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Synthetic studies towards the total synthesis of discorhabdin C

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SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF DISCORHABDIN C

by

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

DOCTOR OF PHILOSOPHY

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May, 1994
Abstract

Synthetic Studies towards the Total Synthesis of Discorhabdin C

by

Tangqing Li

Two synthetic approaches towards the total synthesis of discorhabdin C (3) are described. The general strategy for construction of azacarbocyclic spiro dienone system is to employ an intramolecular para-phenolic alkylation (58 to 43). The key reaction for the first approach is a newly improved aromatic Claisen rearrangement. The key reaction for the second approach is a novel tin-mediated indole synthesis developed in our laboratory.
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CHAPTER 1

Introduction

1.1 Isolations and biological activities

The discorhabdin alkaloids (Figure 1) were isolated by Perry and coworkers at the University of Canterbury from the sponge of Latrunculia du Bocage in New Zealand.\textsuperscript{1-3} Meanwhile, during the course of studies on bioactive substances from Okinawan marine organisms, Kobayashi and coworkers in Japan isolated four polycyclic alkaloids, prianosins A-D (Figure 1), from the Okinawan sponge Prianos melanos, and their structures have proved to be closely related to those of the discorhabdins.\textsuperscript{4-6}

The structure of discorhabdin C (3), which was isolated first and contains the new pyrrolo[1,7]phenanthroline ring system, was established by a single crystal X-ray diffraction study.\textsuperscript{7} Based on the assignment of $^1$H- and $^{13}$C-NMR spectra, structures of discorhabdin A (1), B (2) and D (6) were determined through comparisons with discorhabdin C (3).\textsuperscript{2,3} Discorhabdin A (1) has also been isolated from the Okinawan sponge Prianos melanos. It was confirmed that discorhabdin A (1) is identical to prianosin A (1) by comparison of spectroscopic and biological data.\textsuperscript{2,4} Also, discorhabdin D (6) is identical to prianosin D (6).\textsuperscript{3,6}
Discorhabdins A (1), B (2) and C (3) were isolated because of their strong cytotoxicities found in *in vitro* antiviral assays. Further testing showed that these compounds exhibited high activities against P388 leukemia *in vitro*, with respective ED$_{50}$'s of 0.03, 0.05 and 0.1 µg/ml. However, *in vivo* testing in the P388 leukemia system in mice showed no increase in lifespan with either discorhabdin C (3) or discorhabdin A (1). These two compounds were toxic to mice at about 2 mg per kg of body weight. Discorhabdin B (2) did show some antitumour activity, with a T/C of 117% at a dose of 0.25 mg/kg, but this did not reach the significance level of 120%. Discorhabdin D (6) had a lower *in vitro* activity against the P388 system (IC$_{50}$ 6 µg/mL), but in contrast was considered to have significant *in vivo* P388 activity (T/C 132% at 20 mg/kg). The mode of
action and structural modification studies of the discorhabdins have not yet been reported.

The discorhabdins also showed antimicrobial activity. In a disk assay, with 30 µg/disk, discorhabdins C (3) and A (1) were active against *Escherichia coli*, *Bacillus subtilis* and *Candida albicans*, but not against *Pseudomonas aeruginosa*. Discorhabdin B (2) was active against *E. coli* and *B. subtilis*, but not against *P. aeruginosa* or *C. albicans*.²

The discorhabdins, with their pentacyclic carbon nitrogen framework, are a new type of nitrogenous pigments.³ Three other fused pentacyclic aromatic alkaloids have been reported from marine organisms including a sponge, an ascidian and a sea anemone (Figure 2). Strangely, all these compounds have C₁₈N₃ frameworks, as do the discorhabdins. Amphimedine 7, from a Pacific

![Figure 2](image-url)
sponge of genus *Amphimedon*,\(^{10}\) was active against P388 cells *in vitro* (ED\(_{50}\) 2.8 µg/ml) but was inactive *in vivo*.\(^{8}\) 2-Bromoleptoclinidone 8 (*in vitro* P388 assay: ED\(_{50}\) 0.4 µg/ml) was isolated from an ascidian.\(^{11}\) Two alternative structures have been proposed for calliactine (9 or 10), a pigment from a sea anemone.\(^{12}\) It is conceivable that the discorhabdins and these other compounds are produced by related microorganisms, which are either part of the diets of these filter feeders or are present as symbionts.\(^{13}\)

The 2,6-dibromocyclohexadienone portion of discorhabdin C (3) is echoed in compound 11 (Figure 3), a product of tyrosine metabolism in the sponge *Aplysina fistularis* (family Aplysinidae, order Verongida).\(^{14}\) This compound is cytotoxic and antimicrobial.\(^{2}\)

![Chemical Structure](image)

11

**Figure 3**

In view of the biological properties of the discorhabdins and their relatively high levels in the *Latrunculia* sponges (>1% of dry weight), they may play defensive roles. It is reported that sponges containing antimicrobial substances are rarely overgrown and underwater observations of these *Latrunculia* species showed no evidence of predation or of epibionts.\(^{2}\)
1.2 Synthetic background

The interesting biological properties and novel structural features of discorhabdins C (3) have attracted a number of synthetic chemists since the structural elucidation was published in 1986. The inherent challenges are centered on its unique highly fused ring structure consisting of an unprecedented pyrrolo[1,7]phenanthroline skeleton of a iminoquinone chromophore. Furthermore, this iminoquinone chromophore is coupled with a very unusual azacarbocyclic spirodienone system.

It soon became apparent that the problem was far more challenging than people had anticipated. Because of the instability of the indoloquinone imine skeleton, one of the most important decisions in any total synthesis of 3 is the determination of the precise order of the synthetic transformations required. These transformations must be carried out in the presence of the easily oxidizable heteroatoms and the functionalities sensitive to reduction.\textsuperscript{15} Consideration of the retrosynthesis of discorhabdins C (3) clearly indicated that a critical decision needed to be made, namely, what would constitute the final step of the synthesis. Such monumental puzzles have generated more than ten different approaches, yet there have been only two successful total syntheses, both using phenolic oxidative coupling to form the spiro dienone system through the same intermediate.\textsuperscript{21,25} Most of the other synthetic studies were focused on the construction of the azacarbocyclic spirodienone skeleton using more stable model systems. Since these approaches have been adequately described in a number of reviews\textsuperscript{15,16} and articles,\textsuperscript{17-25} only some of the representative ones are highlighted in chronological order.
We started our own efforts in this area in 1989. After striving for more than four years, we established two new approaches and came within a couple of steps from achieving the total synthesis of discorhabdin C (3). This project will be continued by another graduate student in our laboratories. Details of our efforts are described in the next two chapters.

Confalone's Approach$^{15,18}$

The first published approach to discorhabdin C (3) was reported by Confalone and coworkers, who achieved the synthesis of a novel tetracyclic intermediate 22 by applying an intramolecular para-phenolic alkylation for the spirodienone system formation.

Bromination of 5-methoxysalicylaldehyde 12 in acetic acid selectively inserted bromine ortho to the phenol, giving bromodimethoxy benzaldehyde 13 after methylation with dimethyl sulfate (Scheme 1). For construction of the

![Scheme 1](image-url)
indole, methodology based on thermolysis of azidocinnamates was selected. Thus, treatment of benzaldehyde 13 with methyl azidoacetate in the presence of sodium methoxide yielded azido methyl ester 14, which was heated in xylene at 140° C to afford 5-bromo-4,7-dimethoxyindole-2-carboxylic acid methyl ester 15. This product underwent a palladium-mediated arylboronic acid coupling reaction to produce the arylxy derivative 16.

A three-step conversion of 16 to the 3-carboxaldehyde derivative 17 was performed by saponification of the ester, followed by decarboxylation and a Vilsmeier reaction (Scheme 2). Further elaboration of the indole carboxaldehyde 17 to tribromo indoloquinone 18 was achieved by oxidation with ceric ammonium nitrate (CAN) in acetonitrile, hydrolysis with 6N HCl to remove the MOM group, and tribromination with pyridinium bromide perbromide.
The phenol 18 was first reprotected with chloromethyl methyl ether. The resulting bis-MOM derivative underwent a substitution reaction with ethanolamine in \(N, N\)-dimethylformamide (DMF) to provide the aminoquinone product which was treated with methanesulfonyl chloride, yielding mesyloxy aminoquinone 19. After selective removal of the phenolic MOM group, the key spirocyclization reaction was carried out by treating with potassium \(t\)-butoxide, affording spirocycle 20 (Scheme 3).

\[
\begin{align*}
\text{18} & \xrightarrow{1) \text{MOMCl, CH}_2\text{Cl}_2, 2) \text{HO(CH}_2\text{H}_2\text{NH}_2, DMF, 3) \text{MsCl, Py, CH}_2\text{Cl}_2} \text{MOM} & \rightarrow \text{19} \\
& & \text{CHO} & \text{OMs} \\
& & \text{Br} & \text{Br} \\
\end{align*}
\]

\[
\begin{align*}
& \xrightarrow{1) 6\text{N HCl, THF, 2) t-\text{BuOK, DMF}} \text{MOM} & \rightarrow \text{20} \\
& & \text{CHO} & \text{Br} \\
& & \text{Br} & \text{O} \\
\end{align*}
\]

Scheme 3

Condensation of aldehyde 20 with nitromethane yielded the nitroethylene derivative (21) (Scheme 4). Sodium borohydride reduction of 21 resulted in the formation of the nitroethyl indole 22. Unfortunately, attempts to
reduce the primary nitro group of 22 to an amine prior to the final cyclodehydration were unsuccessful.

![Chemical structures and reaction schemes](image)

**Scheme 4**

**Yamamura's Total Synthesis**

Unlike Confalone's approach, an anodic oxidation was employed for the construction of the crucial azacarbocyclic spiro dienone system in the synthesis reported by Yamamura and coworkers.

Starting from 3,4-dimethoxy-5-nitrobenzaldehyde, the carbobenzylxoy (Cbz) derivative 23 was prepared in two steps. Transformation of 23 to 24 was achieved in four steps by Jones oxidation with formation of a carboxylic acid from aldehyde 23, followed by Curtius rearrangement of the acid to 24 after
trapping the intermediate isocyanate with 2-[(trimethylsilyl)ethanol. Selective removal of the Cbz group in 24 followed by N-benzylation afforded 25, which was then reacted with ethyl γ-chloroacetoacetate in refluxing ethanol to give indole 26 (Scheme 5).

Indole 26 was then converted to the lactam 27 in three steps. Reduction of 27 with BH₃•Me₂S gave the corresponding amine, which on oxidation with CAN yielded a rather unstable iminodienone. Coupling of this iminodienone with 3,5-dibromotyramine hydrobromide in the presence of NaHCO₃ in ethanol provided the phenolic product 28. Upon anodic oxidation of 28, the target discorhabdin C (3) was obtained, but only as a minor product in low yield (Scheme 6).
Kita's Total Synthesis of Discorhabdin C.25

As a continuation of their studies on hypervalent iodine chemistry,24 Kita and coworkers reported in detail their total synthesis of 3. As outlined in Scheme 7, benzylation of 2-hydroxy-4-methoxybenzaldehyde (29) followed by condensation with ethyl azidoacetate in ethanolic sodium ethoxide gave the vinyl azide, which was decomposed in boiling xylene to give 2-(ethoxycarbonyl)indole 30. Hydrolysis of the ester group of 30 gave the indolecarboxylic acid, which was subjected to thermal decarboxylation to give the 2-unsubstituted indole 31. Treatment of indole 31 with dimethyl(methylene)ammonium iodide gave the 3-(dimethylamino)methyl
derivative. The dimethylamino group was replaced by a cyano group with sodium cyanide via a methiodide to yield 3-(cyanomethyl)indole 32. Catalytic hydrogenation of the cyano group of 32, followed by protection of the resulting amino group with the [(trimethylsilyl)ethoxy]carbonyl (TEOC) group afforded 33.

![Scheme 7 Diagram]

Debenzylation of 33 followed by oxidation with Fremy's salt gave the corresponding quinone. Treatment of the quinone with p-toluenesulfonyl chloride gave the N-tosylate 34. Deprotection of the TEOC group of 34 with p-toluenesulfonic acid in acetonitrile in the presence of 3A molecular sieves and sodium bicarbonate yielded an unstable indoloquinone imine 35, which was subjected to the following one-pot transformation without further purification. When treated with 3,5-dibromotyramine hydrobromide in ethanol, the indoloquinone imine 35 underwent a facile substitution reaction at the C-6 position, and subsequent detosylation furnished the phenolic aminooindoloquinone imine 28. Conversion of 28 into the corresponding silyl
ether and a subsequent oxidative coupling reaction using [bis(trifluoroacetoxy)iodo]benzene (PIFA) gave rise to discorhabdin C (3) (Scheme 8).

Scheme 8
CHAPTER 2

Synthetic Studies Towards  
the Total Synthesis of Discorhabdin C

2.1 General strategy

As mentioned in Chapter 1, the two previous total syntheses of discorhabdin C shared the same intermediate 28 to reach the final compound by different oxidative coupling reactions. The biggest drawback of those approaches is the low yields of the final oxidation steps. In order to improve the synthesis of discorhabdin C, we have developed two different synthetic approaches.

Our target molecule 3 is unstable under acidic conditions, undergoing transformation to non-spiro dibromophenol 36 through a dienone-phenol rearrangement\textsuperscript{21} (Scheme 9). We envisioned that the crucial azacarbocyclic

![Scheme 9](image-url)
spiro dienone system could be formed by an intramolecular para-phenolic alkylation 37 to 38 under mild basic conditions (Scheme 10).

![Chemical structures](image)

**Scheme 10**

Meanwhile, formation of a properly substituted indole is essential for construction of the indoloiminquinone skeleton. During our synthetic studies, we have developed two effective pathways to such indole systems. One of them is based on an improved aromatic Claisen rearrangement. The other is based on a novel tin-mediated radical indole synthesis. These two pathways enable us to establish the Claisen rearrangement approach and the radical indole formation approach toward the total synthesis of discorhabdin C.

### 2.2 The Claisen rearrangement approach

#### 2.2.1 Retrosynthetic analysis

The key retrosynthetic disconnection is shown in Scheme 11. Our strategy for the spiro dienone system formation enables us to concentrate on the synthesis of precursor 37. It is reasonable to assume that the amine functionality of bromoethyl amine 37 could be introduced by a Beckmann rearrangement of ketone 39. The successful construction of the tricyclic system
of 37 relies heavily on the crucial carbon-carbon bond formation between the ortho position of the phenol and the allyl side chain in 39, which could be installed by a Claisen rearrangement of a properly substituted allyl aryl ether 40. The nitrogen functionality responsible for the indole formation could be introduced through nitration of the partially protected hydroquinone 41. We envisaged starting this approach from commercially available 2,5-dihydroxyacetophenone (42).

\[ 
\begin{array}{c}
\text{37} \\
\text{39} \\
\text{40} \\
\text{41} \\
\text{42}
\end{array}
\]

\text{Scheme 11}

2.2.2 Model study

One of the challenging problems that inspired us to pursue the total synthesis of discorhabdin C is the construction of the azacarbocyclic spiro dienone system. In order to concentrate on the synthesis of the spiro system, we chose the compound 43 as a target in our initial model studies, which has exactly the same spiro dienone portion as that in discorhabdin C (3) (Figure 4).
Tempted by the prospect of a Friedel-Crafts-type reaction of the electron deficient quinone 44 with a variety of aromatic compounds 45\textsuperscript{28} (Scheme 12), we elected to examine the formation of phenyl acetohydroquinone 41.

\begin{align*}
44 \quad & + \quad 45 \quad \xrightarrow{\text{TFA}} \quad 46 \\
47 \quad & \xrightarrow{\text{Ag}_2\text{O} \quad \text{benzene}} \quad 48
\end{align*}

Scheme 12

2,5-Dihydroxyacetophenone (42) was first oxidized to quinone 48 by treatment with freshly prepared silver oxide\textsuperscript{29} in benzene (Scheme 13). The
resultant acetobenzoquinone was isolated and treated with trifluoroacetic acid and benzyl phenyl ether in dichloromethane. Instead of the expected adduct 41, we found two products in roughly a one to one ratio at the end of the reaction. They were the coupled quinone 49 and 2,5-dihydroxyacetophenone (42).

\[ \text{42} \xrightarrow{\text{Ag}_2\text{O, benzene}} \text{48} \xrightarrow{\text{PhOBn, TFA}} \text{49} + \text{42} \]

Scheme 13

Since quinone 48 is the only possible oxidizing agent present in the reaction system, initial adduct 41 must have been immediately oxidized to its quinone form 49. This problem could be solved by carrying out the same coupling reaction in the presence of excess lead dioxide. Lead dioxide was able to oxidize the initial adduct 41 to quinone 49, blocking the redox reaction between 41 and starting material 48. Furthermore, it would be advantageous to start the oxidative coupling reaction directly with commercially available
dihydroxyacetophenone 42, because if 42 were to be oxidized by lead dioxide
in situ, subsequent coupling between 48 and benzyl phenyl ether would
necessarily follow. Gratifyingly, the desired coupling product 49 was isolated in
nearly quantitative yield when 42 was used as starting material (Scheme 14).

\[
\text{Scheme 14}
\]

Coupled hydroquinone 41, obtained by standard hydrogenation of 49,
was protected for the model study as its dimethyl ether 50 by conventional
methylation (Scheme 15). The introduction of the required amine functionality

\[
\text{Scheme 15}
\]

was accomplished at this stage by Beckmann rearrangement\textsuperscript{30} of ketone 50
(Scheme 16).
The acetyl and benzyl protecting groups in rearrangement product 52 could both be removed by an acidic methanolysis, yielding amino phenol 53 as the major product. Chloroacetamidophenol 54, generated from 53 through treatment with chloroacetyl chloride and \( N,N \)-dimethylaniline, served as a precursor for the dibromination. By using pyridinium bromide perbromide, dibromination of phenol 54 proceeded smoothly and was followed by benzylolation to afford benzyl ether 55 (Scheme 17).
Since attempts to reduce the carbonyl group of chloroacetamide 55 were unsuccessful, hydroxyl acetamide 56 was prepared through substitution of the chloride with an acetate followed by basic hydrolysis (Scheme 18). Upon treatment with borane-methyl sulfide complex, reduction of acetamide 56 to hydroxyethyl amine 57 could be achieved. Dibromophenol 58, precursor of the final para-phenolic alkylation, was obtained through mesylate formation, lithium bromide substitution and debenzylation.

\[
\text{Scheme 18}
\]

In order to find suitable spiro cyclization conditions, a series of experiments using different combinations of base and solvent were conducted. We were delighted to discover that, by using potassium carbonate in DMF with
catalytic sodium iodide, target compound 43 was isolated after 2 hours of stirring at 80 °C (Scheme 19).

![Reactions](image)

Scheme 19

This discovery set the stage for our synthetic approaches. The problems remaining to be addressed were whether we could successfully construct the special pyrrolo[1,7]phenanthroline skeleton, and whether we could find a suitable intermediate to perform the spiro cyclization at a late stage of the synthesis.

2.2.3 Synthetic approach

Having succeeded in forming the critical biaryl carbon-carbon bond with our oxidative coupling reaction, we were ready to concentrate on assembling the indole system. For the purpose of introducing the indole nitrogen, the quinone 49 was reduced with zinc and the subsequent acetylation afforded diacetate 59, which was subjected to the selective aminolysis with piperidine to give monoacetate 60. Nitration of 60 with sodium nitrite in acetic acid in the presence of trifluoroacetic acid cleanly furnished nitrophenol 61. The phenolic hydroxyl group was immediately protected as a methyl ether (Scheme 20).
Conversion of intermediate 62 to phenol 63 was accomplished in 83% yield in a three-step sequence involving zinc reduction, acetylation and hydrolysis (Scheme 21).

Preparation of the Claisen rearrangement precursor 65, shown in Scheme 22, was accomplished in 100% yield by using the Mitsunobu
reaction\textsuperscript{31} of phenol 63 with the alcohol 64\textsuperscript{32}. Unfortunately heating 65 at 210 °C in \textit{N},\textit{N}-diethylaniline resulted in the formation of a one to one mixture of the normal and abnormal rearrangement products, 66 and 67 (Scheme 23).

As illustrated in Scheme 24, it has been demonstrated that the normal product 69 is transformed to the thermodynamically more favorable, abnormal product 71 via the spiro intermediate 70 through consecutive forward and
reverse enol-ene rearrangements. The abnormal Claisen rearrangement could, in theory, be blocked by protecting the incipient phenol 69 before it undergoes the first enol-ene reaction. However, use of acetic or butyric anhydride as a trapping agent caused extensive decomposition of the products.

![Chemical Structures](image)

Scheme 24

Therefore, attention was directed to milder trapping agents, especially such silylating reagents as 1,1,1,3,3,3-hexamethyldisilazane or \( N,O \)-bis-(trimethylsilyl)acetamide. Gratifyingly, the Claisen rearrangement of 65 in \( N,N \)-diethylaniline in the presence of 10 equivalents of hexamethyldisilazane proceeded smoothly at 210 °C to give, upon acidic workup, normal product 66 in 72% yield (Scheme 25), without appreciable formation of abnormal product.

In order to demonstrate the general applicability of this method, five other compounds were prepared and were subjected to the thermal rearrangement conditions in the presence of either 1,1,1,3,3,3-hexamethyldisilazane or \( N,O \)-
bis-(trimethylsilyl)acetamide. Both silylating agents have proven to be excellent blockers of the detrimental abnormal Claisen rearrangement.

Scheme 25

Once the abnormal Claisen rearrangement problem was solved, indole 72 was synthesized from 66 in three steps (Scheme 25). The sequence started with acetylation of the phenol, followed by ozonolysis of the olefin, and finally, condensation of acetamide and aldehyde with camphorsulfonic acid and quinoline in refluxing benzene, providing indole 72 in 52% overall yield. In order to form the pyrrolo[1,7]phenanthroline skeleton, the para-methoxybenzyl
protecting group was removed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)\textsuperscript{36}, yielding alcohol 73 in 83% yield.

With the protected indole 72 in hand, the next task was to transform the methyl ketone into an amine functionality by Beckmann rearrangement (Scheme 26). To our great consternation, the oxime formation of ketone 73 did not proceed under the standard reaction conditions. When the reaction was pushed too hard, it resulted in an intractable mixture of products. After numerous unsuccessful attempts, it became emphatically clear that we would have to develop new tactics to introduce this particular amino group.

![Scheme 26](image)

It appeared to us that the failure of the oxime formation was caused by the steric hindrance of the acetyl group. Although the Beckmann rearrangement of this system failed to provide us with an avenue to introduce the second amino group, we nevertheless were optimistic about obtaining the desired amine 78 by a Curtius rearrangement\textsuperscript{37} of ester 77, which could be synthesized from benzoate 75 using the aforementioned protocol (Scheme 27). This modified approach is currently under investigation in our laboratories.
2.3 The radical indole formation approach

2.3.1 Background

A novel tin-mediated indole synthesis, especially useful for the preparation of 3-substituted and 2,3-disubstituted indoles, was discovered recently in our laboratories (Scheme 28). When isonitrile 79 was heated in the presence of tributyltin hydride and AIBN in benzene or acetonitrile, 3-substituted indole 80 was isolated in excellent yield after acidic workup. The proposed mechanism of this transformation is shown in Scheme 29.
Under the tin hydride radical reaction conditions, isonitrile 79 reacted with tributyltin radical first to form tinimidoyl radical 81. This newly formed tinimidoyl radical caused ring closure by addition to the olefin, generating intermediate 82 with formation of a carbon-carbon bond and a new radical center. Subsequent radical reduction and tautomerization gave an indole, substituted at the 2-position by tributyltin 83. Destannylation by mild acidic treatment furnished desired indole 80.

Formation of imidoyl radicals by addition of tributyltin radicals to isonitriles has been known for some time, along with the strong synthetic potential of different imidoyl radicals. However, simple tinimidoyl radicals
have seldom been used to construct carbon-carbon bonds. In Scheme 30, a typical example of tin-mediated indole synthesis is illustrated.

**Scheme 30**

Formamide 84 was transformed to vinyl substituted isonitrile 85 in 79% yield through Heck reaction followed by phosgene treatment. Indole 87 was obtained in 91% yield by heating 85 in benzene with tributyltin hydride and a catalytic amount of AIBN, followed by acidic workup. Due to the mild nature of the reaction conditions a wide variety of functional groups are expected to tolerate the reaction, which makes this a versatile method for the synthesis of complex natural products.

2.3.2 Retrosynthetic analysis

In light of this newly developed indole synthesis and a successful spirodienone system formation, a new approach, outlined in Scheme 31, was considered.
We anticipated no major difficulties remaining in the synthesis once advanced intermediate 88 was in hand. Meanwhile, we envisioned that the two nitro groups on the central aromatic ring could be introduced after indole 89 was formed. To synthesize the indole 89 using our tin-mediated radical indole synthesis, the requisite isonitrile 90 needed to be prepared from readily available benzoate 91.
2.3.3 Synthetic approach

In order to introduce the nitrogen functionality of the indole, benzoate 91 was stirred with excess fuming nitric acid and acetic acid at 85 °C (Scheme 32). Pure mononitro compound 92 could be obtained from the mixture of the isomers by recrystallization. Since the next goal was to hydroxylate the position ortho to the nitro group under strongly basic conditions, the phenolic benzoate was changed to a methoxymethyl group, providing intermediate 93. Oxidative hydroxylation of 93 was carried out by heating with potassium hydroxide and diphenyl ether at 110 °C in the presence of oxygen. The resulting phenol was protected as its benzyl ether 94.

![Scheme 32](image)

At this stage of the synthesis, attention was directed towards the preparation of the isonitrile 97, a precursor of the indole synthesis (Scheme 33). Compound 94 was reduced to amine 95 by zinc dust in acetic acid. After
numerous attempts to brominate the ortho position of the amino group in 95, we found that the yield of this bromination could be greatly improved by using propylene oxide instead of normal amine base as an acid scavenger. With bromoamine 96 in hand, indole precursor 97 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 98 was obtained in 95% yield by application of our standard radical cyclization procedure (Scheme 34). Having succeeded in the construction of indole 98, we were ready to undertake introduction of the dinitro functionalities. To this end, the reactive indole was protected by N-benzoylation. Debenzylation of intermediate 99 was then carried out to activate the central aromatic ring towards nitration.
The stage was now set for the crucial nitration of phenol 100. Our effort is briefly summarized in Scheme 35. The initial attempts were aimed at synthesis of dinitro phenol 101. Unfortunately, attempts to dinitrate 100, including the use of concentrated nitric acid or fuming nitric acid in different combinations of other acids or solvents, were unsuccessful. Most of the reactions eventually resulted in a complex mixture of products which could not be characterized. We pondered the results and came to the conclusion that, after the first nitro group was introduced onto the central phenol ring, the electron-withdrawing nitro group greatly reduced the reactivity of the phenol towards the second nitration. It appeared to us that these two nitro groups had to be introduced in a stepwise fashion. Accordingly, studies were continued and focused at mononitration of 100. In the event, it was found that good overall yield of mononitration products of phenol 100 could be obtained by
using isoamyl nitrite in the presence of trifluoroacetic acid in dichloromethane at 0 °C. However, both nitrophenols 102 and 103 were isolated in nearly one to one ratio, indicating the lack of regioselectivity of this mononitration. These two products were separated at this stage, and pure nitrophenol 102 was used for further exploration.

Scheme 35

Prior to the second nitration, the nitro group in 102 was reduced to an amine by activated zinc in the presence of trifluoroacetic acid to increase the electron density of the phenol ring. Meanwhile, the resultant amine condensed intramolecularly with the ethyl ester, yielding lactam 104 as the zinc reduction product (Scheme 36). It was obvious that lactam 104 should be an appropriate stage to perform the second nitration, because not only was the central phenol ring activated towards nitration, but also the amine functionality was protected as an amide to stabilize the rather unstable 4-amino phenol intermediate. Much
to our dismay, attempted nitration of lactam 104 under various conditions were unsuccessful, only resulting in decomposition of the starting material 104. The only viable functional group that could be introduced in reasonable yield was a bromide. It was hoped that once the iminoquinone is formed, the third amine functionality could be brought in through an addition-elimination process at the

\[
\text{Scheme 36}
\]

position of this bromide. The phenol was to be protected as a methyl ether following the bromination of 104, but all our methylation attempts were thwarted by the instability of the lactam substrate, resulting in a very low yield of the methyl ether. A mesylate was temporarily formed to further stabilize this intermediate, providing bromomesylate 105. At this point, the synthesis was continued by removal of methoxymethyl group, dibromination of the resultant
phenol and protection of the phenolic hydroxyl group with a silyl ether, furnishing tribromide 106.

Having succeeded in introducing the dibromide, we then turned our attention to the construction of the iminoquinone system. Lactam 106 could be cleanly reduced to an amine upon treatment with borane-methyl sulfide complex in dichloromethane at room temperature, providing amine 107 as a precursor of iminoquinone 108 (Scheme 37).

![Scheme 37](image)

To our great disappointment, oxidation of 107 with a variety of oxidizing agents failed to generate target iminoquinone 108 (Scheme 38). Based on our previous experience, it was clear that the failure of the oxidation is related to the presence of the mesylate in 107. Once we had a methyl ether instead of a mesylate, iminoquinone formation would more likely be successful. Considering the difficulties of converting 107 to iminoquinone 108, along with the lack of regioselectivity for the nitration of 100, this approach was discontinued at this stage.
From the previous approach, we learned that the two nitro groups in compound 88 had to be introduced prior to the indole formation. On the other hand, in order to form iminoquinone successfully by oxidation, a methyl ether instead of mesylate had to be used to protect the central phenolic hydroxyl group. Based on these considerations, a modified route was designed to meet those specific challenges. The retrosynthetic approach is outlined in Scheme 39.
It was believed that diamino indole intermediate 109, which is very similar to compound 88, is essential for this synthesis. By analyzing the previous attempt, we realized that indole synthesis had to occur with the diamino functionality present, meanwhile, the methoxy group, which will serve as a handle for the iminoquinone formation, was brought into the synthesis at much earlier stage. In order to simplify the nitration process, the biaryl carbon-carbon bond was disconnected leading to two aromatic precursors, 110 and 111. It appeared that we could take advantages of the dinitro substitution pattern by connecting this biaryl carbon-carbon bond through an Ullmann reaction.40 The Ullmann reaction plays an important role in biaryl synthesis, among many interesting applications, there is one example41 reported in the literature which shows the potential to be used in discorhabdin C synthesis (Scheme 40).

When picryl chloride 112 was heated together with iodobenzene in the presence of copper powder, biaryl carbon-carbon bond was formed affording 113 in good yield. A quick model study was conducted to examine the possibility of applying this coupling reaction. The biaryl, 115 and 116 in Figure 5, were synthesized from dinitro chloride 114 by reacting with iodobenzene or
para-benzyloxy-iodobenzene, respectively, under the reported conditions. Based on the above experiment, it seemed plausible to form biaryl compound 118 directly from p-benzyloxy-iodobenzene and 117 (Figure 6). The effect of the electron donating methoxy group on the Ullmann coupling was unknown at this point.

The first task for this new approach was to prepare 117 in large quantities. Nitration of the protected chlorosalicylic acid 119 was performed using fuming nitric acid and trifluoroacetic anhydride to provide desired dinitro chloride 117 in pure form after recrystallization in 67% yield. The stage is now set for the critical Ullmann reaction between 117 and p-benzyloxy-iodobenzene. To our great excitement, the coupled product 118 was isolated as the only product in the reaction mixture by following the literature conditions,
and surprisingly, in a quantitative yield (Scheme 41). With the success of the Ullmann reaction, we were able to obtain a key intermediate containing the dinitro and methoxy functionalities in just two steps.

![Chemical structure images](image1)

**Scheme 41**

The nitrogen functionality in the indole system could be brought in by taking advantage of the Curtius rearrangement of benzoic acid 120 (Scheme 42), generated from 118 by alkaline hydrolysis in 93% yield. To perform the rearrangement, the acid azide was prepared by addition of sodium azide to the mixed anhydride derived from acid 120. The rearranged product allyl urethane 121 was obtained in an overall yield of 97% when the acid azide was heated in toluene in the presence of allyl alcohol. Subsequent removal of the allyl carbamate protecting group resulted in 95% yield of free amine 122.
With dinitroamine 122 in hand, we were able to focus on the indole formation using tin-mediated radical cyclization. Since the nitro groups might interfere with the radical chain reaction, it was determined that indole formation would be carried out on the diamine. As illustrated in Scheme 43, the free amino group was first converted into a formamide using mixed anhydride conditions, affording formamide 123 in 92% yield. The two nitro groups were reduced at this stage by activated zinc. Due to the activation of the two amino groups, diamino iodide 124 could be easily obtained in nearly 80% yield with the use of iodine monochloride.
The indole precursor 125 could be prepared in 73% yield through Heck reaction\(^4\) of iodide 124 with methyl acrylate followed by dehydration of the formamide using triphenylphosphine, carbon tetrachloride and triethylamine. Radical cyclization proceeded smoothly when isonitrile 125 was heated with tributyltin hydride and AIBN in acetonitrile, providing the rather unstable diaminoindole 126 in 76% yield (Scheme 44). At this point, the two amino

\[
\text{Scheme 44}
\]
groups in 126 needed to be differentiated and protected to stabilize this indole intermediate. To do so, effort was directed towards the formation of lactam 127, which we thought was ideal for the above purposes. However, despite the fact that lactam 127 could be obtained by using trimethylaluminum or trifluoroacetic acid, we were unable to prevent the migration of the double bond from the indole to the adjacent lactam ring, resulted in the formation of the side product 128.

An alternative sequence was quickly tested (Scheme 45). Instead of forming lactam 127, the two amines were protected as two different urethanes. Since the 4-amino group is more reactive, its allyl urethane was first formed with one equivalent of allyl chloroformate, the other amine was then protected as a 2-trimethylsilyl ethyl urethane. The protected indole 129, which is now a very stable intermediate, was obtained in 55% yield from diaminindo1e 126.

Construction of tricyclic skeleton 131 was accomplished by a three-step transformation from 129 in 99% yield. Reduction of 129 with diisobutylaluminum hydride (DIBAL) afforded alcohol 130 in 100% yield. The primary alcohol was converted to a mesylate, which upon treatment with potassium t-butoxide, furnished intermediate 131 without any difficulties.
At this point, it was safe to remove the trimethylsilylthoxyl carbonyl group from tricyclic intermediate 131 by trifluoroacetic acid treatment, yielding amine 132 (Scheme 46). Bromoethylation of the resultant amine was the next task. In order to obtain bromoethylamine 134 in high yield, hydroxylethylamine was first prepared through reductive alkylation of amine 132 with glycolaldehyde. By controlling the amount of aldehyde and sodium cyanoborohydride carefully, the alkylation could be stopped at the mono alkylation stage. After mesylation of the hydroxyl group in 131,
bromoethylamine 134 could be obtained in reasonable yield by substitution with bromide. After the secondary amine in 134 was protected as a trifluoroacetamide (Scheme 47), the palladium-mediated deprotection of the
allyl carbamate furnished the iminoquinone precursor 135. As expected, the iminoquinone 136 could be obtained by CAN oxidation of 135 (Scheme 48).

![Chemical structures](image)

**Scheme 48**

With the formation of 136, all the difficulties related to the indole and iminoquinone formation were overcome and the stage was set for constructing the final spiro dienone system. However, because of the low yield for the oxidation of 135, the accessibility of iminoquinone 136 was rather limited. It was extremely difficult to pursue further transformations without substantial improvement of this step. Once enough iminoquinone 136 is obtained, the synthesis will be continued according to our plan shown in Scheme 49. The indole in 136 will be protected by a BOC group before debenzylation. Dibromo phenol 138 could then be prepared using pyridinium bromide perbromide. Finally, intramolecular para-phenolic alkylation may be realized by using potassium carbonate or potassium t-butoxide as base to finish the total synthesis of discorhabdin C (3). Synthetic effort in this direction is currently underway in our laboratories.
In summary, with the discoveries of the improved aromatic Claisen rearrangement conditions as well as a new tin-mediated radical indole formation in our laboratories, two different approaches for the total synthesis of discorhabdin C have been developed. During the course of our research, we have learned both from our past failures and successes on this project. Much insight into the chemistry of this system has been gained. We have no doubt that the total synthesis of discorhabdin C shall be realized in the very near future.
CHAPTER 3

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\(^{-1}\)).

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

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

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 × 20 cm or 20 × 20 cm plates prepared with a 2 mm layer of Merck silica gel 60 PF\(_{254}\). Compounds were eluted from the adsorbent with 10% methanol in dichloromethane.
All evaporations were performed under reduced pressure on a rotary evaporator.

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

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

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

Dichloromethane and ether: distilled through a 24 inch Snyder column.
Tetrahydrofuran (dry): distilled from sodium benzophenone ketyl.
Pyridine, triethylamine, and diisopropylethylamine: dried over potassium hydroxide pellets.
\(t\)-Butanol: distilled from calcium hydride.
\(N, N\)-Dimethylformamide, benzene, toluene, acetonitrile, and methanol: dried over 4Å molecular sieves.
Methanesulfonyl chloride and thionyl chloride: distilled over phosphorus pentoxide.

All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.
2-Acetyl-3-(4'-benzyloxyphenyl)-1,4-benzoquinone (49)

A stirred solution of 2.00 g (13.1 mmol) of 42, 7.26 g (39.3 mmol) of benzyl phenyl ether, 20 ml (0.262 mol) of trifluoroacetic acid in 40 ml of dichloromethane was added carefully 7.85 g (32.8 mmol) of lead dioxide over a period of 10 min. The mixture was stirred at room temperature for another 5 min and quenched with brine. The aqueous layer was thoroughly extracted with dichloromethane (50 ml × 2). The combined extracts were washed with 100 ml of brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated at reduced pressure. The crude product was triturated with three portions of 30% ether-hexanes and finally with 50 ml of methanol. The solid product was filtered and then pumped overnight under vacuum (0.5 mmHg) to give 4.15 g (95%) of 49 as dark brown crystals.
Characterization of 49:

mp (ether): 150-151 °C

IR (NaCl): 3130, 3070, 3000, 2930, 1760, 1680, 1650, 1600, 1510, 1300, 1250, 1180

$^1$H NMR (CDCl$_3$): 2.07 (3H, s), 5.08 (2H, s), 6.84 (2H, $J_{ab}$ = 10.3 Hz), 7.00-7.45 (9H, m)

$^{13}$C NMR (CDCl$_3$): 31.3, 70.1, 114.9, 122.5, 127.5, 128.2, 128.6, 131.6, 136.0, 136.2, 136.5, 140.0, 142.0, 160.5, 185.3, 186.8, 200.2

MS: 334([M+2]+, 31), 332 (M+, 35), 243 (18), 241 (44), 199 (10), 115 (43), 91 (100)

Exact Mass: Calculated for C$_{21}$H$_{16}$O$_4$ 332.10484
Found 332.10463
Compound 49 continued
3.6-Diacetoxy-2-(4'-benzyloxyphenyl)-acetophenone (59)

To a solution of 4.15 g (12.5 mmol) of benzoquinone 49 in a mixture of 200 ml of ether and 100 ml of dichloromethane was added an excess amount of activated zinc dust and 2.5 ml (43.6 mmol) of glacial acetic acid. After stirring at room temperature for 10 min, the reaction mixture was filtered and the residue was washed carefully with ether (40 ml × 3). The filtrate and the washings were combined and washed with 100 ml of an aqueous sodium bicarbonate solution. The aqueous layer was thoroughly extracted with 70 ml of ether. The ethereal layers were combined, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give 4.67 g of crude product.

To the above crude product was added of 10 ml of acetic anhydride and 10 ml of pyridine. The mixture was allowed to stand at room temperature for 20 min before it was evaporated under reduced pressure to give 5.72 g of the product as a yellow oil. The crude product was separated by flash chromatography, eluting with 40 to 80% ether-hexanes, to give 5.23 g (100%) of 59 as a light yellow oil.
Characterization of 59:

IR (NaCl): 3050, 1780, 1700, 1610, 1520, 1460, 1390, 1200, 1090, 1010

$^1$H NMR (CDCl$_3$): 1.90 (3H, s), 2.00 (3H, s), 2.25 (3H, s), 5.08 (2H, s), 6.98-7.46 (11H, m)

$^{13}$C NMR (CDCl$_3$): 20.5, 20.8, 31.2, 70.0, 102.7, 114.8, 122.6, 124.3, 126.4, 127.5, 128.1, 128.6, 130.8, 132.7, 136.3, 136.48, 144.0, 145.7, 158.1, 169.2, 201.6.

MS: 418 (M$^+$, 61), 376 (31), 345 (99), 344 (93), 292 (38), 285 (41), 243 (99), 115 (97), 91 (80), 90 (100)

Exact Mass: Calculated for C$_{25}$H$_{22}$O$_6$ 418.14161
Found 418.14229
Compound 59 continued
3-Acetoxy-6-hydroxyl-2-(4'-benzyloxyphenyl)-acetophenone (60)

To a stirred solution of 5.72 g (13.1 mmol) of 59 in 100 ml of dichloromethane was added 3.71 ml (37.5 mmol) of piperidine over a period of 30 min. The reaction mixture was kept stirring at room temperature for additional 2.5 h. The reaction mixture was partitioned between 150 ml of dichloromethane and 100 ml of 3 N hydrochloric acid. The organic layer was then separated, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. Separation by flash column chromatography, eluting with dichloromethane, afforded 3.33 g (68%) of 60.
Characterization of 60:

mp (ether-hexanes): 95-95.5 °C

IR (NaCl): 3450, 2950, 1770, 1640, 1610, 1520, 1450, 1210

$^1$H NMR (CDCl$_3$): 1.79 (3H, s), 1.93 (3H, s), 5.11 (2H, s), 7.00-7.47 (11H, m), 11.71 (1H, s)

$^{13}$C NMR (CDCl$_3$): 20.4, 31.9, 70.1, 115.0, 118.3, 121.9, 127.6, 128.2, 128.6, 128.8, 129.2, 130.9, 135.7, 136.5, 140.8, 158.9, 159.4, 169.9, 206.5

MS: 376 (M+, 44), 334 (95), 243 (96), 115 (41), 92 (100), 91 (93)

Exact Mass: Calculated for C$_{23}$H$_{20}$O$_5$ 376.13105

Found 376.13074
Compound 60 continued
3-Acetoxy-6-hydroxy-2-(4'-benzylxoyphenyl)-5-nitro-acetophenone (61)

To a stirred solution of 3.32 g (8.83 mmol) of 60 in the mixture of 20 ml glacial acetic acid and 1.9 ml (24.7 mmol) of trifluoroacetic acid was carefully added 1.22 g (17.7 mmol) of sodium nitrite over a period of 5 min. The reaction mixture was kept stirring at room temperature for another 30 min and was poured into a 250 ml of separational funnel containing 80 ml of water. The mixture was thoroughly extracted with dichloromethane (75 ml x 2). The combined organic extracts were washed with 100 ml of brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure, to afford 3.61 g (97%) of desired nitro product 61 as a yellow solid which was used in the next step without further purification.
Characterization of 61

mp (ether): 142-142.5 °C

IR (NaCl): 3300, 3080, 2990, 1780, 1700, 1600, 1520, 1440, 1250, 1190

$^1$H NMR (CDCl$_3$): 1.99 (3H, s), 2.18 (3H, s), 5.08 (2H, s), 6.99-7.43 (9H, m), 7.92 (1H, s), 10.80, (1H, s)

$^{13}$C NMR (CDCl$_3$): 20.3, 31.9, 70.0, 114.9, 119.2, 124.6, 127.5, 128.2, 128.6, 130.4, 132.1, 134.2, 136.3, 140.7, 141.8, 149.3, 159.4, 169.0, 200.3

MS: 421 (M$^+$, 65), 379 (93), 313 (25), 288 (50), 93 (100), 90 (99)

Exact Mass: Calculated for C$_{23}$H$_{19}$NO$_7$ 421.11612

Found 412.11574
Compound 61 continued
Methyl 2-acetyl-4-acetoxy-6-nitro-3-(4'-bezyloxyphenyl)-phenol ether (62)

Nitrophenol 61 (2.01 g, 4.77 mmol) was dissolved in 20 ml of \( N,N \)-dimethylformamide, and 3.6 g (26.0 mmol) of potassium carbonate powder followed by 0.64 ml (10.3 mmol) of iodomethane was added. The mixture was heated in an oil bath at 60 °C for 2 h. The reaction mixture was then cooled to room temperature, quenched by pouring into 70 ml of water, and extracted thoroughly with ether (75 ml \( \times \) 2). The ethereal extracts were combined and washed with 100 ml of water. The organic layer was then separated, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography, eluting with 40% ether-hexanes solution, to give 1.97 g (95%) of pure 62.
Characterization of 62

mp (ether): 112-113.5 °C

IR (NaCl): 3100, 3040, 2950, 2870, 1780, 1700, 1590, 1510, 1350, 1230, 1190

$^1$H NMR (CDCl$_3$): 2.01 (3H, s), 2.09 (3H, s), 3.94 (3H, s), 5.08 (2H, s), 7.00-7.45 (9H, m), 7.76 (1H, s)

$^{13}$C NMR (CDCl$_3$): 20.3, 32.0, 64.8, 70.0, 114.9, 120.3, 124.4, 127.6, 128.2, 128.6, 130.7, 138.1, 141.0, 141.9, 143.9, 147.9, 159.3, 168.8, 201.0

MS: 435 (M$^+$, 71), 393 (94), 302 (41), 185 (34), 142 (33), 115 (39), 94 (100), 90 (95)

Exact Mass: Calculated for C$_{24}$H$_{21}$NO$_7$ 435.13177

Found 435.13261
Compound 62 continued

[Graphs showing infrared spectra with wave numbers and transmission values]
3-Acetyl-5-acetamido-4-methoxy-2-(4'-benzyl(oxyphenyl)-phenol (63)

To a solution of 1.76 g (4.04 mmol) of methyl ether 62 in a mixture of 30 ml of ether and 30 ml of dichloromethane was added an excess amount of activated zinc and 3 ml (39.0 mmol) of trifluoroacetic acid. After stirring at room temperature for 30 min, it was filtered and the residue was washed with ether. The filtrate and the washings were combined and washed with an aqueous sodium bicarbonate solution. The ethereal layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure, to give 1.85 g of the crude product.

To the above crude product was added 5 ml of acetic anhydride and 5 ml of pyridine. The mixture was allowed to stand at room temperature for 10 min before it was evaporated under reduced pressure to give 2.12 g of the crude product which was used in the next step without further purification.

To a solution of the above crude product in 25 ml of methanol was added 3 ml (9 mmol) of a 3 N aqueous sodium hydroxide solution with stirring. After 30 min, the reaction was quenched by pouring the mixture into 40 ml of 3N hydrochloric acid. The mixture was extracted thoroughly with dichloromethane (50 ml × 3). The combined organic layers were washed with 70 ml of an aqueous saturated sodium bicarbonate solution. The organic layer was then separated, dried over magnesium sulfate, filtered and evaporated under
reduced pressure, to afford 1.69 g of the crude product. This crude product was washed with two portions of 30 ml of 50% ether-hexanes to give 1.36 g (83%) of pure phenol 63 as yellow crystals.

Characterization of 63

mp (ether-hexanes): 203.5-204.5 °C

IR (NaCl): 3250, 1700, 1660, 1600, 1520, 1390, 1240

$^1$H NMR (CDCl$_3$): 2.02 (3H, s), 2.24 (3H, s), 3.75 (3H, s), 5.07 (2H, s), 7.00-7.46 (9H, m), 7.82 (1H, s), 8.12 (1H, s), 8.33 (1H, s)

$^{13}$C NMR (CDCl$_3$): 24.8, 32.1, 63.3, 69.9, 108.3, 114.8, 120.3, 127.0, 127.5, 127.9, 128.5, 130.8, 131.5, 136.7, 136.8, 137.4, 150.8, 158.3, 169.3, 203.7

MS: 406 ([M+1]+, 70), 405 (M+, 67), 363 (12), 348 (20), 315 (98), 314 (95), 272 (98), 257 (97), 239 (42), 229 (58), 228 (54), 214 (56), 186 (39), 93 (100), 91 (67)

Exact Mass: Calculated for C$_{24}$H$_{23}$NO$_5$ 405.15760
           Found 405.15665
Compound 63 continued
**γ-Substituted allyl phenol ether (65)**

To a stirred solution of 2.18 g (5.38 mmol) of phenol 63 and 1.5 g (6.76 mmol) of γ-substituted allyl alcohol 64 in 100 ml dichloromethane under argon at 0 °C was added 1.84 g (7.02 mmol) of triphenylphosphine and 1.10 ml (7.00 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred for additional 5 min at 0 °C and warmed to room temperature. After washed with brine, the organic layer was dried over sodium sulfate, filtered and evaporated under reduced pressure. The crude product was extracted by two portions of 50 ml of 10% ether-hexanes. The combined extracts were filtered and evaporated under reduced pressure. The residue was separated by flash column chromatography, eluting with 40 to 90% ether-hexanes, to give 4.17 g (100%) of 65 as a light brown oil.
Characterization of 65

IR (NaCl): 3300, 2900, 2820, 1700, 1600, 1510, 1240, 1180

$^1$H NMR (CDCl$_3$): 1.98 (3H, s), 2.23 (3H, s), 2.30 (2H, dt, $J_1 = 6.6$ Hz, $J_2 = 6.6$ Hz), 3.45 (2H, t, $J = 6.7$ Hz), 3.76 (3H, s), 3.78 (3H, s), 4.41 (2H, s), 4.43 (2H, d, $J = 5.0$ Hz), 5.05 (2H, s), 5.68 (2H, m), 6.84-7.46 (13 H, m), 7.68 (1H, s), 8.15 (1H, s)

$^{13}$C NMR (CDCl$_3$): 24.9, 32.1, 32.7, 55.2, 63.2, 69.2, 69.7, 69.9, 72.5, 106.2, 113.7, 114.3, 122.8, 126.4, 127.3, 127.5, 127.9, 128.5, 129.2, 130.3, 130.4, 130.9, 131.2, 131.7, 136.8, 137.8, 152.3, 158.2, 159.1, 168.3, 203.6

MS: 610 ((M+1)$^+$, 9), 609 (M$^+$, 0.4), 406 (18), 405 (17), 362 (8), 314 (61), 272 (13), 205 (36), 123 (100), 92 (82)

Exact Mass: Calculated for C$_{37}$H$_{39}$NO$_7$ 609.27262

Found 609.27245
Compound 65 continued
**Phenol (66)**

Allyl phenol ether 65 (57 mg, 0.09 mmol) was dissolved in the mixture of 0.25 ml (1.20 mmol) of 1,1,1,3,3,3-hexamethyldisilazane and 5 ml of N,N-diethyl aniline. The mixture was placed in a 10-ml culture tube. After argon was bubbled through the mixture for 5 min, the tightly capped culture tube was heated at 215 °C for 3h in an oil bath. After cooling to room temperature, the reaction mixture was partitioned between 25 ml of ether and 20 ml 3 N HCl. The ethereal layer was separated and evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of methanol, treated with 1 ml of 3N hydrochloric acid for 30 min at room temperature to complete the desilylation. The mixture was diluted with 20 ml of ether and washed with brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated on preparative silica gel TLC, eluting with ether, to give 43 mg (75%) of phenol 66 as a pale yellow oil.
Characterization of 66

IR (NaCl): 3300, 3250, 3090, 1700, 1640, 1530, 1440, 1250, 1190, 1130

$^1$H NMR (CDCl$_3$): 1.82 (3H, s), 2.06 (2H, m), 2.13 (3H, s), 3.28 (1H, m), 3.53 (1H, m), 3.61 (3H, s), 3.80 (3H, s), 3.89 (1H, m), 4.31 (2H, AB, J = 10.8 Hz), 5.08 (2H, s), 5.16 (2H, m), 5.38 (1H, s), 6.41 (1H, m), 6.88-7.47 (14 H, m)

$^{13}$C NMR (CDCl$_3$): 22.7, 30.8, 32.3, 38.7, 55.2, 62.5, 68.1, 70.0, 72.7, 113.9, 115.4, 115.6, 122.5, 124.5, 125.0, 125.4, 127.5, 128.1, 128.6, 129.4, 129.8, 131.5, 136.0, 136.5, 139.8, 145.8, 148.0, 158.9, 159.5, 169.3, 203.6

MS: 610 ([M+1]+, 5), 609 (M+, 0.7), 524 (5), 488 (14), 471 (56), 428 (100), 380 (99), 348 (52), 123 (89), 91 (48)

Exact Mass: Calculated for C$_{37}$H$_{39}$NO$_7$ 609.27262

Found 609.27354
Compound 66 continued
3-Substituted indole (72)

To 370 mg (0.61 mmol) of phenol 66 were added 5 ml of pyridine and 5 ml of acetic anhydride. The reaction mixture was allowed to stand at room temperature overnight before it was evaporated to dryness under reduced pressure. The crude product (430 mg) was used in the next step without further purification.

Ozone was bubbled through the solution of the above crude product in 10 ml of dichloromethane at -78 °C for 3 min. After purging with argon over a period of 5 min, the reaction mixture was warmed up to room temperature and treated with 0.2 ml of dimethyl sulfide for 30 min with stirring. The solution was evaporated to dryness under reduced pressure.

To the solution of the above residue in 15 ml of benzene were added 564 mg (2.43 mmol) of camphorsulfonic acid and 0.31 ml (2.61 mmol) of quinoline. The solution was reflux in an oil bath for 3 h while Dean-Stark trap was used to remove water from the reaction mixture. After cooling to room temperature, the reaction mixture was washed with 3 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated on preparative silica gel
TLC, eluting with 80% ether-hexanes, to give 202 mg (52%) of acetyl protected indole 72 as a pale yellow oil.

Characterization of 72

**IR (NaCl):**
2960, 1770, 1610, 1510, 1360, 1240, 1200

**¹H NMR (CDCl₃):**
1.94 (3H, s), 2.18 (3H, s), 2.66 (3H, s), 2.93 (2H, t, J = 6.9 Hz), 3.71 (2H, t, J = 6.7 Hz), 3.74 (3H, s), 3.80 (3H, s), 4.47 (2H, s), 5.08 (2H, s), 6.90 (4H, m), 6.86-7.99 (10 H, m)

**¹³C NMR (CDCl₃):**
20.4, 25.1, 26.4, 32.8, 55.2, 62.7, 68.9, 70.0, 72.7, 113.7, 113.8, 114.5, 117.3, 122.4, 126.8, 127.6, 127.8, 128.0, 128.6, 129.3, 130.1, 131.2, 131.5, 134.8, 136.7, 137.7, 141.9, 158.4, 159.2, 168.0, 169.5, 203.2

**MS:**
636 ([M+1]+, 3), 635 (M+, 1), 607 (18), 593 (19), 472 (65), 455 (50), 413 (100), 370 (49), 322 (86), 136 (97), 122 (96), 92 (93)

**Exact Mass:**
Calculated for C₃₈H₃₇NO₈
635.25188

Found
635.25048
Compound 72 continued
3-(2'-Hydroxyethyl)-indole (73)

To a stirred solution of 25 mg (0.04 mmol) of indole 72 in 5 ml of dichloromethane and water (5 : 1) was added 45 mg (0.20 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at room temperature. After stirred for 2 h, the reaction mixture was partitioned between 20 ml of ethyl acetate and 20 ml of an aqueous sodium sulfite solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated on silica gel TLC, eluting with ethyl acetate, to give 16.9 mg (83%) of hydroxyethyl indole 73 as a pale yellow oil.
Characterization of 73

IR (NaCl): 3430, 2920, 1770, 1730, 1700, 1610, 1510, 1450, 1400, 1370, 1250, 1200

$^1$H NMR (CDCl$_3$): 1.97 (3H, s), 2.18 (3H, s), 2.71 (3H, s), 2.89 (2H, t, J = 6.5 Hz), 3.75 (3H, s), 3.92 (2H, t, J = 6.5 Hz), 5.08 (2H, s), 6.97-7.48 (10H, m)

$^{13}$C NMR (CDCl$_3$): 20.4, 25.2, 29.3, 32.8, 61.9, 62.7, 70.0, 114.6, 116.8, 126.5, 126.7, 127.4, 127.6, 127.8, 128.1, 128.3, 128.6, 131.2, 135.0, 136.7, 137.7, 141.9, 158.5, 168.1, 169.6, 203.1

MS: 515 (M$^+$, 72), 473 (97), 431 (98), 413 (97), 400 (47), 382 (54), 340 (97), 322 (100), 307 (34), 92 (98), 91 (91)

Exact Mass: Calculated for C$_{30}$H$_{29}$NO$_7$ 515.19437
Found 515.19486
Compound 73 continued
Methyl 4-chloro-2-methoxy-3,5-dinitro-benzoate (117)

To a mixture of 40 g (199 mmol) of 119, 50 ml of dichloromethane and 180 ml of trifluoroacetic acid was added 30 ml (674 mmol) of fuming nitric acid over a period of 1 h. The reaction mixture was allowed stirred overnight in a well ventilated hood. The reaction mixture was washed with water. The aqueous layer was extracted with 200 ml of dichloromethane. The combined organic layers were washed with an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was recrystallized from 10% dichloromethane-hexanes solution to give 38.8 g (67%) of 117 as light yellow crystals.
Characterization of 117

mp (ether): 65-66 °C

IR (NaCl): 3070, 2990, 1740, 1560, 1540, 1350, 1300, 1150, 1030

$^1$H NMR (CDCl$_3$): 4.01 (3H, s), 4.05 (3H, s), 8.63 (1H, s)

$^{13}$C NMR (CDCl$_3$): 53.5, 65.2, 124.2, 124.6, 129.7, 142.5, 155.5, 162.0

MS: 290 (M$^+$, 4), 259 (23), 230 (72), 183 (32), 110 (83), 96 (84), 74 (80), 59 (95), 30 (100)

Exact Mass: Calculated for C$_9$H$_7$ClN$_2$O$_7$ 289.99414

Found 289.99407
Compound 117 continued
Methyl 3,5-dinitro-2-methoxy-4-(4'-benzylxyloxyphenyl)-benzoate (118)

A mixture of 18.0 g (62 mmol) of 117, 28.8 g (93 mmol) of 4-iodophenyl benzyl ether and 29.5 g (465 mmol) were placed in a 250 ml three neck round bottom flask equipped with a mechanical stirrer. The stirred mixture was heated at 170 °C in an oil bath under argon over a period of 6 h. After cooling to room temperature, the reaction mixture were extracted with dichloromethane (100 ml × 4) and filtered. The extracts were combined, dried over anhydrous magnesium and evaporated to dryness under reduced pressure. The residue was crystallized in methanol. The solid product was washed with three portions of 100 ml of methanol, to give 28.1 g (100%) of 118 as a yellow solid.
Characterization of 118

mp (ether): 89-90 °C

IR (NaCl): 3090, 3040, 2960, 1740, 1600, 1550, 1520, 1350, 1260, 1180, 1170, 1000

$^1$H NMR (CDCl$_3$): 4.01 (3H, s), 4.05 (3H, s), 5.06 (2H, s), 7.00-7.43 (9H, m), 8.54 (1H, s)

$^{13}$C NMR (CDCl$_3$): 53.3, 65.0, 70.1, 115.3, 121.4, 124.5, 127.6, 128.2, 128.6, 128.7, 129.3, 135.8, 136.3, 144.5, 148.1, 154.4, 160.1, 162.6

MS: 438 (M$^+$, 82), 421 (3), 407 (10), 347 (21), 126 (27), 113 (26), 90 (100)

Exact Mass: Calculated for C$_{22}$H$_{18}$N$_2$O$_8$ 438.10627

Found 438.10550
Compound 118 continued
3.5-Dinitro-2-methoxy-4-(4'-benzyl oxyphenyl)-benzoic acid (120)

To a mixture of 25.3 g (57.7 mmol) of 118, 150 ml of methanol and 50 ml of dichloromethane was added 40 ml (120 mmol) of a 3 N aqueous sodium hydroxide solution. After 4.5 h, the reaction was quenched by neutralizing the reaction mixture with concentrate hydrochloric acid. The mixture was extracted with dichloromethane (200 ml × 3). The combined organic layers were washed with 400 ml of water. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was crystallized with 50% ether-hexanes solution. The solid product was washed with three portions of 40% ether-hexanes, to give 22.8 g (93%) of benzoic acid 120 as light green crystals.
Characterization of 120

mp (ether): 182.5-184 °C

IR (NaCl): 2500-3300 (broad), 1700, 1600, 1550, 1520, 1350, 1250, 1170

$^1$H NMR (CDCl$_3$): 4.11 (3H, s), 5.08 (2H, s), 7.02-7.44 (9H, m), 8.67 (1H, s)

$^{13}$C NMR (CDCl$_3$): 64.8, 70.0, 115.1, 121.6, 125.6, 127.6, 128.1, 129.3, 133.1, 136.2, 144.2, 147.9, 154.4, 159.9, 164.0

MS: 424 (M$^+$, 19), 333 (9), 155 (9), 126 (19), 93 (100), 91 (53)

Exact Mass: Calculated for C$_{21}$H$_{16}$N$_2$O$_8$ 424.09062
              Found 424.09117
Compound 120 continued
Dinitro allyl urethane (121)

To a stirred solution of 18.7 g (44.1 mmol) of benzoic acid 120 in 300 ml of dichloromethane at 0 °C was carefully added 6.6 ml (69.0 mmol) of ethyl chloroformate and 8.3 ml (59.5 mmol) of triethylamine under argon over a period of 25 min. After stirred at 0 °C for additional 20 min, 17 g (59.9 mmol) of tetrabutylammonium azide was added and the reaction mixture was kept stirring for 30 min. The reaction mixture was washed with 200 ml of 3 N hydrochloric acid followed by 200 ml of an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 26.7 g of the crude product.

The crude product was dissolved in a mixture of 150 ml of toluene and 10 ml of allyl alcohol. After heated at 80 °C under argon over a period of 45 min, the reaction mixture was cooled to room temperature and partitioned between dichloromethane and an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was purified by a short silica gel column, eluting with ether, to furnish 20.5 g (97%) of 121.
Characterization of 121

mp (Chloroform): 160-161 °C

IR (NaCl): 3300, 2900, 1720, 1600, 1540, 1500, 1340, 1250, 1220

$^1$H NMR (CDCl$_3$): 3.95 (3H, s), 4.73 (2H, d, J = 5.9 Hz), 5.05 (2H, s), 5.38 (2H, m), 5.96 (1H, m), 6.97-7.46 (9H, m), 8.84 (1H, s)

$^{13}$C NMR (CDCl$_3$): 63.0, 67.0, 70.1, 115.1, 115.2, 119.5, 121.9, 123.4, 127.6, 127.9, 128.1, 129.9, 131.5, 132.7, 136.4, 141.6, 145.7, 146.0, 152.4, 159.7

MS: 480 ([M+1]$^+$, 75), 479 (M$^+$, 62, 421 (5), 402 (20), 388 (20), 181 (68), 141 (40), 113 (80), 94 (100), 91 (99)

Exact Mass: Calculated for C$_{24}$H$_{21}$N$_3$O$_8$ 479.13282

Found 479.13282
Compound 121 continued
3,5-Dinitro-2-methoxy-4-(4'-benzyloxyphenyl)-aniline (122)

To a solution of 20.5 g (42.8 mmol) of 121, 56.1 mg (0.21 mmol) of triphenylphosphine and 5.4 ml (64.2 mmol) of pyrrolidine in 250 ml of dichloromethane was added 124 mg (0.11 mmol) of tetrakis(triphenylphosphine)palladium(0) at room temperature. The solution was stirred over a period of 2 h. The reaction mixture was washed with 250 ml of 3 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 60 to 90% ether-hexanes, to furnish 16.1 g (95%) of 122 as an yellow oil.
Characterization of 122

IR (NaCl): 3500, 3350, 3000, 2890, 1630, 1600, 1540, 1500, 1360, 1240, 1230, 1190

$^1$H NMR (CDCl$_3$): 3.91 (3H, s), 4.32 (2H, bs), 5.05 (2H, s), 6.96-7.42 (10H, m)

$^{13}$C NMR (CDCl$_3$): 61.5, 70.1, 114.3, 114.9, 118.7, 122.7, 127.6, 128.1, 128.6, 130.1, 136.6, 140.2, 140.8, 145.8, 146.9, 159.4

MS: 395 (M+, 100), 304 (25), 213 (8), 185 (16), 169 (29), 141 (51), 127 (37), 115 (64), 102 (44), 93 (99), 90 (91)

Exact Mass: Calculated for C$_{20}$H$_{17}$N$_3$O$_6$ 395.11170
Found 395.11148
Compound 122 continued
Dinitroformamide (123)

To a solution of 16.1 g (40.8 mmol) of 122 in 100 ml of formic acid was added 11.5 ml (122 mmol) of acetic anhydride at room temperature. After stirred over a period of 2 h, the reaction mixture was partitioned between 500 ml of dichloromethane and 300 ml of water. The organic layer was washed by 300 ml of an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The residue was crystallized with 50% ether-hexanes solution. The solid product was triturated with three portions of 100 ml of ether, to give 15.8 g (92%) of formamide 123 as pale yellow crystals.
Characterization of 123

mp (ether): 180-181 °C

IR (NaCl): 3350, 2850, 1700, 1620, 1540, 1490, 1350, 1240

$^1$H NMR (CDCl$_3$): 4.00 (3H, s), 5.06 (2H, s), 6.98-7.46 (9H, m), 7.90 (1H, s), 8.59 (1H, s), 9.09 (1H, s)

$^{13}$C NMR (CDCl$_3$): 63.0, 69.8, 114.8, 117.3, 121.8, 123.9, 127.4, 127.9, 128.4, 129.6, 132.2, 136.2, 142.6, 145.4, 159.4, 160.3

MS: 423 (M$^+$, 76), 332 (16), 140 (17), 103 (28), 93 (100), 90 (99)

Exact Mass: Calculated for C$_{21}$H$_{17}$N$_3$O$_7$ 423.10661

Found 423.10754
Compound 123 continued
Diamino iodide (124)

Formamide 123 (6.7 g, 15.8 mmol) was divided into six portions evenly. Each portion was dissolved in a mixture of 60 ml of glacial acetic acid and 5 ml of dichloromethane. While vigorously stirred at room temperature, an excess amount of activated zinc was added. After stirred for 30 min, six portions were combined and filtered through celite. The filtrate was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure.

To a solution of the above crude product in 150 ml of dichloromethane were added 6.4 ml (79 mmol) of pyridine and 2.6 g (15.8 mmol) of freshly prepared iodochloride. After stirred at room temperature for 30 min, the reaction mixture was partitioned between dichloromethane and water. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with ethyl acetate, to give 4.96 g (78%) of 124 as a reddish foam.
Characterization of 124

IR (NaCl): 3470, 3400, 2920, 1700, 1610, 1520, 1450, 1420, 1270, 1240

$^1$H NMR (CDCl$_3$): 3.65 (3H, s), 3.78 (2H, s), 3.87 (2H, s), 5.12 (2H, s), 7.06 (1H, d, J = 11.3 Hz), 7.11-7.49 (9H, m), 8.57 (1H, d, J = 11.3 Hz)

$^{13}$C NMR (CDCl$_3$): 59.2, 70.0, 111.0, 116.4, 126.9, 127.4, 128.1, 128.6, 130.0, 131.5, 133.6, 136.6, 139.6, 142.3, 158.8, 164.7

MS: 363 (18), 362 (5), 348 (58), 347 (14), 320 (12), 254 (92), 229 (30), 201 (14), 152 (61), 151 (11), 127 (88), 91 (100)

Exact Mass: Calculated for C$_{21}$H$_{20}$I$_3$N$_3$O$_3$ 489.05492
Found 489.05537
Compound 124 continued
Vinyl substituted diamino isonitrile (125)

A solution of 1.51 g (3.1 mmol) of iodide 124, 2.2 ml (25.0 mmol) of methyl acrylate, and 1.3 ml (9.3 mmol) of triethylamine in 20 ml of acetyl nitrile was bubbled through argon. After addition of 189 mg (0.63 mmol) of tri-o-tolyliophosphine and 70 mg (0.31 mmol) of palladium(II) acetate, the mixture was reflux under argon over a period of 45 mins. It was cooled to room temperature before partitioned between dichloromethane and water. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, yielded 1.97 g of a dark brown oil.

The above crude product was dissolved in 50 ml of dichloromethane in the presence of 1.6 ml (15.5 mmol) of carbon tetrachloride, 1.6 g (6.2 mmol) of triphenylphosphine and 1.3 ml (9.3 mmol) of triethylamine. The mixture was refluxed under argon over a period of 1.5 h. After cooled to room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 40 to 90% ether-hexanes, to give 0.96 g (73%) of 125 as a yellow foam.
Characterization of 125

IR (NaCl): 3490, 3370, 2920, 2270, 1700, 1610, 1570, 1520, 1470, 1460, 1290, 1250, 1180

$^1$H NMR (CDCl$_3$): 3.80 (3H, s), 3.85 (2H, s), 3.88 (3H, s), 4.00 (2H, s), 5.12 (2H, s), 6.43 (1H, d, J = 16.3 Hz), 7.13-7.49 (9H, m), 7.81 (1H, d, J = 16.3 Hz)

$^{13}$C NMR (CDCl$_3$): 51.5, 60.0, 69.9, 105.2, 113.7, 116.4, 118.9, 119.4, 125.2, 127.3, 128.0, 128.5, 131.4, 132.3, 136.4, 137.5, 140.9, 141.6, 158.9, 167.7, 171.7

MS: 429 (M+, 51), 414 (51), 398 (25), 382 (9), 370 (13), 323 (45), 262 (41), 234 (25), 92 (100), 91 (88)

Exact Mass: Calculated for C$_{25}$H$_{23}$N$_3$O$_4$ 429.16883

Found 429.16920
Compound 125 continued
**Diamino indole (126)**

A solution of 0.961 mg (2.2 mmol) of isonitrile 125, 1.21 ml (4.5 mmol) of tributyltin hydride, and 20 mg of AIBN in 150 ml of acetyl nitrile was purged with argon for 5 min. The solution was refluxed over a period of 40 min under argon. After cooled to room temperature, the reaction mixture was treated with 0.2 ml trifluoroacetic acid for 10 min. The mixture was washed with 100 ml of hexanes and evaporated to small volume. The residue was dissolved with 50 ml of dichloromethane and washed with an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, yielded 0.732 mg (76%) of 126 as a dark brown foam. This product was used in the next step without further purification.
Characterization of 126

IR (NaCl): 3450, 2990, 2930, 1720, 1630, 1600, 1510, 1490, 1450, 1440, 1240, 1180

\(^1\)H NMR (CDCl\(_3\)): 3.69 (3H, s), 3.84 (5H, b), 5.12 (2H, s), 6.82 (1H, s), 7.08-7.50 (9H, m), 7.95 (1H, s)

\(^{13}\)C NMR (CDCl\(_3\)): 32.8, 52.2, 59.7, 70.0, 108.9, 110.5, 115.9, 120.5, 125.3, 125.5, 127.5, 128.0, 128.3, 128.6, 131.8, 132.0, 132.6, 132.9, 136.9, 158.2, 173.9

MS: 431 (M\(^+\), 19), 416 (58), 325 (28), 293 (12), 265 (9), 236 (12), 91 (100)

Exact Mass: Calculated for C\(_{25}\)H\(_{25}\)N\(_3\)O\(_4\) 431.18448

Found 431.18408
Compound 126 continued
Protected indole (129)

To a solution of 706 mg (1.6 mmol) of diamino indole 126 in 20 ml dichloromethane was added 0.86 ml (6.8 mmol) of N,N-dimethyl aniline followed by 0.16 ml (1.6 mmol) of allyl chloroformate. The reaction mixture was allowed stirred at room temperature overnight. The reaction mixture was washed with 3 N hydrochloric acid. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 713 mg of the crude product.

The above crude product was dissolved in 20 ml of dichloromethane with 0.4 ml (4.8 mmol) of pyridine. After addition of 870 mg (4.8 mmol) of 2-trimethylsilylethyl chloroformate at room temperature, the mixture was stirred over a period of 1 h. The reaction mixture was washed with 3 N hydrochloric acid followed by an aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 60 to 80% ethyl acetate-hexanes, to furnish 505 mg (55%) of 129 as a brown oil.
Characterization of 129

IR (NaCl): 3300, 2960, 1700, 1520, 1250, 1180, 1170

$^1$H NMR (CDCl$_3$): 0.00 (9H, s), 0.91 (2H, t, J = 8.5 Hz), 3.69 (3H, s), 3.76 (2H, s), 3.92 (3H, s), 4.10 (2H, t, J = 8.6 Hz), 4.53 (2H, d, J = 4.5 Hz), 5.09 (2H, s), 5.17 (2H, m), 5.79 (1H, s), 5.80 (1H, m), 6.60 (1H, s), 6.98 (1H, s), 7.01-7.49 (9H, m), 8.61 (1H, s)

$^{13}$CNMR (CDCl$_3$): -1.5, 17.6, 31.5, 52.0, 60.5, 63.5, 65.6, 69.9, 108.1, 114.4, 117.3, 121.0, 121.6, 125.5, 125.6, 127.5, 127.9, 128.6, 128.8, 129.8, 131.1, 132.8, 137.0, 141.8, 155.6, 155.8, 157.9, 173.7

MS: 660 ([M+1]$^+$, 8), 659 (M$^+$, 4), 602 (12), 541 (21), 483 (51), 410 (29), 392 (39), 350 (16), 262 (16), 234 (23), 91 (100)

Exact Mass: Calculated for $\text{C}_{35}\text{H}_{41}\text{N}_3\text{O}_8\text{Si}$ 659.26624
Found 659.26646
Compound 129 continued
3-(2'-Hydroxyethyl)-indole (130)

To a stirred solution of 480 mg (0.73 mmol) of indole 129 in 10 ml THF was added 1.45 ml (2.2 mmol) of DIBAL at 0 °C under argon. After stirred over a period of 30 min, the reaction mixture was warmed to room temperature followed by addition of 5 ml of ethanol and an excess amount of sodium borohydride. The reaction was quenched by pouring into 3 N hydrochloric acid. The mixture was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to furnish 535 mg (100%) of indole 130 as a light brown oil. This product was used in the next step without further purification.
Characterization of 130

IR (NaCl): 3300, 2990, 1710, 1520, 1250, 1170, 1040

$^1$H NMR (CDCl$_3$): 0.00 (9H, s), .91 (2H, t, $J = 8.2$ Hz), 2.89 (2H, b), 3.75 (2H, b), 3.84 (3H, s), 4.10 (2H, t, $J = 8.3$ Hz), 4.52 (2H, d, $J = 4.4$ Hz), 5.08 (2H, s), 5.16 (2H, m), 5.83 (1H, m), 5.95 (1H, s), 6.76 (1H, s), 6.79 (1H, s), 6.94-7.49 (9H, m), 9.01 (1H, s)

$^{13}$C NMR (CDCl$_3$): -1.5, 17.6, 25.6, 28.8, 60.6, 63.4, 67.9, 69.9, 102.7, 112.9, 114.4, 117.4, 120.6, 122.1, 124.8, 127.5, 127.9, 128.5, 128.9, 129.9, 131.1, 132.2, 132.7, 132.8, 137.0, 141.6, 155.8, 157.9

MS: 631 (M+, 23), 613 (5), 573 (16), 529 (9), 513 (5), 495 (8), 471 (10), 455 (11), 368 (29), 350 (17), 337 (15), 322 (13), 305 (10), 295 (10), 91 (100)

Exact Mass: Calculated for C$_{34}$H$_{41}$N$_3$O$_7$Si 631.27133
Found 631.27184
Compound 130 continued
**Tricyclic indole (131)**

To a solution of 501 mg (0.79 mmol) of indole 130 in 20 ml dichloromethane was added 0.44 ml (3.2 mmol) of triethylamine followed by 0.18 ml (2.4 mmol) of methanesulfonyle chloride. The solution was stirred at room temperature over a period of 30 min. The reaction mixture was partitioned between dichloromethane and 3 N hydrochloric acid followed by an aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 525 mg of the crude product.

To the stirred solution of the above product in 10 ml of dry THF was added 2.9 ml (2.8 mmol) of 0.95 M potassium t-butoxide at room temperature. After stirred for 45 min, the reaction mixture was partitioned between dichloromethane and 3 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 481 mg (99%) of 131.
Characterization of 131

mp (ether): 180.5-181.5 °C

IR (NaCl): 3310, 2950, 1700, 1640, 1520, 1470, 1250, 1180

$^1$H NMR (CDCl$_3$): 0.00 (9H, s), 0.92 (2H, t, J = 8.4 Hz), 3.16 (2H, t, J = 7.4 Hz), 3.68 (2H, t, J = 7.4 Hz), 3.88 (3H, s), 4.13 (2H, t, J = 8.5 Hz), 4.57 (2H, d, J = 5.2 Hz), 5.09 (2H, s), 5.20 (2H, m), 5.82 (1H, m), 6.10 (1H, s), 6.95-7.50 (10H, m), 8.73 (1H, s)

$^{13}$C NMR (CDCl$_3$): -1.5, 17.6, 29.7, 45.3, 60.6, 63.5, 65.8, 70.0, 112.9, 114.6, 117.8, 120.8, 121.8, 124.9, 125.3, 127.5, 128.0, 128.5, 128.6, 130.0, 130.9, 131.4, 132.6, 136.9, 141.7, 155.6, 156.0, 158.1

MS: 613 (M$^+$, 5), 591 (6), 531 (6), 505 (5), 495 (13), 473 (15), 304 (13), 278 (13), 248 (10), 147 (100), 92 (96), 91 (71)

Exact Mass: Calculated for C$_{34}$H$_{39}$N$_3$O$_6$Si 613.26077
Found 613.26215
Compound 131 continued
Tricyclic amine (132)

To a stirred solution of 447 mg (0.73 mmol) of tricyclicindole 131 in 10 ml dichloromethane was added 0.56 ml (7.3 mmol) of trifluoroacetic acid at room temperature. The reaction mixture was stirred over a period of 30 min. The reaction mixture was partitioned between dichloromethane and an aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 60 to 80% ethyl acetate-hexanes, to give 334 mg (97%) of 132 as a brown oil.
Characterization of **132**

**IR (NaCl):**
3360, 3260, 2900, 2550, 1700, 1640, 1520, 1460, 1430, 1350, 1250, 1230, 1190

**\(^1\)H NMR (CDCl\(_3\)):**
3.10 (2H, bs), 3.16 (2H, t, J = 7.4 Hz), 3.70 (2H, t, J = 7.4 Hz), 3.87 (3H, s), 4.56 (2H, d, J = 4.3 Hz), 5.10 (2H, s), 5.18 (2H, m), 5.90 (1H, m), 6.00 (2H, s), 6.87, (1H, s), 7.03-7.49 (9H, m), 8.10 (1H, s)

**\(^13\)C NMR (CDCl\(_3\)):**
30.0, 45.3, 59.5, 65.7, 70.0, 113.1, 115.4, 117.8, 118.8, 121.9, 122.4, 127.5, 128.0, 128.2, 128.6, 130.8, 131.1, 131.4, 132.6, 132.7, 136.9, 155.8, 158.3

**MS:**
469 (M\(^+\), 0.4), 454 (0.2), 314 (10), 91 (100)

**Exact Mass:**
Calculated for C\(_{28}\)H\(_{27}\)N\(_3\)O\(_4\) 469.20013
Found 469.20036
Compound 132 continued

![Graph 1](image1)

![Graph 2](image2)

![Graph 3](image3)
2-Hydroxyethyl amine (133)

To a stirred solution of 330 mg (0.70 mmol) of amine 132 and 42.2 mg (0.70 mmol) of glycoaldehyde in 15 ml of methanol was added 0.08 ml (1.05 mmol) of trifluoroacetic acid and 44.2 mg (0.70 mmol) of sodium cyanoborohydride. The solution was stirred over a period of 3.5 h. The reaction mixture was partitioned between dichloromethane and an aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 80 to 100% ethyl acetate-hexanes, to give 247 mg (68%) of 133 as a pale yellow oil.
Characterization of 133

IR (NaCl): 3310, 2950, 1710, 1620, 1520, 1470, 1250, 1170

$^1$H NMR (CDCl$_3$): 1.95 (1H, b), 3.12 (2H, t, $J = 4.8$ Hz), 3.18 (2H, t, $J = 7.5$ Hz), 3.50 (2H, t, $J = 4.8$ Hz), 3.72 (2H, t, $J = 7.5$ Hz), 3.90 (3H, s), 4.56 (2H, d, $J = 5.4$ Hz), 5.11 (2H, s), 5.20 (2H, m), 5.85 (1H, m), 5.93 (1H, s), 6.96 (1H, s), 7.03-7.50 (9H, m), 8.17 (1H, s)

$^{13}$C NMR (CDCl$_3$): 29.9, 45.3, 49.7, 59.3, 61.6, 65.8, 70.0, 112.7, 115.2, 117.8, 120.7, 122.1, 122.8, 126.7, 127.5, 128.0, 128.4, 128.6, 131.2, 131.4, 132.6, 133.4, 135.5, 136.8, 155.9, 158.2

MS: 513 (M$^+$, 5), 462 (7), 428 (6), 403 (49), 91 (100)

Exact Mass: Calculated for C$_{30}$H$_{31}$N$_3$O$_5$ 513.22633
Found 513.22657
Compound 133 continued
2-Bromoethyl amine (134)

To a solution of 220 mg (0.43 mmol) of 2-hydroxyethyl indole 133 in 10 ml dichloromethane was added 0.24 ml (1.72 mmol) of triethylamine followed by 0.10 ml (1.29 mmol) of methanesulfonyl chloride. The solution was stirred at room temperature over a period of 30 min. The reaction mixture was washed with 3 N hydrochloric acid followed by an aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 270 mg of the crude product.

The above crude product was dissolved in 5 ml of N,N-dimethyl formamide along with 400 mg (4.2 mmol) of lithium bromide and 10 mg of 12-crown-4. The solution was placed in a tightly capped culture tube and heated at 60 °C for 2 h in an oil bath with stirring. After cooled to room temperature, the reaction mixture was partitioned between 25 ml of ethyl acetate and 20 ml of water. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 60 to 80% ethyl acetate-hexanes, to give 220 mg (89%) of 2-bromoethyl indole 134.
Characterization of 134

IR (NaCl): 3310, 2970, 1730, 1620, 1510, 1500, 1250, 1180, 1170

$^1$H NMR (CDCl$_3$): 3.18 (2H, t, J = 7.4 Hz), 3.30 (2H, m), 3.43 (2H, m), 3.72 (2H, t, J = 7.4 Hz), 3.89 (3H, s), 4.55 (2H, d, J = 5.0 Hz), 5.12 (2H, s), 5.17 (2H, m), 5.85 (1H, m), 5.90 (1H, s), 6.98 (1H, s), 7.04-7.49 (9H, m), 8.12 (1H, s)

$^{13}$C NMR (CDCl$_3$): 29.9, 33.5, 45.3, 48.5, 59.2, 65.8, 70.0, 113.1, 115.4, 117.8, 120.4, 122.4, 122.5, 126.2, 127.5, 128.0, 128.1, 128.6, 131.4, 131.6, 132.5, 132.6, 13408, 136.8, 155.8, 158.3

MS: 577((M+2)$^+$, 1), 575 (M$^+$, 1), 567 (10), 552 (3), 531 (4), 495 (4), 462 (11), 402 (18), 376 (7), 340 (9), 91 (100)

Exact Mass: Calculated for C$_{30}$H$_{30}$BrN$_3$O$_4$ 575.14193

Found 575.14216
Compound 134 continued
Trifluoroacetamide (135)

To a solution of 190 mg (0.33 mmol) of 2-bromoethyl indole 134 in 10 ml dichloromethane was added 0.37 ml (2.64 mmol) of triethylamine followed by 0.23 ml (1.65 mmol) of trifluoroacetic anhydride. The solution was stirred at room temperature over a period of 30 min. The reaction mixture was washed with 3 N hydrochloric acid followed by an aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure, to give 210 mg of the crude product.

To a stirred solution of the above crude product, 16 mg (0.06 mmol) of triphenylphosphine and 0.04 ml (0.5 mmol) of pyrrolidine in 10 ml of dichloromethane was added 35 mg (0.03 mmol) of tetrakis(triphenylphosphine)palladium(0) at room temperature. The solution was stirred over a period of 2 h. The reaction mixture was washed with 10 ml of 3 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated by flash column chromatography, eluting with 60 to 90% ether-hexanes, to give 179 mg (93%) of 135 as a light brown oil.
Characterization of 135

IR (NaCl): 3380, 2990, 1690, 1620, 1530, 1490, 1470, 1250, 1220, 1180, 1160

$^1$H NMR (CDCl$_3$): 3.31 (4H, m), 3.83 (4H, m), 3.90 (3H, s), 5.12 (2H, s), 7.06-7.49 (11H, m), 8.21 (1H, s)

$^{13}$C NMR (CDCl$_3$): 23.4, 25.6, 30.8, 44.9, 55.0, 61.0, 70.0, 113.5, 115.6, 116.1, 118.2, 123.4, 126.8, 127.3, 128.0, 128.1, 128.6, 129.1, 130.0, 131.7, 132.0, 134.9, 136.7, 158.6

MS: 589 ([M+2]$^+$, 10), 587 (M$^+$, 9), 574 (6), 572 (7), 543 (37), 528 (35), 452 (3), 396 (7), 371 (9), 340 (5), 305 (10), 279 (15), 263 (7), 91 (100)

Exact Mass: Calculated for C$_{28}$H$_{25}$BrF$_3$N$_3$O$_3$ 587.10310

Found 587.10232
Compound 135 continued
Iminoquinone (136)

To a stirred solution of 150 mg (0.25 mmol) of trifluoroacetamide 135 in 10 ml of mixture of acetonitrile and water (5 : 1) was added 280 mg (0.51 mmol) of ceric ammonium nitrate at room temperature. The solution was stirred over a period of 35 min. The reaction mixture was partitioned between 30 ml of ethyl acetate and 20 ml of aqueous sodium sulfite solution. The aqueous layer was extracted with 20 ml of ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The residue was separated on silica gel TLC, eluting with 80% ethyl acetate-hexanes, to give 39.5 mg (27%) of iminoquinone 136 as a yellow oil.
Characterization of 136

IR (NaCl): 3350, 3250, 2950, 1690, 1650, 1590, 1510, 1480, 1340, 1280, 1240, 1220, 1170, 1150, 1130

$^1$H NMR (CDCl₃): 2.93 (2H, t, $J = 6.1$ Hz), 3.15 (2H, t, $J = 6.1$ Hz), 3.30 (2H, t, $J = 6.7$ Hz), 3.85 (2H, t, $J = 6.7$ Hz), 5.13 (2H, s), 5.63 (1H, b), 7.05-7.49 (10H, m)

$^{13}$C NMR (CDCl₃): 23.4, 30.0, 31.9, 44.2, 45.4, 70.1, 111.8, 115.3, 118.8, 123.1, 127.0, 127.4, 127.5, 127.9, 128.1, 128.6, 132.7, 133.1, 136.3, 136.5, 155.9, 159.6, 164.1

MS: 572 ((M+1)$^+$, 0.1), 395 (19), 304 (69), 207 (23), 91 (100)

Exact Mass: Calculated for $C_{27}H_{21}BrF_3N_3O_3$ 571.07180

Found 571.07163
Compound 136 continued
References


32) γ-Substituted allyl alcohol 64 was prepared through a three step sequence shown below in 63% overall yield.


Appendix

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The Radical Indole Synthesis Approach (continued)

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