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A NOVEL TIN-MEDIATED INDOLE SYNTHESIS
AND ITS APPLICATION TO
NATURAL PRODUCT SYNTHESIS

by
GE PENG

A THESIS SUBMITTED
IN PARTIAL FULFILLMENT OF THE
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Houston, Texas
March, 1996
Abstract

A Novel Tin-Mediated Indole Synthesis and
Its Application to Natural Product Synthesis

by

Ge Peng

A new indole synthesis is described. The key step involves a novel tin-mediated free radical reaction to generate unstable 2-tri-n-butylstanny1-3-substituted indoles, which upon mild acidic workup, furnishes 3-substituted indoles. The 2-tri-n-butylstanny1-3-substituted indoles are also subjected to a one-pot Stille coupling to provide 2,3-disubstituted indoles.

Two applications of the above methodology are also described. The efficient total synthesis of (±)-vincadifformine involves the construction of the indole skeleton by using this indole formation reaction and a novel amine protection-deprotection procedure as crucial steps.

A new synthetic approach is explored towards the total synthesis of antitumor agent discorhabdin C. The key step towards the key intermediate has greatly contributed to the development of the novel indole synthesis methodology.
Acknowledgments

First and foremost, I would like to thank my advisor, Professor Tohru Fukuyama for his excellent guidance and unfailing support over the years. His dedication, enthusiasm and love for research are always inspirations to me.

I am indebted to Dr. Xiaogi Chen and Dr. Tangqi Li for their cooperation with me for the indole synthesis methodology and the Discorhabdin C synthetic approach. I am grateful to Dr. Terry Marriot for providing most of the high resolution mass spectral data presented in this manuscript and Dr. Marco Ciufolini for his work in the MNDO calculation and useful discussion.

I also owe a big thank you to all of my former and present labmates for their friendship and creating an exciting and rewarding research environment. Special thanks go to Dr. Lianhong Xu for her help during the early months of my graduate career, Dennis Lovett for the valuable assistance in the preparation of this manuscript.

I would like to express my special thanks to my parents and my grandmother for their support and sacrifice throughout my education years.

Finally, I would like to thank the Department of Chemistry, Rice University and the National Institutes of Health for their support of both myself and this research project.
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To my grandmother and my parents
Chapter One

A Novel Tin-Mediated Indole Synthesis

Introduction

The indole nucleus is found in a large number of natural products having significant biological activity. Such products range in nature from the CNS (central nervous system) acting ibogaine 1 (*iboga* alkaloid)\(^1\) to the cardioactive principles eburnamonine 2 (*Eburna* alkaloids)\(^2\) and ajmaline 3 (Sarpagine-Ajmaline alkaloids),\(^3\) to the potent antitumor agent vincristine 4 (*Vinca* alkaloid).\(^4\)

![Chemical structures](image)

**Figure 1**

The natural paucity of such important substances and the chemical challenges that their structures pose have engendered a great deal of interest in the
development of fully synthetic routes to these indole alkaloids. It is not surprising, therefore, that the search for efficient syntheses of indoles has been both a goal and a problem in organic synthesis for nearly a century.

The immense volume of literature available on indole synthesis has been summarized in many excellent reviews. Therefore, it is not necessary to survey classical solutions to the foregoing problems, and the reader is referred to some recent monographs on the subject.⁵ On the other hand, efforts directed towards new methods for indole syntheses have continued well past the date of publication of those landmark reviews. A brief outline of the most significant developments in this area follows.

![Chemical structures](image)

**Scheme 1**

In 1987, Wender and coworkers published a new indole synthesis based on triazole photochemistry.⁶ Thus, Dimroth condensation of aryl azide 5 with ethyl 6-triisopropylsiloxy-3-ketohexanoate was conducted at 105 °C in DMF in the presence of potassium t-butoxide to give triazole ester 6. Photolysis of triazole 6 in acetonitrile afforded indole 7 in 67% yield (Scheme 1).
The above synthesis is a concise and efficient route to 2,3-disubstituted indoles. However, triazole formation requires application of heat under strongly basic conditions to promote the Dimroth condensation. This step restricts the scope of the approach.

![Chemical structures](image)

**Scheme 2**

Johnson and coworkers described another 2,3-disubstituted indole formation through a base-induced cyclization. Treatment of N-(2,2,2-trifluoroethyl)-N-methyl-m-anisidine 8 with four equivalents of n-butyllithium at low temperature generated lithium species 9, which spontaneously cyclized to provide 2-lithioindole 10. This intermediate may be further functionalized by reaction with electrophiles (Scheme 2). This indole-forming reaction requires an acetylenic intermediate which limits the substitution pattern. Moreover, the indole nitrogen has to be protected under the above reaction conditions.

A 2,3-disubstituted indole synthesis was also reported by Saegusa et al. (Scheme 3). Methylation of o-(acylmethyl)phenyl isocyanide 12 with iodomethane in the presence of sodium hydride produces o-(1-acylmethyl)phenyl isocyanide 13. Upon acid hydrolysis followed by
neutralization, 13 is converted to 2,3-disubstituted indole 14. Although this reaction can give a fairly good yield of the 2,3-disubstituted indole, nevertheless, strongly acidic conditions are required for the ring cyclization.

![Scheme 3](image)

**Scheme 3**

Recent work from our laboratories uncovered a need for an efficient synthesis of 2,3-disubstituted indoles under the mildest possible conditions. In particular, we concluded that avoidance of strong acids or bases would be highly desirable. Under such boundary conditions, the desired heterocycles cannot be synthesized through classical methods.

In the next part of this chapter, a versatile tin-mediated indole synthesis which is particularly suited for the preparation of 3-mono- or 2,3-disubstituted indoles will be described. This method has significant implication for syntheses of a variety of indole alkaloids, as will be shown in connection with a total synthesis of (±)-vincadifformine. Application to the synthesis of an advanced intermediate for the discorhabdin/prianosin group of natural products will also be illustrated.

**Background**

The need to exclude acidic or basic conditions in the preparation of our desired indoles induced us to consider a radical process. There has been a great deal of interest in the chemistry of isonitriles in our research group. The
well known propensity of such functionalities to participate in radical processes led us to reason that the α-stannooimidoyl radical 16, generated from the α-isocyanostyrene derivative 15 by addition of a tri-\(n\)-butyltin radical, should lead to the formation of the 2-stannyldione 18 through a radical cyclization and subsequent tautomerization as illustrated in Scheme 4. The 2-stannyldione 18 would in turn be an ideal precursor for the 3-substituted indole 19 upon acidic workup.

Scheme 4

Ample precedent exists to support the premises outlined above. For instance, in 1967 Shaw and Pritchard reported the radical-initiated vapor phase isomerization of alkyl isocyanides.\(^\text{10}\) It was initiated by a radical from the decomposition of di-\(t\)-butyl peroxide. The isomerization is a chain reaction as shown in Scheme 5.

\[
\text{CH}_3\text{N}=\text{C}: + \text{C}_2\text{H}_5^* \quad \rightarrow \quad \text{CH}_3\text{N}=\text{C}-\text{C}_2\text{H}_6 \quad \rightarrow \quad \text{CH}_3^* + \text{C}_2\text{H}_5-\text{C≡N}
\]

Scheme 5

Saegusa and coworkers observed that isonitriles react with organotin hydride to form imidoyl radicals.\(^\text{11}\) This event may be followed by β-scission
and hydrogen transfer to produce tri-\(n\)-butyltin cyanide and alkane in high yields (Scheme 6).

\[
\begin{align*}
\text{NC} & \quad \text{SnBu}_3 \quad \beta \text{ scission} \\
\text{苯} & \quad n\text{-Bu}_3\text{SnH}, (t\text{-BuO})_2 \\
120 \degree \text{C}, 8 \text{ h} & \\
\end{align*}
\]

\[n\text{-Bu}_3\text{SnCN} + \text{苯} \xrightarrow{n\text{-Bu}_3\text{SnH}} \text{苯CH}_3 (82\%)
\]

**Scheme 6**

This reaction was applied by Barton and associates for a selective modification of neamine through a radical-induced deamination.\(^{12}\) The reaction of neamine tetraformamide tetraacetate 20 with phosphorus oxychloride and triethylamine generates the isonitrile 21. The radical-induced reduction by tri-\(n\)-butylstannane leads to the corresponding deaminated amino glycoside derivative 22 via the imidoyl radical intermediate (Scheme 7).

\[
\begin{align*}
\text{NHCHO} & \quad \text{POCl}_3, \text{Et}_3\text{N} \\
\text{20} & \quad \text{NC} \\
\text{O} & \quad \text{AcO} \\
\text{OHCHN} & \quad \text{AcO} \\
\text{O} & \quad \text{AcO} \\
\text{NHCHO} & \quad \text{21} \\
\text{NHCHO} & \quad \text{NC} \\
\text{O} & \quad \text{AcO} \\
\text{O} & \quad \text{AcO} \\
\text{NHCHO} & \quad \text{NC}
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{22} \\
\text{AcO} & \quad \text{H} \\
\text{O} & \quad \text{AcO} \\
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{AcO} \\
\text{H} & \quad \text{AcO}
\end{align*}
\]

**Scheme 7**
Bimolecular radical reactions of isocyanides have also been demonstrated. In particular, the usefulness of imidoyl radicals resulting from addition of an external radical to an isonitrile in the synthesis of heterocyclic compounds is apparent from Scheme 8. Sunlamp irradiation of 1-methyl-5-iodo-1-pentyne 23 in the presence of hexamethylditin in t-butylbenzene at 150 °C generates alkyl radical 24. Addition of 24 to phenyl isocyanide produces imidoyl radical 25, which undergoes a cascade of intramolecular cyclizations to form quinoline 28 as the ultimate product (70% yield).

Scheme 8

The foregoing discussion clearly reveals the strong synthetic potential of imidoyl radicals. Nevertheless, these reactive intermediates have attracted little attention from the synthetic community.

A Novel Tin-Mediated Indole Synthesis

The first substrate we prepared to test our hypothesis was methyl o-isocyanocinnamate 32. This substance was prepared from o-iodoaniline 29 in a three-step sequence and in 86% overall yield. Formylation of 29 with acetic
formic anhydride in the presence of pyridine afforded the o-iodoformanilide 30 in quantitative yield. Palladium-mediated Heck reaction\textsuperscript{14} introduced the methyl acrylate moiety. Phosgene and triethylamine in dichloromethane proved to be a very efficient combination for the dehydration of formamide 31 to isonitrile 32 (Scheme 9).

$$\text{Scheme 9}$$

Treatment of isonitrile 32 with tributyltin hydride and a catalytic amount of AIBN in acetonitrile at 100 °C indeed gave the desired 3-substituted indole 34 in 91% yield upon mild acidic workup. A mild acid treatment was necessary to release the tin group from the indole (Scheme 10).

$$\text{Scheme 10}$$

An additional example of our new indole synthesis is shown in Scheme 11. This experiment was designed to probe the suitability of cis-olefin substrates. Smooth alkynylation of o-iodoformanilide 30 with tetrahydropyranyl propargyl ether 35 under modified Castro-Stephens conditions\textsuperscript{15} afforded
acetylene 36. Partial hydrogenation of 36 over Lindlar catalyst provided a cis-olefin. Formamide dehydration with phosgene generated isonitrile 37 in 55% overall yield. The tin radical-promoted cyclization was carried out under conventional conditions to provide the desired 3-substituted indole 38 in 83% yield.

Scheme 11

The success of the foregoing experiments engendered cautious optimism concerning the synthetic versatility of the radical-induced indole formation. At this juncture, however, we realized that a more practical way to prepare the requisite \( \sigma \)-isocyanostyrene derivatives was necessary, especially for possible large scale syntheses. In that connection, we recognized that a viable, and general, approach could employ suitable Wittig or Horner-Wadsworth-Emmons (HWE) reagents\(^\text{16}\) 39 as carriers of the benzenoid portion.

Scheme 12
of the indole. These would then be combined with appropriate aldehydes 40, resulting in the desired styrenes 41 (Scheme 12).

Typically, HWE reagents 42 are more reactive than a phosphonium ylides (Wittig reagents) 43; furthermore, by-products of the HWE olefination are water soluble, hence, can be easily separated from the products. Phosphonates are also cheaper than phosphonium salts, and are readily prepared through Arbuzov reactions. The above considerations led us to favor Horner-Wadsworth-Emmons reagent 39 as the most appropriate synthon.

![Figure 2](image_url)

The preparation of 39 was readily achieved through reaction of 2-nitrobenzyl bromide 44 with triethyl phosphite (95% yield, Scheme 13), followed by hydrogenation of the nitro group to an amine, formylation (acetic formic anhydride), and dehydration of the formamide with phosgene. While this method was chemically satisfactory, 2-nitrobenzyl bromide 44 is costly; nor it is particularly practical to prepare it in-house, by radical bromination of inexpensive 2-nitrotoluene. Photobromination (tungsten lamp, \(N\)-bromosuccinimide, carbon tetrachloride) was slow and recrystallization of the volatile bromide, a potent lachrymator, was painstaking.
An improved synthesis of 39 was sought through the agency of a nucleophilic aromatic substitution (S$_{NAr}$) of halogen by the anion of phosphonoacetate ester in substrate 47. The new synthesis was based on the well known mechanism of nucleophilic substitution of halogens, or other nucleofugal groups X, located ortho or para to a nitro group in nitroarenes.\textsuperscript{18} Such processes occur via ipso addition of the nucleophile, resulting in the formation of a so-called Meisenheimer complex, which subsequently expels the $X^-$ ion to form the final product as shown in Scheme 14.

$$\begin{align*}
X \text{NO}_2 + \begin{array}{c}
\text{base}\end{array} & \rightarrow \begin{array}{c}
X \text{Z} \\
\text{Y} \text{NO}_2
\end{array} \\
\begin{array}{c}
\text{base}\end{array} & \rightarrow \begin{array}{c}
Y \text{Z} \\
\text{NO}_2
\end{array}
\end{align*}$$

$X = \text{Br, Cl, F, NO}_2 \text{ etc.}$

$Y, Z = \text{CO}_2\text{Et, CN, SO}_2\text{Ph etc.}$

**Scheme 14**

The procedure outlined in Scheme 15 represents a marked improvement over the synthesis given in Scheme 13. The crucial S$_{NAr}$ reaction was initiated by adding 1-fluoro-2-nitrobenzene 47 to a mixture of triethyl phosphonacetate 48 and potassium hydride. The resultant substitution product 49 was quantitatively converted to 46 upon basic hydrolysis and in situ decarboxylation. Catalytic reduction of the nitro group followed by formylation with acetic formic anhydride furnished formamide 51, which was advanced to isonitrile 39 in excellent yield by treatment with phosgene and triethylamine.
Horner-Wadsworth-Emmons reagent 39 condensed with several aldehydes under conventional conditions (LDA, THF) to furnish the expected olefins in excellent yield. Table I summarizes representative examples, and demonstrates that a wide range of α-isocyanostyrenes are available through this new procedure. With our indole precursors securely in hand, we were ready to test the generality of our radical-induced indole synthesis.
Table I. Representative Horner-Wadsworth-Emmons Reactions.

\[
\begin{align*}
\text{entry} & \quad \text{RCHO} & \quad \text{Product} & \quad \text{yield (\%)} \\
1 & \quad \text{PhCHO} & \quad \text{PhNC-} & \quad 52 & \quad 90 \\
2 & \quad \text{NaphCHO} & \quad \text{NaphNC-} & \quad 53 & \quad 91 \\
3 & \quad n-C_7H_{15}CHO & \quad \text{C}_7H_{15}NC- & \quad 54 & \quad 91 \\
4 & \quad \text{BzCHO} & \quad \text{PhNC-} & \quad 55 & \quad 95 \\
5 & \quad \text{BuCHO} & \quad \text{BuNC-} & \quad 56 & \quad 93 
\end{align*}
\]
Exposure of the above substrates to the action of tributyltin hydride and AIBN in CH$_3$CN at 100 °C resulted in indole formation. The reasons behind the choice of these conditions will be discussed shortly; in any event, Table II outlines the results of these studies.

**Table II. Synthesis of 3-Substituted Indoles**

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
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<tr>
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<td></td>
<td><img src="image14" alt="Structure 67" /></td>
<td></td>
<td>14</td>
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</tbody>
</table>
Perusal of the table above reveals that substrates bearing radical stabilizing substituents (ester, phenyl, 2-naphthyl; entries 1, 3 and 4) at the olefinic β-position gave excellent yields of indoles. However, yields of indoles from substrates 60, 54, 55 and 63, which lack such stabilizing groups, were not uniformly satisfactory, and in some instances they were rather poor. Substantial amounts of tetrahydroquinoline side-products were formed in these reactions. Interestingly, in the case of entry 6 this problem could be partially alleviated by employing the corresponding Z-geometric isomer 63; yet, quinoline formation could not be fully suppressed. To reach this goal, it became critical to gain more detailed mechanistic insight into the reaction.

Tetrahydroquinoline formation may be rationalized by the mechanism shown in Scheme 16. An α-stannimidoyl radical 16, generated from o-isocyanostyrene derivative 15 by addition of tri-n-butyltin radical probably undergoes 6-endo cyclization to form intermediate 68. Subsequent hydrogen atom transfer to 68 provides the 2-stannylidihydroquinoline derivative 69. At this stage, a second molecule of tri-n-butyltin hydride presumably reduces the imino linkage of 69 to furnish a tetrahydroquinoline, which undergoes facile protiodestannylation upon acidic workup. However, the fine details of this

Scheme 16
second reductive event are not fully clear. On the other hand, the indole is probably produced through 5-exo cyclization of radical 16, followed by hydrogen atom transfer. This second mode of cyclization should be kinetically favored over the unwanted 6-endo pathway,\textsuperscript{19} which therefore was likely to be the result of imperfect kinetic control in the overall reaction (Figure 3).

\[
\begin{align*}
\text{17} & \xrightleftharpoons{5\text{-exo}} \text{16} & \xrightleftharpoons{6\text{-endo}} \text{68}
\end{align*}
\]

**Figure 3**

The foregoing conclusion finds support in a semi-empirical study of simplified analogs of the presumed radical intermediates 17 and 68. The heat of formation of MNDO\textsuperscript{20} (UHF) optimized structures of the simplified analogs was calculated to be 58.4 and 37.2 kcal/mol, respectively, while the dipole moment of the two structures was calculated as 2.02 and 1.75 D, respectively.\textsuperscript{21} Thus, the radical intermediate leading to the unwanted quinoline is more thermodynamically stable and less polar than the one leading to the indole.

\[
\begin{align*}
\Delta H_f &= 58.4 \text{ kcal/mol} \\
\mu &= 2.02 \text{ D} \\
\Delta H_f &= 37.2 \text{ kcal/mol} \\
\mu &= 1.75 \text{ D}
\end{align*}
\]

**Figure 4**

Evidently, under our reaction conditions, cyclization of 16 to 17 is kinetically favored, but the new radical 17 may revert to 16, which then may produce 68 in a thermodynamically driven secondary process. Suppression of the undesired side reaction could therefore be achievable by any of three strategies:
• A more polar solvent could be used, in order to favor the more polar radical intermediate 17 leading to the indole;

• A greater concentration of tri-n-butyltin hydride might be utilized, in order to trap the kinetic radical 17 more effectively;

• The reaction might be conducted at a lower temperature, in order to disfavor equilibration of 17 with 16 and thence with 68.

Examination of various solvents indicated that acetonitrile is the most polar medium suitable for the radical reaction. Furthermore, higher concentrations of tributyltin hydride did reduce the extent of formation of the tetrahydroquinolone by-product, which nevertheless was still isolated in substantial amounts even from the most concentrated reactions. Fortunately, complete suppression of the side reaction was achieved by running our radical cyclization at room temperature.

This new protocol required a different mode of initiation of the free radical chain, since AIBN would not be effective below 50-60 °C. Two options for initiation were therefore available: use of triethylborane and catalytic oxygen, or photolysis of hexabutylditin. Attempted triethylborane-oxygen-promoted indole formation in the presence of tri-n-butyltin hydride gave no reaction. By contrast, highly successful results were obtained from photolytic experiments. Thus, irradiation of a mixture of 56 (1 equivalent), tributyltin hydride (2 equivalents) and hexabutylditin (0.5 equivalents), at ambient temperature, with a 500 W high-pressure mercury lamp, resulted in exclusive formation of the desired indole, after the now familiar destannyative acidic workup. A slightly longer reaction time was required compared with the thermal reaction, but the overall yield was greatly improved.
Table III summarizes data for several examples of the new photochemical indole synthesis. Tetrahydroquinoline formation was suppressed in every case. We conclude that reaction temperature is the dominant factor in determining product distribution.

**Table III. Examples of Photolytic Indole Formation**

<table>
<thead>
<tr>
<th>entry</th>
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<th>product</th>
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<td>2</td>
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<td>4</td>
<td><img src="image" alt="Structure 7" /></td>
<td>4.5</td>
<td><img src="image" alt="Structure 8" /></td>
<td>86</td>
</tr>
</tbody>
</table>

It was soon realized that 2-stannyldindoles 18, the primary products of the foregoing radical reaction, are exceptionally useful synthetic intermediates for the preparation of more complex structures, for instance, through the agency of
transition metal-mediated processes. To the best of our knowledge, their chemistry has not been studied extensively. Until now, lithiation/stannylation of N-protected indoles was the only practical method to prepare them,24,25 but the advent of our radical technology has rendered these intermediates considerably more readily available.

Our expectation that 2-stannyldioles 18 may be useful building blocks was immediately realized. For instance, Stille coupling26 with appropriate halides or triflates afforded 2,3-disubstituted indoles in good to excellent yield. Stille coupling was best performed directly on the crude reaction mixture, because 2-stannyldioles were prone to undergo facile protiodestannylation during workup. A typical one-pot preparation of a 2,3-disubstituted indole proceeded as follows. Addition of bromobenzene, triethylamine and tetrakis(triphenylphosphine)palladium(0) (the best catalyst for this type of coupling reaction) to crude stannyldiole 33, followed by heating at 100 °C, furnished the coupling product 71 in 82% yield (Scheme 17).
We surveyed the generality of this one-pot Stille coupling procedure with respect to several 2-stannyldindole intermediates and a variety of halides and triflates. Results of representative experiments are summarized in Table IV.

**Table IV. One-Pot Synthesis of 2,3-Disubstituted Indoles**

```
\[
\begin{array}{cccccc}
\text{entry} & \text{substrate} & \text{R'}X & \text{equiv} & \text{time (h)} & \text{product} & \text{yield (%)} \\
1 & \text{phenyl} - \text{Br} & 1.2 & 5 & \text{product} & 71 & 82 \\
2 & \text{phenyl} - \text{I} & 1.2 & 8 & 71 & 68 \\
3 & \text{Ac} - \text{phenyl} - \text{Br} & 1.2 & 12 & \text{product} & 72 & 81 \\
4 & \text{phenyl} - \text{I} & 1.2 & 3 & 72 & 75 \\
5 & \text{phenyl} - \text{I} & 3.0 & 8 & \text{product} & 73 & 58 \\
\end{array}
\]
```
Table IV continued:

<p>| | | | | | |</p>
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In accord with Stille's reports, addition of lithium chloride was essential for successful couplings with triflates (entries 4, 6 and 10). Moreover, when trans-1-iodohexene was used as a coupling partner, addition of 1 equivalent of
cuprous iodide was needed to suppress the formation of the undesired 2-(1-butylethenyl)indole (entry 8).\textsuperscript{28}

**Conclusions**

Many functional groups tolerate both free radical and palladium-mediated reactions, so our methodology should facilitate construction of a wide range of 3-mono- or 2,3-disubstituted indoles from readily accessible isonitriles. This strategy should provide more direct routes to the preparation of natural products incorporating such ring systems. Both the indoles and the starting materials used to create the isonitriles are easily made. This, combined with the high yields of the indole formation and the ensuing Stille coupling reactions, renders the method quite valuable for the preparation of complex heterocyclic frameworks. Applications of this methodology to the total syntheses of indole alkaloids will be discussed in the following chapters.
Chapter Two

Total Synthesis Of (±)-Vincadifformine

Background

Even at the early stage of its development, we recognized that the new indole-forming reaction offered important advantages over existing methods. Accordingly, a search for possible synthetic applications was undertaken. A target was readily identified among several biologically active substances, as discussed below.

Aspidosperma alkaloids, exemplified by vincadifformine 90, are prominent representatives of a large family of natural products based on the indole nucleus. These substances have attracted a great deal of attention on accounts of their important medicinal properties. Their biogenesis has been elucidated through the combined efforts of many research groups, and excellent reviews exist on this subject. Their origin has been traced to tryptophan and loganin, as shown in the simplified biosynthetic scheme of Figure 5.
Legend:
80 geraniol  
83 strictosidine  
86 dehydrosecodine  
89 tabersonine  
81 logain  
84 catenamine  
87 secodine  
90 vincadifformine  
82 secologanin  
85 prekuammicine  
88 catharanthine  

Figure 5
Dehydrolecrodine 86 is a pivotal precursor to *Aspidosperma* (i.e., tabersonine, 89) and *Iboga* (i.e., catharanthine, 88) alkaloids by alternative reactions of the acrylic ester and dienamine moieties. Furthermore, reduction of dehydrolecrodine 86 will furnish secodine 87, cyclization of which may now occur only to form vincadifformine 90.30

Isolated in 1962 from *Vinca minor* Linn,31 (+)-vincadifformine is representative of the *Aspidosperma* alkaloids. Since the first total synthesis published in 1968, a plethora of papers on the synthesis of vincadifformine have been reported reflecting continuing interests in this molecule.32 However, despite admirable efforts and great contributions towards its synthesis, there is still the need for an efficient synthetic route. Our indole formation methodology should allow facile construction of the secodine intermediate 87, which is known to cyclize to (+)-vincadifformine via a biomimetic pathway.

**Synthetic Strategy**

![Scheme 18](image-url)
According to the Wenkert-Scott biogenetic hypotheses,\textsuperscript{33} secodeine 87 is the immediate biogenetic precursor of (\pm\)-vincadifformine 90. Disconnection of the enamine linkage in 87 leads to recognition of compound 91 as a key synthon. It is apparent that compound 91 can be synthesized in a relatively straightforward fashion from 92 through our indole formation reaction, as shown in Scheme 18.

**Model Study**

At the outset of this research, scope and limitations of the Stille coupling\textsuperscript{34} leading to 2,3-disubstituted indoles had not been explored. A model study was therefore undertaken to examine the feasibility of the planned transformations. Indole precursor 37 was chosen as a model (Scheme 19).

![Chemical Structures]

**Scheme 19**

Attempted Stille coupling of 2-stannyllindole intermediate 93 with methyl 2-bromoacrylate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium under the usual conditions gave 94 in a very poor yield. The low yield could be attributed to the instability of methyl 2-bromoacrylate, which polymerizes rapidly even at low temperatures.
Fortunately, methyl 2-tributylstannylacrylate proved to be much more stable under Stille coupling conditions than the 2-bromoacrylate ester; therefore, the problem of instability was solved by interchanging the roles of the coupling reactants (Scheme 20). Treatment of 2-stannyldione 33 with N-iodosuccinimide at room temperature furnished 2-idoindole 95 in 91% yield. The modified Stille coupling was carried out by heating 2-idoindole 95 with methyl 2-tributylstannylacrylate and bis(triphenylphosphine)benzylpalladium chloride in the presence of copper(I) iodide and triphenylarsine in a mixed solvent of DMF and HMPA to generate the desired product 96 in 54% yield. The palladium-based catalytic system used in this reaction proved superior to several other complexes/ligands. The success of the coupling step augured well for the ultimate application of our methodology to an efficient total synthesis of (±)-vincadifformine.

Scheme 20
Initial Approach

The important intermediate 100 was prepared in a conventional manner. Thus, cyano dimethyl acetal 97 was obtained from butyraldehyde as described by Ziegler. Reduction of the cyano group in 97 with DIBAL-H provided aldehyde 98, which was reductively aminated with propargylamine in the presence of zinc chloride and sodium cyanoborohydride in methanol to afford secondary amine 99. The amine was then protected as t-butyl carbamate 100.

![Chemical structure and reaction scheme](image)

Scheme 21

Castro-Stephens type coupling of 100 with o-iodoformanilide 30 gave the alkynylation product 101, which was partially hydrogenated over Lindlar catalyst prior to formamide dehydration with phosgene and triethylamine to provide isonitrile 102. Our novel indole-forming reaction was followed by treatment of the intermediate stannyllindole (not isolated) with N-iodosuccinimide to furnish 2-iodoindole 103. However, compound 103 was obtained in fairly low yield, together with unknown byproducts. The major byproduct appeared to arise from 102 through loss of the side-chain. Despite this disappointing result, we elected to postpone optimization of this reaction, and to advance the crucial iodoindole into the synthesis, in order to explore more substantive issues.
Scheme 22

Indole 103 was N-protected as a Boc derivative and subjected to Stille coupling with methyl 2-tributylstannylacrylate under the conditions optimized in the course of our model study. The desired coupling product 105 thus emerged. At this stage, simultaneous deprotection of both Boc groups and dimethyl acetal was achieved by treatment with trifluoroacetic acid. Upon workup, (±)-vincadiiformine was isolated in fairly low yield (Scheme 23).

The reasons for the poor efficiency of the foregoing process became apparent soon. Briefly, it may be expected that release of all protecting groups upon trifluoroacetic acid treatment of 105 would result in intramolecular condensation of the emerging secondary amine with the aldehyde. The resulting imine would subsequently tautomerize to give the required enamine 87. Model studies in our laboratories suggested that enamine/iminium ion tautomers of the type 87 are not stable to strong protic acids and decompose readily. Therefore, secodine formation, a necessary event en route to (±)-vincadiiformine, is compromised in the presence of excess trifluoroacetic acid.
Scheme 23

The side chain secondary amine in 106 required a blocking group that would be cleavable under considerably milder conditions. An improved synthesis was rapidly developed on the basis of these considerations, as shown in Scheme 24.

Amine 99 was protected as the 2-carbomethoxyethyl carbamate 107, which was subjected to the same sequence illustrated earlier for the conversion of 100 into 106 (Scheme 22), resulting in formation of compound 108. However, the problem with the low yield in the indole forming reaction persisted. Release of the indolic N-Boc group was effected by treatment of 108 with trifluoroacetic acid, which also liberated the aldehyde from its dimethyl...
acetal. Deprotection of the 2-carbomethoxyethyl carbamate with DBU provided the desired (±)-vincadifformine in more than 50% yield. The successful conclusion of this phase of our work induced us to switch our focus to the optimization of the radical indole formation.

![Chemical reaction images]

**Scheme 24**

The studies described above suggested that a more efficient synthesis might result if indole and amine side chain sectors were to be prepared separately, then merged at a later stage to avoid loss of the side chain during the radical reaction. The desired (±)-vincadifformine could then be obtained under mildly basic conditions. Our second approach, based on this premise, is described in the next section.
Total Synthesis of (±)-Vincadifformine

Our modified plan envisioned construction of 110 via the novel indole-forming reaction. Coupling of 110 with 111 would deliver advanced intermediate 91, which was expected to cyclize spontaneously to secodine 87 (Scheme 25), and thence to (±)-vincadifformine.

\[
\begin{align*}
\text{87} & \quad \text{→} \quad \text{91} \\
\text{110} & \quad \text{+} \quad \text{111}
\end{align*}
\]

**Scheme 25**

Indole alcohol 110 was synthesized as shown in Scheme 26. A modified Castro-Stephens reaction of o-iodoformanilide 30, introduced a propargyl alcohol unit. Protection of the alcohol as its acetate 112 and hydrogenation over Lindlar catalyst provided olefin 113. Dehydration of the formamide with phosgene afforded isonitrile 114. Formation of the desired 2-iodoindole occurred very cleanly and without incident, and it was followed by Boc protection of the indole nitrogen under standard conditions. The overall yield of 115 was 71%. The methyl acrylate moiety was introduced in even better yield (62%) than in the model study. Finally, the acetate was cleaved under mildly basic conditions to give alcohol 110.
Scheme 26

Synthesis of the amine part is outlined in Scheme 27. Hydrogenation of cyano dimethylacetal 97 over Raney nickel in ethanol saturated with anhydrous ammonia reduced the cyano group to the primary amine 117. At this juncture, we focused our attention on two of the many available coupling procedures for the merger of 117 with fragment 110: reductive alkylation of the amine with the indole aldehyde using NaBH₃CN, and Mitsunobu alkylation. The first protocol was soon ruled out, because the indole aldehyde obtained upon Swern oxidation of alcohol 110 was unstable. Furthermore, reductive alkylation of
amine 117 furnished some undesired dialkylation product. We therefore concentrated on the Mitsunobu alkylation of 117.

\[
\begin{align*}
97 \xrightarrow{1) \text{ CSA, CH(OMe)_3, MeOH}} & \quad \text{Cl} \xrightarrow{2) \text{ H}_2, \text{ Rh-Ni, EtOH (NH}_3)\text{Et}_3\text{N, CH}_2\text{Cl}_2}
\end{align*}
\]

\[\text{MeO} \xrightarrow{\text{OMe}} \text{NH}_2 \quad \text{CO}_2\text{Me} \quad \text{MeO} \xrightarrow{\text{OMe}} \text{Cl} \xrightarrow{\text{Et}_3\text{N, CH}_2\text{Cl}_2}
\]

110 + 118 \rightarrow \text{Mitsunobu reaction} \rightarrow \text{no reaction}

**Scheme 27**

The Mitsunobu reaction succeeds only if the donor component is a Brønsted acid with pKa around 10.\textsuperscript{36} Therefore, an amine group requires activation in order to participate in that process. Typically, this is accomplished by creation of toluenesulfonamides\textsuperscript{37} or trifluoroacetamides.\textsuperscript{38} An unfortunate problem with these methods, especially with sulfonamides, is that harsh conditions are required for N-deprotection. Attempted Mitsunobu reaction of 2-carboxymethoxyethyl sulfonamide 118, which can be deprotected with DBU under mild conditions, failed to give the coupling product, suggesting that perhaps this sulfonamide is not acidic enough for the Mitsunobu reaction. In summary, it was necessary to create an entirely new protecting group which could meet our requirements.

The reactions shown above suggested that the amine had to be protected as a benzenesulfonamide derivative which could be deprotected under very mild conditions. After many attempts, we found that 2,4-
dinitrobenzenesulfonamides could be cleaved via the S$_{N}$Ar processes$^{39}$ as shown in Scheme 28. After realization of Mitsunobu reaction, facile deprotection of the 2,4-dinitrobenzenesulfonyl group occurs via the Meisenheimer complex upon addition of a soft nucleophile, giving the desired secondary amine.

$$
\begin{align*}
\text{HN-SO}_2^+\text{NO}_2^- & \xrightarrow{\text{Mitsunobu}} \text{RN-SO}_2^+\text{NO}_2^- \\
\text{Y} & \rightarrow \text{RN-SO}_2^+\text{NO}_2^- + \text{R}^- + \text{SO}_2 \\
\end{align*}
$$

**Scheme 28**

Amine 117 reacted with commercially available 2,4-dinitrobenzenesulfonyl chloride to give sulfonamide 118. This substance underwent smooth Mitsunobu coupling with indole alcohol 110 to afford compound 119 in excellent yield as shown in Scheme 29.
As illustrated earlier, both indolic N-Boc group and dimethyl acetal unit were cleaved with trifluoroacetic acid to give aldehyde 120, setting the stage for the crucial release of the sulfonamide function. In that connection, a rigorous requirement existed for a nucleophile that would selectively attack the 2,4-dinitrobenzene nucleus, thus initiating the aromatic addition-elimination process, without reacting at other electrophilic sites such as the methyl acrylate moiety or the aldehyde. PhSH or HSCH$_2$CO$_2$H$^{40}$ were not suitable because the acrylate moiety underwent Michael reaction first. We were delighted to find that treatment of 120 with potassium phenoxide, a very mild nucleophile, gave fully synthetic (±)-vincadifformine in 67% yield over the last two steps, without causing any undesired Michael addition or alternative side reactions (Scheme 30). We could not observe the presumed intermediate secodine in the course
of this transformation. The spectral data of synthetic material were in complete agreement with those reported in the literature for natural (±)-vincadifformine.

![Chemical structures and reactions]

Scheme 30

Conclusions

An efficient total synthesis of (±)-vincadifformine has been achieved through the application of a novel radical indole-forming reaction and through
the use of certain sulfonamide N-protecting groups that are cleavable under extremely mild conditions. The advances in chemical methodology that were necessitated by the many difficulties encountered in the course of this research are likely to remain as generally, perhaps extremely, useful techniques well beyond the conclusion of these experiments.
Chapter Three

A Synthetic Approach To Discorhabdin C: Using A Tin-Mediated Indole Synthesis

Introduction

Much attention has been focused upon isolation and structure determination of biologically active materials from marine sources. One of the most interesting classes of these compounds is the structurally diverse group of alkaloids containing the pyrrolo[4,3,2-de]quinoline nucleus. Representative examples include the discorhabdins and the prianosins.

The discorhabdin alkaloids were first isolated by Perry and coworkers from the sponge of Latrunculia du Bocage in New Zealand. At the same time, Kobayashi and coworkers reported four polycyclic alkaloids, prianosins A-D from the Okinawan sponge Prianos melanos, and their structures have been shown to be closely related to those of the discorhabdins (Figure 6). The isolation process was guided by a bioassay for cytotoxicity against standard tumor cell lines. Further testing showed that these compounds exhibited high activity against P388 leukemia in vitro (IC$_{50}$ values in range 0.03-0.1 µg/ml), but only discorhabdin D was found to have significant in vivo P388 activity (T/C 132% at 20 mg/kg).
Potent anticancer activities, limited availabilities from the natural sources, and novel molecular architecture centered on an unusual, highly fused pyrrolo[1,7]phenanthroline ring system have made the discorhabdins prime synthetic targets. Attention so far has been focused on discorhabdin C, for which two total syntheses\textsuperscript{47} and several synthetic approaches\textsuperscript{48} have been reported since 1991. Activity in this area is briefly reviewed in the following paragraphs, wherein emphasis is given to the synthetic strategies.

Construction of the spirocyclic dienone system seems to be the greatest obstacle to overcome. Three general approaches have been explored in that connection. Oxidative phenolic coupling, originally reported by Yamamura and Kita independently, has been the only successful strategy for the syntheses of discorhabdin C. Recent work by Cava, White and others also rests on similar
principles. An alternative strategy explored by Ciufolini features an early installation of the spirocyclic system. His approach was based on a novel synthesis of 4-aryl-4-alkyl cyclohexanone. The Confalone approach envisions an intramolecular para-phenolic alkylation to form the spirodienone system. Our synthetic strategy is also based on an intramolecular phenolic alkylation. Details of published work follow.

**The Yamamura Synthesis**

The first total synthesis of discorhabdin C featured coupling of a tricyclic system 133 with dibromotyramine to form the oxidative cyclization precursor 135 (Figure 7).

![Diagram](image)

**Figure 7**

Aldehyde 128 was converted into 129 by Jones oxidation followed by Curtius rearrangement in the presence of 2-(trimethylsilyl)ethanol. Compound 129 served as a template for a traditional Bischler indole synthesis. The product 131 was transformed to the lactam 132 in three steps. Lactam 132 was converted to the iminodienone 133 through a sequence of reduction and oxidation reactions (Scheme 31).
Scheme 31

Coupling of iminoquinone 133 with 3,5-dibromotyramine hydrobromide 134 in the presence of NaHCO₃ provided the phenolic product 135. Anodic oxidation of 135 gave discorhabdin C 124 in 24% yield, which is a disappointing step for an otherwise elegant synthesis.
The Kita Synthesis\textsuperscript{50}

In 1992, Kita and coworkers published their total synthesis of discorhabdin C. Their strategy for the construction of the spirocyclic dienone system was the same as Yamamura's, except that a hypervalent iodine reagent was used for the final oxidative coupling. Unfortunately, like in Yamamura's case, the yield of the final oxidation step was low.

As outlined in Scheme 33, a Moody-Rees reaction\textsuperscript{51} was used for the indole formation. Benzylation of aldehyde 136 followed by condensation with ethyl azidoacetate in ethanolic sodium ethoxide provided the vinyl azide, which decomposed in boiling xylene to give indole 137. Decarboxylation, alkylation and substitution afforded the 3-(cyanomethyl)indole 139. Hydrogenation of cyanide 139 gave a primary amine, which was protected prior to oxidation of the benzenoid nucleus to give quinone 141. After protecting the indolic nitrogen with a tosyl group, the critical cyclization gave the tricyclic intermediate 142. Coupling with dibromotyramine transformed 142 to phenol 135, and a subsequent oxidation with [bis(trifluoroacetoxy)iodo]benzene afforded discorhabdin C in moderate yield.
The Cava Approach\textsuperscript{52}

Recently Cava et al. described a more efficient way to synthesize compound 142. Indole-2-carboxylate 144 was prepared by a Moody-Rees reaction from aldehyde 143. Decarboxylation of 144 provided indole 145, alkylation of which was achieved by condensation with oxalyl chloride and
addition of dibenzylamine. The resulting amide 146 was then reduced to amine 147.

Scheme 34

A sequence involving indole N-protection with a tosyl group, hydrogenation and protection of the primary amine by TEOC gave compound 141, which was oxidized to a quinone with CAN. Acid treatment afforded the Kita intermediate 142, thus completing the formal synthesis of discorhabdin C. However, the subsequent coupling of dibromotryptamine and 142 gave 135 in only 35% yield.

Scheme 35
The Ciufolini Approach$^{53}$

Ciufolini elected to install the spirocyclic ring at an early stage. A key step leading to the crucial intermediate 151 involved a new Paterno-Büchi reaction for the spirocyclic ring formation, and heteroannulation through cascade Michael reactions for the construction of the pyrrolidine unit. Specifically, a quinone photochemical product was converted to 4-aryl-4-alkylcyclohexanone$^{54}$ which was protected to give compound 148. Compound 148 was oxidized to a quinone monoketal which served as a template for a Michael addition cascade to construct the pyrrolidine ring. A Mitsunobu reaction and subsequent hydrazinolysis converted the alcohol 150 to a primary amine, which cyclized to give imine 151 as shown in Scheme 36.

Scheme 36

Aromatization of the imine 151 followed by protection of the secondary amine set the stage for nitration. After nitration, the olefin was subjected to
hydroboration-oxidation to furnish the corresponding alcohol 153, which was mesylated. The final ring formation occurred upon the reduction of the nitro group, completing the basic ring system of the discorhabdins.

While several attempts were made to upgrade the oxidation state of the 4,4-dialkylcyclohexanone moiety of the molecule to a bromodienone, no satisfactory halogenation protocol has been found so far.

![Scheme 37](image)

**The Confalone Approach**

The first synthetic approach to discorhabdin C was reported by Confalone and coworkers. They developed a relatively facile intramolecular *para*-phenolic alkylation for spirodienone formation.

Bromination and protection of 155 afforded 156. The indole-2-carboxylate 157 was synthesized according to the Moody-Rees reaction from
bromoaldehyde 156. A palladium-mediated Suzuki coupling introduced another aryl group to give 158. Saponification of ester 158 followed by decarboxylation and Vilsmeier-Haack-Viehe reaction afforded 159. Oxidation of the benzene ring, removal of the MOM group, and tribromination with pyridium bromide perbromide provided 160 (Scheme 38).

Scheme 38

As shown in Scheme 39, treatment of 160 with chloromethyl methyl ether gave the N,O-bis-MOM derivative. This underwent smooth halide displacement with ethanolamine to provide an alkylaminoquinone. Subsequent activation of the hydroxyl group as a mesylate gave 161. The critical spirocyclization reaction was performed after deblocking the MOM
group. Thus, treatment of the free phenol with potassium t-butoxide afforded 162. Condensation of the aldehyde in 162 with nitromethane yielded nitroethylene derivative 163, which was reduced by sodium borohydride to nitroethyl indole 164. However, attempts to further reduce the aliphatic nitro group to an amine, a prerequisite for the final cyclodehydration, failed.

Scheme 39
A Synthetic Approach to Discorhabdin C

Retrosynthetic Strategy

A potential weakness of the successful total syntheses of discorhabdin C resides in the phenolic coupling reaction that installs the spirocyclic subunit. It is plausible that more complex members of the discorhabdin family, especially those containing sulfur, may not survive manipulations involving strong oxidants. Consequently, a synthetic attack on those molecules would probably require a different strategy.

A particularly appealing plan visualized formation of the spirodienone unit through a para-phenolic alkylation. The crucial synthetic intermediate 166 would then be prepared from dinitroindole 167, a logical precursor to which is 168. This substance would fall nicely within the scope of our newly developed methodology for indole synthesis.56
Synthetic Approach

As depicted in Scheme 41, the readily available benzoate 169 was converted to mononitro product 170 upon reaction with excess fuming nitric acid and acetic acid at 85 °C. After recrystallization, the pure mononitro compound 170 was ready for hydroxylation ortho to the nitro group. This operation would be carried out under strongly basic conditions; therefore, the phenol benzoate was changed to a base-resistant methoxymethyl group. The hydroxylation proper was carried out by heating 171 with potassium hydroxide and diphenyl ether at 110 °C in the presence of oxygen. The product 172 was protected as the benzyl ether to give 171.

![Chemical Structure](image)

Scheme 41

An indole fragment of the type 168 was constructed in the following manner. The nitro group of 171 was reduced to amine 172 with zinc dust in acetic acid. This made the aromatic ring more electron-rich and ready for bromination, a goal smoothly achieved upon reaction of 172 with pyridinium bromide perbromide in the presence of propylene oxide as an acid scavenger. The precursor for the indole synthesis was synthesized in a three-step
sequence, involving formylation of amine, Heck reaction to introduce the acrylate moiety, and dehydration of the formamide with phosgene. The desired indole 176 was obtained in 95% yield by our tin-mediated radical indole synthesis (Scheme 42).

Scheme 42

At this stage, incorporation of nitrogen functionalities at the two vacant positions of the central aromatic ring of 176 became necessary. Dinitration seemed to be the easiest way to accomplish our objective. To that end, the benzyl ether was deprotected to form a phenol, which would increases the nucleophilicity of its ortho and para positions, and the indole nitrogen was blocked to give amide 177, which has less nucleophilicity at the carbon atom α to the indole nitrogen. However, attempted nitration of 178 with fuming nitric
acid, or concentrated nitric acid with different combinations of other acids or solvents, was unsuccessful, resulting only in intractable mixtures. Apparently, either the starting material or the mono nitration product are unstable to the strongly acidic conditions.

Scheme 43

A possible way to alleviate the dinitration problem was to introduce each nitro group in a stepwise manner. In principle, once the mononitration product was obtained, reduction of the nitro group to an amine would facilitate introduction of the second nitro group by increasing the nucleophilicity of the aromatic system. To our great disappointment, the best result for the mononitration (isoamyl nitrite in the presence of trifluoroacetic acid in dichloromethane at 0 °C) generated an almost 1:1 mixture of mononitrophensols 179 and 180 (Scheme 44).
Scheme 44

Although we could separate those two isomers and reduce them to the corresponding amines, the procedure was unsuitable for a practical synthesis. The failure of the mononitration forced us to find a better route to obtain a key intermediate which could be transformed to 166.

Revised Synthetic Strategy

We recognized that the two nitrogen functionalities in compound 181 had to be introduced prior to indole formation. To simplify the nitration process,
the biaryl carbon-carbon bond was disconnected, leading to two aromatic fragments 182 and 183, to be joined at an appropriate time.

Synthetic Approach

Creation of the key intermediate 181 required us to research a protocol for the establishment of the indole nucleus in the presence of the two aromatic amino groups. Nitration of protected chlorosalicylic acid 183 was best conducted with fuming nitric acid in trifluoroacetic anhydride and dichloromethane, and provided dinitro product 185 in 67% yield after recrystallization. A biaryl subunit was manufactured at this stage through the merger of 185 and 186 by Ullman coupling.57 This reaction proceeded cleanly in the presence of copper powder to furnish 187 in quantitative yield.

At this juncture, we focused our attention on the construction of the indole ring. This requires an isonitrile group at the ring position where the ester group resides, and an acrylate moiety at its vacant ortho position.

Scheme 46
Curtius rearrangement of benzoic acid 188 installed the requisite nitrogen functionality. Thus, the acyl azide was prepared by addition of tetrabutylammonium azide to a mixed anhydride derived from 188. Curtius rearrangement in refluxing toluene containing allyl alcohol gave allyl carbamate 189 in 97% yield. Palladium-mediated deprotection of the Alloc group produced amine 190, and subsequent formylation of the amine resulted in formamide 191 in 92% yield.

Scheme 47

The two nitro groups in 191 were anticipated to interfere with the indole forming radical reaction; therefore, they were smoothly reduced to amines with activated zinc and acetic acid. At this stage, the diamine product was treated with iodine monochloride to give diamino iodide 192 in 78% yield. Compound 192 reacted with methyl acrylate under standard Heck conditions to provide 193. Dehydration of the formyl group of 193 was best realized using triphenylphosphine, carbon tetrachloride, and triethylamine. To our great excitement, when isonitrile 194 was heated with tri-\(n\)-butyltin hydride and AIBN
in acetonitrile, radical cyclization proceeded smoothly without damaging the sensitive amino groups. Upon acidic workup, the desired diaminoindole 195 was isolated in 76% yield (Scheme 48). The 4,6-diamino indole 195 is quite electron-rich and prone to air oxidation. It is doubtful that a molecule this sensitive might be constructed by other existing methods. This further demonstrated the versatility of our tin-mediated indole synthesis.

\[
\begin{align*}
\text{HCOHN} & \quad \text{OMe} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{O} & \quad \text{Bn} \\
\text{191} & \\
\end{align*}
\]

\[
\begin{align*}
\text{191} & \xrightarrow{1) \ Zn, \text{AcOH}} \text{HCOHN} \\
& \quad \text{OMe} \\
& \quad \text{NH}_2 \\
& \quad \text{OMe} \\
& \quad \text{NH}_2 \\
& \quad \text{2) ICl, py} \\
& \quad \text{192} \\
& \quad \overset{(78\%)}{\text{Pd(OAc)}_2, \text{P(o-tol)}_3} \\
& \quad \text{Et}_3\text{N, CH}_3\text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{HCOHN} & \quad \text{OMe} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{MeO}_2\text{C} & \quad \text{Et}_3\text{N, CH}_2\text{Cl}_2 \\
\text{193} & \xrightarrow{\text{CCl}_4, \text{PPh}_3} \text{CN} \\
& \quad \text{OMe} \\
& \quad \text{NH}_2 \\
& \quad \text{MeO}_2\text{C} \\
& \quad \text{194} \\
& \quad \overset{(73\%)}{\text{Bu}_3\text{SnH, AlBN}} \\
& \quad \text{CH}_3\text{CN, reflux} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{MeO}_2\text{C} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{195} & \xrightarrow{\text{AlMe}_3} \text{N} \\
& \quad \text{OMe} \\
& \quad \text{NH}_2 \\
& \quad \text{O} \\
& \quad \text{196} + \text{197} \\
\end{align*}
\]

\textbf{Scheme 48}

Since compound 195 had to be stabilized, and the two amino groups also had to be differentiated each other to prepare the more advanced intermediate 166, selective protection of the two amino units was then attempted. We envisioned that the easiest way to attain this goal might be to
form lactam 196. Unfortunately, when diaminindoole 195 was treated with trimethylaluminum, the desired 196 was formed together with a substantial amount of unwanted byproduct 197, which results from double bond migration. It was not possible to isomerize 197, clearly the more stable of the two tautomers, back to 196; furthermore, the latter compound rearranged to the undesired isomer upon standing. Interestingly, this troublesome isomerization was not observed upon lactamization of the amine produced upon reduction of the nitro group in compound 180.

Despite the failure of the above lactamization, we were confident that the reactivities of the two amino groups were different enough to allow selective protection. Indeed, when a stoichiometric amount of allyl chloroformate was added to 195, the 4-amino group was selectively protected to give the valuable allyl carbamate, which was advanced to the differentially blocked bis-carbamate 196 by treatment with 2-trimethylsilylethyl chloroformate (TEOC-Cl). Two tasks thus remained in order to convert 196 to 201. The first was formation of the

![Scheme 49](image-url)
tricyclic segment of the discorhabdin C; the second was the bromoethylation of the 2-amino group to build the aminoethylbromide side chain.

The tricyclic skeleton of 198 was created in three steps (Scheme 49). Reduction of ester 196 with DIBAL-H, mesylation of the resultant alcohol 197, and exposure of the mesylate to the action of potassium t-butoxide precipitated an instantaneous and virtually quantitative cyclization to 198.

At this point, the TEOC group was removed with trifluoroacetic acid, whereupon amine 199 emerged. Reductive alkylation of 199 with glycoaldehyde introduced the seeds of the future bromoethylamine 201. Careful control of the amount of glycoaldehyde and sodium cyanoborohydride was necessary in order to arrest the reaction at the mono alkylation stage. Compound 201 proper was reached upon mesylation of alcohol 200 followed by treatment with lithium bromide.

![Chemical Structures](image.png)

**Scheme 50**

With compound 201 in hand, we were now ready to face two major final issues. First, we needed to dibrominate the aromatic system in the presence of
sensitive functionalities. Second, the core of 201 had to be oxidized to an iminoquinone without damaging the rest of the molecule. In that connection, the secondary amine in 201 would probably require protection prior to oxidation, and because the iminoquinone is very acid sensitive, we needed to find a protecting group that could be removed under mildly basic conditions. An even more efficient solution would involve simultaneous deblocking of the amine protecting group and para-phenolic alkylation under basic conditions. A trifluoroacetamide appeared to provide a suitable form of the protection for this purpose. Amine 201 was therefore treated with trifluoroacetic anhydride in the presence of triethylamine to give trifluoroacetamide, which was subjected to a palladium-mediated deprotection of the allyl carbamate\textsuperscript{58} to furnish the iminoquinone precursor 202. Compound 202 was subjected to CAN oxidation to produce iminoquinone 203 in 27% yield (Scheme 51).

Scheme 51

With the formation of 203, all the problems related to the indole and iminoquinone formation were solved. However, because of the low yield of the
iminoquinone formation, it was very difficult to pursue further transformations. Several other intermediates were explored as potential substrates for aromatic ring dibromination prior to iminoquinone formation. However, unexpected difficulties surfaced during such attempts. For instance, bromination of 205 with pyridium bromide perbromide proceeded extremely slowly, and application of gentle heat resulted in rapid decomposition. Treatment with bromine gave a dark intractable material (Scheme 52).

\[
\begin{align*}
\text{202} & \xrightarrow{TMSCH}_2\text{CH}_2\text{OCCl} \quad \text{py, CH}_2\text{Cl}_2 \quad \text{204} \\
\text{205} & \xrightarrow{\text{py-HBr-Br}_2 \text{ or Br}_2} \quad \text{206}
\end{align*}
\]

Scheme 52

Conclusion

The above studies have greatly contributed to the development of the novel indole synthesis. They also form the basis of a modified discorhabdin C synthesis currently underway in our laboratories. The work described here does add to the evidence that our indole forming reaction is likely to facilitate the preparation of other synthetically challenging alkaloids.
Chapter Four

Experimental

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\(^{-1}\)).

\(^1\)H NMR (250 MHz) and \(^{13}\)C NMR (62.5 MHz) spectra were determined on a Bruker AC250 instrument unless otherwise noted. Chemical shifts for \(^1\)H NMR are reported in parts per million (\(\delta\)) downfield from tetramethylsilane as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, sex = sextet, m = multiplet and b = broad. \(^{13}\)C NMR spectra were reported in ppm relative to the center line of a triplet at 77.0 ppm for deuteriochloroform.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole at 70 eV, unless otherwise noted, using direct probe insertion at temperature of 100 to 300 °C. High resolution mass spectra were obtained on a Finnigan Mat95 with electronic impact ion source at 70 eV, unless otherwise noted, using probe insertion at temperatures of 50 to 300 °C.

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 F\(_{254}\). Compounds were eluted from the adsorbent with 10% methanol in dichloromethane.
All evaporations were performed under reduced pressure on a rotary evaporator.

Column chromatography was performed on Woelm silica gel, 230-400 mesh, packed in ACE columns on a flash chromatography system.

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

Dichloromethane and diethyl ether:

   distilled through a 24 inch Snyder column.

Tetrahydrofuran (dry):

   distilled from sodium benzophenone ketyl.

Pyridine, triethylamine, and N,N-diisopropylethylamine:

   dried over potassium hydroxide pellets.

t-Butanol:

   distilled from calcium hydride.

N, N-dimethylformamide, benzene, toluene, acetonitrile, and methanol, Hexamethylphosphoramide:

   dried over 4Å molecular sieves.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
Methyl o-N-formylamino-cinnamate (31)

To a stirred solution of 403 mg (1.63 mmol) of o-iodoformylaniline 30, 3.8 mg (0.018 mmol) of palladium acetate, 0.25 ml (1.80 mmol) triethylamine and 10 mg (0.025 mmol) tri-o-tolylphosphine in 5 ml of dry acetonitrile was added 0.175 ml (1.95 mmol) of methyl acrylate. The reaction mixture was heated at 100 °C for 2.5 h in a tightly sealed culture tube under an argon atmosphere. Upon completion, the reaction mixture was partitioned between 50 ml ethyl ether and 1N HCl (2 x 10 ml), the extracts were combined and washed with 20 ml sodium bicarbonate solution and 20 ml saturated brine, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The crude product was purified by flash silica gel chromatography eluting with 60% ether-hexanes to give 349 mg (90%) of cinnamate 31 as a white solid.

mp: 99-101 °C (dichloromethane-hexanes)

IR (thin film): 3310, 3071, 3054, 3020, 2972, 2894, 1700, 1640, 1583, 1532, 1449, 1403, 1336, 1270, 1200, 1183, 1038, 981, 870, 774

$^1$H NMR (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)

$^{13}$C NMR (CDCl$_3$): 51.7, 119.7, 120.4, 122.8, 124.4, 125.6, 127.6, 130.8, 131.1, 135.0, 139.0, 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 C_{11}H_{11}NO_3  205.0739
              Found  205.0734
Compound 31 continued:
\( \text{o-Isocyanicinnamate (32)} \)

To a stirred solution of 141 mg (0.68 mmol) of cinnamate 31, 287 \( \mu \)l (2.06 mmol) of triethylamine in dichloromethane cooled at 0 °C was added dropwise a 4.0 M phosgene solution in dichloromethane. The progress of the reaction was closely monitored by TLC. Upon the disappearance of the starting material, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and partitioned with ether. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated \textit{in vacuo}. The crude product was purified by flash silica gel chromatography eluting with 20% ether-Hexanes to give 106 mg (87%) of 32 as a white solid.

\text{mp:} \quad 57-59 ^\circ \text{C (ether-hexanes)}

\text{IR (thin film):} \quad 3430, 3051, 3013, 2962, 2119, 1750, 1640, 1483, 1427, 1329, 1294, 1042, 990, 781

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

\text{\(^{13}\text{C NMR (CDCl}_3\):}} \quad 51.9, 121.9, 126.8, 127.2, 129.6, 130.7, 137.8, 166.3, 168.7

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

\text{Exact Mass:} \quad \text{Calculated for } \text{C}_{11}\text{H}_9\text{NO}_2 \quad 187.0633 \\
\text{Found} \quad 187.0635
Compound 32 continued:
**o-N-Formylaminophenyl propargyl ether** (36)

A stirred mixture of 4.17 g (16.8 mmol) of o-iodoformylaniline 30, 236 mg (0.34 mmol) of bis(triphenylphosphine)palladium chloride, 257 mg (1.35 mmol) of copper iodide in 20 ml of dry diethylamine at room temperature under an argon atmosphere was added 4.26 g (30.4 mmol) of propargyl alcohol THP ether 35. The reaction mixture was stirred at room temperature for 8 h and then partitioned between 100 ml of ethyl ether and 3N hydrochloric acid (2 x 30 ml). 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 residue was separated by silica gel chromatography eluting with 20% ether-hexanes to give 3.98 g (91%) of o-N-Formylaminophenyl propargyl ether 36 as a yellow oil.

**IR (thin film):**  3300, 2954, 2871, 2860, 2232, 1700, 1576, 1519, 1455, 1403, 1350, 1303, 1273, 1199, 1122, 1090, 1157, 1026, 904, 870, 821, 760

**$^1$H NMR (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)

**$^{13}$C NMR (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 $\text{C}_{15}\text{H}_{17}\text{N}_{1}\text{O}_{3}$  259.1208
Found  259.1206
Compound 36 continued:
Isonitrile (37)

A solution of 3.98 g (15.3 mmol) of o-N-formylaminophenyl propargyl ether 36 in 40 ml of absolute ethanol was hydrogenated over 400 mg of palladium on barium sulfate (5%) at a hydrogen pressure of 1 atm at room temperature for 3 h. The reaction was closely monitored by TLC until the completion of the reaction, the reaction mixture was filtered through a celite column. The filtrate was evaporated under reduced pressure to yield 2.53 g (63%) of partially reduced N-formylanilide as a dark yellow oil. The crude product was used without purification.

To a stirred solution of 2.53 g (9.68 mmol) of the above N-formylanilide, 4.07 ml (29.3 mmol) of triethylamine in 30 ml of dichloromethane at 0 °C was added dropwise a 4.0 M solution of phosgene in dichloromethane. The reaction was carefully monitored by TLC until the completion of the reaction. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and partitioned with ethyl ether. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash silica gel chromatography to yield 2.27 g (96%) of isonitrile 37 as a colorless oil.

IR (thin film): 3040, 2954, 2861, 2243, 1733, 1447, 1375, 1345, 1340 1274, 1200, 1129, 1037, 971, 898, 770
$^1$H NMR (CDCl$_3$): 1.45 - 1.88 (4H, m), 3.49 (2H, m), 3.86 (2H, 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, $J = 11.9$ Hz), 7.30 (4H, m)

$^{13}$C NMR (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
Compound 37 continued:
1-(2-Nitrophenyl)-triethyl phosphonoacetate (49)

Potassium hydride 0.218 g (1.90 mmol), as a 35 wt.% mineral oil dispersion, was weighed into a 100 milliter flask, into which 5 ml of N, N-dimethylformamide was directly added. The flask was capped with septum cap, flushed with argon, and cooled in an ice bath. To above stirred slurry was added dropwise 0.282 ml (1.42 mmol) triethyl phosphonoacetate 48. After the addition was complete, the resulting mixture was stirred at 0 °C for additional 10 min. To above mixture was then added 0.1 ml (0.948 mmol) 1-fluoro-2-nitrobenzene 47 in a dropwise manner. The orange color reaction mixture was stirred for 10 min. The reaction mixture was then allowed to warm to room temperature and then stirred in an oil bath at 50 °C for additional 5 h. The reaction mixture was then cooled to room temperature, quenched by pouring into 5 ml of water, and extracted thoroughly with ethyl ether (2x25 ml). The ethereal extracts were combined, washed with 2x10 ml of water and 5 ml of saturated brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was then separated by flash chromatography eluting with 40%-60% ether in hexanes to give 287 mg (87%) of 49 as a colorless oil.

IR (film): 3640, 3555, 3482, 2990, 2938, 2911, 1735, 1616, 1530, 1443, 1344, 1264, 1158, 1052, 1018, 979, 852, 793

$^1$H NMR (CDCl$_3$): 1.16 (3H, t, J = 7.1 Hz), 1.27 - 1.34 (6H, m), 3.41 - 4.32 (6H, m), 5.35 (1H, J = 25.7), 7.51 (1H, ddd, J$_1$ = 1.2 Hz, J$_2$ =
7.6 Hz, J₃ = 7.7 Hz), 7.66 (1H, ddd, J₁ = 0.90 Hz, J₂ = 7.4 Hz, J₃ = 8.6 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.05 (1H, dd, J₁ = 1.8 Hz, J₂ = 7.9 Hz)

¹³C NMR (CDCl₃): 13.86, 15.89, 15.99, 16.08, 16.18, 44.46, 46.61, 62.19, 63.15, 63.26, 63.34, 63.45, 124.64, 124.66, 125.85, 125.96, 128.59, 128.62, 132.25, 132.33, 132.61, 132.65, 149.18, 149.31, 166.47, 166.53

MS: 347 (12, M+2), 346 (48, M+1), 345 (6, M⁺), 300 (12), 299 (47), 298 (7), 271 (10), 243 (10), 215 (5), 200 (14), 199 (4), 198 (22), 197 (41), 196 (11), 191 (17), 185 (13), 172 (8), 169 (45), 163 (32), 146 (38), 136 (23), 135 (35), 134 (25), 120 (31), 119 (52), 118 (17), 109 (65), 105 (32), 99 (22), 92 (86), 91 (22), 90 (43), 87 (43), 81 (88), 80 (22), 79 (32), 78 (28), 77 (53), 65 (47), 64 (22), 63 (17), 52 (11), 29 (100), 27 (52)

Exact Mass: Calculated for C₁₄H₂₀O₇N₁P₁  345.0977
           Found                345.0974
Compound 49 continued:
2-Nitro benzylidethyl phosphonate (46)

To a stirred solution of 0.5 g (1.45 mmol) of 49 in 20 ml of tetrahydrofuran at room temperature was added 4.85 ml (29.1 mmol) of 6N sodium hydroxide solution. The reaction was allowed to warm to 70 °C and stirred for additional 4 h. The mixture was evaporated to a small volume and partitioned between 30 ml of dichloromethane and 2x10 ml of 3N hydrochloric acid. The aqueous layer was extracted thoroughly with dichloromethane. The extracts were combined, washed with a saturated aqueous sodium bicarbonate solution and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by a flash silica gel column chromatography eluting with 40%-60% ether in hexanes and afforded 0.38 g (96%) of 46 as a colorless oil.

IR (film): 3635, 3469, 2991, 2931, 2911, 1609, 1523, 1357, 1257, 1051, 1032, 972, 779

$^1$H NMR (CDCl$_3$): 1.22 (6H, t, J = 7.1 Hz), 3.70 (2H, d, J = 22.6 Hz), 4.00 (2H, q, J = 7.1 Hz), 4.03 (2H, q, J = 7.0 Hz), 7.37-7.58 (3H, m), 7.95 (1H, d, J = 8.1 Hz)

$^{13}$C NMR (CDCl$_3$): 16.09, 16.18, 29.28, 31.48, 62.23, 62.34, 108.73, 125.09, 125.13, 127.10, 127.25, 127.89, 127.95, 132.84, 132.90, 133.05, 133.14

MS: 274 (M+1), 273 (9, M+), 236 (27), 199 (33), 170 (88), 120 (57), 106 (76), 99 (100), 78 (88), 64 (96), 28 (72)

Exact Mass: Calculated for C$_{11}$H$_{16}$N$_1$O$_5$P$_1$ 273.0766
Found 273.0763
Compound 46 continued:
2-Amino benzyl(diethyl)phosphonate (50)

A solution of 14.0 g (51.3 mmol) of nitrobenzene 46 in 30 ml of absolute ethanol was hydrogenated over 1.0 g of palladium charcoal (10%) at a hydrogen pressure of 1,500 psi at room temperature for 3 h. Upon completion, the reaction mixture was filtered through a Celite column, the catalyst was washed with 50 ml of dichloromethane. The filtrate and washings were combined, evaporated under reduced pressure to yield 11.7 g (94%) of amine 50 as a light yellow oil. The crude product was used without purification.

IR (film): 3422, 3356, 3250, 2991, 2911, 1643, 1609, 1576, 1497, 1450, 1390, 1218, 1164, 1058, 1025, 959, 753

$^1$H NMR (CDCl$_3$): 1.22 (6H, t, J = 7.0 Hz), 3.10 (1H, d, J = 20.8 Hz), 3.91 - 4.0 (4H, m), 4.24 (2H, s), 6.67 - 6.74 (2H, m), 6.99 - 7.08 (2H, m)

$^{13}$C NMR (CDCl$_3$): 16.17, 16.26, 29.31, 31.52, 62.21, 62.32, 116.95, 117.00, 117.05, 117.11, 118.88, 118.93, 128.02, 128.07, 131.36, 131.46, 145.78, 145.85

MS: 243 (M$^+$), 169 (57), 106 (6), 44 (7), 32 (100), 27 (98)

Exact Mass: Calculated for C$_{11}$H$_{18}$N$_1$O$_3$P$_1$ 243.1024
                     Found                  243.1019
Compound 50 continued:
2-N-Formylamino benzyl diethyl phosphonate (51)

To a stirred solution of 11.7 g (48.1 mmol) of amine 50, and 7.78 ml (96.2 mmol) of pyridine in 60 ml of formic acid at room temperature, 5.45 ml (57.7 mmol) of acetic anhydride was added through dropping funnel over a period of 15 min, the mixture was allowed to stir for additional 30 min. The solution was then evaporated in vacuo with toluene to give a brown oil. The resulting residue was partitioned between 100 ml of dichloromethane and 75 ml of water. The organic layer was washed by an aqueous sodium bicarbonate solution. The combined organic extracts were dried over magnesium sulfate, filtered, evaporated to yield 11.9 g (91%) of formamide 51 as a light yellow oil. The crude product was used without purification.

IR (film): 3456, 3270, 2991, 2911, 1702, 1689, 1596, 1543, 1457, 1397, 1304, 1270, 1231, 1170, 1058, 1025, 965, 799, 766

¹H NMR (CDCl₃): (observed as a mixture of two atropisomers)
1.23 (6H, t, J = 7.1 Hz), 3.18 (2H, dd, J₁ = 6.4 Hz, J₂ = 21.2 Hz), 3.92 - 4.08 (4H, m), 7.09 - 7.30 (3H, m), 7.80 (1H, d, J = 8.0 Hz), 8.43 (1H, d, J = 9.5 Hz), 9.32 (1H, d, J = 11.1 Hz), 9.47 (1H, s)

¹³C NMR (CDCl₃): 16.05, 16.14, 29.43, 29.65, 31.32, 31.50, 62.51, 62.63, 62.66, 62.77, 122.88, 122.93, 123.25, 123.40, 124.56, 125.04, 125.36, 125.41, 125.56, 125.61, 126.15, 126.20, 127.81, 127.87, 128.32, 128.38, 131.11, 131.15, 131.26, 131.64, 131.75, 135.23, 135.31, 136.01, 136.19, 159.60, 162.92
MS: 273 (<1, M+2), 272 (3, M+1), 271 (<1, M+), 215 (18), 214 (10), 213 (2), 200 (2), 197 (14), 187 (14), 170 (13), 169 (38), 168 (12), 152 (5), 151 (9), 150 (7), 132 (22), 107 (38), 106 (100), 105 (36), 104 (24), 91 (28), 81 (20), 78 (27), 77 (49), 65 (14), 51 (22), 43 (25), 30 (15), 29 (94), 27 (97), 26 (50)

Exact Mass: Calculated for C₁₂H₁₈O₄N₁P₁ 271.0973
Found 271.0967
Compound 51 continued:
2-Isocyano-benzyl(diethyl) phosphonate (39)

To a solution of 8.0 g (29.5 mmol) of formamide 51 and 10.3 ml (73.8 mmol) of triethylamine in 75 ml of dichloromethane cooled at 0 °C was added phosgene, a 4.6 M solution in dichloromethane, in a dropwise manner. The progress of the reaction was carefully monitored by TLC. Upon the disappearance of the starting material, the reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and partitioned with ethyl ether. The organic layer was dried over sodium sulfate, filtered and evaporated in vacuo. The crude product was purified by flash silica gel chromatography to yield 6.79 g (91%) of 39 as a colorless oil.

IR (film): 3481, 2991, 2938, 2917, 2121, 1642, 1484, 1450, 1416, 1383, 1257, 1197, 1164, 1051, 1025, 965, 858, 832, 766

\(^1\)H NMR (CDCl\(_3\)): 1.28 (6H, t, J = 7.0 Hz), 3.33 (2H, d, J = 22.2 Hz), 4.06 (2H, q, J = 7.2 Hz), 7.25 - 7.52 (4H, m)

\(^13\)C NMR (CDCl\(_3\)): 15.99, 16.09, 28.56, 30.77, 62.04, 62.15, 126.14, 126.17, 126.21, 126.30, 126.75, 126.77, 126.79, 127.67, 127.73, 128.77, 128.91, 129.12, 129.14, 129.17, 129.19, 130.88, 130.96, 166.63

MS: 253 (<1, M\(^+\)), 243 (4), 224 (2), 214 (2), 132 (20), 106 (28), 81 (19), 77 (17), 58 (48), 23 (100), 20 (69)

Exact Mass: Calculated for C\(_{12}\)H\(_{16}\)O\(_3\)N\(_1\)P\(_1\) 253.0868
Found 253.0871
Compound 39 continued:
General Procedure For Horner-Emmons Reaction

To a stirred solution of 0.741 ml (5.65 mmol) of diisopropylamine in 30 ml of tetrahydrofuran at 0 °C under argon was added dropwise 2.40 ml (5 mmol) of 2.08 M of n-butyllithium in hexanes. The mixture was stirred at 0 °C for 20 minutes and then cooled to -78 °C, to which 1.10 g (4.35 mmol) of Horner-Emmons reagent 39 was added. The mixture was stirred at -78 °C for 30 minutes before 3.92 mmol of aldehyde was added. The reaction mixture was stirred for additional 20 minutes at -78 °C and then allowed to warm to room temperature and stirred for another 1 h before it was quenched by addition of 3 ml of water. The biphasic mixture was stried at room temperature for 10 minutes and partitioned between ethyl ether and a saturated ammonium chloride solution. The aqueous layer was thoroughly extracted with ethyl ether. The extracts were combined and washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. Generally the residue was then purified by flash silica gel chromatography eluting with 5-25% ether in hexanes. Yields range from 90-95%.
Isonitrile (52)

IR (film): 3037, 2951, 2924, 2120, 1955, 1809, 1729, 1636, 1490, 1450, 1257, 1198, 1098, 958, 759, 690

$^1$H NMR (CDCl$_3$): 7.10 - 7.40 (9H, m), 7.53 (2H, dd, $J_1 = 0.71$ Hz, $J_2 = 8.5$ Hz), 7.67 (1H, d, $J = 8.0$ Hz)

$^{13}$C NMR (CDCl$_3$): 121.9, 124.5, 126.7, 126.9, 127.7, 128.5, 129.1, 132.4, 133.3, 136.1, 167.4

MS: 206 (14, M+1), 205 (84, M$^+$), 204 (100), 203 (19), 190 (8), 177 (9), 178 (11), 151 (4), 103 (5), 102 (26), 101 (8), 89 (13), 88 (13), 87 (7), 78 (16), 77 (18), 76 (19), 75 (18), 74 (15), 63 (16), 62 (13), 61 (5), 52 (7), 51 (24), 50 (28), 39 (13), 38 (8), 37 (8)

Exact Mass: Calculated for C$_{15}$H$_{11}$N$_1$ 205.0891
      Found                                           205.0887
Compound 52 continued:
Isonitrile (53)

IR (film): 3389, 3055, 2925, 2117, 1690, 1627, 1593, 1509, 1481, 1448, 1394, 1278, 1250, 1167, 1088, 960, 792, 779

$^1$H NMR (CDCl$_3$): 7.20 - 7.56 (7H, m), 7.78 - 7.87 (4H, m), 7.95 (1H, d, J = 16.0 Hz), 7.15 (1H, d, J = 8.3 Hz)

$^{13}$C NMR (CDCl$_3$): 123.4, 124.2, 124.8, 125.1, 125.7, 125.8, 125.9, 126.3, 127.3, 128.1, 128.7, 128.9, 129.4, 129.8, 131.3, 132.3, 133.6, 133.9, 167.2

MS: 256 (6, M+1), 255 (43, M$^+$), 254 (66), 253 (12), 226 (6), 152 (9), 128 (41), 127 (100), 126 (36), 113 (66), 112 (22), 99 (26), 88 (8), 77 (6), 74 (7), 63 (8), 51 (9)

Exact Mass: Calculated for C$_{19}$H$_{13}$N 255.1048
Found 255.1041
Compound 53 continued:
Isonitrile (54)

IR (film): 3071, 2956, 2926, 2855, 2118, 1649, 1482, 1466, 1450, 1378, 1286, 1179, 1041, 965, 755, 723

$^1$H NMR (CDCl$_3$): 0.86 - 0.91 (3H, m), 1.25 - 1.59 (10H, m), 2.29 (2H, ddt, $J_1 = 1.4$ Hz, $J_2 = 6.8$ Hz, $J_3 = 7.2$ Hz), 6.35 (1H, dt, $J_1 = 6.8$ Hz, $J_2 = 15.8$ Hz), 6.69 (1H, d, $J = 15.8$ Hz), 7.16 - 7.35 (3H, m), 7.54 (1H, dd, $J_1 = 1.6$ Hz, $J_2 = 7.5$ Hz)

$^{13}$C NMR (CDCl$_3$): 14.0, 22.6, 29.0, 29.1, 29.3, 31.7, 33.2, 123.8, 124.1, 125.5, 126.9, 127.1, 129.1, 134.2, 135.9, 166.4

MS: 227 (2, M$^+$), 198 (2), 184(9), 170 (23), 156 (30), 143 (52), 142 (47), 130 (50), 129 (100), 128 (23), 116 (27), 115 (46), 101 (11), 89 (13), 77 (8), 55 (10), 43 (32), 41 (42), 39 (20), 29 (31), 27 (28)

Exact Mass: Calculated for C$_{16}$H$_{21}$N$_1$ 227.1674
Found 227.1669
Compound 54 continued:
**ISONITRILE (55)**

IR (film): 3064, 3031, 2931, 2858, 2120, 1649, 1603, 1490, 1483, 1450, 965, 805, 745, 699

$^1$H NMR (CDCl$_3$): 2.59 (2H, dt, $J_1 = 6.9$ Hz, $J_2 = 7.2$ Hz), 2.83 (2H, t, $J = 7.1$ Hz), 6.36 (1H, dd, $J_1 = 6.9$ Hz, $J_2 = 15.8$ Hz), 6.73 (1H, d, $J = 15.8$ Hz), 7.17 - 7.34 (3H, m), 7.51 (1H, d, $J = 7.6$ Hz)

$^{13}$C NMR (CDCl$_3$): 34.9, 35.5, 124.2, 124.5, 125.7, 126.1, 127.0, 127.5, 128.5, 129.3, 134.0, 134.7, 141.3, 167.0

MS: 234 (11, M+1), 233 (49, M+), 218 (6), 142 (19), 114 (6), 116 (19), 115 (42), 91 (100), 89 (12), 65 (28), 56 (6), 44 (23), 22 (43)

Exact Mass: Calculated for $C_{17}H_{15}N$ 233.1204

Found 233.1160
Compound 55 continued:
Isonitrile (56)

IR (film): 3384, 2959, 2867, 2118, 1646, 1476, 1455, 1364, 1265, 1090, 1040, 972, 756

$^1$H NMR (CDCl$_3$): 1.57 (9H, s), 6.35 (1H, d, J = 16.0 Hz), 6.62 (1H, d, J = 16.0 Hz), 7.22 (1H, dd, J$_1$ = 1.2 Hz, J$_2$ = 7.4 Hz), 7.29 - 7.32 (2H, m), 7.55 (1H, d, J = 7.5 Hz)

$^{13}$C NMR (CDCl$_3$): 29.2, 33.8, 119.0, 124.4, 125.6, 126.9, 127.2, 129.1, 134.4, 146.3, 166.3

MS: 185 (2, M$^+$), 184 (10, M-1), 170 (42), 160 (51), 145 (13), 144 (45), 143 (26), 142 (14), 132 (52), 130 (18), 129 (17), 128 (16), 118 (17), 117 (15), 115 (11), 106 (11), 91 (7), 77 (17), 57 (13), 51 (11), 44 (100), 43 (12), 41 (34), 39 (28), 32 (58), 29 (34), 27 (33)

Exact Mass: Calculated for C$_{13}$H$_{15}$N$_1$ 185.1204
Found 185.1203
Compound 56 continued:
General Procedure For The Indole Formation Reaction

A mixture of 0.83 mmol of isonitrile, 0.245 ml (0.91 mmol) of \( n\)-tributyltinhydride and 7 mg (0.04 mmol) of 2,2'-azobisisobutyronitrile in 5 ml of dry acetonitrile in culture tube was bubbled with argon for 5 min. The tube was then capped and heated at 95-100 °C for 1 hour under an argon atmosphere. Upon cooling to room temperature, the reaction mixture was partitioned between ethyl ether and 3N hydrochloric acid. The organic layer was then washed with a one third saturated aqueous potassium fluoride solution. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The resulting residue was separated by flash silica gel chromatography eluted with ethyl ether-hexanes to afford indole in 32-91% yield.
Methyl 2-indolylacetate (34)

IR (film): 3512, 3063, 2961, 1734, 1620, 1459, 1439, 1344, 1270, 1202, 1163, 1099, 1020, 751,

$^1$H NMR (CDCl$_3$): 3.72 (1H, 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, t, J = 7.9 Hz), 7.64 (1H, d, J = 7.4 Hz), 8.16 (1H, s)

$^{13}$C NMR (CDCl$_3$): 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 C$_{11}$H$_{11}$N$_1$O$_2$ 189.0790
Found 189.0792
Compound 34 continued:
2-Indolyethyl alcohol THP ether (38)

IR (film): 3421, 3058, 2950, 2878, 1662, 1581, 1458, 1347, 1211, 1072, 1028, 754

\(^1\)H NMR (CDCl\(_3\)): 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\(_3\)): 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 \(\text{C}_{15}\text{H}_{19}\text{N}_{1}\text{O}_{2}\) 245.1416

Found 245.1416
Compound 38 continued:
3-Benzyl indole (57)

mp: \(107-108^\circ\text{C}\) (ether-hexanes)

IR (KBr): \(3393, 3218, 3000, 2140, 1631, 1604, 1479, 1351, 1333, 1071, 904, 737, 700\)

\(^1\text{H NMR (CDCl}_3\)): \(4.11\) (2H, s), \(6.93\) (1H, d, J = 1.2 Hz), \(7.10\) (1H, m), \(7.21\) (2H, m), \(7.30\) (4H, m), \(7.37\) (1H, d, J = 7.8 Hz), \(7.54\) (1H, d, J = 7.8 Hz), \(7.95\) (1H, s)

\(^{13}\text{C NMR (CDCl}_3\)): \(31.7, 111.0, 119.1, 119.3, 122.0, 122.2, 125.8, 128.3, 128.7\)

MS: \(207\) (66, M\(^+\)), \(206\) (55, M\(^+\)-1), \(129\) (100), \(103\) (16), \(102\) (31), \(86\) (20), \(77\) (22), \(44\) (12), \(18\) (18), \(17\) (47)

Exact Mass: Calculated for \(C_{15}H_{13}N_1\) = 207.1048

Found = 207.1048
Compound 57 continued:
3-Naphthylmethyl indole (58)

mp 121.5-123 °C (CH₂Cl₂-Hexanes)

IR (film): 3422, 3054, 2918, 2850, 1596, 1509, 1419, 1397, 1351, 1338, 1223, 1091, 1010, 908, 781, 743

¹H NMR (CDCl₃): 4.51 (2H, s), 6.56 (1H, t, J = 1.2 Hz), 7.07 - 7.47 (7H, m), 7.61 (1H, d, J = 7.7 Hz), 7.71 - 7.74 (2H, m), 7.84 (1H, dd, J₁ = 2.4 Hz, J₂ = 7.7 Hz), 8.06 (1H, dd, J₁ = 2.3 Hz, J₂ = 7.3 Hz)

¹³C NMR (CDCl₃): 28.9, 111.1, 115.2, 119.0, 119.3, 122.0, 122.7, 124.3, 125.4, 125.6, 125.7, 126.6, 126.8, 127.4, 128.6, 132.1, 133.8, 136.3, 136.7

MS: 257 (22, M⁺), 256 (20, M-1), 254 (3), 130 (62), 129 (23), 128 (23), 127 (32), 126 (31), 77 (7), 51 (37), 49 (99), 48 (3)

Exact Mass: Calculated for C₁₉H₁₅N₁ 257.1191
Found 257.1192
Compound 58 continued:

![Graph 1](image1)

![Graph 2](image2)
General Procedure For The Photolysis Indole Formation Reaction

A mixture of 0.19 mmol of isonitrile, 0.10 ml (0.38 mmol) of n-tributyltinhydride and 46.7 μl (0.09 mmol) of Bis(tributyltin) in 1.3 ml of dry acetonitrile in a pyrex culture tube was bubbled with argon for 3 minutes. The tube was then capped and irradiated with 500 Watt high pressure mercury lamp at room temperature for 3.5 h under an argon atmosphere. Upon completion of the reaction, the reaction mixture was partitioned between acetonitrile and hexanes. The acetonitrile layer was then partitioned between ethyl ether and 3N hydrochloric acid twice. The organic layer was washed with a one third saturated aqueous potassium fluoride solution. The organic extract was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The resulting residue was separated by flash silica gel chromatography eluted with ethyl ether-hexanes to afford indole in 82-55% yield.
3-t-Butylmethyl indole (59)

IR (film): 3418, 2951, 2904, 2864, 2842, 1475, 1456, 1421, 1391, 1363, 1339, 1244, 1232, 1093, 1066, 1010, 770, 741

$^1$H NMR (CDCl$_3$): 0.96 (9H, s), 2.64 (2H, s), 6.94 (1H, d, J = 2.1 Hz), 7.08 (1H, ddd, J$_1$ = 1.0 Hz, J$_2$ = 7.0 Hz, J$_3$ = 7.5 Hz), 7.17 (1H, ddd, J$_1$ = 1.1 Hz, J$_2$ = 7.0 Hz, J$_3$ = 7.5 Hz), 7.34 (1H, d, J = 7.5 Hz), 7.60 (1H, d, J = 7.5 Hz), 7.95 (1H, s)

$^{13}$C NMR (CDCl$_3$): 29.6, 32.1, 39.0, 110.7, 114.1, 119.0, 119.5, 121.3, 122.9, 128.8, 135.8

MS: 187 (14, M$^+$), 131 (15), 130 (100), 129 (35), 128 (10), 77 (6), 57 (4), 51 (1), 44 (3), 43 (3), 41 (7), 39 (5), 29 (6)

Exact Mass: Calculated for C$_{13}$H$_{17}$N$_1$ 187.1838
Found 187.1839
Compound 59 continued:
3-Heptyl indole (61)

mp 41-42 °C (methanol)

IR (film): 3316, 3054, 2962, 2850, 1618, 1460, 1423, 1343, 1234, 1101, 1010, 743

$^1$H NMR (CDCl$_3$): 0.92 (3H, t, J = 6.6 Hz), 1.14 (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)

$^{13}$C NMR (CDCl$_3$): 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 (28, M$^+$), 156 (6), 144 (12), 143 (12), 130 (99), 118 (13), 106 (5)

Exact Mass: Calculated for C$_{26}$H$_{32}$N$_2$O$_6$ 187.1361
Found 187.1363
Compound 61 continued:
3-Octyl indole (64)

IR (film): 3418, 3058, 2853, 2870, 1619, 1488, 1456, 1420, 1351, 1337, 1224, 1091, 1010, 801, 763, 741

$^1$H NMR (CDCl$_3$): 0.93 (3H, t, J = 6.2 Hz), 1.33 - 1.46 (10H, m), 1.74 (2H, sep, J = 7.5 Hz), 2.79 (2H, t, J = 7.5 Hz), 6.98 (1H, d, J = 2.0 Hz), 7.15 (1H, t, J = 7.3 Hz), 7.23 (1H, t, J = 7.3 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.65 (1H, d, J = 7.6 Hz), 7.85 (1H, s)

$^{13}$C NMR (CDCl$_3$): 14.0, 22.6, 25.1, 29.3, 29.5, 29.6, 30.1, 31.8, 110.9, 117.1, 118.9, 120.9, 121.7, 127.6, 136.3

MS: 230 (12, M+1), 229 (47, M$^+$), 228 (3), 144 (11), 143 (9), 132 (7), 131 (100), 130 (99), 129 (58), 128 (15), 118 (9), 117 (12), 116 (4), 115 (8), 103 (23), 102 (14), 89 (3), 77 (33), 57 (7), 55 (7), 43 (13), 41 (26), 39 (8), 32 (5), 29 (27), 27 (56), 26 (4)

Exact Mass: Calculated for C$_{16}$H$_{23}$N$_1$ 229.1830
Found 229.1832
Compound 64 continued:
1-(3-phenyl)propyl indole (66)

mp 47-48 °C (Et<sub>2</sub>O)

IR (film): 3422, 3057, 3024, 2931, 2858, 1603, 1497, 1457, 1410, 1337, 1231, 1091, 1011, 799, 740, 693

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.05 (2H, tt, J<sub>1</sub> = 7.5 Hz, J<sub>2</sub> = 7.9 Hz), 2.71 (2H, t, J = 7.9 Hz), 2.79 (2H, t, J = 7.5 Hz), 6.94 (1H, d, J = 1.3 Hz), 6.95 - 7.34 (3H, m), 7.58 (1H, d, J = 7.7 Hz), 7.84 (1H, s)

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 24.6, 31.6, 35.6, 110.9, 116.5, 118.9, 119.0, 121.0, 121.8, 125.6, 127.5, 128.2, 128.4, 136.3, 142.4

MS: 236 (14, M+1), 235 (62, M<sup>+</sup>), 234 (6, M-1), 144 (17), 143 (26), 142 (8), 132 (16), 131 (100), 130 (100), 129 (85), 128 (22), 118 (12), 117 (32), 116 (12), 115 (29), 105 (7), 104 (17), 103 (53), 102 (32), 101 (7), 91 (67), 90 (17), 89 (20), 79 (7), 78 (17), 77 (92), 76 (17), 75 (7), 65 (28), 63 (17), 51 (27), 50 (9), 39 (21), 27 (23)

Exact Mass: Calculated for C<sub>17</sub>H<sub>17</sub>N<sub>1</sub> 235.1361

Found 235.1360
Compound 66 continued:
**o-N-Formylaminophenyl propargyl acetate (112)**

A stirred mixture of 10 g (40.5 mmol) of o-idoformylaniline 33, 710 mg (1.01 mmol) of bis(triphenylphosphine)palladium chloride, 1.54 g (8.1 mmol) of copper iodide in 30 ml of dry diethylamine at room temperature under an argon atmosphere was added 3.54 ml (60.8 mmol) of propargyl alcohol in a dropwise manner. The reaction mixture was stirred at room temperature for 1 h and then partitioned between 150 ml of dichloromethane and 3N hydrochloric acid (2x50 ml). 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 above residue was dissolved in 8.8 ml (93.2 mmol) of acetic anhydride and 7.5 ml (93.2 mmol) of pyridine. The resulting mixture was left at room temperature for 30 min. The solution was then evaporated with toluene under reduced pressure and separated by silica gel chromatography eluting with 40-60% ether-hexanes to give 7.79 g (87%) of o-N-Formylaminophenyl propargyl acetate 112 as a colorless crystal.

**mp**
86-87 °C (Et₂O/ Hexanes)

**IR (film):**
3482, 3336, 2898, 2240, 1749, 1696, 1583, 1443, 1218, 1025, 760

**¹H NMR (CDCl₃):** (observed as a mixture of two atropisomers)
2.11 (3H, s), 4.88 (2H, s), 7.00 (1H, m), 7.19 - 7.46 (3H, m), 8.20 (1H, s), 8.40 (1H, d, J = 8.3 Hz), 8.48 (1H, d, J = 1.6 Hz), 8.78 (1H, d, J = 11.2 Hz)
$^{13}$C NMR (CDCl$_3$): 20.7, 52.5, 52.8, 81.8, 90.7, 108.4, 110.7, 116.1, 119.9, 123.6, 124.3, 130.2, 131.6, 133.1, 139.0, 159.2, 161.3, 170.7

MS: 217 (32, M$^+$), 200 (18), 174 (12), 158 (8), 157 (3), 156 (6), 147 (17), 146 (67), 145 (3), 133 (4), 130 (43), 129 (67), 128 (46), 118 (21), 117 (6), 103 (26), 102 (60), 101 (11), 92 (8), 91 (18), 90 (12), 89 (22), 78 (8), 77 (32), 76 (17), 75 (11), 65 (9), 63 (17), 62 (7), 52 (7), 51 (16), 50 (12), 43 (99), 39 (14), 29 (52)

Exact Mass: Calculated for $\text{C}_{12}\text{H}_{11}\text{N}_1\text{O}_3$ 217.0739
Found 217.0737
Compound 112 continued:
\textit{o-N-Formylaminophenyl cis-allyl acetate (113)}

A solution of 14.5 g (66.8 mmol) of \textit{o-N-formylaminophenyl propargyl acetate 112} in 60 ml of absolute ethanol was hydrogenated over 1.1 g of palladium on barium sulfate (5\%) at a hydrogen pressure of 1 atmosphere at room temperature for 5 h. The reaction was closely monitored by TLC until the completion of the reaction, the reaction mixture was filtered through a celite column. The filtrate was evaporated under reduced pressure to yield 13.6 g (93\%) of partially reduced \textit{N-formylaniline} as a dark yellow oil. The crude product was used without purification.

\textbf{IR (film):} 3535, 3469, 3302, 3037, 2878, 1756, 1696, 1530, 1463, 1377, 1244, 1032, 759

\textbf{\textsuperscript{1}H NMR (CDCl\textsubscript{3}):} (observed as a mixture of two atropisomers)
2.04 (3H, s), 4.60 (2H, dt, J\textsubscript{1} = 1.5 Hz, J\textsubscript{2} = 6.8 Hz), 5.99 (1H, dt, J\textsubscript{1} = 6.8 Hz, J\textsubscript{2} = 11.2 Hz), 6.62 (1H, d, J = 11.2 Hz), 7.08 - 7.35 (4H, m), 7.64 (1H, s), 8.15 (1H, d, J = 8.2 Hz), 8.04 (1H, d, J = 1.7 Hz), 8.56 (1H, d, J = 11.3 Hz)

\textbf{\textsuperscript{13}C NMR (CDCl\textsubscript{3}):} 20.8, 61.2, 61.6, 120.3, 122.3, 124.7, 125.5, 126.7, 128.1, 128.6, 128.7, 129.1, 129.2, 129.4, 129.7, 130.4, 134.2, 134.5, 159.4, 162.9, 170.8, 171.0

\textbf{MS:} 219 (4, M\textsuperscript{+}), 177 (25), 160 (32), 159 (99), 158 (90), 148 (13), 132 (52), 131 (100), 130 (98), 129 (37), 128 (12), 120 (23), 119 (8), 118 (66), 117 (47), 116 (8), 115 (29), 106 (17), 105 (8), 104 (8), 103 (42), 102 (11), 93 (24), 91 (33), 90 (26), 89 (35), 78 (10), 77 (84), 76 (16), 65 (27), 63 (34), 62 (7), 52 (17), 51 (38), 50 (33), 44 (59), 43 (100), 42 (37), 39 (49), 29 (95), 27 (32)
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Compound 113 continued:
**o-isocyanoaminophenyl cis-allyl acetate (114)**

To a stirred solution of 4.50 g (20.5 mmol) of the N-formylanilide 113, 7.16 ml (51.3 mmol) of triethylamine in 50 ml of dichloromethane at 0 °C was added dropwise a 4.0 M solution of phosgene in dichloromethane. The reaction was carefully monitored by TLC until the completion of the reaction. The reaction mixture was poured into a saturated aqueous sodium bicarbonate solution and partitioned with ethyl ether. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography eluting with 10-40% ether-hexanes to yield 3.79 g (92%) of isonitrile 114 as a colorless oil.

**IR (film):** 3622, 3535, 3462, 3077, 3031, 2944, 2121, 1736, 1477, 1443, 1377, 1244, 1032, 766

**1H NMR (CDCl₃):** 2.07 (3H, s), 4.74 (2H, dd, J₁ = 1.4 Hz, J₂ = 6.7 Hz), 6.06 (1H, dt, J₁ = 6.7 Hz, J₂ = 11.8 Hz), 6.79 (1H, d, J = 11.8 Hz), 7.28 - 7.43 (4H, m)

**13C NMR (CDCl₃):** 20.4, 60.6, 126.5, 127.2, 128.2, 128.7, 129.0, 129.2, 132.3, 167.0, 171.1

**MS:** 201 (<1, M⁺), 160 (7), 159 (52), 158 (34), 157 (10), 140 (29), 131 (38), 130 (99), 129 (71), 128 (21), 116 (17), 115 (31), 114 (17), 113 (7), 103 (16), 102 (19), 101 (11), 89 (19), 77 (28), 76 (21), 75 (22), 63 (27), 51 (24), 50 (23), 44 (67), 43 (99), 42 (34), 39 (38)

**Exact Mass:** Calculated for C₁₂H₁₁N₁O₂ 201.0790  Found 201.0790
Compound 114 continued:
**2-Iodoindole acetate (115)**

A mixture of 3.80 g (19.8 mmol) of isonitrile 114, 5.09 ml (28.4 mmol) of \(\text{n-tributyltinhydride}\) and 155 mg (0.99 mmol) of 2,2'-azobisisobutyronitrile in 80 ml of dry acetonitrile was bubbled with argon for 10 min. The solution was then heated at 95-100 °C for 30 min under an argon atmosphere. Upon cooling to room temperature, 4.68 g (21.8 mmol) of \(N\)-iodosuccinimide was added and the reaction mixture was stirred at room temperature for 20 min. After the completion of the reaction, the reaction mixture was partitioned between acetonitrile and hexanes twice. The acetonitrile layer was separated for the next step.

To the stirred solution of the above product was added 5.61 g (25.7 mmol) of di-\(t\)-butyl dicarbonate, 0.24 g (2.0 mmol) of 4-dimethylamino pyridine and 3.95 ml (29.7 mmol) of triethylamine. After stirring at room temperature for 1 h, the reaction was partitioned between ethyl ether and saturated ammonium chloride two times and then washed with sodium bicarbonate and brine. The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The resulting residue was separated by flash silica gel chromatography eluted with ethyl ether-hexanes to afford 5.74 g (71%) of iodoindole 115 as a yellow oil.

IR (film): 2984, 1742, 1443, 1364, 1317, 1244, 1164, 1091, 1052, 739
\(^1\)H NMR (CDCl\textsubscript{3}): 1.71 (9H, s), 2.02 (3H, s), 3.10 (2H, t, J = 7.1 Hz), 4.27 (2H, t, J = 7.1 Hz), 7.17 - 7.26 (2H, m), 7.51 - 7.55 (1H, m), 8.06 - 8.09 (1H, m)

\(^{13}\)C NMR (CDCl\textsubscript{3}): 20.7, 27.2, 28.0, 62.7, 79.2, 84.8, 115.3, 117.9, 122.4, 124.2, 125.4, 129.5, 137.8, 148.9, 170.6

MS: 429 (M\(^+\)), 313 (5), 270 (7), 269 (64), 268 (3), 256 (18), 143 (4), 142 (7), 141 (6), 140 (2), 130 (8), 129 (9), 128 (9), 127 (3), 115 (5), 102 (2), 101 (2), 58 (3), 57 (99), 56 (7), 44 (4), 43 (42), 42 (2), 41 (23), 39 (7), 37 (3)

Exact Mass: Calculated for C\textsubscript{17}H\textsubscript{20}I\textsubscript{1}NO\textsubscript{4} 429.0439
Found 429.0437
Compound 115 continued:
2-Methylacrylate indole acetate (116)

A stirred mixture of 1.0 g (2.33 mmol) of 2-iodoindole 115, 356 mg (0.47 mmol) of trans-benzyl(chloro)bis-(triphenylphosphine)palladium, 447 mg (2.33 mmol) of copper iodide and 288 mg of triphenylarsine in 10 ml of dry DMF and 3.3 ml of dry HMPA was added 2.66 g (6.99 mmol) of methyl 2-tributylstannylacrylate, the reaction mixture was bubbled with argon for 10 min and then heated at 85 °C for 3.5 h under an argon atmosphere. The resulting mixture was then allowed to cool to room temperature and partitioned between ethyl ether and a diluted aqueous potassium fluoride solution. The aqueous layer was washed thoroughly with ethyl ether. The extracts were combined, dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo. Flash silica gel chromatography separation of the crude product eluted with 20-40% ether-hexanes afforded 0.61 g (62%) of 116 as light yellow oil.

IR (film): 2977, 2951, 1729, 1636, 1463, 1370, 1330, 1244, 1151, 1091, 1045, 826, 759

$^1$H NMR (CDCl$_3$): 1.60 (9H, s), 2.01 (3H, s), 3.01 (2H, t, br), 3.73 (3H, s), 4.26 (2H, t, J = 7.2), 5.86 (1H, d, J = 1.6 Hz), 6.64 (1H, d, J = 1.6 Hz), 7.25 - 7.35 (2H, m), 7.61 (1H, d, J = 6.9 Hz), 8.13 (1H, d, J = 8.0 Hz)

$^{13}$C NMR (CDCl$_3$): 20.8, 24.0, 27.9, 52.0, 63.8, 84.3, 115.6, 117.2, 119.1, 122.6, 124.9, 128.1, 129.2, 132.7, 133.7, 135.6, 150.0, 166.2, 170.8
MS: 387 (<1, M), 331 (<1), 287 (8), 238 (9), 237 (44), 236 (8), 214 (23), 196 (14), 195 (89), 194 (7), 182 (8), 168 (27), 167 (38), 166 (8), 156 (5), 155 (11), 154 (46), 153 (5), 140 (3), 128 (9), 127 (12), 75 (8), 56 (100), 55 (7), 44 (11), 43 (32), 42 (30), 29 (21)

Exact Mass: Calculated for C_{22}H_{25}N_{1}O_{6} 387.1682
Found 387.1683
Compound 116 continued:
2-Methyl acrylate indole alcohol (110)

A solution of 600 mg (1.55 mmol) of 116 and 1.0 ml of sodium carbonate solution in 3 ml of methanol was stirred at room temperature for 2 h. The resulting biphasic solution was extracted with dichloromethane thoroughly. The extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude reaction mixture was purified by flash silica gel chromatography eluted with ethyl ether-hexanes to afford 481 mg (90%) of indole alcohol 110 as a colorless oil.

IR (film): 3522, 3436, 2984, 2951, 2878, 1736, 1623, 1457, 1370, 1331, 1251, 1224, 1151, 1091, 1038, 759

$^1$H NMR (CDCl$_3$): 1.59 (9H, s), 2.23 (1H, s), 2.92 (1H, t, J = 6.4 Hz), 3.72 (3H, s) 3.79 (2H, d, J = 6.4 Hz), 5.87 (1H, d, J = 1.3 Hz), 6.59 (1H, d, J = 1.3 Hz), 7.20 - 7.32 (2H, m), 7.55 (1H, d, J = 7.7 Hz), 8.13 (1H, d, J = 8.3 Hz)

$^{13}$C NMR (CDCl$_3$): 27.6, 27.8, 52.0, 61.9, 76.5, 84.3, 115.5, 117.8, 119.0, 122.6, 124.8, 128.2, 129.2, 132.7, 133.6, 135.6, 149.9, 166.5

MS: 345 (<1, M$^+$), 245 (16), 215 (17), 214 (79), 213 (9), 182 (10), 155 (17), 154 (40), 153 (6), 128 (12), 127 (18), 57 (100), 39 (32), 29 (28)

Exact Mass: Calculated for C$_{19}$H$_{23}$N$_1$O$_5$ 345.1576
Found 345.1570
Compound 110 continued:
2,4-Dinitrobenzenesulfonamide (118)

A solution of 1.05 g (6.14 mmol) of 98 in 20 ml of ammonia saturated absolute ethanol was hydrogenated over 10 ml of Raney nickel at a hydrogen pressure of 1,500 psi at 80 °C for 4 h. Upon completion, the reaction mixture was decanted from catalyst. The catalyst was washed with hot ethanol until all of the product had been eluted. The washings were combined, evaporated under reduced pressure to yield 0.91 g (94%) of amine 117 as a brown oil. The crude product was used without purification.

To a stirred solution of 0.91g (5.62 mmol) of amine 117 and 0.91 ml (11.2 mmol) in 20 ml of dry dichloromethane under argon at room temperature was added 1.65 g (6.18 mmol) of 2,4-dinitrobenzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then partitioned between ethyl ether and 1N hydrochloric acid two times. The aqueous layer was extracted thoroughly with ethyl ether. The extracts were washed with aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by a flash silica gel chromatography and gave 2.04 g (82%) of the sulfonamide 118 as a yellow oil.

IR (film): 3356, 3104, 2944, 1550, 1357, 1171, 1105, 1065, 746
$^1$H NMR (CDCl$_3$): 0.85 (3H, t, J = 7.4 Hz), 1.19 - 1.63 (7H, m), 3.17 (2H, dd, J$_1$ = 6.5 Hz, J$_2$ = 6.6 Hz), 3.32 (3H, s), 3.34 (3H, s), 4.09 (1H, d, J = 5.6 Hz), 5.53 (1H, t, J = 5.9), 8.35 (1H, d, J = 8.6 Hz), 8.54 (1H, dd, J$_1$ = 2.1 Hz, J$_2$ = 8.6 Hz), 8.67 (1H, d, J = 2.2)

$^{13}$C NMR (CDCl$_3$): 11.0, 22.0, 25.0, 27.2, 41.3, 44.2, 54.2, 54.9, 107.5, 120.6, 127.0, 132.5, 139.4, 148.1, 149.7

MS: 404 (<1, M-1), 343 (9), 342 (41) 259 (7), 232 (66), 231 (9), 142 (18), 111 (18), 110 (19), 99 (67), 95 (32), 93 (19), 86 (22), 85 (20), 79 (32), 77 (100), 76 (100), 75 (95), 74 (87), 72 (29), 71 (46), 70 (9), 69 (23), 63 (17), 62 (14), 59 (12), 56 (18), 55 (82), 47 (49), 45 (83), 42 (39), 41 (78), 39 (37), 31 (82), 30 (69), 29 (62), 27 (53)

Exact Mass: Calculated for C$_{15}$H$_{23}$N$_{3}$O$_{8}$S 405.1206
Found not found
Compound 118 continued:
Coupling product (119)

To a stirred solution of 70 mg (0.20 mmol) of indole alcohol 110, 162 mg (0.4 mmol) of sulfonamide 118 and 106 mg (0.4 mmol) triphenylphosphine in 3 ml of dry benzene was added at room temperature 44.7 µl (0.28 mmol) of diethyl azodicarboxylate (DEAD) under an argon atmosphere. The mixture was stirred for 40 min and then partitioned between ethyl ether and brine. The aqueous layer was extracted thoroughly with ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by means of preparative TLC with 30% ether-hexanes to afford 115 mg (91%) of 119 as colorless crystals.

**mp** 179-180 °C (Et₂O-MeOH)

**IR (film):** 3110, 2944, 2825, 1729, 1556, 1463, 1377, 1244, 1151, 1111, 759

**¹H NMR (CDCl₃):** 0.88 (3H, t, J = 7.3 Hz), 1.18 - 1.70 (7H, m), 1.62 (9H, s), 2.97 (2H, t, br), 3.34 (6H, d, J = 1.9 Hz), 3.41 (2H, t, J = 7.2 Hz), 3.57 (2H, t, br), 3.80 (3H, s), 4.12 (1H, d, J = 5.7 Hz), 5.81 (1H, d, J = 1.1 Hz), 6.62 (1H, d, J = 1.1 Hz), 7.17 - 7.30 (2H, m), 7.48 (1H, dd, J₁ = 1.0 Hz, J₂ = 10.3 Hz), 7.94 (1H, d, J = 8.1 Hz), 8.02 (1H, dd, J₁ = 1.7 Hz, J₂ = 7.9 Hz), 8.19 (2H, m)
$^{13}$C NMR (CDCl$_3$): 11.0, 21.8, 23.3, 25.1, 25.4, 27.9, 41.4, 46.6, 47.7, 52.2, 54.2, 54.7, 84.8, 107.5, 115.3, 117.3, 118.9, 119.1, 122.7, 125.0, 125.5, 128.1, 128.6, 131.9, 132.7, 133.7, 135.2, 138.4, 147.4, 149.0, 149.8, 166.0

MS:
632 (>1, M-Boc), 369 (4), 215 (27), 214 (99), 213 (11), 193 (5), 182 (13), 170 (6), 169 (4), 168 (21), 167 (6), 156 (13), 155 (14), 154 (57), 127 (9), 124 (7), 122 (6), 99 (8), 76 (8), 75 (23), 74 (7), 64 (21), 22 (18), 21 (37), 19 (75)

Exact Mass:
Calculated for C$_{34}$H$_{44}$N$_4$O$_{12}$S = 732.2676
Found not found
Compound 119 continued:
(±)-Vincadifformine (90)

To a stirred solution of 40 mg (0.055 mmol) of 119 in 0.3 ml of dichloromethane was added 169 µl (2.0 mmol) of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 15 min. The mixture was evaporated to dryness under reduced pressure and 0.5 ml of dry denzene was added and then evaporated to dryness under reduced pressure.

The residue was dissolved in 1.0 ml of acetonitrile and 108 mg (0.825 mmol) of potassium phenoxide was introduced under an argon atmosphere. The reaction mixture was stirred at room temperature for 4 h. Upon the completion of the reaction, the reaction mixture was partitioned between ethyl ether and brine. The crude product was separated on a silica gel TLC (40% ether-hexanes) to give 12.5 mg (67%) of (±)-vincadifformine as colorless crystals.

mp 122-124 °C (ether-hexanes)

IR (film): 3369, 2956, 2930, 2851, 2771, 1675, 1609, 1477, 1436, 1250, 1157, 1111, 1038, 746

$^1$H NMR (CDCl$_3$): 0.60 (3H, m), 0.85 - 1.04 (1H, m), 1.19 - 1.34 (1H, m), 1.50 - 1.60 (1H, m), 1.70 - 1.90 (2H, m), 2.00 - 2.12 (1H, m), 2.28 (1H, d, J = 15.2 Hz), 2.35-2.65 (3H, m), 2.71 (1H, d, J = 15.2 Hz)
Hz), 2.94 (1H, t, J = 6.7 Hz), 3.09 - 3.17 (1H, d, br), 3.77 (3H, s), 6.78 - 7.23 (4H, m), 8.90 (1H, s, br)

$^{13}$C NMR (CDCl$_3$): 7.10, 21.8, 25.7, 29.4, 32.9, 38.1, 45.2, 50.5, 51.0, 51.7, 55.5, 72.5, 92.5, 109.3, 120.5, 121.1, 127.4, 137.9, 143.3, 167.7, 169.2

MS: 338 (15, M$^+$), 154 (4), 153 (4), 125 (9), 124 (100), 49 (31)

Exact Mass: Calculated for C$_{21}$H$_{16}$N$_2$O$_2$ 338.1994

Found 338.1989
Compound 90 continued:

[Images of spectra and graphs related to compound 90]

[Note: The images are not described in detail due to the limitations of text-based interpretation.]
References


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21 Computational work was carried out with the HYPERCHEM® package, available from Autodesk, Inc., Sausalito, CA, and running on a Windows®-based 486 PC system.


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