimeric bromides furnished two stereoisomeric azides, 39 and 40, in 34% and 29% yield,
respectively. The azide 39 was then reduced with lithium aluminum hydride to give a mixture of several amines including the ones resulting from an unexpected reduction of the tetrasubstituted olefin in 41% combined yield. The desired product was further transformed to hapalindole J (9) and M (10) in 30% and 35% yield, respectively in a conventional manner. Although these syntheses
of (±)-hapalindole J and M are rather short, very little stereo- and regioselectivity was achieved throughout the synthesis (Scheme 1).

Scheme 2

The same strategy was adopted for the synthesis of hapalindole H and U. The difference was that, instead of the azide displacing the bromide, a hydroxyl group was used to replace the bromide to yield 34% of the desired epimeric allylic alcohol 43. The remaining 31% of the undesired regioisomeric alcohol was recycled by acid treatment. After the tetrasubstituted olefin was reduced with lithium aluminum hydride, the alcohol was oxidized to a ketone in order to
perform a reductive amination. However, the reductive amination of ketone 44 and 45 did not offer any substantial improvement in terms of stereoselectivity of the reaction compared to the aforementioned route. The two desired precursors to hapalindole H (12) and U (8) were obtained in 22% and 42% yield, respectively, after formylation of the intermediate amine. (±)-Hapalindole H and U were obtained upon dehydration of the formamide (Scheme 2).

Scheme 3

The total synthesis of (+)-hapalindole Q was recently reported. By incorporating the brominated camphor derivative 46 as a six-membered ring chiral building block, (+)-hapalindole Q was elegantly synthesized in eight steps (Scheme 3). The key α-arylation was achieved by a palladium-mediated
coupling reaction of the protected 3-bromoindole 49 with the tin enolate of 9-bromocamphor, which was generated in situ from the enol acetate 47. The resultant arylation product 50 underwent fragmentation of the C-1 and C-7 bond upon treatment with sodium naphthalenide at −78 °C. The enolate from the fragmentation reaction was directly alkylated with acetaldehyde, resulting in an epimeric mixture of the aldol adducts 51. After mesylation of the carbinol under standard conditions, an olefin was generated by a thermal elimination promoted by sodium iodide. Reductive amination of the ketone 52 for seven days furnished, after treatment with 1,1'-thiocarbonyldiimidazole, (+)-hapalindole Q (18) in 62% yield along with 19% of its epimer. The absolute stereochemistry of hapalindole Q was thus confirmed to be 10R, 11R, 12 R, 15R.

Although Albizati's total synthesis of (+)-hapalindole Q is a well designed and well executed success, it precluded the possibility of introducing the chlorine atom at the C-13 position of the hapalindole framework, because any hetero atom at the C-6 position of camphor would undergo facile elimination during the fragmentation. The approaches developed thus far are not suited for the synthesis of more challenging chlorine containing hapalindoles. The inherent challenges in an enantiospecific total synthesis of (−)-hapalindole A or G are centered upon the construction of the five contiguous stereogenic centers around the hitherto unknown tetracyclic indoloterpene skeleton. More importantly, the introduction of the chlorine atom adjacent to the quaternary carbon with high stereochemical control requires an entirely different approach.
Chapter II
Total Synthesis of (−)-Hapalindole G

On the outset of our retrosynthetic analysis, we envisioned that the isonitrile function needed to be installed as late as possible, ideally at the last step of the synthesis due to its instability under acidic conditions. We also noticed the reaction reported in the literature that hapalindole E (5) cyclizes to form a tetracyclic product 54 when treated with 1:1 mixture of 2 N hydrochloric acid and ethanol (Scheme 4). It seemed reasonable to introduce the nitrogen

![Reaction Scheme](image)

**Scheme 4**

function from ketone 55 by a reductive amination. The active methylene of the ketone 56 could be used for installation of the requisite indole. After the construction of the indole moiety, an acid-catalyzed cationic cyclization with the isopropenyl group would provide us with the desired tetracyclic framework. The ketone 56 in turn could be derived from readily available (−)-carvone (59). Our original and the most critical plan was to introduce the chlorine atom adjacent to the quaternary center by $S_N$2 cleavage of the activated cyclopropane
intermediate 57. We were mindful of the possibility that a detrimental elimination reaction might compete with the nucleophilic process. Such elimination might occur through the usual anti mechanism as shown in the diagram below. However, the alignment of the axial hydrogen atom, HA, with the departing of the cyclopropane bond appeared to be less than ideal for a facile elimination to occur.\textsuperscript{11} Moreover, the low basicity of chloride ion augured well for the success of the planned reaction. The cyclopropane intermediate 57 could be prepared by an intramolecular cyclopropanation of an appropriate diazo compound. Since the chlorine of hapalindole G is on the same side as the isopropenyl group, the cyclopropane ring should be attached from the \(\alpha\)-face of the molecule. Therefore, the \textit{trans}-carveol 58 was our starting material of choice.
(Scheme 5). Bearing the above retrosynthetic perspective in mind, we started the venture into the total synthesis of \((-\))-hapalindole \(G\).

\((-\))-Carvone (59) was first oxidized with alkaline hydrogen peroxide to give epoxy ketone 60. The resultant keto epoxide was subjected to Wharton rearrangement to afford trans-carveol (58).\(^\text{12}\) Incidentally, reduction of \((+\))-carvone with lithium aluminum hydride provided exclusively the cis-carveol. The carveol 58 was then condensed with methyl (chloroformyl)acetate in the presence of triethylamine at \(-30^\circ\text{C}\) to furnish an ester, which was treated with \(p\)-acetamidobenzenesulfonyl azide\(^\text{13}\) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile to give the diazo intermediate 61 in 88% yield after chromatography. \(p\)-Acetamidobenzenesulfonyl azide was preferred over tosyl azide because of the readily removable sulfonamide byproduct on a large scale preparation. The crucial cyclopropanation was achieved in 60% yield to furnish 57 upon thermolysis of the diazo 61 in methylene chloride using copper(II) bis(salicylidene-\textit{tert}-butylamine) as a catalyst.\(^\text{14}\) This homogenous copper

![Scheme 6](image-url)
catalyst was practically the only one that gave satisfactory yield for the
cyclopropanation (Scheme 6).

With the key cyclopropane intermediate in hand, we focused our
attention on the cleavage of the cyclopropane 57 with such Lewis acid-type
reagents as TMSCl, BCl₃, ZnCl₂, and HCl, with a hope to activate the malonate
system of 57. Unfortunately, the isopropenyl group could hardly tolerate these
reaction conditions. When treated with hydrogen chloride, 57 gave exclusively
the isopropyl chloride 62 without forming any trace of ring opening product.
Finally, we realized that the cleavage of the cyclopropane could be facilitated at
high temperature under less acidic conditions. The chloro lactone 63 was
formed for the first time, albeit in low yield, when Li₂CuCl₄ was used in THF at
100 °C in a sealed tube. A combination of LiCl and acetic acid in N,N-
dimethylformamide at 140 °C improved the yield to 61%, and the yield was
further optimized to 71% by changing acetic acid to camphorsulfonic acid. The
chloride ion, as expected, attacked at the less substituted carbon of the
cyclopropane 57 to give the lactone 63 as a result of a concomitant Krapcho
decarboxylation. The stereochemistry of the chloride was confirmed to be β on
the basis of extensive NMR studies (Scheme 7).

Scheme 7

With the chloride successfully introduced to the C-13 position, our efforts
were then directed at conversion of the lactone to the desired vinyl ketone 56.
To this end, three approaches have been developed to achieve the aforementioned transformation. Our first route features a Cope elimination reaction (Scheme 8). The lactone 63 was partially reduced with diisobutylaluminum hydride (DIBAL) to lactol 64, which was treated with hydroxylamine hydrochloride in methanol to yield oxime 65. The oxime was then reduced with sodium cyanoborohydride in the presence of titanium trichloride and formaldehyde to give directly a tertiary amine. In order to block the nucleophilic attack to C-21 position, it was protected as an acetate. The tertiary amine 66 was cleanly oxidized to the amine oxide 67 with mCPBA. When heated at 110 °C in toluene, the amine oxide 67 underwent elimination to give the olefin 68 in low yield along with a large amount of byproduct, which was later identified as amine acetate 66. Even the standard Cope elimination conditions, vacuum thermolysis at 160 °C, did not afford the desired olefin 68 in
satisfactory yield. Since extensive endeavors to improve the reaction were futile, we decided to explore an alternative approach.

The second approach, illustrated in Scheme 9, called for a selenoxide elimination reaction. First the lactone 63 was reduced with lithium aluminum hydride to give diol 69. The diol 69 was directly subjected to the Grieco selenide formation conditions with a hope to take advantage of the different reactivity of the primary and the secondary hydroxyl groups. Unfortunately, the expected selenide was not the product isolated from the reaction, which gave instead the tetrahydrofuran 70. In order to avoid this undesired cyclization, extra steps had to be taken to differentiate those two hydroxyl groups. Thus, the primary and secondary alcohols were protected as their t-butyldimethylsilyl ether and acetate, respectively. Surprisingly, removal of the t-butyldimethylsilyl group with tetrabutylammonium fluoride (TBAF) conditions caused facile migration of
the acetate to the deprotected primary alcohol. Fortunately, by using acidic conditions, the deprotection of the silyl group was successful without causing any acetate migration. The primary alcohol of 72 was then converted to ortho-nitrophenyl selenide 73 according to Grieco's procedure. Exposure of the selenide 73 to hydrogen peroxide induced a clean elimination to give, after chromatography, the desired vinyl acetate 68. The vinyl ketone 56 was subsequently prepared from 68 in a conventional manner involving alkaline hydrolysis and Jones oxidation. While the above pathway provided a reasonable amount of the key intermediate 56 for the synthesis of hapalindole G, it was far from being practical due mainly to the tedious protection-deprotection scheme. Therefore we decided to explore a more efficient route which is amenable to a large scale preparation.

The third and the last approach turned out to be much better designed than the previous ones (Scheme 10). The lactone 63 was first converted to the α-bromo lactone 74 in 81% yield by treatment with LDA at low temperature followed by quenching with carbon tetrabromide. A one-pot, two-stage reduction transformed the α-bromo lactone 74 to the bromohydrin 75. In order
to minimize any undesired debromination, which was caused by other reducing agents we used, it was essential to first reduce the lactone with DIBAL at −78 °C to the corresponding lactol. The reduction was completed by addition of ethanol and sodium borohydride to the reaction mixture. The desired vinyl ketone 56 was obtained by zinc copper couple reduction in refluxing ethanol and subsequent Jones oxidation in an overall yield of 94% from 75. With this key intermediate in hand, the stage was set for the introduction of the indole moiety.

Before proceeding further in the synthetic studies, a model study was conducted on ketone 77 to find a suitable way to construct the indole. The successful route leading to indole 82 is summarized as follows (Scheme 11). The lithium enolate of the model ketone 77, prepared from (−)-carvone by L-Selectride reduction and subsequent alkylation with methyl iodide, was treated with o-nitro-β-nitro styrene in the presence of N′,N-dimethyl-propyleneurea (DMPU). The aliphatic nitro group of adduct 78 was transformed to aldehyde 79 by the standard Nef reaction conditions. The other conditions like Ti3+ reduction did not work in this particular case. The aromatic nitro group of 79 was reduced with zinc and acetic acid to the amine, which was trapped by the aldehyde function to furnish the indole 80 spontaneously. Treatment of the ketone 80 with hydroxylamine gave oxime 81. This oxime was surprisingly stable under reductive conditions. It remained intact during an attempted lithium aluminum hydride reduction even in refluxing THF. Finally, it was found that the combination of titanium trichloride and sodium cyanoborohydride could successfully reduce the oxime 81 to the amine. Acetamide 82 was prepared to help us determine the stereochemistry of this compound. It was disappointing for us to find that the coupling constant between the H-10 and H-11 was 10 Hz, which clearly indicated the undesired
axial-axial relation between these two protons. The corresponding coupling constant for the natural products is 2-3 Hz. Nevertheless, we shifted our attention to the real system because at least an efficient method had been established to assemble the indole moiety.

Scheme 11

The yield of the Michael addition of ketone 56 to the α-nitro-β-dinitro styrene was at first not as good as the model study. However, a significant improvement was made by adding one equivalent of boron trifluoride etherate and allowing the reaction mixture to slowly warm to room temperature. Also,
Nef reaction on the aliphatic nitro did not proceed under the same reaction conditions employed in the model study. However, after the ketone was reduced to alcohol 84, direct reduction of the dinitro compound 84 in the presence of acetic acid and iron furnished indole 85 in moderate yield. Conversion of hindered alcohol 85 to its mesylate or triflate, unfortunately, failed to yield any desired product. The powerful Mitsunobu reaction could not introduce the nitrogen functionality either. It was suspected that the failure of the substitution reactions was due to the severe steric congestion on the neopentyllic site of the indole 85. We reasoned that blocking the free rotation of the indole moiety would result in increased accessibility of nucleophiles to the neopentyllic site. To this end, cationic cyclization to the 4-position of the indole 85 was attempted under a variety of acidic conditions. Although a clean cyclization did take place, the 2-position of the indole was preferred to the 4-
position, providing exclusively the tetracyclic compound 86. The structure assignment was made on the basis of the comparison of the $^1$H NMR spectra of several natural products and the product obtained. Deactivation of the 2-position of the indole by protecting the indole nitrogen with an acetyl or a tosyl group, however, did not change the outcome of the cyclization (Scheme 12).

Scheme 13

Since it was difficult to form the C-4 - C-16 bond with the preformed
indole ring, we started exploring the possibility of assembling the indole after
the formation of the strategic C-4 - C-16 bond. A major breakthrough of this
approach was achieved with the phenol ether adduct 87. A clean cyclization
took place when it was treated with trimethylsilyl triflate to yield two
regioisomers, 88 and 89, albeit in 1:1 ratio. In addition, the mesylated phenol
substrate also underwent the same clean cyclization upon treatment with
trimethylsilyl triflate. If the phenol moiety is essential for the success of the
cyclization, it would have to be subsequently removed by hydrogenolysis of the
 corresponding triflate. In order to construct an indole, however, it is necessary
to have an amine equivalent at the ortho position of the phenyl precursor. To
this end, a series of model compounds 92-102 were synthesized to test the
cyclization. It was very disappointing to find that none of these compounds
behaved in the same manner as the simple phenol or its mesylate. No clean
cyclization was observed on any of those substrates. Finally, a compromise was
made to use o-iodo phenyl compound as an alternative to the more direct o-
amine phenyl derivative. The iodide could be later converted to an amine
functionality through a palladium-mediated carbonylation and subsequent
Curtius rearrangement. Moreover, the iodide appears to be useful because its
low electronegativity would not suppress the electrophilic aromatic substitution.
We were delighted to find that the iodide 103 gave a virtually quantitative yield
of the desired tricyclic compound upon acid treatment (Scheme 13).

Tempted by the prospect of utilizing the new isonitrile indole synthesis\textsuperscript{17}
developed recently in our laboratories, the enone 105 was prepared from 104 by
\textit{N}-bromosuccinimide oxidation of trimethylsilyl enol ether and subsequent
dehydrobromination using DBU. The aryl iodide 105, as planned, was
converted to carboxylic acid 106 by a palladium-mediated carbonylation using
sodium hydroxide as a base.\textsuperscript{18} Conversion of the acid 106 to \textit{t}-butyl urethane 107 was effected by heating with diphenylphosphoryl azide, triethylamine, and \textit{t}-butanol in toluene.\textsuperscript{19} Standard functional group manipulation provided the
isonitrile precursor 109 ready for the tin-mediated indole synthesis. Unfortunately, this seemingly sound approach failed to yield any desired indole under the normal radical reaction conditions. Under somewhat forceful conditions, involving elevated temperature and longer reaction time, the reaction did proceed to give amine 108 in low yield. No indole formation was observed by modification of the reagent combination and substrate (such as 109) (Scheme 14). The failure of the reaction can be rationalized by the frontier orbitals theory. A simplified explanation is that, due to this rigid tricyclic system, the LUMO of the olefin remaining almost orthogonal to the HOMO of the tin substituted imidoyl radical. There seems to be no substantial overlap between the HOMO and the LUMO during the bond formation process. Accordingly, the tin substituted imidoyl radical cannot attack the proximal olefin but instead gets reduced by the tributyltin hydride to give the observed amine.

Having failed to capitalize on the novel indole synthesis protocol for construction of the indole, we started exploring different procedures to introduce the key carbon unit corresponding to the 2-position of the indole. An umpolung approach was planned to introduce an aldehyde functionality to the enone like 113. Following the scheme developed in the model studies, were attempted to synthesize the enone 113 from ketone 56. In contrast to the model studies, however, the reaction between ketone 56 and o-iodobenzyl bromide gave only an unacceptably poor yield of alkylation product 111. Use of o-iodobenzyl iodide with addition of N',N-dimethylpropyleneurea (DMPU) gave somewhat higher, but still unsatisfactory yield. Fortunately, titanium-mediated aldol condensation\(^{20}\) between ketone 56 and o-iodobenzaldehyde furnished aldol adducts 112 in 68\% yield. A mixture of the epimeric aldol adducts (in 4:1 ratio)
was transformed directly to enone 113 by treatment with trifluoroacetic acid. A three-step sequence, however, gave a higher overall yield and more reproducible results than the direct acid treatment. This sequence, which involves acetylation, elimination of acetic acid with DBU, and exposure to a mixture of trifluoroacetic acid and methanesulfonic acid in 10:1 ratio, provided crystalline enone 113 in an overall yield of 88%.

Conversion aryl iodide 113 to the carboxylic acid by means of the palladium-catalyzed carbonylation was much more problematic than that of
Scheme 16
model studies. Commonly used strong bases such as sodium hydroxide unexpectedly replaced the somewhat hindered neopentyl chloride to give alcohol 115 during the course of the reaction. After extensive studies, it was found that triethylamine was a superior reagent to serve our purpose which provided the acid 116 in 80% yield with the chloride intact. The Curtius rearrangement was performed according to the Shioiri-Yamada procedure to furnish the allyl urethane 117 in 90% yield. Methyl (methylthio)methyl sulfoxide was called for as an umpoled aldehyde equivalent in the reaction used to form the indole moiety. Addition of enone 117 to the preformed lithium methyl (methylthio)methyl sulfoxide at -78 °C gave a conjugate addition product 118. The reaction was quenched with water at low temperature followed by addition of excess mercuric chloride and perchloric acid to deprotect the thioacetal sulfoxide. After heating the mixture at 60 °C for an hour, the indole 119 was isolated by flash chromatography in 69% yield as a single stereoisomer. The β-isomer could not be detected in the reaction mixture. Since the coupling constant between H-9 and H-10 was 12.7 Hz, the stereochemistry of the ring junction in 119 was assigned as trans as shown. In the absence of mercuric chloride, hydrolysis of 118 resulted in a complex mixture (Scheme 16).

With this advanced intermediate in hand, one of the major hurdles remaining for the total synthesis of hapalindole G was to construct the isonitrile functionality. Upon treatment with hydroxylamine hydrochloride and pyridine in ethanol, ketone 119 was transformed to oxime 120. It was found that the combination of titanium trichloride and sodium cyanoborohydride could successfully reduce this relatively unreactive oxime to the amine. The resultant amine was formylated with acetic formic anhydride to provide formamide 121.
Deprotection of the allyl carbamate of 121 by Pd(0) catalyst turned out to be quite precarious. Commonly used bases, like piperidine and pyrrolidine, caused extensive decomposition of the product. The reaction did not proceed by changing the nucleophile to malonate<sup>21</sup> or dimedone.<sup>22</sup> However, by using less basic N-methylaniline, the deprotection finally proceeded smoothly. Dehydration of the formamide with phosgene and triethylamine provided us the indole isonitrile 123. To our great disappointment, there were noticeable differences between the <sup>1</sup>HNMR data of synthetic and natural hapalindole G. We therefore concluded that the configuration of the isonitrile of synthetic sample is opposite to the natural one. Trying to reverse the stereochemistry of the amine by using different reducing agents and also by reducing to the corresponding oxime ether met with no success (Scheme 16).

![Scheme 17](image)

In view of the failure of the above approach, we decided to explore the feasibility of converting the ketone 121 to the desired amine by way of the hydroxyl intermediate (Scheme 17). Toward this end, ketone 119 was reduced with sodium borohydride in methanol at 0 °C. As expected, the β-isomer 124 was obtained as the predominant product in 91% yield. Not surprisingly, the Mitsunobu reaction of the neopentylic alcohol 124, using such azide sources as
diphenyl phosphoril azide, hydroazoic acid, and zinc azide, did not take place at all. Trying to activate the alcohol with triflate or mesylate under standard conditions, met with failure. After extensive experimentation, a clean mesylation was finally realized in 82% yield when the compound 124 was treated with methanesulfonic anhydride and pyridine at 65 °C. Heating this mesylate with lithium azide in wet N,N-dimethylformamide (2% H₂O) for 36 hours caused a clean substitution to give the desired azide 126. The allyl

Scheme 18
carbamate was also removed during the course of the azide displacement presumably via a $S_{N}2'$ mechanism. The $^1$HNMR coupling constant between H-10 and H-11 of azide 126 was 2 Hz, indicating the axial-equatorial relationship between these two protons. It was a pleasant surprise to find the reaction proceeded so cleanly. Having secured the stereochemistry of the azide, the rest of the functional group manipulations were straightforward. Although the hindered azide 126 resisted the attempted reduction with Zn-AcOH, Ph$_3$P, $n$-Bu$_3$P, or H$_2$S-Py, it was smoothly reduced to the amine 127 with sodium amalgam in ethanol. The amine was formylated in a conventional manner to provide formamide 128 in an overall yield of 84% for two steps. As illustrated in Scheme 18, dehydration of the formamide with phosgene furnished (−)-hapalindole G (7) ([α]$_D^{25}$ -45.0° (c = 0.037, CH$_2$Cl$_2$), lit.$^2$ ([α]$_D^{23}$ -43.9° (c = 0.28, CH$_2$Cl$_2$)) in 90% yield. The synthetic (−)-hapalindole G was identical to an authentic sample by spectroscopic comparison ($^1$HNMR, [α]$_D^{23}$, MS, IR, CD).$^{23}$

In conclusion, we have developed an enantiospecific total synthesis of (−)-hapalindole G (7) in twenty one steps from (−)-carveol. Our synthesis features a stereospecific introduction of chlorine next to a quaternary center via cleavage of the cyclopropane intermediate and facile elaboration of the indole moiety through a conjugate addition of lithium methyl (methylthio)methyl sulfoxide to an enone system followed by hydrolysis of the resultant adduct. An unusual neopentyllic $S_{N}2$ substitution further established the stereochemistry of the isonitrile moiety. The absolute configuration of (−)-hapalindole G has been subsequently confirmed on the basis of the specific rotation of our synthetic sample.
Technical notes:

Melting points (mp), determined on a Mel-Temp, were uncorrected.

Infrared (IR) spectra were recorded on Nicolet 205 Infrared Spectrophotometer and are reported in wavenumbers (cm$^{-1}$).

Nuclear magnetic resonance (NMR) spectra were determined on a Bruker AC250 instrument unless otherwise noted. Chemical shifts are reported in parts per million downfield from tetramethylsilane (d) as the internal standard. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, and br = broad.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole mass spectrometer at 70 eV, unless otherwise noted, using direct probe insertion at temperatures of 50 to 300 °C. High resolution mass spectra were obtained under similar conditions using a CEC 21-110B instrument.

Optical rotations were measured on a Jasco DP-370 polarimeter at ambient temperature.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F$_{254}$. Preparative TLC separations were made on 10 x 20 cm or 20 x 20 cm plates prepared with a 2 mm layer of Merck silica gel 60 PF$_{254}$. Compounds were eluted from the adsorbent with 10% methanol in dichloromethane.

All evaporation was performed under reduced pressure on a rotary evaporator.
Column chromatography was performed on Baxter silica gel, 32-63 or 230-400 mesh, packed in Ace columns on a flash chromatography system.

Hydrogenations were carried out in a stainless steel Parr general purpose autoclave unless otherwise noted.

Commercial grade reagents and solvents were used as supplied with the following exceptions:

Dichloromethane and ether: distilled through a 24 inch Snyder column.
Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl.
Pyridine, triethylamine, and diisopropylethylamine: dried over potassium hydroxide pellets.

t-Butanol: distilled from calcium hydride.

\( N,N \)-dimethylformamide, benzene, toluene, acetonitrile, and methanol: dried over 4Å molecular sieves.

Methanesulfonyl chloride and thionyl chloride: distilled over phosphorus pentoxide.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
Methyl malonyl ester

To a stirred solution of 27.19 g (179 mmol) of 58 and 37.3 ml (268 mmol) of triethylamine in 300 ml of methylene chloride, cooled at -30 °C, was added dropwise 23.0 ml (215 mmol) of methyl (chloroformyl)acetate. The mixture was allowed to stir at -30 °C for 10 min, then warmed to room temperature. After the reaction was complete as monitored by TLC, the mixture was poured into a 3 N hydrochloric acid solution. The aqueous layer was extracted thoroughly with ether, and the combined organic layers were washed with a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium chloride solution. The extracts were combined, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 43.7 g (97%) of malonate ester as a yellow oil.

Characterization of malonate ester:

IR (film): 3090, 2950, 2920, 1755, 1740, 1645, 1440, 1330, 1270, 1200, 1150, 1025, 970, 910, 890, 830, 800

$^1$HNMR (CDCl$_3$): 1.71 (3H, s), 1.73 (3H, s), 1.63 (1H, m), 1.82-2.04 (2H, m), 2.17-2.29 (2H, m), 3.41 (2H, s) 3.74 (3H, s), 4.73 (2H, d, J = 10.3 Hz), 5.31 (1H, m), 5.76 (1H, m)

$^{13}$CNMR (CDCl$_3$): 20.4, 20.7, 30.8, 33.4, 35.7, 41.7, 52.4, 72.1, 109.3, 128.3, 130.4, 148.5, 166.3, 167.0
MS: 252 (<1, M+), 209 (6), 152 (48), 134 (66), 119 (91), 109 (90), 105 (92), 101 (99), 93 (93), 92 (99), 91 (79), 79 (74), 59 (40)

$[\alpha]_D^{23}$: +141.08° (c=1.38, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{14}$H$_{20}$O$_4$ 252.1361
Found 252.1360
Diazomalonate ester (61)

To a mixture of 43.70 g (173 mmol) of malonate ester and 42.9 g (173 mmol) of p-acetamidobenzenesulfonyl azide in 350 ml of acetonitrile was added dropwise 26.7 ml (173 mmol) of DBU over a period of 15 min. After stirring at room temperature for additional 15 min, the reaction was complete as monitored by TLC. The reaction mixture was then partitioned between ether and a combined solution of 3 N hydrochloric acid and brine. The aqueous layer was extracted thoroughly with a 1:1 ether-hexanes and the combined organic layers were washed with a saturated sodium bicarbonate solution and brine. The combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to provide 47.21 g (98%) of diazoester 61 as a yellow oil.

Characterization of 61:

IR (film): 3100, 2955, 2940, 2140, 1780, 1730, 1650, 1640, 1430, 1320, 1270, 1080, 920, 890, 770

$^1$HNMR (CDCl$_3$): 1.65 (1H, m), 1.71 (3H, s), 1.75 (3H, s), 1.81-2.06 (2H, m), 2.16-2.27 (2H, m), 3.85 (3H, s), 4.73 (2H, d, J = 11.5 Hz), 5.41 (1H, m), 5.76 (1H, m)

$^{13}$CNMR (CDCl$_3$): 20.5, 20.8, 30.8, 33.7, 35.7, 52.4, 72.2, 109.3, 128.6, 130.3, 148.3, 160.6, 161.6

MS: 278 (<1, M$^+$), 238 (12), 151 (62), 134 (100), 127 (100), 119 (100), 109 (100), 107 (100), 105 (100), 94 (100), 93
(100), 92 (100), 91 (100), 79 (100), 77 (100), 69 (100),
55 (100)

$[\alpha]_D^{23}$: +131.21° (c=1.77, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{14}$H$_{18}$N$_2$O$_4$ 278.1266
Found 278.1265
Cyclopropyl ester (57)

A solution of 10.67 g (38 mmol) of 61 and 1.56 g (3.8 mmol) of copper(II) bis(salicylidene-tert-butyamine) in 200 ml of methylene chloride was heated at 70 °C in a tightly capped tube for 8 h under an atmosphere of argon. After cooling to room temperature, the solvent was removed under reduced pressure to give a brown residue. Another 30.49 g (0.11 mol) of diazo 61 was subjected to the same reaction conditions as mentioned above on a 10-g scale for three different runs. The combined residues were purified by flash chromatography on a silica gel column eluting with hexanes to 40% ether-hexanes, giving 22.32 g (60.3%) of 57 as a yellow oil.

Characterization of 57:

IR (film): 3100, 2955, 2940, 1780, 1730, 1650, 1440, 1330, 1320, 1230, 1070, 910

$^1$HNMR (CDCl$_3$): 1.42 (3H, s), 1.50 (1H, m), 1.69 (3H, s), 1.86 (1H, m), 2.01 (1H, dt, $J_1 = 4.3$ Hz, $J_2 = 13.9$ Hz), 2.13 (1H, dd, $J_1 = 6.7$ Hz, $J_2 = 15.2$ Hz), 2.34 (1H, m), 2.39 (1H, d, J = 6.7 Hz), 3.79 (3H, s), 4.63 (1H, d, J = 4.3 Hz), 4.72 (2H, d, J = 8.8 Hz)

$^{13}$CNMR (CDCl$_3$): 15.2, 20.3, 23.8, 29.6, 31.5, 34.1, 40.3, 41.3, 52.8, 77.5, 110.1, 147.6, 166.8, 171.0

MS: 250 (9, M$^+$), 235 (12), 232 (10), 218 (35), 200 (17), 169 (61), 156 (58), 124 (97), 123 (71), 95 (97), 91 (97), 77 (59), 67 (80), 59 (48)
\([\alpha]_D^{23}\): \(-7.37^\circ\) (c=1.615, CH\(_2\)Cl\(_2\))

Exact Mass:

- Calculated for C\(_{14}\)H\(_{18}\)O\(_4\) 250.1205
- Found 250.1204
Chloro lactone (63)

To a stirred solution of 7.12 g (28.5 mmol) of cyclopropane ester 57 in 70 ml of \(N,N\)-dimethylformamide was added 14.55 g (62.7 mmol) of camphorsulfonic acid (CSA) and 9.11 g (285 mmol) of lithium chloride. The reaction mixture was heated at 140 °C for 1 h, at which time an additional 6.62 g (28.5 mmol) of CSA was added. After heating at 140 °C for another 30 min, the reaction mixture was cooled to room temperature, and then partitioned between ether and a diluted aqueous sodium chloride solution. The aqueous layer was thoroughly extracted with ether. The ethereal layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. Flash chromatography separation eluting with hexanes to 40% ether-hexanes afforded 4.63 g (71.3%) of 63 as a pale yellow oil.

Characterization of 63:

IR (film): 3100, 2990, 2950, 2930, 1790, 1650, 1460, 1420, 1210, 1140, 940, 900, 860, 780

\(^1\)HNMR (CDCl\(_3\)): 1.26 (3H, s), 1.58 (2H, m), 1.73 (3H, s), 2.17 (3H, m), 2.39 (1H, \(d, J_{AB} = 17.2\) Hz), 2.82 (1H, \(d, J_{AB} = 17.2\) Hz), 3.94 (1H, dd, \(J_1 = 3.9\) Hz, \(J_2 = 12.7\) Hz), 4.44 (1H, \(t, J = 2.9\) Hz), 4.76 (2H, \(d, J = 12.8\) Hz)

\(^{13}\)CNMR (CDCl\(_3\)): 16.2, 20.7, 29.1, 36.4, 39.2, 43.2, 44.6, 63.2, 85.1, 110.3, 146.5, 175.0
MS: 230 (2, M+2), 228 (8, M+), 193 (49), 168 (78), 133 (99), 105 (23), 93 (26), 79 (29), 67 (26), 53 (18)

$[\alpha]_D^{23}$: +51.74° (c=1.190, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{12}$H$_{17}$Cl$_1$O$_2$ 228.0917
Found 228.0917
Bromo lactone (74)

To a solution of 2.89 ml (23.8 mmol) of diisopropylamine in 30 ml of tetrahydrofuran at 0 °C was added 8.50 ml (2.33 M, 19.8 mmol) of n-butyl lithium. After the solution was stirred at 0 °C for 15 min, it was added via a syringe to a tetrahydrofuran solution of 3.01 g (13.2 mmol) of 63 at −78 °C. The temperature was maintained at −78 °C for 15 min before a solution of 4.82 g (14.5 mmol) of carbon tetrabromide in 15 ml of tetrahydrofuran was added by means of syringe. The reaction mixture was allowed to stir at −78 °C for 10 min and then poured into a saturated aqueous sodium chloride solution. The biphasic mixture was acidified with 3 N aqueous hydrochloric acid and extracted thoroughly with ether. The etheral layers were washed with a saturated sodium bicarbonate solution and brine consecutively, then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. Flash silica gel chromatography eluting with hexanes to 40% ether-hexanes yielded 3.29 g (81.2%) of 74 as a light yellow oil.

Characterization of 74:

IR (film): 3100, 2950, 2930, 1790, 1645, 1460, 1440, 1200, 1130, 970, 940, 920, 900, 790

$^1$HNMR (CDCl$_3$): 1.33 (3H, s), 1.59 (1H, m), 1.73 (3H, s), 1.78 (1H, m), 2.23 (3H, m), 3.88 (1H, dd, $J_1 = 3.9$ Hz, $J_2 = 12.3$ Hz), 4.44 (1H, s), 4.67 (1H, t, $J = 2.9$ Hz), 4.78 (2H, d, $J = 15.3$ Hz)
\(^{13}\text{CNMR (CDCl}_3\): 14.6, 20.7, 28.5, 37.1, 38.7, 48.1, 49.9, 60.6, 82.9, 110.6, 145.9, 171.7

\textbf{MS:} 308 (4, M+2), 306 (3, M+), 273 (6), 271 (6), 227 (9), 191 (53), 168 (74), 145 (25), 133 (99), 119 (26), 105 (67), 91 (67), 79 (33), 67 (32), 53 (38), 41 (77)

\([\alpha]_p^{23}\): +52.80° (c=1.87, CH\(_2\)Cl\(_2\))

\textbf{Exact Mass:} Calculated for C\(_{12}\)H\(_{16}\)Br\(_1\)Cl\(_1\)O\(_2\) 306.0022

\textbf{Found} 306.0024
Bromo diol (75)

To a stirred solution of 3.29 g (10.7 mmol) of 74 in 30 ml of dichloromethane at −78 °C under argon was added 7.8 ml (1.5 M, 11.7 mmol) of diisobutyl-aluminum hydride in toluene over a 10 min period. The mixture was stirred at −78 °C for 15 min and then warmed to 0 °C for 5 min before it was treated with 15 ml of ethanol and 1.98 g (53.5 mmol) of sodium borohydride. The reaction mixture was kept at room temperature for 3.5 h until the TLC indicated the disappearance of the lactol intermediate. It was then partitioned between dichloromethane and a 3 N hydrochloric acid solution. The aqueous layer was thoroughly extracted with dichloromethane. The organic layers were combined, washed with a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified by flash silica gel chromatography eluting with 20% to 60% ether-hexanes to give 2.37 g (71.2%) of 75 as white crystals.

Characterization of 75:

mp: 111-112 °C (ether-hexanes)

IR (film): 3250, 3120, 2950, 2870, 1650, 1470, 1430, 1100, 950, 890, 760

$^1$HNMR (CDCl$_3$): 1.18 (3H, s), 1.69 (1H, dd, $J_1 = 2.4$ Hz, $J_2 = 12.1$ Hz), 1.74 (3H, s), 1.88 (1H, q, $J = 12.1$ Hz), 2.17 (1H, m), 2.63 (1H, tt, $J_1 = 4.3$ Hz, $J_2 = 12.3$ Hz), 3.90 (1H, dd, $J_1 = 4.0$ Hz, $J_2 = 13.4$ Hz), 4.17 (1H, t, $J = 4.0$ Hz),
4.20 (1H, dd, J$_1$ = 4.0 Hz, J$_2$ = 13.4 Hz), 4.51 (1H, t, J = 3.3 Hz), 4.56 (1H, dd, J$_1$ = 4.3 Hz, J$_2$ = 12.1 Hz), 4.75 (2H, d, J = 4.8 Hz)

$^{13}$CNMR (CDCl$_3$): 19.6, 20.9, 33.2, 38.0, 38.2, 48.1, 61.5, 61.8, 69.1, 71.1, 109.7, 147.6

MS: 294 (1, M$^+$-18), 259 (1), 195 (4), 169 (6), 133 (74), 119 (17), 107 (12), 79 (37), 67 (28), 53 (34)

$[\alpha]_D^{23}$: $-22.57^\circ$ (c=2.075, CH$_2$Cl$_2$)
Vinyl alcohol (76)

To a refluxing solution of 2.37 g (7.6 mmol) of 75 in 20 ml of ethanol was added 11 g (168 mmol) of zinc copper couple. The reaction mixture was heated at 78 °C for 45 min, and an additional 1 g (15 mmol) of zinc copper couple was added. The temperature was maintained at 78 °C for another 15 min, then the solvent was evaporated under reduced pressure to a small volume. Dichloromethane was added to the reaction mixture, filtered, and the filtrate was washed with a 3 N hydrochloric acid solution. The aqueous layer was thoroughly extracted with dichloromethane. The extracts were combined, washed with a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give 1.54 g (94.6%) of 76 as a pale yellow oil.

Characterization of 76:

IR (film): 3470, 3100, 2950, 2880, 1645, 1475, 1440, 1380, 1005, 990, 960, 920, 900, 760, 670

$^1$HNMR (CDCl$_3$): 1.14 (3H, s), 1.66 (1H, dd, $J_1 = 1.7$ Hz, $J_2 = 14.1$ Hz), 1.74 (3H, s), 1.83 (2H, q, $J = 12.7$ Hz), 2.14 (1H, dt, $J_1 = 4.0$ Hz, $J_2 = 13.0$ Hz), 2.55 (1H, tt, $J_1 = 3.8$ Hz, $J_2 = 12.6$ Hz), 3.78 (1H, t, $J = 2.6$ Hz), 4.45 (1H, dd, $J_1 = 4.4$ Hz, $J_2 = 12.3$ Hz), 4.74 (3H, s), 5.31 (2H, dd, $J_1 = 11.0$ Hz, $J_2 = 17.7$ Hz), 5.93 (1H, dd, $J_1 = 11.0$ Hz, $J_2 = 17.7$ Hz)
$^{13}$CNMR (CDCl$_3$): 17.2, 20.8, 31.8, 37.1, 38.3, 46.7, 62.5, 74.9, 109.5, 116.0, 143.3, 147.9

MS: 199 (12, M$^+$−18), 198 (11), 196 (23), 178 (31), 170 (51), 161 (99), 145 (29), 135 (57), 119 (19), 84 (8), 67 (6), 49 (25)

[α]$_D^{23}$: −79.74° (c=1.51, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{12}$H$_{19}$Cl$_1$O$_1$ 214.1124
Found 214.1124
Vinyl ketone (56)

To a solution of 1.54 g (7.2 mmol) of alcohol 76 in 10 ml of acetone was added Jones reagent dropwise until TLC indicated the completion of the reaction. Excess Jones reagent was destroyed by adding a small amount of isopropanol. The solution was evaporated to a small volume before it was taken up in water and dichloromethane. The aqueous layer was extracted thoroughly with dichloromethane. The combined extracts were washed with a sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Purification by flash chromatography eluting with 10% ether in hexanes afforded 1.52 g (99%) of 56 as white crystals.

Characterization of 56:

mp: 58-59 °C (30% ether-hexanes)

IR (film): 3100, 2990, 2950, 1720, 1650, 1445, 1375, 1240, 995, 925, 890, 850, 740

$^1$HNMR (CDCl$_3$): 1.14 (3H, s), 1.66 (1H, dd, $J_1 = 1.7$ Hz, $J_2 = 14.1$ Hz), 1.74 (3H, s), 1.83 (2H, q, $J = 12.7$ Hz), 2.14 (1H, dt, $J_1 = 4.0$ Hz, $J_2 = 13.0$ Hz), 2.55 (1H, tt, $J_1 = 3.8$ Hz, $J_2 = 12.6$ Hz), 3.78 (1H, t, $J = 2.6$ Hz), 4.45 (1H, dd, $J_1 = 4.4$ Hz, $J_2 = 12.3$ Hz), 4.74 (3H, s), 5.31 (2H, dd, $J_1 = 11.0$ Hz, $J_2 = 17.7$ Hz), 5.93 (1H, dd, $J_1 = 11.0$ Hz, $J_2 = 17.7$ Hz)
$^{13}$CNMR (CDCl$_3$): 15.9, 20.2, 36.6, 41.4, 42.1, 57.0, 64.0, 110.8, 116.6, 138.7, 145.4, 209.5

MS: 214 (<1, M+2), 212 (1, M+), 149 (6), 135 (10), 102 (16), 91 (21), 81 (79), 66 (83), 52 (81), 41 (100), 39 (100)

$[\alpha]_D^{23}$: +7.34° (c=1.775, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{12}$H$_{17}$ClO$_1$ 212.0968
Found 212.0968
Aldol products (112)

To a solution of 459 mg (2.17 mmol) of ketone 56 in 5 ml of tetrahydrofuran at −78 °C under argon was added 3.85 ml (0.619 M, 2.38 mmol) of lithium diisopropylamide in tetrahydrofuran. After stirring for 5 min at −78 °C, 644 μl (2.17 mmol) of titanium tetra(isopropoxide) was introduced followed by 603 mg (2.60 mmol) of o-iodobenzaldehyde in tetrahydrofuran. The reaction mixture was stirred at −78 °C for 30 min before it was poured into a 1:1 mixture of saturated aqueous sodium chloride solution and 3 N hydrochloric acid solution. The aqueous layer was thoroughly extracted with ether. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The crude product was separated by flash chromatography eluting with 20%-40% ether in hexanes to give 658 mg (68.4%) of 112 as a pale yellow oil.

Characterization of major isomer 112a:

IR (film): 3510, 3100, 2960, 2920, 1700, 1650, 1460, 1440, 1290, 1010, 930, 895, 760

¹HNMR (CDCl₃): 1.08 (3H, s), 1.51 (3H, s), 2.15 (1H, m), 2.10 (1H, d, J_AB = 13.1 Hz), 2.25 (1H, d, J_AB = 13.1 Hz), 2.83 (1H, dt, J₁ = 4.5 Hz, J₂ = 12.2 Hz), 3.58 (1H, dd, J₁ = 1.4 Hz, J₂ = 12.1 Hz), 4.11 (1H, dd, J₁ = 4.8 Hz, J₂ = 12.1 Hz), 4.47 (1H, s), 4.75 (1H, s), 5.23 (1H, d, J = 17.4 Hz)
Hz), 5.39 (1H, d, J = 10.9 Hz), 6.91 (1H, t, J = 7.6 Hz), 7.23 (1H, t, J = 7.6 Hz), 7.53 (1H, d, J = 7.6 Hz), 7.72 (1H, d, J = 7.6 Hz)

\(^{13}\)CNMR (CDCl\(_3\)):
15.6, 17.2, 38.2, 43.4, 50.4, 57.4, 63.2, 73.5, 97.0, 114.4, 116.4, 127.2, 128.8, 130.1, 138.7, 138.9, 143.1, 144.8, 211.6

MS:
408 (6, M–36), 363 (1), 317 (2), 273 (8), 233 (31), 203 (10), 127 (21), 105 (38), 91 (33), 77 (84), 67 (56), 53 (43), 41 (93)

\([\alpha]_D^{23}\):
–45.96° (c=1.175, CH\(_2\)Cl\(_2\))

Characterization of minor isomer 112b:

IR (film):
3540, 3080, 2940, 2920, 1700, 1640, 1570, 1550, 1460, 1430, 1210, 1140, 1010, 960, 930, 900, 810, 750

\(^{1}\)HNMR (CDCl\(_3\)):
1.30 (3H, s), 1.93 (3H, s), 2.29 (1H, d, J\(_{AB}\) = 12.1 Hz), 2.32 (1H, m), 2.39 (1H, d, J\(_{AB}\) = 12.1 Hz), 2.78 (1H, dt, J\(_1\) = 4.6 Hz, J\(_2\) = 12.2 Hz), 3.54 (1H, dd, J\(_1\) = 2.7 Hz, J\(_2\) = 12.1 Hz), 3.74 (1H, d, J = 10.5 Hz), 4.06 (1H, dd, J\(_1\) = 5.3 Hz, J\(_2\) = 11.6 Hz), 4.83 (1H, d, J = 8.8 Hz), 5.09 (2H, d, J = 25.3 Hz), 5.30 (1H, d, J = 11.0 Hz), 5.88 (1H, dd, J\(_1\) = 11.0 Hz, J\(_2\) = 17.5 Hz), 6.94 (1H, t, J = 7.7 Hz), 7.33 (1H, t, J = 7.7 Hz), 7.60 (1H, d, J = 7.7 Hz), 7.75 (1H, d, J = 7.7 Hz)

\(^{13}\)CNMR (CDCl\(_3\)):
14.8, 20.4, 37.0, 46.3, 50.9, 58.2, 63.7, 75.0, 96.7, 115.6, 116.5, 128.0, 129.0, 129.3, 138.2, 139.5, 142.5, 143.8, 212.6

MS:
445 (<1, M+1), 444 (1, M\(^+\)), 409 (20), 363 (5), 317 (8), 233 (52), 203 (9), 176 (9), 127 (32), 79 (51), 77 (53), 67 (42), 39 (65)

\([\alpha]_D^{23}\):
+35.94° (c=1.320, CH\(_2\)Cl\(_2\))
Tricyclic enone (113)

To 479 mg (0.37 mmol) of alcohol 112 was added 2 ml of acetic anhydride and 2 ml of pyridine. After stirring at 60 °C for 8 h, the reaction mixture was cooled and evaporated to dryness at room temperature.

The above residue was dissolved in 2 ml of benzene and treated with 148 µl (0.99 mmol) of DBU. The reaction mixture was refluxed for 2 h, then partitioned between ether and a 3 N hydrochloric acid solution. The organic extracts were washed with a saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure.

To the above residue was added 700 µl of trifluoroacetic acid and 70 µl of methanesulfonic acid. After the reaction mixture was stirred at room temperature for 10 min, it was poured into a saturated aqueous sodium bicarbonate solution. The aqueous layer was thoroughly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. A flash silica gel chromatography separation employing a solvent gradient from 20% to 60% ether-hexanes afforded 405 mg (88.2%) of 113 as yellow crystals.
Characterization of 113:

**mp:** 187-188 °C (30% ether-hexanes)

**IR (film):**
3090, 2970, 2930, 1670, 1590, 1550, 1440, 1370, 1240, 1140, 1080, 1010, 930, 780

**$^1$HNMR (CDCl$_3$):**
0.99 (3H, s), 1.39 (3H, s), 1.46 (3H, s), 2.24 (1H, t, J = 11.9 Hz), 2.45 (1H, m), 2.82 (1H, m), 4.36 (1H, dd, J$_1$ = 3.5 Hz, J$_2$ = 11.5 Hz), 5.29 (1H, d, J = 17.4 Hz), 5.35 (1H, d, J = 10.8 Hz), 5.89 (1H, dd, J$_1$ = 10.8 Hz, J$_2$ = 17.4 Hz), 7.02 (1H, t, J = 7.8 Hz), 7.35 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.94 (1H, d, J = 3.1 Hz)

**$^{13}$CNMR (CDCl$_3$):**
17.3, 22.0, 24.0, 29.5, 38.9, 41.6, 55.3, 62.9, 102.9, 116.8, 123.9, 131.9, 132.6, 133.2, 138.2, 139.1, 140.0, 148.9, 198.1

**MS:**
427 (14, M+1), 426 (27, M$^+$), 425 (31), 344 (82), 316 (32), 309 (38), 294 (25), 282 (32), 267 (10), 218 (12), 183 (32), 153 (49), 152 (49), 139 (57), 81 (91), 53 (63), 41 (73)

**[$\alpha$]$_D^{23}$:**
+56.30° (c=0.341, CH$_2$Cl$_2$)

**Exact Mass:**
Calculated for C$_{19}$H$_{20}$Cl$_2$I$_1$O$_1$ 426.0247
Found 426.0249
Tricyclic acid (116)

To a solution of 301 mg (0.71 mmol) of 113 in 4 ml of 8:1 acetonitrile and water was added 393 μl (2.84 mmol) of triethylamine, 55 mg (0.21 mmol) of triphenyl phosphine and 16 mg (0.07 mmol) of palladium acetate. After the reaction mixture was heated at 80 °C for 1 h under 1 atm of carbon monoxide, an additional 16 mg (0.07 mmol) of palladium acetate was added. The heating was continued for 2 h before it was partitioned between water and ether. The aqueous layer was acidified with a 3 N hydrochloric acid solution and thoroughly extracted with dichloromethane. The combined dichloromethane layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 80% ether-hexanes to give 195 mg (80.2%) of 116 as a pale white solid.

Characterization of 116:

mp: 230-232 °C (dichloromethane)

IR (film): 3570-3100, 2990, 2950, 1730, 1670, 1600, 1560, 1450, 1370, 1250, 1200, 1140, 1000, 930, 820, 760

$^1$HNMR (CDCl$_3$): 1.01 (3H, s), 1.39 (3H, s), 1.51 (3H, s), 2.26 (1H, t, J = 12.1 Hz), 2.46 (1H, m), 2.83 (1H, m), 4.37 (1H, dd, $J_1$ = 3.5 Hz, $J_2$ = 11.7 Hz), 5.31 (2H, dd, $J_1$ = 10.8 Hz, $J_2$
= 17.3 Hz), 5.88 (1H, dd, J1 = 10.8 Hz, J2 = 17.3 Hz),
7.43 (1H, t, J = 7.7 Hz), 7.60 (1H, d, J = 7.7 Hz), 7.89
(1H, d, J = 7.7 Hz), 8.59 (1H, d, J = 2.6 Hz)

13C NMR (CDCl3): 17.1, 21.9, 24.2, 29.5, 37.9, 40.8, 55.3, 62.8, 102.8,
116.7, 128.1, 129.6, 130.2, 131.1, 132.3, 134.2, 139.1,
147.9, 172.0, 198.6

MS: 344 (2, M+), 263 (6), 227 (99), 213 (13), 199 (10), 165
(10), 128 (21), 115 (14), 81 (40), 53 (18), 41 (17)

[α]D25: +3.94° (c=1.04, CH2Cl2)

Exact Mass: Calculated for C20H21Cl1O3 
Found 344.1179
344.1183
Allyl urethane (117)

To a solution of 100 mg (0.29 mmol) of 116 in 2 ml of toluene was added 81 μl (0.58 mmol) of triethylamine, 200 μl (2.9 mmol) of allyl alcohol and 94 μl (0.44 mmol) of diphenylphosphoryl azide. The reaction mixture was refluxed for 1 h before it was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 20% ether-hexanes to give 105 mg (90.0%) of 117 as a yellow oil.

Characterization of 117:

mp: 74-75 °C (ether-hexanes)

IR (film): 3120, 3080, 2980, 2950, 1730, 1670, 1590, 1570, 1530, 1460, 1280, 1220, 1070, 1000, 920, 780

$^1$HNMR (CDCl$_3$): 0.96 (3H, s), 1.38 (3H, s), 1.47 (3H, s), 2.23 (1H, t, J = 11.9 Hz), 2.43 (1H, m), 2.76 (1H, m), 4.35 (1H, dd, J$_1$ = 3.5 Hz, J$_2$ = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz), 5.26 (1H, d, J = 17.4 Hz), 5.26 (1H, d, J = 11.1 Hz), 5.32 (1H, d, J = 11.5 Hz), 5.36 (1H, d, J = 17.4 Hz), 5.86 (1H, dd, J$_1$ = 11.5 Hz, J$_2$ = 17.4 Hz), 5.95 (1H, m), 6.93 (1H, s), 7.17 (1H, d, J = 7.9 Hz), 7.36 (1H, t, J =
7.9 Hz), 7.66 (1H, d, J = 7.9 Hz), 7.85 (1H, d, J = 3.0 Hz)

$^{13}$CNMR (CDCl$_3$): 17.3, 21.9, 24.1, 29.4, 38.1, 41.2, 55.2, 62.9, 66.2, 116.7, 118.4, 120.0, 121.1, 129.9, 130.1, 131.3, 131.6, 132.2, 136.1, 139.2, 147.6, 153.7, 198.6

MS: 399 (8, M$^+$), 318 (49), 282 (99), 242 (23), 197 (45), 170 (21), 154 (29), 143 (12), 127 (14), 115 (12), 81 (21), 41 (99)

$[\alpha]_D^{23}$: +143.76° (c=0.882, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{23}$H$_{26}$Cl$_1$N$_1$O$_3$ 399.1601
Found 399.1600
Indole ketone (119)

To a solution of 157 µl (1.5 mmol) of methyl (methylthio)methyl sulfoxide in 1.5 ml of tetrahydrofuran at -78 °C was added 645 µl (2.33M, 1.5 mmol) of n-butyllithium. After stirring for 5 min, 120 mg (0.3 mmol) of 117 in 2.5 ml of tetrahydrofuran was introduced via syringe. The reaction mixture was stirred at -78 °C for 15 min before it was quenched by adding 1 ml of water. The reaction was warmed to room temperature, and 500 µl of perchloric acid (60% in water) was added followed by 408 mg (1.5 mmol) of mercuric chloride. The reaction mixture was refluxed for 1 h. After cooling to room temperature, the reaction mixture was passed through a small celite pad and partitioned between ether and a saturated sodium bicarbonate solution. The extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crude residue was purified on a preparative silica gel TLC developed with 40% ether-hexanes to give 85 mg (68.8%) of 119 as a yellow oil.

Characterization of 119:

IR (film): 3140, 2990, 2910, 1740, 1640, 1600, 1570, 1440, 1390, 1270, 1230, 1170, 1110, 1080, 930, 750, 700

$^1$HNMR (CDCl$_3$): 1.21 (3H, s), 1.53 (3H, s), 1.54 (3H, s), 1.96 (1H, dt, $J_1$ = 3.7 Hz, $J_2$ = 12.7 Hz), 2.37 (1H, d, $J$ = 11.9 Hz), 2.59
\begin{itemize}
  \item \(1H, \text{ dt, } J_1 = 4.3 \text{ Hz, } J_2 = 13.6 \text{ Hz} \), \(3.90 \text{ (1H, dd, } J_1 = 1.6 \text{ Hz, } J_2 = 12.7 \text{ Hz}) \), \(4.19 \text{ (1H, dd, } J_1 = 4.3 \text{ Hz, } J_2 = 11.3 \text{ Hz}) \), \(4.89 \text{ (2H, d, } J = 5.7 \text{ Hz}) \), \(5.92 \text{ (1H, dd, } J_1 = 10.7 \text{ Hz, } J_2 = 17.3 \text{ Hz}) \), \(6.05 \text{ (1H, m), } 7.17 \text{ (1H, d, } J = 7.6 \text{ Hz}) \), \(7.29 \text{ (1H, t, } J = 7.6 \text{ Hz}) \), \(7.89 \text{ (1H, d, } J = 1.6 \text{ Hz}) \), \(7.90 \text{ (1H, d, } J = 7.6 \text{ Hz}) \)

\begin{itemize}
  \item \( ^{13} \text{CNMR (CDCl}_3) \): \(16.9, 24.5, 24.6, 32.3, 37.9, 42.9, 46.4, 57.3, 64.2, 67.3, 112.8, 112.9, 116.7, 117.0, 119.2, 121.8, 125.2, 127.2, 131.5, 133.3, 138.8, 139.3, 150.9, 207.5 \)

\begin{itemize}
  \item \( \text{MS:} \) \(413 \text{ (18, } M+2) \), \(411 \text{ (69, } M^+) \), \(368 \text{ (8) \), 348 (13) \), 314 (13) \), \(252 (35) \), \(208 (65) \), \(182 (58) \), \(168 (44) \), \(154 (23) \), \(128 (99) \), \(115 (17) \), \(84 (45) \), \(81 (65) \), \(67 (19) \), \(57 (39) \), \(41(73) \)

\begin{itemize}
  \item \([\alpha]_D^{23}: +63.15^\circ \text{ (c}=1.67, \text{ CH}_2\text{Cl}_2)\)

\begin{itemize}
  \item \( \text{Exact Mass:} \) Calculated for \( \text{C}_{24}\text{H}_{26}\text{Cl}_1\text{N}_1\text{O}_3 \) \(411.1601 \)
  \item Found \(411.1603 \)
\end{itemize}
\end{itemize}
\end{itemize}
\end{itemize}
Indole alcohol (124)

To a stirred solution of 65 mg (0.16 mmol) of 119 in 1 ml of methanol at room temperature was added 29 mg (0.79 mmol) of sodium borohydride. The reaction mixture was stirred for 10 min before it was taken up in dichloromethane, and washed with a 1:1 mixture of 3 N hydrochloric acid solution and brine. The aqueous layer was thoroughly extracted with dichloromethane, and the combined extracts were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, evaporated, and separated on a preparative silica gel TLC developed with 40% ether-hexanes to give 60 mg (91.4%) of 124 as a white foam.

Characterization of 124:

IR (film): 3560, 3100, 3070, 2970, 2890, 1730, 1600, 1440, 1390, 1350, 1280, 1260, 1220, 1110, 930, 760, 700

$^1$HNMR (CDCl$_3$): 1.15 (3H, s), 1.28 (3H, s), 1.46 (3H, s), 1.61 (1H, dt, $J_1$ = 3.5 Hz, $J_2$ = 12.5 Hz), 2.02 (1H, t, $J$ = 12.6 Hz), 2.27 (1H, dt, $J_1$ = 3.8 Hz, $J_2$ = 13.1 Hz), 2.94 (1H, t, $J$ = 10.5 Hz), 3.47 (1H, t, $J$ = 5.4 Hz), 3.93 (1H, dd, $J_1$ = 4.1 Hz, $J_2$ = 12.2 Hz), 4.87 (2H, d, $J$ = 5.8 Hz), 5.38 (4H, m), 5.76 (1H, dd, $J_1$ = 10.7 Hz, $J_2$ = 17.3 Hz), 6.03 (1H, m), 7.16 (1H, d, $J$ = 7.6 Hz), 7.29 (1H, t, $J$ = 7.6 Hz), 7.75 (1H, s), 7.87 (1H, d, $J$ = 7.6 Hz)
$^{13}$CNMR (CDCl$_3$): 9.76, 24.7, 24.8, 31.8, 34.8, 37.1, 46.7, 49.5, 65.6, 67.2,
77.4, 112.7, 116.8, 117.4, 119.0, 119.3, 120.6, 125.1,
127.6, 131.6, 133.4, 140.7, 144.0, 151.1

MS: 415 (10, M+2), 413 (45, M$^+$), 354 (17), 329 (6), 262
(10), 218 (12), 208 (15), 182 (26), 168 (36), 154 (21),
128 (39), 105 (35), 84 (99), 55 (36), 51 (68), 41 (66)

$[\alpha]_D^{23} -5.38^\circ$ (c=2.515, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{24}$H$_{28}$Cl$_1$N$_1$O$_3$ 413.1758
Found 413.1759
**Indole mesylate (125)**

To a stirred solution of 55 mg (0.13 mmol) of alcohol 124 in 1 ml of pyridine was added 100 mg (0.39 mmol) of methanesulfonic anhydride. After the reaction mixture was heated at 65 °C for 30 min, an additional 50 mg (0.20 mmol) of methanesulfonic anhydride was introduced. The heating was continued for 30 min while the progress of the reaction was carefully monitored by TLC. After the reaction was completed, as indicated by TLC, it was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid solution and brine. The combined extracts were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, evaporated, and separated on a preparative silica gel TLC developed with 40% ether-hexanes to give 54 mg (82.1%) of 125 as a white solid.

**Characterization of 125:**

mp: 181-182 °C (CH₂Cl₂)

**IR (KBr):**

3160, 3100, 2970, 2900, 1740, 1440, 1390, 1350, 1270, 1175, 1120, 1080, 940, 910, 760, 730, 700

**¹H NMR (CDCl₃):**

1.12 (3H, s), 1.38 (3H, s), 1.47 (3H, s), 1.72 (1H, dt, J₁ = 3.0 Hz, J₂ = 12.0 Hz), 1.93 (1H, q, J = 12.7 Hz), 2.35 (1H, dt, J₁ = 3.7 Hz, J₂ = 13.1 Hz), 3.22 (3H, s), 3.32 (1H, dt, J₁ = 1.6 Hz, J₂ = 11.7 Hz), 3.82 (1H, dd, J₁ =
4.1 Hz, J₂ = 12.2 Hz), 4.91 (3H, m), 5.31 (1H, d, J = 10.5 Hz), 5.47 (2H, m), 6.04 (2H, m), 5.98 (1H, dd, J₁ = 10.8 Hz, J₂ = 17.7 Hz), 6.03 (1H, m), 7.15 (1H, d, J = 7.7 Hz), 7.29 (1H, t, J = 7.7 Hz), 7.91 (1H, d, J = 7.7 Hz), 8.38 (1H, d, J = 1.6 Hz)

$^{13}$CNMR (CDCl₃):
10.1, 24.8, 24.9, 31.7, 35.1, 37.3, 41.0, 46.5, 49.4, 63.7, 67.2, 89.9, 112.7, 116.0, 116.5, 118.3, 118.5, 121.0, 125.1, 127.4, 131.5, 133.3, 139.8, 143.5, 150.9

MS:
493 (14, M⁺2), 491 (36, M⁺), 395 (28), 380 (40), 360 (10), 333 (12), 318 (22), 274 (23), 252 (28), 208 (48), 182 (45), 168 (55), 154 (18), 141 (18), 79 (30), 41 (55)

$[\alpha]_D^{23}$: -11.38° (c=1.950, CH₂Cl₂)

Exact Mass:
Calculated for C₂₅H₃₀Cl₇N₇O₅S₇ 491.1533
Found 491.1537
Indole azide (126)

To a stirred solution of 45 mg (0.092 mmol) of 125 and 90 mg (1.85 mmol) of lithium azide in 1 ml of N,N-dimethylformamide was added 20 µl of water. The mixture was stirred at 100 °C for 36 h before it was partitioned between ether and a diluted brine. The aqueous layer was thoroughly extracted with ether. The combined extracts were washed with a saturated aqueous sodium chloride solution once again, dried over anhydrous sodium sulfate and evaporated to dryness in vacuo. A preparative silic gel TLC separation developed with 2:1 hexanes-ethyl acetate gave 31 mg (95.8%) of indole azide 126 as a white solid.

Characterization of 126:

mp : 242-243 °C (decomposed) (50% ether-hexanes)

IR (KBr): 3400, 3080, 2960, 2910, 2105, 1620, 1600, 1470, 1440, 1350, 1340, 1290, 1180, 960, 930, 780, 750, 690

$^1$HNMR (CDCl$_3$): 1.14 (3H, s), 1.41 (3H, s), 1.50 (3H, s), 1.98 (1H, t, J = 12.4 Hz), 2.07 (1H, dt, J$_1$ = 2.8 Hz, J$_2$ = 12.7 Hz), 2.34 (1H, m), 3.39 (1H, d, J = 10.9 Hz), 4.09 (1H, d, J = 2.6 Hz), 4.40 (1H, dd, J$_1$ = 4.7 Hz, J$_2$ = 11.9 Hz), 5.35 (1H, d, J = 17.6 Hz), 5.38 (1H, d, J = 10.9 Hz), 6.14 (1H, dd, J$_1$ = 11.0 Hz, J$_2$ = 17.6 Hz), 6.88 (1H, d, J = 1.9 Hz), 7.05 (2H, m), 7.18 (1H, m), 8.07 (1H, s)
$^{13}$CNMR (CDCl$_3$): 16.7, 24.3, 24.9, 32.6, 34.8, 37.2, 43.8, 46.4, 63.7, 73.7, 108.4, 112.8, 113.0, 115.6, 116.2, 123.2, 125.3, 134.1, 140.5, 143.8

MS: 356 (2, M+2), 454 (6, M+), 284 (1), 264 (1), 182 (21), 168 (99), 154 (13), 81 (8)

$[\alpha]_D^{23}$: $-52.66^\circ$ (c=0.970, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{20}$H$_{23}$Cl$_1$N$_4$ 354.1611
Found 354.1614
Indole formamide (128)

To a solution of 14.5 mg (0.041 mmol) of 126 in 2 ml of ethanol at 78 °C was added portionwise 140 mg of sodium amalgam (3%). After 15 min, another 140 mg of sodium amalgam (3%) was added. The progress of the reaction was carefully monitored by TLC. An additional 140 mg of sodium amalgam (3%) was added after 30 min. After the TLC indicated the completion of the reaction, the reaction mixture was partitioned between dichloromethane and a saturated aqueous sodium chloride solution. The aqueous layer was thoroughly extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*.

The above residue was dissolved in 1 ml of dichloromethane and was treated successively with 8 μl (0.2 mmol) of formic acid, 33 μl (0.4 mmol) of pyridine, and 8 μl (0.08 mmol) of acetic anhydride. The reaction was allowed to stirred at room temperature for 15 min. Then it was partitioned between dichloromethane and a 1:1 mixture of 3 N hydrochloric acid and brine. The aqueous layer was thoroughly extracted with dichloromethane. The combined extracts were washed with a saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified on a preparative silica gel TLC which was
developed with 5% methanol-dichloromethane to give 12.3 mg (84.4%) of 118 as a white solid.

Characterization of 118:

mp: 252-254 °C (decomposed) (MeOH)

IR (KBr): 3400, 3300, 3050, 2960, 2900, 1675, 1500, 1440, 1380, 1190, 1100, 930, 780, 760, 720

$^1$HNMR (DMSO-d$_6$):
0.24 (3H, s), 0.52 (3H, s), 0.60 (3H, s), 1.13 (1H, qd, J$_1$ = 12.6 Hz, J$_2$ = 16.5 Hz), 1.42 (1H, m), 1.67 (1H, s), 2.45 (1H), 3.69 (1H, dd, J$_1$ = 4.3 Hz, J$_2$ = 11.5 Hz), 3.87 (1H, dd, J$_1$ = 3.5 Hz, J$_2$ = 10.8 Hz), 4.26 (1H, d, J = 11.2 Hz), 4.38 (1H, d, J = 18.3 Hz), 4.94 (1H, dd, J$_1$ = 10.9 Hz, J$_2$ = 18.3 Hz), 5.92 (1H, s), 6.07 (1H, d, J = 7.4 Hz), 6.17 (1H, t, J = 7.4 Hz), 6.27 (1H, d, J = 7.4 Hz), 6.99 (1H, s), 7.12 (1H, d, J = 11.2 Hz), 9.79 (1H, s)

$^{13}$CNMR (DMSO-d$_6$):
16.7, 24.4, 24.9, 32.6, 33.2, 36.9, 43.8, 45.2, 53.6, 64.6, 108.4, 110.0, 111.6, 114.3, 117.2, 121.7, 125.2, 133.7, 139.6, 143.3, 160.8

MS:
358 (5, M+2), 356 (26, M+), 341 (5), 311 (9), 296 (13), 234 (8), 194 (15), 182 (16), 180 (16), 168 (44), 154 (11), 141 (11), 115 (13), 44 (78)

$[\alpha]_D^{23}$: −88.39° (c=0.445, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_{21}$H$_{25}$N$_2$Cl$_1$O 356.1655
Found 356.1655
(-)-Hapalindole G (7)

To an ice cold solution of 8.4 mg (0.02 mmol) of 128 and 50 µl (0.35 mmol) of triethylamine in 1 ml of dichloromethane was added dropwise a solution of phosgene in dichloromethane. The progress of the reaction was carefully monitored by TLC. After the TLC indicated the complete consumption of 128, the reaction mixture was warmed to room temperature, taken up into dichloromethane and a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted thoroughly with dichloromethane. The extracts were combined, washed with brine, dried over sodium sulfate, filtered, and evaporated in vacuo. The crude product was purified on a preparative silica gel TLC developed with 4:2:1 hexanes-ethyl acetate-dichloromethane to give 7.2 mg (90.3%) of 7 as a white solid.

Characterization of 7:

mp: 186-188 °C (decomposed) (CH₂Cl₂)

IR (KBr): 3410, 3050, 2960, 2930, 2860, 2150, 1720, 1640, 1610, 1470, 1440, 1350, 1180, 1080, 780, 690

¹HNMR (CDCl₃): 1.17 (3H, s), 1.39 (3H, s), 1.52 (3H, s), 2.02 (1H, t, J = 12.4 Hz), 2.12 (1H, dt, J₁ = 2.7 Hz, J₂ = 12.7 Hz), 2.41 (1H, m), 3.32 (1H, d, J = 10.2 Hz), 4.24 (1H, d, J = 3.1 Hz), 4.43 (1H, dd, J₁ = 4.7 Hz, J₂ = 11.9 Hz), 5.36 (1H, d, J = 11.0 Hz), 5.39 (1H, d, J = 17.4 Hz), 6.14
(1H, dd, $J_1 = 11.0$ Hz, $J_2 = 17.4$ Hz), 6.89 (1H, s), 7.04 (1H, m), 7.18 (1H, m), 7.20 (1H, m), 8.05 (1H, s)

$^{13}$CNMR (CDCl$_3$): 16.0, 24.3, 25.1, 30.0, 32.4, 33.5, 37.4, 44.2, 62.3, 64.7, 108.5, 111.4, 113.1, 116.3, 116.5, 123.2, 125.3, 134.1, 140.0, 142.2, 158.7

MS: 340 (1, M+2), 338 (5, M+), 323 (8), 260 (4), 206 (17), 182 (43), 168 (99), 154 (43), 140 (29), 115 (42), 79 (40), 67 (27), 53 (24), 41 (61)

$[\alpha]_D^{23}$: $-45.04^\circ$ (c=0.037, CH$_2$Cl$_2$)

Exact Mass: Calculated for C$_21$H$_{23}$N$_2$Cl$_1$ 338.1550

Found 338.1548

Reported data for (−)-hapalindole G:$^2$

mp: >184 °C (decompose)

$^1$HNMR (CDCl$_3$): 1.17 (3H, s), 1.39 (3H, s), 1.52 (3H, s), 2.01 (1H, d, $J = 12.5$ Hz), 2.11 (1H, ddd, $J_1 = 3.0$ Hz, $J_2 = 12.5$ Hz, $J_3 = 4.5$ Hz), 2.41 (1H, ddd, $J_1 = 3.0$ Hz, $J_2 = 12.5$ Hz, $J_3 = 4.5$ Hz), 3.32 (1H, br dm), 4.24 (1H, br d, $J = 3.1$ Hz), 4.43 (1H, dd, $J_1 = 4.5$ Hz, $J_2 = 11.9$ Hz), 5.34 (1H, dd, $J_1 = 17.4$ Hz, $J_2 = 0.5$ Hz), 5.39 (1H, dd, $J_1 = 10.9$ Hz, $J_2 = 0.5$ Hz), 6.14 (1H, dd, $J_1 = 10.9$ Hz, $J_2 = 17.4$ Hz), 6.89 (1H, dd, $J_1 = 1.6$ Hz, $J_2 = 2.2$ Hz), 7.04 (1H, m), 7.18 (1H, m), 7.20 (1H, m), 8.04 (1H, br)

$[\alpha]_D^{23}$: $-43.9^\circ$ (c=0.28, CH$_2$Cl$_2$)

Exact Mass: Found 338.1530
PART TWO: A NOVEL TIN-MEDIATED INDOLE SYNTHESIS

Chapter I

Introduction

The indole nucleus is a very important constituent of a wide variety of natural products. The significance of the indole moiety is not only demonstrated by the role it plays in the medicinally important compounds, but also by the wealth of synthetic methodology developed to construct this aromatic ring system. A search for efficient syntheses of indoles has been the subject of intensive investigation for nearly a century. Starting with the discovery of the most classical Fischer indole synthesis, a large number of preeminent methods have been developed to date. However, the need for the development of new, versatile, and regiospecific indole syntheses has never ceased. During the course of our search for novel indole formation reactions, we discovered a novel tin-mediated indole synthesis, which is especially suited for the regiospecific formation of 3-substituted and 2,3-disubstituted indoles. Before discussing our results on this new indole synthesis in detail, it may be necessary to survey existing methods. Since there have been several excellent reviews that cover different aspects of this particular area, the following introduction is going to illustrate only newly developed and versatile methods that have significant potential in the synthesis of complex natural products.

Synthesis of indoles can be divided into five categories according to the mechanism of the key bond formation during the cyclization process. Type A-D can be classified as indolization reactions by using selectively functionalized arenes. As indicated in Figure 1, different bond dissections around the pyrrole
ring, shown by the dashed bond, classifies types A - D indolization processes. The fifth synthetic method does not fall in the A - D categories because it is based on strategies exemplified by benzannulation.

![Figure 1](image)

The first type of indolization, the most highly developed one, permits the preparation of indoles with a wide range of substituents at position 2 and on the benzene ring. The majority of indole syntheses belong to this category. The modified Batcho-Leimgruber method, using the o-nitrotoluene and N,N-dimethylformamide dimethyl-acetal strategy (entry 1 - 5), is perhaps the most well known among these newly developed methods. Modifications of this reaction have been developed to meet some specific requirements, however, a strategic similarity is noticeable in all of those variations. Several newly developed indole syntheses rely with application of a hetero-Cope rearrangement (entry 6 - 13). All of the precursors are elegantly set up for the sigmatropic rearrangement. The famous Fischer and Gassman indole syntheses are the forerunners of these rearrangement strategies. It is worth mentioning that the reaction in entry 13 is accelerated by the free radical initiator AIBN, which suggests the involvement of an acyl nitroxide radical that rearranges to provide an O-acyl phenylhydroxylamine derivative capable of undergoing a hetero-Cope rearrangement.3 The long known regioselectivity problem of the classical Fischer indole synthesis has also been improved recently (entry 32). The
widespread use of transition metals in organic synthesis has strongly influenced the recent strategy for indole synthesis. The substrates usually have functional groups, like vinyl or acetylene group, which can be coordinated to a transition metal to form stable reactive, organometallic intermediates. The indoles are subsequently formed after the collapse of those complexes. The transition-metal indole syntheses allow the use of somewhat unconventional starting materials with unusual reactivity patterns to produce complex indole products. These synthetic methods have and will continue to have wide usage in the preparation of natural products and medicinally important compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Intermediate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate Image" /></td>
<td>(1) (MeO)_2CHNMe_2&lt;br&gt;DMF, 105 °C&lt;br&gt;(2) H_2, Pd/C, MeCO_2Et</td>
<td><img src="image2.png" alt="Intermediate Image" /></td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Substrate Image" /></td>
<td>Ni_2B, N_2H_4 H_2O, Δ</td>
<td><img src="image5.png" alt="Intermediate Image" /></td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Substrate Image" /></td>
<td>Cl·Me_2N=NN·Me_2&lt;br&gt;NaH&lt;br&gt;then H_2, Pd/C</td>
<td><img src="image8.png" alt="Intermediate Image" /></td>
<td><img src="image9.png" alt="Product Image" /></td>
<td>6</td>
</tr>
</tbody>
</table>
9. 
\[
\begin{align*}
\begin{array}{c}
\text{H} \\
\text{MgBr}
\end{array}
\end{align*}
\]
(1) H₂O, KHSO₄
(2) 110 °C
(3) R₁ = H, OMe, Br
R₂ = H, OMe

10. 
\[
\begin{align*}
\begin{array}{c}
\text{OH} \\
\text{O-Ph}
\end{array}
\end{align*}
\]
(1) R₁R₂CHCCl
(2) LDA, -90 °C, TMSCl
(3) DCC

11. 
\[
\begin{align*}
\begin{array}{c}
\text{S} \\
\text{CH₂CH₂O₂CCH₃}
\end{array}
\end{align*}
\]
(1) PhSO₂Cl
(2) H⁺
(3) Et₃N

12. 
\[
\begin{align*}
\begin{array}{c}
\text{CO₂Me}
\end{array}
\end{align*}
\]
R₃N

13. 
\[
\begin{align*}
\begin{array}{c}
\text{OH}
\end{array}
\end{align*}
\]
Δ or AIBN

14. 
\[
\begin{align*}
\begin{array}{c}
\text{SO₂Ph}
\end{array}
\end{align*}
\]
63 - 93%

15. 
\[
\begin{align*}
\begin{array}{c}
\text{CO₂Me}
\end{array}
\end{align*}
\]
89%

43 - 87%
19
\[
\begin{align*}
\text{(1) } & \text{Pd}^\text{cat} \quad \text{(2) } \text{H}^+ \\
\text{C}:=\text{CH} & \\
\text{NH}_2 & \\
\end{align*}
\]

20
\[
\begin{align*}
\text{(1) } & \text{ROTF, Pd(PPH}_3)_4 \quad \text{Cul, Et}_2\text{NH} \\
\text{Cl} & \\
\text{NH}_2 & \\
\text{NR}_1 & \\
\end{align*}
\]

21
\[
\begin{align*}
\text{(1) } & \text{RCCH, Et}_3\text{N} \quad \text{L}_2\text{PdCl}_2 \\
\text{Br} & \\
\text{NHCO}_2\text{Et} & \\
\text{C}:=\text{CR} & \\
\text{NR}_1 & \\
\end{align*}
\]

22
\[
\begin{align*}
\text{(1) } & \text{PdCl}_2 \quad \text{CuCl, O}_2 \quad \text{HO(CH}_2\text{)_2OH} \\
\text{C}:=\text{CH} & \\
\text{NO}_2 & \\
\text{X} & \\
\end{align*}
\]

23
\[
\begin{align*}
\text{(1) } & \text{CH}_2=\text{CH}_2 \quad \text{Pd(OAc)}_2 \\
\text{Br} & \\
\text{NH}_\text{Ac} & \\
\text{X} & \\
\end{align*}
\]

24
\[
\begin{align*}
\text{C}:=\text{CH} & \\
\text{NH}_\text{Ac} & \\
\text{X} & \\
\end{align*}
\]

60 - 95%  
\[\text{R}_1 = \text{H, Ac} \]  
\[\text{R}_2 = \text{H, n-C}_6\text{H}_{13} \]  

21 - 87%  
\[\text{R} = \text{vinyl, aryl} \]  

65 - 93%  
\[\text{R} = \text{H, Bu, Ph} \]  

49 - 68%  
\[\text{X} = \text{H, 7-CO}_2\text{Me, 5-Me,} \]
\[4\text{-CO}_2\text{Me, 5-CO}_2\text{Me,} \]
\[5\text{-OMe, 6-Me, 6-OMe,} \]
\[6\text{-CO}_2\text{Me,} \]  

26 - 46%  
\[\text{X} = \text{H, 7-CO}_2\text{Me, 5-Me,} \]
\[4\text{-CO}_2\text{Me, 5-CO}_2\text{Me,} \]
\[5\text{-OMe, 6-Me, 6-OMe,} \]
\[6\text{-CO}_2\text{Me, 4-Me, 6-Cl} \]
(1) Pd(II), MeOH
RONO
(2) Fe, CH$_3$COOH

15 - 70%
X = H, 4-OMe, 4-Me,
4-Cl, 4-CO$_2$Me,
5-OMe, 6-Me

Fe(CO)$_5$
or Ru$_5$(CO)$_{12}$
or Rh$_6$(CO)$_{16}$

30 - 70%
R = H, Me,
CO$_2$Me, 2-py

R$_2$=NH$_2$
Ph
R$_2$=N Ph
PhNE$_2$, $\Delta$

60 - 75%
R$_1$ = H, Me
R$_2$ = H, Me

P$_2$O$_5$/CH$_3$SO$_2$H

78 : 22 yield 56%
85 : 15 yield 71%
90 : 10 yield 81%

(1) DMF
(2) H$^+$

40 - 86%
R$_1$ = H, 4-Cl, 5-Cl, 4-F,
5-F, 7-F, 5-OMe, 6-OMe,
5-Me, 4,5-(OMe)$_2$
R$_2$ = H, Me, Et, Ph
Figure 2

The type B indolization process is the formation of the indole 3/3a bond. Few classical methods are well accepted for this strategy of bond formation due to the harsh reaction conditions and strict substrate requirement. Not until recently did organometallic chemistry provide a very nice entry into this type of indolization under mild conditions. As illustrated in Figure 3, a large number of type B indole formations are catalyzed by transition metals. Because o-bromoanilines are easily N-allylated or N-alkynylated to provide ideally suited substrates for palladium-mediated oxidative addition and insertion reactions, extensive research has been conducted on this type of process. Both activated and simple olefins undergo this type of insertion reaction to give indoles in good to excellent yield. Some other types of reagents like SmI₂, Ni(PPh₃)₄, and n-BuLi, are also known to induce the insertion reactions. However, they do not appear to be as attractive as palladium catalysts due to the fact that a range of functional groups are known to tolerate the mild palladium-mediated reaction conditions. Rh₂(OAc)₄ catalyzed decomposition of stabilized diazo compounds provides oxindoles as a result of carbene insertion (entry 43). Because oxindoles are easily transformed to indoles, this method can be regarded as a good supplementary method to the palladium insertion chemistry.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Intermediate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td><img src="image1" alt="Substrate" /></td>
<td>(CF&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;)O&lt;br&gt;CF&lt;sub&gt;3&lt;/sub&gt;COOH, 65 °C</td>
<td><img src="image2" alt="Intermediate" /></td>
<td><img src="image3" alt="Product" /></td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td><img src="image4" alt="Substrate" /></td>
<td>(1) RLi&lt;br&gt;(2) H&lt;sup&gt;+&lt;/sup&gt;</td>
<td><img src="image5" alt="Intermediate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td><img src="image7" alt="Substrate" /></td>
<td>(1) PdCl&lt;sub&gt;2&lt;/sub&gt;(MeCN)&lt;sub&gt;2&lt;/sub&gt;&lt;br&gt;quinone&lt;br&gt;(2) Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, Tol&lt;sub&gt;2&lt;/sub&gt;Br,&lt;br&gt;Et&lt;sub&gt;3&lt;/sub&gt;N, 100 °C</td>
<td><img src="image8" alt="Intermediate" /></td>
<td><img src="image9" alt="Product" /></td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td><img src="image10" alt="Substrate" /></td>
<td>Pd&lt;sup&gt;0&lt;/sup&gt;, 125 °C</td>
<td><img src="image11" alt="Intermediate" /></td>
<td><img src="image12" alt="Product" /></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td><img src="image13" alt="Substrate" /></td>
<td>(1) N&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;&lt;br&gt;(2) O&lt;sub&gt;2&lt;/sub&gt;</td>
<td><img src="image14" alt="Intermediate" /></td>
<td><img src="image15" alt="Product" /></td>
<td>40</td>
</tr>
</tbody>
</table>
40 \[
\begin{align*}
&X \\
&\text{Pd(OAc)}_2 \\
&\text{R}_1 \\
&\text{R}_2 \\
&\text{R}_3 \\
&\text{R}_4
\end{align*}
\]

80 - 95%

\[X = Br, I\]

\[\text{R}_1 = H, Me, CH_2CO_2Et\]

\[\text{R}_2 = Me, OR, Ph\]

41

42

70 - 90%

\[\text{R}_1 = H, Me, Ac\]

\[\text{R}_2 = H, Me, Ph\]

43

44

67 - 98%

\[\text{R}_1 = H, 2-Me, 2,3-Me, 3-Me, 2,3-\text{CH}_2(\text{O})_2, 3,4-\text{CH}_2(\text{O})_2\]

\[\text{R}_2 = Me, Et, En\]

\[\text{R}_3 = H, \text{Ac}\]

45

59 - 77%

\[\text{R} = H, Me, Ph\]
Figure 3

It has been shown that type C indolization has been primarily used for the preparation of 2-substituted indoles. The method most worthy of mention is entry 48, which is elegantly designed to provide a variety of 2-substituted indoles by using an intramolecular Wittig reaction under mild conditions. Entry 47 is also an interesting reaction. A solvent dependent selective benzylic deprotonation of the o-alkylphenyl isocyanides resulted in subsequent intramolecular ring closure to furnish 3-substituted indoles in high yield. Compared to the other types of indole syntheses, however, this type of indolization process has not been studied extensively as also indicated by the rather small number of examples listed in Figure 4.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Intermediate</th>
<th>Product</th>
<th>Ref.</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td><img src="image1" alt="Substrate" /></td>
<td>(1) Ar₂CHO &lt;br&gt;p-TSA &lt;br&gt;(2) NaOH</td>
<td><img src="image2" alt="Intermediate" /></td>
<td><img src="image3" alt="Product" /></td>
<td>47</td>
<td>74 - 92% &lt;br&gt;R = H, Cl, Ph &lt;br&gt;Ar₁ = Ph, Tol &lt;br&gt;Ar₂ = Sub-Ph, furane</td>
</tr>
<tr>
<td>47</td>
<td><img src="image4" alt="Substrate" /></td>
<td>(1) LDA, RX, diglyme &lt;br&gt;(2) LTMP, −78 °C &lt;br&gt;(3) −78 °C to rt.</td>
<td><img src="image5" alt="Intermediate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>48</td>
<td>78 - 100% &lt;br&gt;R = H, Me, i-Bu</td>
</tr>
<tr>
<td>48</td>
<td><img src="image7" alt="Substrate" /></td>
<td>MeONa or t-BuOK &lt;br&gt;toluene, Δ</td>
<td><img src="image8" alt="Intermediate" /></td>
<td><img src="image9" alt="Product" /></td>
<td>49</td>
<td>93 - 97% &lt;br&gt;R = Me, Ph, isopropenyl</td>
</tr>
<tr>
<td>49</td>
<td><img src="image10" alt="Substrate" /></td>
<td>RuH₂(diphos)₂ cat. &lt;br&gt;140 °C</td>
<td><img src="image11" alt="Intermediate" /></td>
<td><img src="image12" alt="Product" /></td>
<td>50</td>
<td>70%</td>
</tr>
<tr>
<td>50</td>
<td><img src="image13" alt="Substrate" /></td>
<td>Ti/C</td>
<td><img src="image14" alt="Intermediate" /></td>
<td><img src="image15" alt="Product" /></td>
<td>51</td>
<td>70 - 90% &lt;br&gt;R = Me, Ph</td>
</tr>
</tbody>
</table>

Figure 4
The most well known reaction for type D indolization is the thermolysis of α-azidocinnamates to the corresponding indoles. This strategy was used in entry 51 on a rather elaborate substrate. The copper(I) salts have long been known to catalyze the reaction of nucleophiles with aromatic halides, and the combination of sodium hydride and copper(I) demonstrated the capability of achieving indolization on a wide range of readily available starting materials in excellent yields (entry 53-54). Other methods in Figure 5 are also very interesting both synthetically and mechanistically.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Intermediate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td><img src="image1" alt="51 Substrate" /></td>
<td>decalin, 190 °C</td>
<td><img src="image2" alt="51 Intermediate" /></td>
<td><img src="image3" alt="51 Product" /></td>
<td>52</td>
</tr>
<tr>
<td>52</td>
<td><img src="image4" alt="52 Substrate" /></td>
<td>PO(OE)₃, 160 °C</td>
<td><img src="image5" alt="52 Intermediate" /></td>
<td><img src="image6" alt="52 Product" /></td>
<td>53</td>
</tr>
</tbody>
</table>

30, 40%
R = N-methylpyrrole, furane
53
\[
\begin{align*}
\text{(1) 50% NaH/ DMF} \\
\text{(2) CuX} \\
\text{(3) Mg\textsuperscript{0} or MgO\textsubscript{2}}
\end{align*}
\]

54
\[
\text{65 - 88\%} \\
R_1 = H, \text{OMe} \\
R_2 = \text{OMe} \\
R_3 = \text{Ac, CO\textsubscript{2}Me}
\]

54
\[
\begin{align*}
\text{MeO} \\
\text{Me} \\
\text{Me}
\end{align*}
\]
\[
\text{NaH, CuI} \\
\text{DMF, \Delta}
\]

55
\[
\begin{align*}
\text{(1) MeLi} \\
\text{(2) n-BuLi} \\
\text{(3) 15 °C/ 2-3 h} \\
\text{(4) H\textsubscript{2}O} \\
\text{(5) AcCl, py}
\end{align*}
\]

55
\[
\text{85%}
\]

56
\[
\begin{align*}
\text{(1) t-BuOCl} \\
\text{(2) Ag\textsubscript{2}CO\textsubscript{3}} \\
\text{CF\textsubscript{3}CO\textsubscript{2}H}
\end{align*}
\]
\[
\text{64 - 96\%} \\
R_1 = \text{Br, Cl, Me, OMe, NHCOMe} \\
R_2 = \text{H, Me, NPhth}
\]

57
\[
\begin{align*}
\text{(EtO\textsubscript{2})POH}
\end{align*}
\]
\[
\text{78 - 82\%} \\
R_1 = \text{H, Me} \\
R_2 = \text{Me, Et}
\]
Figure 5

The last type of indole formation reaction is benzannulation. For the synthesis of multiply substituted benzene rings of the indoles, benzoannelation is the reaction of choice. Some of the examples in Figure 6 constructed the benzene ring by utilizing a Diels-Alder reaction or other pericyclic reaction. Treatment of readily accessible 1-tosylalkenyl isocyanides with Michael acceptors produce substituted pyrroles which undergo sigmatropic rearrangement to give indoles in high yields after DDQ oxidation (entry 61). The inverse electron demand Diels-Alder reaction method, seems to be another very efficient way to synthesize highly substituted indoles, as demonstrated by Boger's extensive studies (entry 68). Pyrrole chemistry has also been extensively used for the synthesis of indoles. It is typified by the intramolecular version of the Vilsmeier-Haack type reaction as shown in entry 67. The other annelation example that needs to be mentioned is entry 72. The original approach was developed by Magnus and was used on the indole substrates, the same approach is now used to form the indole itself. The $o$-quinodimethane type
intermediate was generated in situ by treating the substrate with methyl chloroformate and Hünig's base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Intermediate</th>
<th>Product</th>
<th>Ref.</th>
</tr>
</thead>
</table>
| 60    | ![Substrate](image1) | (1) CH₂O, i-Pr₂NH, CuBr  
(2) 160 °C  
(3) DDQ or MnO₂ | ![Intermediate](image2) | ![Product](image3) | 61   |
|       |           |                     | 36 - 80%  
R₁, R₂, R₃ = H, Me, Et  
R₄ = H, Bn |                     |       |
| 61    | ![Tos](image4) | (1) Ph(CH₂)₄COPh  
 t-BuOK  
(2) Mel  
(3) DDQ | ![Intermediate](image5) | ![Product](image6) | 62   |
|       |           |                     | 83 - 95%  
R₁, R₂ = (CH₂)₃,  
(CH₂)₄, (CH₂)₅ |                     |       |
| 62    | ![MeO₂C](image7) | Mel, DMF | ![Intermediate](image8) | ![Product](image9) | 63   |
|       |           |                     |                | 63%    |       |
(1) Ac₂O, NaOAc
(2) 160 °C

(1) NaH, BnCl
(2) XH₂ = CHY
(3) DDQ

13 - 30%
X = CO₂Me, CN, CHO
Y = H, CO₂Me

17%

13 - 41%
X, Y = O, H, OAc; H, H
Z = OH, OAc, H

84%
The above introduction is a brief summary of the methodologies of indole synthesis. Some of them may need further refinement to accommodate more useful functional groups. Some of them have already been proved to be quite general and useful for the synthesis of complex indole alkaloids. However, this area has by no means been fully exploited yet. New and versatile methodologies will continue to appear, and will be warmly welcomed by the organic chemical community.
Chapter II
A Novel Tin-Mediated Indole Synthesis

It has been known for quite some time that the tributyltin radical adds to isonitriles to form α-stannoimidoyl radicals. In 1968, Saegusa and co-workers reported the first example of a radical reaction of isocyanide with an organotin hydride. It was reported that the isonitrile reacted with trialkyltin hydride to yield a hydrocarbon in high yield. The reaction mechanism is believed to involve an α-stannoimidoyl radical, generated by addition of trialkyltin radical to the isonitrile, which initiates the cleavage of the carbon nitrogen bond to give an alkyl radical followed by reduction with trialkyltin hydride of the alkyl radical. Since that finding, this reaction was quickly adopted by synthetic chemists as a general procedure for deamination. However, the deamination can only be applied to the aliphatic isonitriles. The aromatic isonitriles cannot be reduced under the tin hydride conditions. Although the trialkyltin radical does

\[
\begin{align*}
C_6H_{11}NC & \xrightarrow{\text{Bu}_3\text{SnH, (t-BuO)₂ \quad 120 °C, 82\%}} C_6H_{12} + \text{Bu}_3\text{SnCN} \\
R-N=\overset{\bullet}{C} & \xrightarrow{\text{Bu}_3\text{Sn}^*} R-N=\overset{\circ}{C} \overset{\bullet}{-}\text{SnBu}_3 \xrightarrow{-\text{Bu}_3\text{SnCN}} R^* \\
\text{Bu}_3\text{SnH} & \xrightarrow{\text{Bu}_3\text{Sn}^*} \text{RH} + \text{Bu}_3\text{Sn}^* \\
\text{Ph-N}=\overset{\bullet}{C} & \xrightarrow{\text{Bu}_3\text{Sn}^*} \text{Ph-N}=\overset{\circ}{C} \overset{\bullet}{-}\text{SnBu}_3 \xrightarrow{\text{X}} \text{Ph}^*
\end{align*}
\]

Scheme 1
add to the isonitrile to form the α-stannnoimidoyl radical, the carbon-nitrogen bond cleavage could not take place presumably due to the unfavorable formation of an aryl radical (Scheme 1).

The first example of utilizing imidoyl radicals for carbon-carbon bond formation was reported in 1984. It was shown that the imine 1 reacted with diisopropyl peroxydicarbonate (DPDC) in benzene at 60 °C to give an imidoyl radical 2 which added to the phenyl acetylene to form a new vinyl radical 3. The radical 3 followed two routes giving either 4, by an intramolecular homolytic aromatic substitution on the phenyl ring linked to the iminic nitrogen, or 5, through an ipso cyclization followed by a rearrangement via cleavage of the carbon-nitrogen bond of the intermediate spirocyclohexadienyl radical. In 1989, Bachi reported an intramolecular version of this cyclization by using chemospecific homolysis of a carbon-selenium bond by trialkyltin radicals to form the imidoyl radical 9. The imidoyl radical then underwent cyclization to give, after hydrolysis, the corresponding ketone 12 in 50% yield. Curran recently extended the scope of the imidoyl radical cyclization by developing a [4 + 1] annulation with isonitriles to form cyclopentane-fused quinolines, 18 and 19. The aryl isonitrile serves as a bridge to relay the carbon radical to the acetylene intramolecularly (Scheme 2).
Scheme 2
Despite the fact that some of the aforementioned imidoyl radicals have been demonstrated to have strong synthetic potential for inter- and intramolecular carbon-carbon bond formation, simple α-stannoimidoyl radicals have attracted little attention among synthetic organic chemists even though they could be easily generated. At the outset of this research, we envisioned that α-stannoimidoyl radical 21, generated from α-isocyanostryrene derivative 20 by the addition of a tri-\(n\)-butyltin radical, will cause radical ring closure by addition to the proximal olefin. Subsequent radical reduction and tautomerization will give 2-stannylindole 24. Destannylation with mild acidic treatment will furnish 3-substituted indole 25 (Scheme 3).

![Scheme 3](image)

The first reaction was conducted on the methyl α-isocyanoacinnamate (28), which was prepared from α-iodoformylaniline (26) by a Heck reaction with methyl acrylate and dehydration with phosgene in an overall yield of 86%. Treatment of the isonitrile 28 with tributyltin hydride and a catalytic amount of AIBN gave the desired 3-substituted indole 30 in 91% yield after acidic workup (Scheme 4). The ideal conditions for this novel reaction were investigated by Miss Ge Peng in this laboratory. Both benzene and acetonitrile are suitable
solvents for this tin-mediated indole synthesis. Using thiophenol instead of tributyltin hydride can also induce cyclization to form phenylthioimines which upon Raney nickel treatment yielded the indoles. Substrates with an acetylenic side chain are not suitable for this radical reaction, because they only lead to intractable mixtures. The results of further investigation of the cyclization on other isonitriles are presented in Table I. It should be noted that the substrates with radical-stabilizing substituents at the β-position gave excellent yields (entry 1-4). The E-substrate 37 reacted anomalously to furnish the tetrahydroquinoline 39 (33% yield) together with the expected indole 38 (51% yield). Formation of 39 is presumed to involve 6-Endo-Trig cyclization of the imidoyl radical and subsequent reduction of the resultant imine by tributyltin hydride. Interestingly, the foregoing problem can be circumvented by using Z-substrate (entry 6) (Scheme 5). The yield of byproduct 39 decreased from 33% to 18%. At the present time, the reaction rate constants of 5-Exo-Trig cyclization and 6-Endo-Trig cyclization have not been determined.

Scheme 4
Table I. Synthesis of 3-substituted Indoles

\[
\begin{align*}
(1) \text{Bu}_3\text{SnH (1.1 equiv)} &\quad \text{AIBN (5\%), CH}_2\text{CN, 100 °C} \\
(2) \text{H}_2\text{O}^+ &
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 28" /></td>
<td><img src="image" alt="Product 30" /></td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 31" /></td>
<td><img src="image" alt="Product 32" /></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 33" /></td>
<td><img src="image" alt="Product 34" /></td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 35" /></td>
<td><img src="image" alt="Product 36" /></td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 37" /></td>
<td><img src="image" alt="Product 38" /></td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Substrate 40" /></td>
<td><img src="image" alt="Product 38" /></td>
<td>72</td>
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<td><img src="image" alt="Product 39" /></td>
<td>33</td>
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<td></td>
<td><img src="image" alt="Substrate 40" /></td>
<td><img src="image" alt="Product 39" /></td>
<td>18</td>
</tr>
</tbody>
</table>
This novel tin-mediated indole synthesis can be classified as a type C indolization. As illustrated in the introduction part, there are only a few methods available for that particular type of indolization process. This newly developed method has some unique advantages over the existing procedures due to the mild conditions of the radical reaction. However, the major advantage of this process lies in the fact that it produces hitherto unknown \(N\)-unprotected 2-stannyindole 45. The chemistry of 2-stannyindole has not been developed extensively presumably because metallation of the \(N\)-protected indole has been the only practical method for generating it.\(^{81, 82}\) However, the tin substituent provides a valuable handle for further manipulation of the 2-position, making this protocol suitable not only for synthesizing 3-substituted indoles, but also 2,3-disubstituted indoles (Scheme 6). A particularly intriguing possibility is to achieve the latter goal by a Stille reaction. However, 2-stannyindoles are prone to undergo facile destannylation during workup, so Stille's palladium-mediated coupling\(^{83}\) was attempted on the crude reaction mixture immediately after the completion of the indole synthesis.
Scheme 6

To our delight, treatment of the primary product 45 with tetrakis-(triphenylphosphine)palladium(0) and coupling reagents provided the 2-functionalized indoles in good yield. The results of this one-pot synthesis of 2,3-disubstituted indoles are summarized in Table II. A few comments are worthy of note. The nature of the palladium catalyst does not appear to make an appreciable difference in the yield of coupling products. Triphenyl phosphine had to be added when (CH$_3$CN)$_2$PdCl$_2$ was used as a catalyst, which indicates that ligands on palladium apparently are important. This ligand dependence is quite consistent with Stille's observation.$^{83a}$ Bromobenzene offered a higher yield of coupling product than iodobenzene (entry 1 vs. 2). As reported by Stille,$^{83c}$ addition of lithium chloride was essential for the success of the coupling reaction with triflate. In entries 6 and 10, 10% volume of N,N-dimethylformamide, a solvent that can both solubilize lithium chloride and act as a ligand for palladium, was introduced to accelerate the reaction and to improve the yields. A benzyl group can also be incorporated onto the 2-position of the indole when benzyl bromide was employed (entry 7). When trans-1-iodohexene is used as the coupling partner, desired product 52 was obtained along with 2-(1-butylethenyl)indole in 1:1 ratio as an inseparable mixture. This problem was circumvented by adding one equivalent of cuprous iodide$^{84}$ which enabled us to achieve a 10:1 ratio in favor of the desired indole (entry 8). Different isonitrile substrates (entries 9 - 12) further demonstrate the attractive
features of this indole synthesis reaction which is generally applicable to a variety of acyclic isonitrile precursors.

Table II. One-Pot Synthesis of 2,3-substituted Indoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R'X</th>
<th>Equiv. (h)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>Br</td>
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<td>5</td>
<td><img src="image1" alt="Product" /></td>
<td>82\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>I</td>
<td>1.5</td>
<td>8</td>
<td><img src="image2" alt="Product" /></td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>Ac-Bz-Br</td>
<td>1.5</td>
<td>12</td>
<td><img src="image3" alt="Product" /></td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>Ac-OTf</td>
<td>1.5</td>
<td>3</td>
<td><img src="image4" alt="Product" /></td>
<td>75\textsuperscript{b}</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>I</td>
<td>3.0</td>
<td>8</td>
<td><img src="image5" alt="Product" /></td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>t-Bu-OTf</td>
<td>3.0</td>
<td>7</td>
<td><img src="image6" alt="Product" /></td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>CH\textsubscript{2}Br</td>
<td>3.0</td>
<td>1</td>
<td><img src="image7" alt="Product" /></td>
<td>71\textsuperscript{c}</td>
</tr>
</tbody>
</table>
8  28  \( nBu \longrightarrow I \)  3.0  8  \[ \text{structure} \]  71\(^d\)

9  31  \( \text{phenyl-Br} \)  3.0  11  \[ \text{structure} \]  63

10  31  \( tBu \longrightarrow \text{phenyl-OTf} \)  3.0  7  \[ \text{structure} \]  49\(^b\)

11  33  \( \text{phenyl-Br} \)  3.0  10  \[ \text{structure} \]  60

12  40  \( \text{phenyl-Br} \)  3.0  8  \[ \text{structure} \]  65

\(^a\) Using Pd(PPh\(_3\))\(_2\)Cl\(_2\) gave coupling product in 71\% yield; Pd(OAc)\(_2\) and PPh\(_3\), 72\% yield, Pd(CH\(_3\)CN)\(_2\)Cl\(_2\) and PPh\(_3\), 74\% yield; Pd(CH\(_3\)CN)\(_2\)Cl\(_2\), 0\% of 47, 87\% of 30. \(^b\) LiCl (5 equiv.) and 10\% volume of DMF were added. \(^c\) No Et\(_3\)N was added. \(^d\) CuI (1 equiv.) was added.

The significance of this one-pot synthesis of 2,3-disubstituted indole is not limited to the Stille coupling with 2-stannyllindole 45. Since the tin-carbon bond is readily oxidized by I\(_2\), we envisioned that this method can pave the way for making N-unprotected 2-iodoindole. There are only few practical procedures in the literature to make N-unprotected 2-iodoindole and, as a result of that, the chemistry of N-unprotected 2-iodoindole has not been studied extensively. Our newly developed method not only makes those 2-iodoindole derivatives more readily accessible, but also extends the versatility of coupling patterns. They are no longer limited to aryl halide, vinyl iodide, vinyl triflate, and benzyl bromide, but also can include acetylene, acrylate, and vinyl tin reagents.
Experimentation on the methyl o-isocyanocinnamate (28) quickly brought our intriguing postulation into reality (Scheme 7). We were delighted to obtain 2-iodoindole 57 from o-isocyanocinnamate 28 in an overall yield of 91% upon in situ iodination of the 2-stannyldole 29. The 2-iodoindole 57 can be purified by flash silica gel chromatography and characterized by standard spectral methods. More importantly, this 2-iodoindole 57 behaved normally in the palladium-mediated cross coupling with methyl acrylate, acetylene, and vinyltin reagents to give excellent yields of the expected products. The results of the coupling reactions are summarized in Table III. Although this 2-iodoindole 57 can be stored in a freezer for several weeks without appreciable decomposition, the cross coupling can also be conveniently performed in one-pot without isolating the iodo intermediate, as shown in entry 1 and entry 2. When the reaction was carried out under the atmosphere of carbon monoxide in the presence of a vinyltin reagent, the α,β-unsaturated ketone 62 was generated as anticipated. The same chemistry was also successfully applied to the iodoindole derivative 59. This iodoindole was obtained from o-isocyanocinnamyl alcohol THP ether 31 in 47% yield. The THP ether underwent deprotection unless pyridine was
Table III. Synthesis of 2,3-substituted Indoles by Coupling with 2-Iodoindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R'X</th>
<th>Equiv.</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>28</td>
<td>CO₂Me</td>
<td>3</td>
<td>8</td>
<td><img src="image1.png" alt="Image" /></td>
<td>81&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>28</td>
<td>n-Bu₂Sn⁻n-Bu</td>
<td>2</td>
<td>10</td>
<td><img src="image2.png" alt="Image" /></td>
<td>66&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>n-Bu</td>
<td>5</td>
<td>8</td>
<td><img src="image3.png" alt="Image" /></td>
<td>89&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>n-Bu₂Sn⁻n-Bu</td>
<td>1.5</td>
<td>12</td>
<td><img src="image4.png" alt="Image" /></td>
<td>78&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>CO₂Me</td>
<td>2</td>
<td>4</td>
<td><img src="image5.png" alt="Image" /></td>
<td>82&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>n-Bu</td>
<td>5</td>
<td>8</td>
<td><img src="image6.png" alt="Image" /></td>
<td>94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> (1) n-Bu₂SnH (1.1 equiv.), AIBN (5% mmol), 80 °C, CH₃CN. (2) I₂, (1.1 equiv.). (3) Pd(OAc)<sub>2</sub> (3% mmol), P(Tol)<sub>3</sub> (0.12 equiv.), Et₂N (2.2 equiv.), 80 °C, one-pot; trans : cis = 2.7 : 1. <sup>b</sup> (1) n-Bu₂SnH (1.1 equiv.), AIBN (5% mmol), 100 °C, CH₃CN. (2) I₂, (1.1 equiv.). (3) Pd(PPh₃)<sub>4</sub> (5% mmol), Cul (1 equiv.), 80 °C, one-pot. <sup>c</sup> Pd(PPh₃)<sub>2</sub>Cl₂ (5% mmol), CuI (5% mmol), Et₂NH, room temperature. <sup>d</sup> PdCl₂(dppf) (5% mmol), BHT (trace), CO, 1 atm, DMF, 70 °C. <sup>e</sup> Same as <sup>a</sup>, 100 °C.
added. The yield indicates that the reaction still requires more optimization. Nevertheless, the preliminary results shown in Table III serve to highlight this strategic breakthrough in making 2,3-disubstituted indoles.

In conclusion, a novel tin-mediated indole synthesis has been developed using α-isocyanostyrene derivatives as starting materials. Because a wide variety of functional groups are known to tolerate both radical and palladium-mediated reactions, our efficient synthesis presented herein constitutes a new and facile construction of a range of 3- or 2,3-substituted indoles from readily accessible isonitriles. This indole synthesis has a significant implication for the synthesis of a variety of indole alkaloids.

Some of the possible target molecules to demonstrate the synthetic potential of our indole synthesis methodology include vincadifformine (66), (−)-tabersonine (65), and catharanthine (67). It has been proposed by Wenkert and Scott that those alkaloids are biogenetically derived from the same postulated precursor dehydrosedecodine (68) via two alternative intramolecular Diels-Alder-

![Figure 7](image-url)
type reactions (Figure 7). Incorporation of specifically labeled precursors and establishment of isotopic label distribution in the final alkaloid products supported a dehydrosecodine pathway. From then on, synthetic chemists have been making enormous efforts to incorporate such hypothetical process into total syntheses of these alkaloids. Kuehne has recently demonstrated the enantioselective total synthesis of (−)- and (+)-vincadifformine and (−)-tabersonine in a biomimetic fashion. Our indole synthesis method will have

Figure 8
advantages in introducing the acrylate moiety efficiently and should provide a unique opportunity to synthesize those alkaloids biomimetically.

One of the possible routes that can lead to tabersonine is illustrated in Figure 8. A palladium-mediated coupling between o-iodoformylaniline (26) and an acetylene side chain, which serves as a masked form of dihydropyridine, will provide the coupling product 69. Hydrogenation of 69 over Lindlar catalyst followed by dehydration of the formamide with phosgene will give isonitrile 70, which will set the stage for the tin-mediated indole formation reaction. Since methyl 2-bromoacrylate is prone to be decompose at elevated temperature, methyl 2-tri-n-butylstannylacrylate can be used to incorporate the acrylate function. Good results have recently been reported for the Stille coupling of methyl 2-tri-n-butylstannylacrylate with aryl iodide.87 Based upon the above consideration, the tin intermediate in the indole formation reaction will be oxidized with I₂ to give 2-iodoindole 71 which will be subjected to the Stille coupling reaction. After securing the coupling product 73, acidic treatment will remove all the protecting groups to generate the enamine 74 which is expected to undergo the Diels-Alder-type reaction to yield (±)-tabersonine 75 after dehydration. In order to enatioselectively synthesize the (−)-tabersonine, a carefully selected bulky chiral auxiliary, indicated as R* in figure 9, can be used.

![Figure 9](image-url)
to affect the face selectivity of the intramolecular Diels-Alder-type reaction. The research directed toward the synthesis of Aspidosperma alkaloids is actively under investigation in our laboratories.
Chapter III
Experimental

Technical notes
See page 31 to 32.
Methyl o-N-formylamino-cinnamate (27):

A mixture of 161 mg (0.65 mmol) of o-iodoformylaniline (26), 70 μl (0.78 mmol) of methyl acrylate, 1.5 mg (0.007 mmol) of Pd(OAc)$_2$, 100 μl (0.72 mmol) of Et$_3$N, and 4 mg (0.01 mmol) of (Tol)$_3$P in 2 ml of dry acetonitrile was heated at 100 °C for 2.5 h in a tightly capped pressure tube under an argon atmosphere. The reaction mixture was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The extracts were washed with sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 60% ether-hexanes to give 141 mg (90.5%) of cinnamate 27 as a white solid.

Characterization of 27:

mp: 99-100 °C (dichloromethane-hexanes)

IR (film): 3310, 3070, 3050, 3020, 2970, 2890, 1700, 1640, 1580, 1530, 1450, 1400, 1330, 1270, 1200, 1180, 1040, 980, 870, 770

$^1$HNMR (CDCl$_3$): (observed as a mixture of two atropisomers)
3.71 (3H, s), 3.74 (3H, s), 6.36 (1H, d, J = 15.8 Hz), 6.39 (1H, d, J = 15.8 Hz), 7.10-7.41 (8H, m), 7.55 (2H, m), 7.88 (2H, m), 8.43 (1H, m), 8.63 (1H, s)

$^{13}$CNMR (CDCl$_3$): 51.7, 119.7, 120.4, 122.8, 124.4, 125.6, 126.8, 127.6, 130.8, 131.1, 135.0, 139.0, 139.4, 163.9, 166.8, 167.4, 168.7, 168.9
MS: 205 (22, M+), 146 (79), 128 (63), 118 (95), 117 (99), 91 (31), 90 (37), 89 (36), 39 (19)

Exact Mass: Calculated for C₁₁H₁₁N₁O₃ 205.0739
Found 205.0734
\[
\begin{array}{c}
\text{27} \quad \text{28}
\end{array}
\]

\textbf{\(p\)-Isocyanocinnamate (28):}

To a solution of 141 mg (0.68 mmol) of cinnamate 27, 287 \(\mu\)l (2.06 mmol) of \(\text{Et}_3\text{N}\) in dichloromethane at 0 °C was added dropwise with a solution of phosgene in methylene chloride. The reaction was closely monitored by TLC until the completion of the reaction. The reaction mixture was partitioned between ether and sodium bicarbonate solution and then brine. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness \textit{in vacuo}. The crude product was purified by flash silica gel chromatography eluting with 20% ether-hexanes to give 106 mg (86.9\%) of 28 as a white solid.

\textbf{Characterization of 28:}

\textbf{mp:} 57-59 °C (ether-hexanes)

\textbf{IR (KBr):} 
3430, 3050, 3010, 2960, 2120, 1750, 1640, 1480, 1430, 1330, 1290, 1200, 1040, 990, 780

\textbf{\(^1\text{HNMR (CDCl}_3\):} 
3.84 (3H, s), 6.55 (1H, d, \(J = 16.0\) Hz), 7.46 (2H, m), 7.67 (2H, m), 7.98 (1H, d, \(J = 16.0\) Hz)

\textbf{\(^{13}\text{CNMR (CDCl}_3\):} 
51.9, 121.9, 126.8, 127.6, 129.6, 130.7, 137.8, 166.3, 168.7

\textbf{MS:} 
187 (6, \(M^+\)), 156 (30), 143 (14), 142 (13), 139 (99), 138 (99), 101 (61), 75 (43), 51 (30), 28 (31)

\textbf{Exact Mass:} 
Calculated for \(\text{C}_{11}\text{H}_9\text{N}_1\text{O}_2\) 187.0633

\textbf{Found} 187.0635
**o-N-Formylaminophenyl propargyl ether:**

A mixture of 4.17 g (16.8 mmol) of o-iodoformylaniline (26), 236 mg (0.34 mmol) of Pd(PPh3)2Cl2, 257 mg (1.35 mmol) of CuI, and 4.26 g (30.4 mmol) of propargyl alcohol THP ether in 20 ml of dry diethylamine was stirred at room temperature for 8 h under an argon atmosphere. The reaction mixture was then partitioned between ether and 3 N hydrochloric acid. The extracts were washed with sodium bicarbonate solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by silica gel chromatography eluting with 20% ether-hexanes to give 3.98 g (91.1%) of o-N-formylaminophenyl propargyl ether as a yellow oil.

**Characterization of o-N-formylaminophenyl propargyl ether:**

IR (film): 3300, 2950, 2870, 2860, 2230, 1700, 1580, 1520, 1450, 1400, 1350, 1300, 1270, 1200, 1120, 1090, 1160, 1030, 900, 870, 820, 760

$^1$HNMR (CDCl$_3$): (observed as a mixture of two atropisomers)

- 1.56-1.90 (4H, m), 3.60 (2H, m), 3.91 (2H, m), 4.56 (2H, m), 4.90 (1H, m), 7.06 (1H, m), 7.22-7.48 (3H, m), 7.28 (1H, s), 8.42 (1H, d, J = 8.3 Hz), 8.47 (1H, d, J = 1.6 Hz), 8.82 (1H, d, J = 11.3 Hz)

$^{13}$CNMR (CDCl$_3$): 18.9, 25.2, 29.6, 30.3, 54.9, 55.4, 62.2, 80.9, 92.9, 97.5, 97.9, 113.3, 115.8, 119.8, 123.7, 124.3, 129.8, 131.7, 133.1, 138.6, 159.1, 161.2

MS: 259 (M$^+$), 243 (2), 175 (45), 158 (34), 146 (10), 130 (99), 102 (23), 101 (23), 77 (23), 55 (22), 41 (39)
Exact Mass:  
Calculated for C$_{15}$H$_{17}$N$_1$O$_3$  
259.1208  
Found  
259.1206
Isonitrile (31):

A mixture of 3.98 g (15.3 mmol) of o-N-formylaminophenyl propargyl ether, and 200 mg of Pd/BaSO₄ in 40 ml of ethanol was stirred at room temperature for 2.5 h under 1 atm of hydrogen. The reaction was closely monitored by TLC until the completion of the reaction. The reaction mixture was passed through a celite pad, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 30% ether-hexanes to give 2.53 g (63.1%) of partially reduced N-formylanilide as a dark yellow oil.

To a solution of 2.53 g (9.68 mmol) of the above N-formylanilide, 4.07 ml (29.3 mmol) of Et₃N in dichloromethane at 0 °C was added dropwise a solution of phosgene in methylene chloride. The reaction was closely monitored by TLC until the completion of the reaction. The reaction mixture was partitioned between ether and aqueous sodium bicarbonate solution and then brine. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 10% ether-hexanes to give 2.27 g (96.5%) of 31 as a colorless oil.

Characterization of 31:

IR (film): 3040, 2950, 2860, 2140, 1730, 1450, 1375, 1340, 1270, 1200, 1130, 1030, 970, 900, 770
$^1$HNMR (CDCl$_3$): 1.45-1.88 (4H, m), 3.49 (1H, m), 3.86 (1H, m), 4.18 (2H, dd, $J_1 = 6.5$ Hz, $J_2 = 12.9$ Hz), 4.43 (2H, dd, $J_1 = 6.5$ Hz, $J_2 = 12.9$ Hz), 4.65 (1H, t, $J = 3.0$ Hz), 6.12 (1H, dt, $J_1 = 6.5$ Hz, $J_2 = 11.9$ Hz), 6.74 (1H, d, $J = 11.9$ Hz), 7.30 (4H, m)

$^{13}$CNMR (CDCl$_3$): 19.3, 25.3, 30.6, 62.2, 63.9, 98.4, 126.1, 126.8, 128.1, 128.9, 129.8, 132.4, 133.3

MS: 243 (1, M$^+$), 214 (2), 200 (4), 199 (30), 143 (55), 142 (99), 130 (36), 115 (82), 85 (96), 43 (57), 41 (62)

Exact Mass: Calculated for C$_{15}$H$_{17}$N$_1$O$_2$ 243.1259
Found 243.1259
**Methyl 2-indolyl acetate (30)**

A mixture of 155 mg (0.83 mmol) of isonitrile 28, 245 µl (0.91 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was partitioned between ether and 3 N hydrochloric acid. The ethereal layer was washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 141 mg (90.5%) of 30 as a light yellow oil.

**Characterization of 30:**

**IR (film):**
3510, 3060, 2960, 1730, 1620, 1460, 1440, 1340, 1270, 1200, 1160, 1100, 1020, 750

**¹HNMR (CDCl₃):**
3.72 (3H, s), 3.81 (2H, s), 7.08 (1H, s), 7.13 (1H, t, J = 7.4 Hz), 7.22 (1H, t, J = 7.9 Hz), 7.32 (1H, d, J = 7.9 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.16 (1H, s)

**¹³CNR (CDCl₃):**
31.0, 51.9, 108.0, 111.2, 118.6, 119.5, 122.0, 123.2, 136.0, 172.7

**MS:**
189 (40, M⁺), 130 (99), 103 (17), 77 (19)

**Exact Mass:**
Calculated for C₁₁H₁₁N₁O₂ 189.0790  
Found 189.0792
2-Indolyl ethyl alcohol THP ether (32)

A mixture of 123 mg (0.51 mmol) of isonitrile 31, 150 μl (0.56 mmol) of \( \text{Bu}_3\text{SnH} \), and 4 mg (0.024 mmol) of AIBN in 3 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was partitioned between ether and 3 N hydrochloric acid. The ethereal layer was washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness \textit{in vacuo}. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 102 mg (82.2%) of 32 as a light yellow oil.

Characterization of 32:

**IR (film):**
3420, 3060, 2950, 2880, 1660, 1580, 1530, 1460, 1350, 1120, 1070, 1030, 750

**\(^1\)HNMR (CDCl\textsubscript{3}):**
1.48-1.96 (6H, m), 3.09 (2H, t, \( J = 7.3 \) Hz), 3.52 (1H, m), 3.75 (1H, m), 3.88 (1H, m), 4.04 (1H, m), 4.66 (1H, t, \( J = 2.6 \) Hz), 7.05 (1H, d, \( J = 1.5 \) Hz), 7.12 (1H, t, \( J = 7.1 \) Hz), 7.19 (1H, t, \( J = 7.1 \) Hz), 7.35 (1H, d, \( J = 7.9 \) Hz), 7.65 (1H, d, \( J = 7.9 \) Hz), 8.04 (1H, s)

**\(^13\)CNMR (CDCl\textsubscript{3}):**
19.7, 25.5, 25.8, 30.8, 62.4, 67.8, 99.0, 111.0, 113.2, 118.9, 119.2, 121.9, 127.6, 136.1

**MS:**
245 (18, \( M^+ \)), 144 (36), 143 (99), 130 (38), 117 (34), 85 (70), 41 (12), 28 (32)

**Exact Mass:**
Calculated for C\(_{15}\)H\(_{19}\)N\(_1\)O\(_2\) 245.1416
Found 245.1416
2-Indolyl ethyl alcohol benzyl ether (34)

A mixture of 88 mg (0.35 mmol) of isonitrile 33, 139 µl (0.52 mmol) of n-Bu₃SnH, and 6 mg (0.03 mmol) of AIBN in 2 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was partitioned between ether and 3 N hydrochloric acid. The ethereal layer was washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 61 mg (68.5%) of 34 as a light yellow oil.

Characterization of 34:

IR (film): 3520, 3320, 3050, 2940, 2860, 1660, 1630, 1500, 1450, 1360, 1230, 1100, 1030, 800, 740, 710

¹H NMR (CDCl₃): 3.11 (2H, t, J = 7.2 Hz), 3.80 (2H, t, J = 7.2 Hz), 4.58 (2H, s), 7.05 (1H, s), 7.12 (1H, t, J = 7.1 Hz), 7.20 (1H, t, J = 7.5 Hz), 7.31 (1H), 7.35 (5H, m), 7.62 (1H, d, J = 7.5 Hz), 7.98 (1H, s)

¹³C NMR (CDCl₃): 25.8, 70.6, 72.9, 111.0, 113.0, 118.8, 119.2, 121.9, 127.5, 127.7, 128.3, 136.1, 138.5

MS: 251 (M⁺), 145 (10), 130 (99), 127 (23), 103 (13), 91 (16), 77 (12), 65 (9)

Exact Mass: Calculated for C₁₇H₁₇N₁O₁ 251.1310
Found 251.1312
3-Heptyl indole (38)

A mixture of 101 mg (0.55 mmol) of isonitrile 37, 220 µl (0.82 mmol) of n-Bu₃SnH, and 9 mg (0.05 mmol) of AIBN in 4 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was partitioned between ether and 3 N hydrochloric acid. The ethereal layer was washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 34 mg (32.9%) of 39 and 52 mg (50.9%) of 38 as light yellow oils.

Characterization of 38:

mp: 41-42 °C (hexanes)

IR (film): 3520, 3050, 2960, 2930, 2850, 1620, 1460, 1420, 1340, 1230, 1100, 1010, 740

¹H NMR (CDCl₃): 0.92 (3H, t, J = 6.6 Hz), 1.41 (4H, m), 1.74 (1H, sep, J = 7.4 Hz), 2.77 (2H, t, J = 7.4 Hz), 6.97 (1H, s), 7.12 (1H, t, J = 7.1 Hz), 7.20 (1H, t, J = 7.3 Hz), 7.36 (1H, d, J = 7.3 Hz), 7.63 (1H, d, J = 7.1 Hz), 7.88 (1H, s)

¹³C NMR (CDCl₃): 14.1, 22.6, 29.8, 30.7, 31.8, 111.0, 117.2, 119.0, 120.9, 121.8, 127.6, 132.2

MS: 187 (M⁺), 156 (6), 144 (12), 143 (12), 130 (99), 118 (13), 106 (5)
Exact Mass: Calculated for C_{13}H_{17}N_1 187.1361
         Found 187.1363

Characterization of 39:

IR (film): 3400, 3050, 3020, 2920, 2850, 1610, 1500, 1470, 1370, 1270, 1090, 740

{\textsuperscript{1}H}NMR (CDCl\textsubscript{3}): 0.93 (3H, t, J = 6.8 Hz), 1.37 (4H, m), 1.91 (1H, m),
2.44 (1H, dd, J\textsubscript{1} = 10.5 Hz, J\textsubscript{2} = 16.0 Hz), 2.82 (1H, dd, J\textsubscript{1} = 4.9 Hz, J\textsubscript{2} = 11.1 Hz), 2.92 (2H, dd, J\textsubscript{1} = 9.8 Hz, J\textsubscript{2} = 10.5 Hz), 3.32 (1H, dm, J = 11.1 Hz), 6.49 (1H, d, J = 7.7 Hz), 6.61 (1H, t, J = 7.2 Hz), 6.97 (2H, m)

{\textsuperscript{13}C}NMR (CDCl\textsubscript{3}): 14.1, 22.9, 29.1, 32.2, 33.5, 33.7, 47.3, 113.8, 116.9, 121.1, 126.6, 129.6, 144.6

MS: 189 (32, M\textsuperscript{+}), 167 (8), 158 (5), 149 (66), 144 (19), 130 (99), 118 (19), 106 (13), 85 (19)

Exact Mass: Calculated for C_{13}H_{19}N_1 189.1517
         Found 189.1518
3-Heptyl indole (38)

A mixture of 101 mg (0.55 mmol) of isonitrile 40, 191 µl (0.72 mmol) of n-Bu₃SnH, and 9 mg (0.05 mmol) of AIBN in 4 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was partitioned between ether and 3 N hydrochloric acid. The ethereal layer was washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 19 mg (18.4%) of 39 and 74 mg (72.5%) of 38 as light yellow oil.
Indoleacetate (47)

A mixture of 159 mg (0.85 mmol) of isonitrile 28, 251 µl (0.93 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 142 µl (1.02 mmol) of Et₃N, 49 mg (0.04 mmol) of Pd(PPh₃)₄, and 107 µl (1.02 mmol) of bromobenzene was added to the reaction mixture. The heating was continued for an additional 5 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. Ether was added to the combined hexanes layer and the organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were then washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 30% ether-hexanes to give 186 mg (82.4%) of 47 as a light yellow foam.

Characterization of 47:

mp: 106-107 °C (dichloromethane)

IR (film): 3480, 3050, 2950, 2860, 1730, 1610, 1450, 1320, 1270, 1170, 1010, 750, 700

¹HNMR (CDCl₃): 3.75 (3H, s), 3.91 (2H, s), 7.21 (1H, t, J = 5.8 Hz), 7.26 (1H, t, J = 5.8 Hz), 7.36 (1H, d, J = 8.8 Hz), 7.45 (1H, t, J = 7.3 Hz), 7.51 (2H, t, J = 6.8 Hz), 7.67 (2H, d, J = 7.5 Hz), 7.72 (1H, d, J = 6.8 Hz), 8.32 (1H, s)
$^{13}$CNMR (CDCl$_3$): 30.9, 52.0, 105.3, 110.9, 119.1, 120.0, 122.5, 128.0, 128.2, 128.8, 132.2, 135.7, 136.1, 172.8

MS: 265 (19, $M^+$), 206 (99), 178 (19), 102 (4), 59 (5)

Exact Mass:
- Calculated for C$_{17}$H$_{15}$N$_1$O$_2$ 265.1103
- Found 265.1102
**Indoleacetate (47)**

A mixture of 105 mg (0.56 mmol) of isonitrile 28, 165 μl (0.62 mmol) of $n$-Bu$_3$SnH, and 5 mg (0.03 mmol) of AIBN in 3 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 93 μl (0.67 mmol) of Et$_3$N, 32.3 mg (0.03 mmol) of Pd(PPh$_3$)$_4$, and 75 μl (0.67 mmol) of iodobenzene was added to the reaction mixture. The heating was continued for an additional 8 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. Ether was added to the combined hexanes layer and the organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were then washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The crude product was purified by flash silica gel chromatography eluting with 30% ether-hexanes to give 100 mg (67.7%) of 47 as a light yellow foam.
Indoleacetate (48)

A mixture of 165 mg (0.88 mmol) of isonitrile 28, 261 µl (0.97 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 147 µl (1.06 mmol) of Et₃N, 51 mg (0.04 mmol) of Pd(PPh₃)₄, and 211 mg (1.06 mmol) of p-acetyl bromobenzene was added to the reaction mixture. The heating was continued for an additional 12 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. Ether was added to the combined hexanes layer and the organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were then washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 60% ether-hexanes to give 218 mg (80.5%) of 48 as light yellow crystals.

Characterization of 48:

mp: 153-154 °C (ether-hexanes)

IR (KBr):

3390, 3050, 2940, 1730, 1670, 1600, 1440, 1360, 1260, 1200, 1000, 960, 830, 740

¹H NMR (CDCl₃):

2.63 (3H, s), 3.73 (3H, s), 3.87 (2H, s), 7.17 (1H, t, J = 8.1 Hz), 7.25 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.68 (1H, d, J = 8.1 Hz), 7.73 (2H, d, J = 7.5 Hz), 8.03 (2H, d, J = 7.5 Hz), 8.44 (1H, s)
$^{13}$CNMR (CDCl$_3$): 26.5, 30.8, 52.1, 106.7, 111.1, 119.2, 120.1, 123.1, 127.3, 127.8, 128.8, 128.9, 134.7, 135.7, 136.1, 136.8, 172.6, 197.8

MS: 
307 (44, M$^+$), 248 (44), 206 (89), 205 (99), 204 (99), 179 (21), 176 (21), 102 (22), 43 (40)

Exact Mass: 
Calculated for C$_{19}$H$_{17}$N$_1$O$_3$ 307.1208
Found 307.1210
**Indoleacetate (48)**

A mixture of 166 mg (0.88 mmol) of isonitrile 28, 262 μl (0.97 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 148 μl (1.06 mmol) of Et₃N, 51 mg (0.04 mmol) of Pd(PPh₃)₄, 113 mg (2.67 mmol) of LiCl, and 211 mg (1.06 mmol) of p-acetophenyl triflate was added to the reaction mixture. The heating was continued for an additional 3 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. Ether was added to the combined hexanes layer and the organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The extracts were then washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 60% ether-hexanes to give 218 mg (80.5%) of 48 as light yellow crystals.
Indoleacetate (49)

A mixture of 159 mg (0.85 mmol) of isonitrile 28, 252 μl (0.94 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 ºC for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 355 μl (2.55 mmol) of Et₃N, 49 mg (0.04 mmol) of Pd(PPh₃)₄, and 530 mg (2.55 mmol) of 1-iodocyclohexene was added to the reaction mixture. The heating was continued for an additional 8 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. Ether was added to the combined hexanes layer and the organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were then washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 30% ether-hexanes to give 134 mg (58.6%) of 49 as a light yellow oil.

Characterization of 49:

IR (film): 3400, 3050, 2940, 1730, 1650, 1580, 1520, 1440, 1340, 1270, 1200, 1160, 1010, 740

¹H NMR (CDCl₃): 1.69-1.83 (4H, m), 2.26 (2H, m), 2.39 (2H, m), 3.70 (3H, s), 3.84 (2H, s), 6.16 (1H, sep, J = 1.7 Hz), 7.12 (1H, dt, J₁ = 1.5 Hz, J₂ = 6.9 Hz), 7.17 (1H, dt, J₁ = 1.5 Hz, J₂ = 6.7 Hz), 7.27 (1H, d, J = 6.7 Hz), 7.58 (1H, d, J = 6.9 Hz), 8.03 (1H, s)
$^{13}$C NMR (CDCl$_3$): 21.9, 22.7, 25.6, 28.1, 31.1, 51.9, 104.0, 110.5, 118.6, 119.6, 121.9, 128.9, 129.0, 134.9, 138.2, 172.8

MS: 269 (24, M$^+$), 210 (99), 196 (30), 180 (34), 168 (38), 167 (39), 144 (36), 109 (17)

Exact Mass: Calculated for C$_{17}$H$_{19}$N$_3$O$_2$ 269.1416
Found 269.1415
Indoleacetate (50)

A mixture of 155 mg (0.83 mmol) of isonitrile 28, 246 µl (0.91 mmol) of n-Bu3SnH, and 7 mg (0.04 mmol) of AIBN in 5 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 346 µl (2.49 mmol) of Et3N, 48 mg (0.04 mmol) of Pd(PPh3)4, 176 mg (4.13 mmol) of LiCl, 500 µl of DMF, and 712 mg (2.49 mmol) of 4-t-butylocyclohexenyl triflate was added to the reaction mixture. The heating was continued for an additional 7 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 40% ether-hexanes to give 171 mg (63.5%) of 50 as a light yellow oil.

Characterization of 50:

IR (film): 3480, 3030, 2950, 2860, 1730, 1660, 1580, 1530, 1440, 1370, 1200, 1170, 1040, 750

1HNMR (CDCl3): 0.93 (9H, s), 1.37 (2H, m), 2.00 (2H, m), 2.31 (1H, m), 2.46 (2H, m), 3.69 (3H, s), 3.83 (2H, s), 6.16 (1H, m), 7.11 (1H, t, J = 7.9 Hz), 7.16 (1H, t, J = 6.4 Hz), 7.28 (1H, d, J = 7.9 Hz), 7.58 (1H, d, J = 6.4 Hz), 7.98 (1H, s)
$^{13}$CNMR (CDCl$_3$): 24.2, 27.1, 27.3, 29.6, 31.1, 32.2, 43.6, 51.9, 104.1, 110.5, 118.7, 119.7, 121.9, 128.8, 128.9, 129.2, 134.9, 137.8, 172.8

MS: 325 (6, M$^+$), 323 (6), 282 (18), 266 (13), 206 (99), 193 (31), 167 (36), 165 (76), 161 (45), 146 (69), 145 (68), 130 (62), 117 (29), 96 (27), 57 (47), 41 (48), 29 (65)

Exact Mass: Calculated for C$_{21}$H$_{27}$N$_1$O$_2$ 325.2042
       Found 325.2041
Indoleacetate (51)

A mixture of 105 mg (0.56 mmol) of isonitrile 28, 167 μl (0.62 mmol) of $n$-Bu$_3$SnH, and 5 mg (0.03 mmol) of AIBN in 4 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 20 mg (0.02 mmol) of Pd(PPh$_3$)$_4$ and 204 μl (1.69 mmol) of benzyl bromide was added to the reaction mixture. The heating was continued for an additional 1 h under argon, at which time it was partitioned twice between hexanes and acetonitrile. The combined acetonitrile layer was evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 20-40% ether-hexanes to give 112 mg (71.5%) of 51 as a light yellow oil.

Characterization of 51:

mp: 97-98 °C (ether-hexanes)

IR (film): 3390, 3060, 3040, 2960, 2920, 1730, 1600, 1490, 1460, 1270, 1160, 1020, 850, 740, 700

$^1$HNMR (CDCl$_3$): 3.68 (3H, s), 3.81 (2H, s), 4.13 (2H, s), 7.18 (5H, m), 7.31 (3H, m), 7.63 (1H, m), 7.87 (1H, s)

$^{13}$CNMR (CDCl$_3$): 30.1, 32.2, 51.8, 105.0, 110.5, 118.3, 119.6, 121.5, 126.6, 128.2, 128.7, 134.9, 135.3, 138.2, 172.4

MS: 279 (71, M$^+$), 220 (99), 218 (55), 206 (34), 191 (5), 178 (6), 142 (9), 115 (21)

Exact Mass: Calculated for C$_{18}$H$_{17}$N$_1$O$_2$ 279.1259
Found 279.1258
Indoleacetate (52)

A mixture of 49 mg (0.26 mmol) of isonitrile 28, 78 μl (0.28 mmol) of n-Bu₃SnH, and 2 mg (0.01 mmol) of AIBN in 2 ml of dry acetonitrile was heated at 100 °C for 1.5 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 15 mg (0.01 mmol) of Pd(PPh₃)₄, 50 mg (0.26 mmol) of CuI, and 110 mg (0.52 mmol) of 1-iodohexene was added to the reaction mixture. The heating was continued for an additional 8 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The extracts were washed with a one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 40% ether-hexanes to give 50 mg (70.4%) of 52 as a light yellow oil.

Characterization of 52:

IR (film): 3400, 3030, 2950, 2930, 2860, 1730, 1450, 1310, 1270, 1160, 1020, 960, 740

¹H NMR (CDCl₃): 0.94 (3H, t, J = 7.0 Hz), 1.42 (4H, m), 2.27 (2H, dd, J₁ = 6.6 Hz, J₂ = 6.9 Hz), 3.66 (3H, s), 3.77 (2H, s), 6.03 (1H, dt, J₁ = 6.9 Hz, J₂ = 16.0 Hz), 6.52 (1H, d, J = 16.0 Hz), 7.08 (1H, t, J = 6.9 Hz), 7.16 (1H, t, J = 7.0 Hz), 7.27 (1H, d, J = 7.0 Hz), 7.55 (1H, d, J = 7.1 Hz), 8.06 (1H, s)
$^{13}$CNMR (CDCl$_3$): 13.9, 22.2, 30.1, 31.4, 32.9, 52.0, 106.0, 110.4, 118.4, 118.7, 119.7, 122.5, 128.7, 130.8, 133.7, 135.7, 172.2

MS: 271 (71, $M^+$), 228 (11), 212 (99), 198 (13), 182 (11), 168 (94), 154 (31), 130 (23), 28 (46)

Exact Mass: Calculated for $C_{17}H_{21}N_1O_2$ 271.1572
Found 271.1574
2-(3-Indolyl)ethanol THP ether (53)

A mixture of 134 mg (0.56 mmol) of isonitrile 31, 165 µl (0.61 mmol) of \( \text{Bu}_3\text{SnH} \), and 5 mg (0.03 mmol) of AIBN in 3 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 155 µl (1.11 mmol) of \( \text{Et}_3\text{N} \), 32 mg (0.03 mmol) of \( \text{Pd(PPh}_3)_4 \), and 88 µl (0.84 mmol) of bromobenzene was added to the reaction mixture. The heating was continued for an additional 11 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 50% ether-hexanes to give 112 mg (62.8%) of 53 as a light yellow oil.

Characterization of 53:

mp: 105-106 °C (ether-hexanes)

IR (film): 3420, 2950, 2860, 1725, 1630, 1530, 1455, 1360, 1250, 1200, 1140, 1080, 1030, 920, 750

\(^1\text{HNMR (CDCl}_3\): 1.48-1.92 (6H, m), 3.23 (2H, t, J = 7.2 Hz), 3.49 (1H, m), 3.76 (1H, m), 3.82 (1H, m), 4.09 (1H, m), 4.64 (1H, t, J = 3.1 Hz), 7.15 (1H, t, J = 6.6 Hz), 7.22 (1H, t, J = 9.5 Hz), 7.37 (1H), 7.38 (1H, d, J = 6.6 Hz), 7.47 (2H, t, J = 7.1 Hz), 7.65 (2H, d, J = 7.1 Hz), 7.69 (1H, d, J = 9.5 Hz), 8.17 (1H, s)
$^{13}$C NMR (CDCl₃): 19.4, 25.3, 25.4, 30.6, 62.1, 67.6, 98.7, 109.8, 110.7, 119.3, 119.5, 122.2, 127.6, 128.0, 128.7, 129.3, 132.1, 135.2, 135.8

MS: 321 (6, M⁺), 269 (9), 253 (18), 206 (99), 193 (66), 179 (25), 148 (18), 105 (75), 85 (67), 77 (42), 41 (36), 29 (38)

Exact Mass: Calculated for C$_{21}$H$_{23}$N$_{1}$O$_{2}$ 321.1729
Found 321.1727
2-(3-Indoly)ethanol THP ether (54)

A mixture of 128 mg (0.53 mmol) of isonitrile 31, 157 μl (0.58 mmol) of n-Bu₃SnH, and 4 mg (0.02 mmol) of AIBN in 3 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 221 μl (1.59 mmol) of Et₃N, 31 mg (0.03 mmol) of Pd(PPh₃)₄, 113 mg (2.65 mmol) of LiCl, 300 μl of DMF, and 455 mg (1.59 mmol) of 4-t-butylcyclohexenyl triflate was added to the reaction mixture. The heating was continued for an additional 7 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 40% ether-hexanes to give 97 mg (48.2%) of 54 as a light yellow oil.

Characterization of 54:

IR (film): 3420, 2950, 2860, 1725, 1630, 1530, 1455, 1360, 1250, 1200, 1140, 1080, 1030, 920, 750

¹HNMR (CDCl₃): 0.92 (9H, s), 1.36 (2H, m), 1.53 (5H, m), 2.00 (2H, m), 2.24 (2H, m), 2.48 (2H, m), 3.14 (2H, t, J = 7.7 Hz), 3.48 (1H, m), 3.65 (1H, m), 3.85 (1H, m), 3.95 (1H, m), 4.62 (1H, t, J = 3.8 Hz), 6.08 (1H, m), 7.07 (1H, t,
J = 7.2 Hz), 7.13 (1H, t, J = 6.6 Hz), 7.28 (1H, m), 7.58 (1H, d, J = 7.2 Hz), 7.87 (1H, s)

$^{13}$CNMR (CDCl$_3$):

19.6, 24.2, 25.5, 25.6, 27.2, 27.3, 29.7, 30.7, 32.2, 43.7, 62.3, 67.9, 98.8, 108.2, 110.3, 118.7, 119.2, 121.6, 127.9, 129.4, 129.7, 134.9, 136.8

MS:

397 (<1, M$^+$), 379 (1), 329 (3), 313 (2), 256 (5), 238 (91), 220 (18), 208 (18), 206 (18), 165 (40), 147 (43), 129 (48), 85 (99), 57 (83), 41 (45)

Exact Mass:

Calculated for C$_{25}$H$_{35}$N$_1$O$_3$ 397.2617

Found 397.2617
2-(3-Indolyl)ethanol benzyl ether (55)

A mixture of 104 mg (0.42 mmol) of isonitrile 33, 157 µl (0.59 mmol) of n-Bu$_3$SnH, and 7 mg (0.04 mmol) of AIBN in 3 ml of dry acetonitrile was heated at 100 ºC for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 175 µl (1.26 mmol) of Et$_3$N, 24 mg (0.02 mmol) of Pd(PPh$_3$)$_4$, and 221 µl (2.10 mmol) of bromobenzene was added to the reaction mixture. The heating was continued for an additional 10 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 30% ether-hexanes to give 82 mg (60.0%) of 55 as a light yellow oil.

Characterization of 55:

IR (film): 3410, 3050, 2920, 2850, 1650, 1600, 1540, 1500, 1450, 1370, 1310, 1260, 1200, 1100, 1040, 740, 700

$^{1}$HNMR (CDCl$_3$): 3.25 (2H, t, J = 7.6 Hz), 3.83 (2H, t, J = 7.6 Hz), 4.55 (2H, s), 7.15 (1H, t, J = 7.6 Hz), 7.19 (1H, t, J = 7.5 Hz), 7.33 (7H, m), 7.47 (2H, t, J = 7.0 Hz), 7.60 (2H, d, J = 6.8 Hz), 7.64 (1H, d, J = 7.6 Hz), 8.09 (1H, s)
$^{13}$CNMR (CDCl$_3$): 25.4, 70.4, 72.9, 109.5, 110.8, 119.1, 119.6, 122.3, 127.4, 127.6, 127.7, 128.0, 128.3, 128.8, 129.2, 132.9, 135.1, 135.8, 138.5

MS: 327 (24, M$^+$), 252 (21), 222 (29), 206 (99), 193 (13), 178 (16), 105 (14), 91 (63), 77 (21), 65 (11)

Exact Mass: Calculated for C$_{23}$H$_{21}$N$_1$O$_1$ 327.1623
Found 327.1624
3-Heptyl indole (56)

A mixture of 114 mg (0.62 mmol) of isonitrile 40, 197 µl (0.73 mmol) of n-Bu3SnH, and 10 mg (0.06 mmol) of AIBN in 4 ml of dry acetonitrile was heated at 100 °C for 2 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 256 µl (1.84 mmol) of Et3N, 35 mg (0.03 mmol) of Pd(PPh3)4, and 194 µl (1.84 mmol) of bromobenzene was added to the reaction mixture. The heating was continued for an additional 8 h under argon, at which time ether was added to the reaction mixture. The organic layer was washed with a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a one third of saturated aqueous potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 10% ether-hexanes to give 104 mg (64.2%) of 56 as a light yellow oil.

Characterization of 56:

IR (film):

3330, 3060, 2940, 2860, 1650, 1580, 1530, 1450, 1320, 1260, 1200, 1080, 750, 700

1H NMR (CDCl3):

0.91 (3H, t, J = 6.9 Hz), 1.40 (4H, m), 1.76 (2H, sep, J = 7.6 Hz), 2.90 (2H, t, J = 7.6 Hz), 7.16 (1H, t, J = 7.9 Hz), 7.23 (1H, t, J = 6.7 Hz), 7.39 (2H, m), 7.49 (3H, m), 7.58 (3H, m), 7.67 (1H, d, J = 7.6 Hz), 7.98 (1H, s)

13C NMR (CDCl3):

14.1, 22.5, 24.5, 30.7, 32.1, 110.7, 114.1, 119.0, 119.3, 119.4, 122.1, 127.4, 127.9, 128.8, 129.3, 133.5, 135.9
MS: 263 (12, M+), 222 (42), 206 (84), 180 (39), 174 (35), 146 (37), 118 (29), 105 (99), 72 (64), 29 (27)

Exact Mass: Calculated for C_{19}H_{21}N_1 263.1674
Found 263.1675
2-Iodoindoleacetate (57)

A mixture of 202 mg (1.08 mmol) of isonitrile 28, 320 µl (1.19 mmol) of \( n \)-Bu\(_3\)SnH, and 9 mg (0.05 mmol) of AIBN in 6 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After the reaction mixture was cooled to room temperature, 302 mg (1.19 mmol) of I\(_2\) was added in one portion. The reaction was allowed to stir at room temperature for 10 min before it was partitioned twice between hexanes and acetonitrile. The combined acetonitrile extracts were evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 60% ether-hexanes to give 308 mg (90.5%) of 57 as a colorless oil.

Characterization of 57:

IR (film): 3350, 3050, 3000, 2950, 2850, 1730, 1440, 1340, 1270, 1200, 1170, 1010, 940, 750

\(^1\)HNMR (CDCl\(_3\)): 3.70 (3H, s), 3.74 (2H, s), 7.13 (2H, m), 7.26 (1H, m), 7.54 (1H, m), 8.22 (1H, s)

\(^13\)CNMR (CDCl\(_3\)): 32.9, 52.1, 79.8, 110.4, 115.0, 118.1, 120.2, 127.3, 138.7, 171.6

MS: 315 (69, M\(^+\)), 256 (86), 188 (12), 145 (13), 129 (99), 117 (14), 102 (56), 75 (22), 59 (9)

Exact Mass: Calculated for C\(_{11}\)H\(_{10}\)N\(_1\)O\(_2\)I\(_1\) 314.9756
Found 314.9755
2-(3-(2-Iodoindolyl))ethanol THP ether (59)

A mixture of 216 mg (0.90 mmol) of isonitrile 31, 264 μl (0.98 mmol) of n-Bu₃SnH, and 7 mg (0.04 mmol) of AIBN in 6 ml of dry acetonitrile was heated at 100 °C for 1 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, 80 μl (0.99 mmol) of pyridine and 249 mg (0.98 mmol) of I₂ was added in one portion to the reaction mixture. The reaction mixture was allowed to stir at room temperature for 10 min, at which time it was partitioned twice between hexanes and acetonitrile. The combined acetonitrile extracts were evaporated to dryness in vacuo. The crude product was purified by flash silica gel chromatography eluting with 40% ether-hexanes to give 156 mg (47.2%) of 31 as a colorless oil.

Characterization of 31:

IR (film): 3390, 3250, 3050, 2940, 2860, 1450, 1350, 1280, 1200, 1140, 1120, 1070, 1020, 900, 870, 800, 740

¹HNMR (CDCl₃): 1.25-1.89 (6H, m), 3.02 (2H, t, J = 7.4 Hz), 3.47 (1H, m), 3.61 (1H, q, J = 9.6 Hz), 3.81 (1H, m), 3.93 (1H, q, J = 9.6 Hz), 4.64 (1H, t, J = 3.2 Hz), 7.07 (1H, t, J = 7.4 Hz), 7.12 (1H, t, J = 7.0 Hz), 7.27 (1H, d, J = 7.0 Hz), 7.58 (1H, d, J = 7.4 Hz), 8.20 (1H, s)

¹³CNMR (CDCl₃): 19.4, 25.4, 27.6, 30.6, 62.1, 66.9, 78.5, 98.6, 110.2, 118.2, 119.0, 119.6, 122.1, 127.6, 138.8

MS: 371 (1, M⁺), 256 (8), 193 (22), 176 (14), 165 (13), 158 (17), 148 (55), 130 (33), 85 (99), 55 (99), 39 (29)
<table>
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<td>Found</td>
<td>371.0381</td>
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</table>
Indoleacetate (60)

A mixture of 52 mg (0.28 mmol) of isonitrile 28, 82 µl (0.30 mmol) of \( n \)-Bu₃SnH, and 2 mg (0.01 mmol) of AIBN in 2 ml of dry acetonitrile was heated at 100 °C for 1.5 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was treated with 78 mg (0.31 mmol) of \( I_2 \) in one portion. The reaction was allowed to stir at room temperature for 10 min prior to the addition of 75 µl (0.84 mmol) of methyl acrylate, 2 mg (0.01 mmol) of \( \text{Pd(OAc)}_2 \), 84 µl (0.60 mmol) of Et₃N, and 10 mg (0.03 mmol) of \((\text{Tol})_3\text{P}\). The mixture was then heated at 80 °C for 8 h under argon, at which time it was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with aqueous sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 40% ether-hexanes to give 17 mg (22.4%) of 60a and 45 mg (59.3%) of 60b as light yellow oil.

Characterization of 60a:

IR (film): 3300, 3050, 3030, 3010, 2970, 1740, 1700, 1600, 1530, 1500, 1450, 1430, 1340, 1270, 1200, 1030, 1010, 830, 750

\(^1\)HNMR (CDCl₃): 3.66 (3H, s), 3.83 (3H, s), 3.89 (2H, s), 5.86 (1H, d, \( J = 12.9 \) Hz), 7.09 (1H, d, \( J = 12.9 \) Hz), 7.12 (1H, t, \( J = 8.1 \) Hz)
Hz), 7.29 (1H, t, J = 8.1 Hz), 7.43 (1H, d, J = 8.1 Hz), 7.65 (1H, d, J = 8.1 Hz), 11.99 (1H, s)

$^{13}$CNMR (CDCl$_3$): 30.4, 52.0, 52.1, 112.0, 112.7, 114.8, 119.7, 120.1, 125.2, 127.2, 130.9, 132.0, 136.4, 169.0, 171.4

MS: 273 (31, M$^+$), 241 (5), 214 (18), 182 (26), 154 (99), 127 (10), 77 (5), 44 (14)

Exact Mass: Calculated for C$_{11}$H$_{11}$N$_1$O$_2$ 273.1001
                       Found 273.1001

Characterization of 60b:

mp: 145-146 °C (ether-hexanes)

IR (film): 3350, 3070, 3050, 3010, 2960, 2850, 1720, 1690, 1630, 1620, 1460, 1440, 1320, 1290, 1200, 1150, 1030, 970, 850, 750

$^1$HNMR (CDCl$_3$): 3.71 (3H, s), 3.80 (3H, s), 3.88 (2H, s), 6.12 (1H, dd, $J_1$ = 1.1 Hz, $J_2$ = 15.8 Hz), 7.09 (1H, t, J = 6.1 Hz), 7.28 (2H, m), 7.58 (1H, d, J = 8.0 Hz), 7.70 (1H, dd, $J_1$ = 2.3 Hz, $J_2$ = 15.8 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.65 (1H, s)

$^{13}$CNMR (CDCl$_3$): 30.1, 51.8, 52.3, 111.2, 114.1, 114.9, 119.8, 120.5, 125.1, 128.2, 130.9, 131.7, 137.2, 167.3, 173.8

MS: 273 (36, M$^+$), 241 (8), 214 (61), 182 (29), 154 (99), 127 (13), 77 (11), 44 (6), 28 (14)

Exact Mass: Calculated for C$_{11}$H$_{11}$N$_1$O$_2$ 273.1001
                       Found 273.1003
Indoleacetate (52)

A mixture of 52 mg (0.28 mmol) of isonitrile 28, 82 μl (0.30 mmol) of n-Bu$_3$SnH, and 2 mg (0.01 mmol) of AIBN in 2 ml of dry acetonitrile was heated at 100 °C for 1.5 h in a tightly capped culture tube under an argon atmosphere. After cooling to room temperature, the reaction mixture was treated with 78 mg (0.31 mmol) of I$_2$ in one portion. The reaction was allowed to stir at room temperature for 10 min prior to the addition of 247 mg (0.56 mmol) of 1-tri-n-butylstannylhexene, 16 mg (0.01 mmol) of Pd(PPh$_3$)$_4$, and 53 mg (0.28 mmol) of CuI. The mixture was then heated at 80 °C for 10 h under argon, at which time it was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a one third of saturated potassium fluoride solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 30% ether-hexanes to give 50 mg (66.0%) of 52 as a light yellow oil.
Indoleacetate (61)

To a mixture of 50 mg (0.16 mmol) of iodoindole 57, 6 mg (0.01 mmol) of Pd(PPh3)2Cl2, and 3 mg (0.02 mmol) of CuI in 2 ml of dry diethylamine was added 92 µl (0.80 mmol) of 1-hexyne at room temperature under an argon atmosphere. The reaction mixture was stirred for 8 h at which time it was partitioned between ether and 3 N hydrochloric acid. The combined extracts were washed with sodium bicarbonate solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 40% ether-hexanes to give 38 mg (89.0%) of 61 as a light yellow oil.

Characterization of 61:

IR (film): 3350, 3050, 2950, 2920, 2870, 2320, 1730, 1460, 1430, 1350, 1300, 1270, 1250, 1170, 1010, 750

1H NMR (CDCl3): 0.98 (3H, t, J = 7.2 Hz), 1.46-1.66 (4H, m), 2.49 (2H, t, J = 6.7 Hz), 3.70 (3H, s), 3.87 (2H, s), 7.14 (2H, m), 7.23 (1H, m), 7.56 (1H, d, J = 7.6 Hz), 8.18 (1H, s)

13C NMR (CDCl3): 13.6, 19.3, 21.9, 30.6, 31.0, 51.9, 71.5, 96.9, 110.7, 112.8, 118.8, 119.0, 120.1, 123.1, 127.0, 135.3, 172.0

MS: 269 (M⁺), 210 (99), 170 (13), 167 (25), 154 (16), 139 (10), 49 (4)

Exact Mass: Calculated for C17H19N1O2 269.1416
Found 269.1418
Indoleacetate (62)

A mixture of 62 mg (0.20 mmol) of iodoindole 57, 131 mg (0.30 mmol) of 1-tri-\(\pi\)-butylstannyhexene, 7 mg (0.01 mmol) of \(\text{PdCl}_2(\text{dpdf})\), and trace amount of 2,6-di-t-butyl-4-methylphenol (BHT) in 1 ml of dry \(\text{N}_2\text{N}\)-dimethylformamide was heated at 70 °C under 1 atm of carbon monoxide. The reaction mixture was stirred for 12 h, at which time it was partitioned between ether and a one third saturated aqueous potassium fluoride solution. The combined extracts were washed with diluted brine, dried over anhydrous sodium sulfate, filtered, and evaporate to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 40% ether-hexanes to give 46 mg (78.2%) of 62 as a light yellow solid.

Characterization of 62:

mp: 78-79 °C (ether-hexanes)

IR (film): 3320, 3050, 2950, 2920, 2860, 1730, 1650, 1600, 1540, 1430, 1340, 1250, 1210, 1170, 1020, 930, 740

\(^1\text{HNMR (CDCl}_3\): 0.93 (3H, t, \(J = 7.1\) Hz), 1.42 (4H, m), 2.27 (2H, q, \(J = 6.6\) Hz), 3.75 (3H, s), 4.16 (2H, s), 6.83 (1H, d, \(J = 15.3\) Hz), 7.03 (1H, t, \(J = 6.7\) Hz), 7.13 (2H, m), 7.32 (2H, m), 7.66 (1H, d, \(J = 8.1\) Hz), 9.58 (1H, s)

\(^{13}\text{CNMR (CDCl}_3\): 13.8, 22.2, 27.8, 30.0, 31.2, 32.4, 52.1, 112.2, 114.2, 120.6, 126.1, 126.5, 129.4, 133.2, 136.1, 148.2, 171.8, 182.8
MS: 299 (22, M+), 242 (38), 240 (55), 226 (19), 210 (22),
196 (45), 182 (99), 168 (60), 156 (34), 128 (34), 101 (9)

Exact Mass: Calculated for C18H21N1O3 299.1521
Found 299.1519
Indoleacrylate (63)

A mixture of 42 mg (0.11 mmol) of iodoindole 59, 21 µl (0.23 mmol) of methyl acrylate, 1 mg (0.005 mmol) of Pd(OAc)$_2$, 17 µl (0.12 mmol) of Et$_3$N, and 4 mg (0.01 mmol) of (Tol)$_3$P in 2 ml of dry acetonitrile was heated at 100 °C for 4 h in a tightly capped culture tube under an argon atmosphere. After the reaction mixture was cooled to room temperature, it was partitioned between ether and a 1:1 mixture of 3 N hydrochloric acid and saturated sodium chloride solution. The combined extracts were washed with a sodium bicarbonate solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 40% ether-hexanes to give 31 mg (82.8%) of 63 as a light yellow solid.

Characterization of 63:

mp: 121-122 °C (ether-hexanes)

IR (film): 3350, 3060, 2950, 2880, 1700, 1620, 1460, 1440, 1330, 1290, 1200, 1180, 1040, 980, 920, 740

$^1$HNMR (CDCl$_3$): 1.49 (4H, m), 1.79 (2H, m), 3.17 (2H, t, J = 6.8 Hz), 3.46 (1H, m), 3.60 (1H, q, J = 7.0 Hz), 3.77 (1H, m), 3.81 (3H, s), 3.97 (1H, q, J = 7.0 Hz), 4.58 (1H, t, J = 2.5 Hz), 6.19 (1H, d, J = 15.9 Hz), 7.08 (1H, t, J = 7.5 Hz), 7.26 (1H, m), 7.27 (1H, d, J = 7.5 Hz), 7.61 (1H, d, J = 7.5 Hz), 7.85 (1H, d, J = 15.9 Hz), 8.61 (1H, s)
$^{13}$CNMR (CDCl$_3$): 19.3, 24.9, 25.3, 30.5, 51.6, 62.0, 67.5, 98.8, 110.9, 113.5, 119.8, 119.9, 124.8, 128.3, 130.5, 132.7, 137.3, 167.6

MS: 329 (21, M$^+$), 227 (29), 214 (33), 201 (99), 167 (69), 154 (75), 128 (6), 115 (6), 85 (67), 67 (19), 57 (19), 28 (23)

Exact Mass: Calculated for C$_{19}$H$_{23}$N$_3$O$_4$ 329.1627

Found 329.1630
Indoleacetylene (64)

To a mixture of 45 mg (0.12 mmol) of iodoindole 59, 4 mg (0.006 mmol) of Pd(PPh₃)₂Cl₂, 2 mg (0.01 mmol) of CuI, and 70 µl (0.61 mmol) of 1-hexyne in 1 ml of dry diethylamine was stirred at room temperature for 8 h under argon, at which time it was partitioned between ether and 3 N hydrochloric acid. The combined extracts were washed with a sodium bicarbonate solution and then with brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. The crude product was purified by preparative thin layer silica gel chromatography eluting with 20% ether-hexanes to give 37 mg (93.4%) of 64 as a light yellow oil.

Characterization of 64:

IR (film): 3410, 3290, 3060, 2940, 2860, 2220, 1620, 1580, 1460, 1350, 1300, 1200, 1120, 1070, 1020, 900, 870, 810, 740

¹H NMR (CDCl₃): 0.96 (3H, t, J = 7.2 Hz), 1.45-1.89 (6H, m), 2.47 (2H, t, J = 6.8 Hz), 3.15 (2H, t, J = 7.6 Hz), 3.50 (1H, m), 3.70 (1H, q, J = 9.3 Hz), 3.86 (1H, m), 4.02 (1H, q, J = 9.3 Hz), 4.68 (1H, t, J = 3.8 Hz), 7.06 (2H, m), 7.22 (1H, m), 7.61 (1H, d, J = 7.7 Hz), 8.27 (1H, s)

¹³C NMR (CDCl₃): 13.5, 19.2, 19.4, 21.9, 25.4, 25.6, 30.6, 62.1, 67.3, 72.2, 96.0, 98.6, 110.5, 117.3, 117.5, 117.8, 119.1, 119.5, 122.8, 127.4, 135.4

MS: 325 (38, M⁺), 283 (3), 223 (51), 210 (99), 197 (62), 170 (50), 168 (21), 167 (21), 155 (14), 85 (5)

Exact Mass: Calculated for C₂₁H₂₇N₁O₂ 325.2042
Found 325.2041
REFERENCES FOR PART ONE


11. CAChe™ molecular mechanics calculation program (Version 3.5 by CAChe Scientific, Inc.) shows that the dihedral angle of Hα and the departing cyclopropane bond is 131.8 °.


23. We are indebted to Professor Richard E. Moore of University of Hawaii for direct comparison of our synthetic sample with the natural (−)-hapalindole G.
REFERENCES FOR PART TWO


79. Other isonitriles in the Table I were similarly prepared in 61 to 82% overall yield from o-iodoformylamide by palladium-mediated coupling reaction unless otherwise mentioned.

80. Results from Miss Ge Peng are greatly appreciated.


82. The Stille coupling of 1-SEM-2-tributylinylindole with a variety of halides has been recently reported: Palmisano, G.; Santagostino, M. Helv. Chim, Acta 1993, 76, 2356.


