AN ABSTRACT OF THE THESIS OF


Title: Synthetic Studies on Marine Natural Products:


Abstract approved: ____________________________

James D. White

Part 1. The synthesis of dihydropallescensin D (82), a sesquiterpenoid related to the sponge metabolite pallescensin D (16), is described. The route begins from α-ionone (86) and required ten steps. Oxidative free-radical cyclization of the olefinic β-keto ester 79 with manganese triacetate in the presence of cupric acetate gave the bicyclo[4.3.1]decane intermediate 81, which was converted to ketone 90. Regioselective enolization of ketone 90 under thermodynamic conditions afforded enol ether 96, which was oxidized to the alcohol 98 with m-chloroperbenzoic acid. Condensation of 98 with lithium trimethylsilylethylcetylide, followed by basic hydrolysis of the silicon group, gave acetylenic diol 109. Intramolecular oxymercuration of 109 with mercuric ion in the presence of acid finally yielded 82.

Part 2. Two approaches to the indoloquinone imine 51, the tricyclic nucleus of the prianosin and discorhabdin alkaloids, are described. The first approach entails cyclization of the amine 94, prepared in four steps
from 3,4-dimethoxybenzaldehyde (88), to the quinone imine ketal 100 by oxidation with iodobenzene diacetate. Reductive aromatization of 100 with hydrogen over a palladium catalyst gave tetrahydroquinoline 97. Strategies for the conversion of 97 to 51 by a third cyclization are discussed.

The second, successful route to 51 proceeded in eleven steps from 3,4-dimethoxybenzoic acid (119). A modified Curtius reaction of 119 with diphenylphosphoryl azide in the presence of ethanol gave the carbamate 124, which was converted to hydrazine 125. A Fischer cyclization of hydrazone 118, prepared by condensation of 125 with 2,3-dihydrofuran, furnished the indole derivative 127. Tosylation of 127 gave 117, which was nitrated at the 4-position of the indole nucleus with acetyl nitrate. Hydrogenation of 132 over a platinum catalyst, followed by heating in the presence of base, produced the tricyclic indole derivative 116 via an intramolecular displacement. Oxidation of 116 with ceric ammonium nitrate afforded 51 in 60% yield. The failure to install nitrogen-containing substituents at C-7 of 51 are discussed, as are the apparent inconsistencies of our results with published routes to discorhabdin C.
Synthetic Studies on Marine Natural Products:

By
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Thesis prepared by Kraig M. Yager
To the memory of my mother

Kathleen M. J. Yager
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Synthetic Studies on Marine Natural Products:

General Introduction

A widely adopted characterization of secondary metabolites, known collectively as natural products, defines them as substances that possess no known role in the internal economy of the producing organism. Secondary metabolites are thereby distinguished from those of the primary metabolic pathways, such as fatty acids, sugars, amino acids and the oligo- and polymeric forms of the latter which are considered essential for cell growth and maintenance of the organism. Presently, there exist several hypotheses concerning the question of why natural products are biosynthesized and how they may benefit or serve the producing organism. The objective of this introduction is not to provide support for, or argue against, this definition, or any of these hypotheses, but rather to introduce a class of molecules that, for the last one hundred and fifty years, has focused scientific research in many disciplines.

Traditionally, investigations aimed at discovering new compounds were performed on the terrestrial flora and fauna and, even though it was as early as 1882 that marine invertebrates were recognized as a source of novel compounds, it has been the last thirty years that have witnessed explosive growth in the area of marine natural products chemistry. A myriad of compounds, the majority of which have no terrestrial parallel, have been characterized from a broad range of marine phyla that include microorganisms, sponges, coelentrates and molluscs. Within these phyla there
exist representative examples of each of the major secondary metabolic subdivisions. Specifically, compounds derived from acetate (fatty acids, polyketides), mevalonate (isoprenoids), amino acids (alkaloids), and mixed biosynthetic origins have been identified.\textsuperscript{5} The boron containing antibiotic aplasmomycin A (1), from a marine strain of \textit{Streptomyces griseus},\textsuperscript{6} and saxitoxin,\textsuperscript{7} the dinoflagellate principle responsible for paralytic shellfish poisoning, attest to the structural diversity and potent biological properties of many of these compounds.

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

There are a few metabolites shared by both terrestrial and marine organisms. This is particularly apparent in the higher terpenes where, for example, (-)-\textsuperscript{δ}-cadinol (3) has been characterized from the brown alga \textit{Dictyopteris divaricata} and the genus \textit{Pinus}. In some instances the absolute configuration is reversed.\textsuperscript{8} Several contrasting features exist between marine and terrestrial metabolites. One of these is the frequent incorporation of halogen and isocyanide\textsuperscript{9a} functionalities in marine compounds where there are few examples in terrestrial natural products. Kalihinol B (4),\textsuperscript{9b} and the haloforms of the red alga \textit{Asparagopsis taxiformis}\textsuperscript{10} illustrate this characteristic.
The research embodied within this thesis concerns synthetic studies on natural products derived from marine sponges. Therefore, this section of the introduction will address those areas of secondary metabolism unique to the phylum porifera. Early work in the natural products chemistry of sponges was concerned primarily with the sterols as a means of establishing chemotaxonomic distinctions between the ever-growing sponge classes. However, according to Scheuer, "...isolation of two unusual nucleosides (5, R=H, Me) from the Jamaican sponge Tethya crypta was, perhaps more than any single discovery, responsible for stimulating wide interest in sponges as a source of novel compounds".3

To date, well over five hundred sponge-derived natural products have been reported.11 The most common nonsteroidal metabolites from this phyla are those of the terpene family, primarily sesquiterpenes (e.g. 6), diterpenes
(e.g. 7), C$_{21}$ furanoterpenes (e.g. 8), sesterterpenes (e.g. 9), carotenoids (e.g. 11) and the terpenoid hydroquinone and quinones of mixed biogenesis (e.g. 10) (Figure 1).$^{12}$

![Chemical structures](image)

**Pallescensin 1 (6)** sesquiterpene  
*Disidea pallescens*

**Nitenin (8)** C$_{21}$ furanoterpene  
*Spongia nitens*

**Isoagatholactone (7)** diterpene  
*Spongia officinallis*

**Nitenin (8)** C$_{21}$ furanoterpene  
*Disidea pallescens*

**Ircinianin (9)** sesterterpene  
*genus Ircinia*

**Panicein B2 (10)** terpenoid hydroquinone  
*Halichondria panicea*

**α-Carotene (11)**

**Figure 1**: Representative Sponge Terpenoids.

The mechanisms and pathways of terpene biosynthesis in sponges have rarely been explored, primarily due to technical problems. The extremely slow rate of sponge metabolism and the fact that metabolites
generally accumulate over the course of years, rather than weeks or months, make incorporation experiments difficult. The majority of the work accomplished in this area has focused on the biosynthesis of sterols and in particular, their side-chain modification. Substantial effort has also been devoted to the biogenetic origins of the isonitrile group found in a number of marine terpenes. The biological roles of these molecules are not well understood but are under active investigation. The sterols are believed to be structural components in cell membranes while many of the terpenes have been implicated in defensive roles against predation and competition.

Introduction

In 1975 a series of reports by Minale and co-workers described the isolation and characterization of ten new furanosesquiterpenes from the marine sponge Disidea pallescens. Three of the metabolites were of the monocyclofarnesyl variety and are represented by pallescensins 1 (6) and 2 (12). The remainder of the pallescensins were previously unknown skeletal types. Pallescensins A (13) and E (14) are illustrative of the two new types of fused bicyclic structures identified, while pallescensins B (15) and D (16) exemplify two bridged-ring systems.
Each of the pallescensin structures was originally assigned on the basis of spectroscopic analyses. Since then, the structure and absolute stereochemistry, where applicable, of the simpler pallescensins 1 (6), 2 (12), A (13) and E (14) have been confirmed by total synthesis. The biological activities of these natural products have not been delineated, although pallescensin A (13) is reported to have fish-antifeedant activity.

Pallescensin D (16) was the first recorded example of a secondary metabolite with the bicyclo[4.3.1]decane carbon skeleton. Aside from the co-metabolite pallescensin C (17), sanadaol (18), from the brown alga *Pachydictyous coriaceum*, nakafuran-9 (19) from *Disidea fragilis* and the unnamed 20 from a New Zealand *Eurypon* sponge species are the only other examples of natural products with this carbon framework.
The biosynthetic origin of the pallescensins is currently unknown. Although it remains to be verified experimentally, Minale has suggested that each of the metabolites could be biogenetically derived from a single furanoid monocyclofarnesane derivative 21 resembling pallescensin 1 (Figure 1.1). In such a pathway, carbon-carbon bond formation between C-12 of the furan (or its biological equivalent) and different sites on the cyclohexane ring gives the various natural product skeletons.16c

**Figure 1.1: Hypothetical Biogenesis of the Pallescensins.**

Bridged carbon frameworks are a common structural motif of many terpenoid natural products. Bridged ring systems can be the core structural element or part of a more complex polycyclic array. Considerable effort has been given to the development of synthetic strategies and methods for bridged ring construction, and approaches toward three naturally occurring bridged arrangements have been the subject of review.24 The large number
of synthetic methods studied and the variety of both natural and unnatural products constructed by them makes a detailed account of recent advances in this area beyond the scope of this introduction. Briefly, among the methods of bridged carbocyclic ring synthesis that have been used are intramolecular alkylation\textsuperscript{24a,25} and aldol condensation\textsuperscript{24,26} of ketones or derived Mannich bases,\textsuperscript{25b} cationic olefin cyclization,\textsuperscript{27} carbone insertion,\textsuperscript{28} transition metal,\textsuperscript{29} and boron-mediated\textsuperscript{30} cyclizations, thermal\textsuperscript{24a,31} and photochemical\textsuperscript{24a,b} cycloadditions, and free-radical\textsuperscript{32} processes. Operations on existing carbocyclic intermediates that involve ring fragmentation,\textsuperscript{24a,25} contraction,\textsuperscript{34} and rearrangement\textsuperscript{35} have also been reported to give bridged carbocycles. The first part of this thesis describes a novel route to the bicyclo[4.3.1]decane framework. For this reason, methods reported in the literature for its construction are summarized in greater detail.

An early report by Shea and Wise described the synthesis of a bicyclo[4.3.1]decene 23 as part of a general study of molecules containing bridgehead double bonds (Scheme 2).\textsuperscript{36} This and other frameworks were accessed via an intramolecular Diels-Alder reaction using a continuous flow pyrolysis technique. Although excellent yields were reported (>80%), the harsh reaction conditions and lack of functionality limit the synthetic utility of this process. Harding and co-workers prepared highly functionalized bicyclic ketones, e.g. 25, by creating the three-carbon bridge in a one-pot, two-step process (Scheme 2).\textsuperscript{25b} Bimolecular Michael addition of cycloheptenyl Mannich base 24 to substituted acryloyl chlorides and subsequent intramolecular acylation gave the product ketones in essentially quantitative yield. Momose and co-workers demonstrated that one-carbon ring enlargement of bicyclo[3.3.1]nonadione 26 with diazomethane gives
bicyclic diketone 27 with substituted three- and four-carbon bridges (Scheme 2).\textsuperscript{37}

\textbf{Scheme 2}

Grob fragmentation\textsuperscript{38} of substituted tricyclodecanes was utilized by two research groups to gain access to bicyclo[4.3.1]decane frameworks. In the first report Seto and co-workers describe the synthesis of differentially functionalized bicyclo[4.3.1]decenone 33 by a sequence involving two successive ring fragmentations (Scheme 3).\textsuperscript{39} In this scheme, intramolecular, crossed photocycloaddition generates tricyclic keto acetate 29 which undergoes ring opening to the presumed diketone 30, followed by
intramolecular aldol condensation to 31 in the presence of base. The unexpected aldol closure provided useful synthetic discrimination between the two essentially equivalent ketone carbonyls. Hydride reduction from the sterically less hindered face of 31 and selective tosylation of the resultant secondary alcohol gave the Grob fragmentation precursor 32. Treatment with potassium t-butoxide gave 33 in excellent yield.

Scheme 3

The second synthesis along these lines was reported by Yamada and co-workers (Scheme 4).40 Bicyclo[4.3.1]decane intermediate 35 was prepared in a highly stereocontrolled fashion en route to (±)-sanadaol (18).
Tricycle 34, synthesized in twelve steps with good overall conversion, underwent ring fragmentation by the actions of sodium hydride under crown ether catalysis to afford 35 in 72% yield.

Two constructions of the bicyclo[4.3.1]decane nucleus involving cationic intermediates have been reported. The first entails silica gel-promoted transannular cyclization (Scheme 5).\textsuperscript{41} It was found that one of the formyl groups of the natural product dictyodial (36) suffers nucleophilic attack by the transannular cyclononadiene double bond to furnish products of tertiary carbocation 37. However, the potential of this sequence as a synthetic process would appear limited by the complex cyclononene precursors required. As part of a general approach towards fused, spirocyclic, and bridged ring systems, Tanis and Harrinton examined furans as terminators in cationic cyclization (Scheme 5).\textsuperscript{42} They found that, in the presence of acid, cyclohexenone 38 was efficiently converted to a diastereomeric mixture of bicyclic ketones 39 in 79% yield. This intermediate was converted to (±)-nakafuran-9 (19) in two steps.
In a recent account, Snider and co-workers described one of the few examples of bridged ring synthesis using free-radical chemistry.\textsuperscript{43} Except for our application, which was reported first and is detailed in the results and discussion section, Snider's is the only other free-radical process reported to give a bicyclo[4.3.1]decane. Intramolecular oxidative free-radical cyclization of readily available β-keto ester 40 afforded bridged products 41 and 42 in approximately equal quantities. Although rapid access to these functionalized molecules was realized in this way, low yield and poor regiochemical control limit the use of this radical cyclization as a preparative method.

\begin{align*}
\text{CO}_2\text{Et} & \quad 40 \\
\text{Mn(OAc)}_3 & \text{Cu(OAc)}_2 \\
\text{CO}_2\text{Et} & \quad 41 \\
\text{CO}_2\text{Et} & \quad 42 \\
\end{align*}

Methods for carbon-carbon bond formation have, historically, been dominated by polar processes, which typically take the form of nucleophile-electrophile coupling. Due to recent advances in free-radical chemistry this less familiar technique for carbon bond construction has assumed an increasingly prominent place in modern organic synthesis and has become an attractive alternative to traditional methods. These advances and their applications are summarized in several comprehensive reviews.\textsuperscript{44} For synthetic purposes, the manner of both radical generation and termination often plays an important role in the overall success of the reaction. One of the more frequently used procedures for radical production entails halogen atom transfer to trialkyl tin radicals. Once the carbon radical is formed, addition, either bi- or unimolecular, to a site of unsaturation produces a
carbon-carbon bond and new alkyl radical. The chain of events is usually terminated by hydrogen atom abstraction. This sequence, exemplified in scheme 6, 43 to 46, is an overall two-electron reduction that typically leads to less functionalized products. Loss of both the halogen atom and the olefin from 43 to 46 is illustrative.

Scheme 6

Radical reactions utilizing transition metal redox couples have become increasingly popular. With this method alkyl radicals are generated without sacrifice of a functional group, and lead to highly functionalized products, for example nucleophilic addends or elimination products of 48, and the conditions are compatible with a variety of existing functionality. Transition metals known to operate in this capacity include Mn(III), Mn(IV), Co(III), Cu(I), Cu(II), Fe(II), Fe(III), Ag(I), Ag(II), Pb(IV), Ce(IV), Cr(II). Of these, the chemistry of manganese(III) has been the most actively and thoroughly explored.

The synthetic potential of manganese triacetate [Mn(OAc)₃] was first realized by two groups in 1968. It was shown that acetic acid solutions of Mn(OAc)₃ produced acetate radicals that reacted with olefins to give γ-
lactones in synthetically useful yields. Several subsequent reviews described synthetic methodology employing Mn(OAc)\(_3\), with particular attention given to formation and reactions of \(\alpha\)-oxo alkyl radicals.\(^{46,47}\) Apart from generating \(\alpha\)-oxo radicals, Mn(OAc)\(_3\) displays other modes of reactivity. Fristad and co-workers have shown that Mn(OAc)\(_3\) with added azide or chloride ions reacts with olefins to give vicinal diazides\(^{48}\) and dichlorides\(^{49}\) respectively. Alkyl free-radicals have been made by oxidative decarboxylation of carboxylic acids\(^{50}\) and by nitrogen-carbon bond homolysis of nitromethane.\(^{51}\) Hirao and co-workers have shown that Mn(OAc)\(_3\) effectively catalyzes epoxidation of styrenes by iodosylbenzene.\(^{52}\) Oxidation of benzylic positions (methyl, methylene), sulfides, and phosphines, afford aldehydes, ketones, methylenated products,\(^{53}\) and heteroatom oxides.\(^{54}\) Oximes are oxidatively hydrolyzed by Mn(OAc)\(_3\) regenerating the parent carbonyl compound.\(^{55}\) An assortment of \(\alpha,\beta\)-unsaturated ketones undergo regioselective \(\alpha'\)-acetoxylation and \(\alpha'\)-acyloxylation with Mn(OAc)\(_3\) in combination with carboxylic acids or Mn(II) carboxylates (Scheme 7).\(^{56}\) The reaction conditions accommodate many existing functional groups\(^{56d}\) and the products from reaction with \(\alpha\)-chloroacetic acid (50, \(R=\text{CH}_2\text{Cl}\)) have proven useful in butenolide syntheses.\(^{56e}\)

\[
\text{Scheme 7}
\]
Recently, the γ-lactonization reaction first described by Bush and Heiba\textsuperscript{46} was extended to include reactions of electron rich olefins.\textsuperscript{57} Two accounts by Bestmann and co-workers describe lactone and dihydrofuran syntheses using conjugated eneynes. One addresses the fate of the propargylic radical upon addition of α-oxo radicals\textsuperscript{58a} while the other demonstrates regiochemical control over the radical addition by hexacarboxylidicobalt complexation of the triple bond.\textsuperscript{58b} Nishino and co-workers were first to characterize 1,2-dioxacyclohexanes from a reaction mixture consisting of 1,1-disubstituted alkenes, β-dicarbonyl compounds, Mn(OAc)\textsubscript{3} and molecular oxygen.\textsuperscript{59} Finally, Nishiguchi and co-workers demonstrated that much of the classical Mn(OAc)\textsubscript{3} chemistry can be performed catalytically by continuous anodic oxidation of Mn(II) \textit{in situ}.\textsuperscript{60}

Manganese (III)-promoted oxidative free-radical processes resulting in cyclization have been, in regard to preparative scale methods, the most intensely studied. In early examples of addition reactions promoted by manganese(III), monocarbonyl compounds were used because the reactions were performed on large excesses of oxidizable substrates. Yields from these reactions were typically based on consumed oxidant. This practice is exemplified in seminal works by Heiba and Dessau, where they showed that moderate yields of tetralones were obtained when acetophenone (51) was oxidized with Mn(OAc)\textsubscript{3} in the presence of olefins (Scheme 8).\textsuperscript{61}
Olefinic compounds containing only one electron withdrawing substituent are unsuitable precursors for intramolecular oxidative cyclization since acetic acid, the most commonly used reaction medium, is oxidized preferentially. For this reason, and others, olefinic β-dicarbonyl systems such as 1,3-diketones, malonates, and β-keto esters have become the substrates of choice as they are more readily oxidized than acetic acid.\textsuperscript{62}

Citterio\textsuperscript{63} and Snider\textsuperscript{64} have studied in detail cyclization reactions of aromatic precursors. Employing substituted α-benzylmalonates and olefins they showed that six-membered ring closure cleanly affords functionalized tetrahydronapthalenes (55) (Scheme 9). Ring formation to give five- and seven-membered cycles were generally lower yielding and were accompanied by products of dimerization and hydrogen atom abstraction.\textsuperscript{63b} Similar modes of reactivity were observed with substituted pyridines.\textsuperscript{63c}

\begin{center}
\includegraphics[width=\textwidth]{scheme9.png}
\end{center}

Polycyclic aromatic compounds were obtained by Snider and co-workers by a cyclization cascade initiated by oxidation with Mn(OAc)\textsubscript{3} (Scheme 10, Eq. 1).\textsuperscript{64} Problems associated with the regiochemistry of the initial radical addition were addressed by this group.\textsuperscript{65} Previous work established that alkyl and aryl substituents on the terminal position of the double bond accelerate exo-cyclization and inhibit endo-cyclization.\textsuperscript{64b}
Generally, however, these can not be used as regiochemical control elements since they are not readily removed from the cyclization product. This limitation was overcome by using terminally substituted chloroalkenes, Scheme 10, Eq. 2, where the chloro group was found to be an efficient directing group and readily expendable.\textsuperscript{65}

\begin{align*}
\text{Scheme 10} \\
\text{Snider}\textsuperscript{66} \text{ and others}\textsuperscript{67} \text{ have shown that } \text{Mn(OAc)}_3, \text{in conjunction with } \text{Cu(OAc)}_2\textsuperscript{68} \text{ and acetic acid or ethanol}\textsuperscript{69} \text{ as solvent, gives highly functionalized cycloalkenes from olefinic } \beta\text{-dicarbonyl compounds (Scheme}
\end{align*}
These reactions, which may involve single or multiple radical additions, generate cycloalkyl radicals (64) from endo-cyclization or cycloalkylmethyl radicals (67) from exo-cyclization. Oxidation of these radicals by Cu(II) terminates the cyclization and forms a new double bond. Single addition reactions afford five-, six-, seven-, and eight-membered rings. Spiroyclic compounds have been similarly prepared.43,68

Scheme 11
Tandem radical cyclization yield fused\textsuperscript{66b} and bridged\textsuperscript{43} bicyclic structures such as bicyclo[4.3.0] and -[3.3.1]nonane derivatives 72 and 75 (Scheme 12).\textsuperscript{43} Higher bridged homologues have also been prepared by this method.\textsuperscript{66b,66d}

\begin{center}
\textbf{Scheme 12}
\end{center}

Current efforts in the area of manganese(III)-based cyclizations are directed towards identifying precursors that cyclize with useful levels of asymmetric induction. Starting from unsaturated β-keto tolyl sulfoxides, Snider and co-workers prepared optically pure bicyclo[3.2.1]octan-2-ones.\textsuperscript{69} Finally, a recent communication by Zoretic and co-workers described preparation of fused bicylononane derivatives 77 and 78 in optically active form utilizing Oppolzer’s\textsuperscript{70} chiral sultam methodology (Scheme 13).\textsuperscript{71}

\begin{center}
\textbf{Scheme 13}
\end{center}
Results and Discussion

Our research group has previously demonstrated the preparative utility of olefinic β-keto esters in synthesis. It was shown that Lewis acid-mediated cationic cyclizations afford highly functionalized mono- and fused bicyclic compounds. As part of a general synthetic approach towards stemodane diterpenes, cyclization reactions of β-keto ester 79 were investigated (Scheme 14). Although cyclization attempts employing selenium reagents and mercuric ion failed to produce the desired decalin 80, treatment of 79 with a mixture of manganese triacetate and cupric acetate in acetic acid resulted in a relatively clean reaction. Spectral analysis of the new product, isolated in 40% yield, indicated that it did not, however, possess the anticipated decalin ring structure. On the basis of NMR, IR, and combustion analysis this compound was assigned the bicyclo[4.3.1]decane structure 81.

Scheme 14
It was recognized that β-keto ester 81 held the bicyclo[4.3.1]decane framework and much of the resident functionality present in pallescensin D (16).\textsuperscript{16c} A total synthesis of this metabolite was envisioned that would utilize this novel mode of cyclization to generate a precursor similar to 81, but with the 2,3-double bond (pallescensin numbering) or functionality for its subsequent generation. Before implementing structural modifications to the cyclization precursor, we chose to test the synthetic viability of 81 in a synthesis of 2,3-dihydropallescensin D (82).

![82](image)

With the bicyclic nucleus of 82 secured, the remaining synthetic challenge would involve elaboration of the β-keto ester group of 81 into a furan. A retrosynthetic analysis of this problem is outlined below (Figure 1.2).

![82](image) \[\rightleftharpoons\] ![83](image) \[\downarrow\] ![85](image) \[\leftleftharpoons\] ![84](image)

**Figure 1.2: Retrosynthetic Analysis of 82.**
Annelation of the fused furan moiety was initially envisioned through the intermediacy of butenolide 84 which, after reduction to lactol 83 and dehydration, would be expected to afford the furan ring of 82. Compound 84 would be accessed via intramolecular aldol condensation of 85, the α-acetoxy group of which should be derivable from limited operations on the ester group present in 81.

Before the synthesis of 82 could be initiated, the chemical yield of the cyclization reaction required optimization. For these and subsequent studies, the cyclization precursor 79 was prepared according to the method of White and Somers (Scheme 15). Thus, α-dihydroionone (87), prepared by dissolving metal reduction of α-ionone (86) with lithium in liquid ammonia, was converted to olefinic β-keto ester 79 by formation of its kinetic enolate with lithium diisopropylamide and then acylation with the Mander reagent, methyl cyanoformate.

**Scheme 15**

Optimum yields of 81 were ultimately realized by implementing three crucial modifications to the original protocol. These were, specifically, the use of degassed solvents, dropwise addition of the manganese-copper salt mixture to dilute solutions to 79, and termination of the reaction prior to complete conversion. The first of these adaptations is particularly significant since it is known that, under certain circumstances, the radical intermediates involved in cyclization will react with oxygen. Although products arising from reaction with oxygen were not characterized from previous
experiments, the use of degassed solvent ensured against this becoming a limiting side reaction. The later changes are meaningful in light of observations by Snider and co-workers who have shown manganese(III) oxidations to be substantially faster for α-unsubstituted β-keto-esters than for α-substituted analogs. Because the cyclization product 81 is capable of further oxidation, addition of the metal salts to 79 along with incomplete conversion maintains an excess of reactive substrate in solution. Unreacted starting material was readily separated from 81 by silica gel chromatography and was reused. This efficient process provided the multi-gram quantities of 81 needed for further studies.

The formation of bridged adduct 81 to the exclusion of 80 is in full accordance with the experimental observations of Snider. They have demonstrated that 7-heptenyl radicals generated oxidatively with manganese triacetate preferentially undergo 7-endo cyclization (Scheme 11, n=1). A plausible mechanistic rationale for the observed mode of cyclization relies on the relative thermodynamic stabilities of the radical species formed upon addition of the α-α'-dioxo radical to the cyclohexene double bond (Scheme 16). Attack of the radical species at the more substituted olefinic site generates secondary radical 80a whereas addition to the less substituted terminus yields the more stable tertiary radical 81a. Cyclizations of β-dicarbonyl radicals with olefins are known to be reversible under certain conditions. The fact that 81 was obtained as a single stereoisomer, assigned the β-configuration shown on the basis of a JHaHb=9Hz trans coupling, which could be equilibrated to a small degree by silica gel suggests, however, that this cyclization is not under thermodynamic control.
A theoretical treatment of the 7-heptenyl radical cyclization by Beckwith and Schiesser explains 7-endo ring closure by invoking a preferred low energy (MM2 minimum) conformation resembling a modified chair.\(^{76}\) This transition state geometry appears to be well adapted to the prototypical 7-heptenyl system studied but needs to be modified for cyclizations of radicals generated oxidatively with manganese(III) for the following reason. Snider and co-workers have provided mechanistic evidence for cyclization of \(\alpha\)-unsubstituted \(\beta\)-keto esters through oxidation of a Mn(III)-\(\beta\)-keto ester-alkene complex\(^{74a}\) such as 88, (Scheme 17) and not
free, non-metal bound radicals as has been demonstrated recently for α-
substituted analogs. These findings, and the fact that calculations do not
take into account conformational perturbation by the bound manganese
atom, makes an explanation of the observed selectivity founded on a simple
conformational preference questionable. A reasonable explanation from
examination of the Dreiding model of 88 is that a conformation which
accommodates tricoordination to the manganese atom predisposes the
latent radical center toward reaction with the less substituted olefin terminus.

We anticipated that the carbomethoxy group of 81 would provide a
convenient means for introducing the oxygen functionality required for
construction of the furan ring. The well preceded, one-step oxidative
decarboxylation-acetoxylation of carboxylic acids using lead tetraacetate in
acetic acid appeared to be well suited for this purpose. Unfortunately, 81
proved surprisingly resilient to basic hydrolysis and, even under forcing
conditions, failed to yield the required carboxylic acid. The persistent yellow
reaction mixture suggested that only enolization at the α-carbon was
occurring. As an alternative, introduction of the oxygen substituent prior to
decarboxylation was investigated. However, treatment of 81 with lead
tetraacetate, or base and a source of electrophilic oxygen, such as the Davis
oxaziridine or MoOPH, failed to effect this transformation.

Since attempts to functionalize β-keto ester 81 were unrewarding,
elaboration of the decarbomethoxylated product 90, was examined
(Scheme 18). Ketone 90 was obtained in excellent yield by heating a
solution of 81 in wet dimethyl sulfoxide in the presence of lithium chloride.
By using these reaction conditions as described by Krapcho and co-
workers, rather than the standard pyrolysis of β-keto acids, problems
encountered during saponification of 81 were circumvented and yields were vastly improved. An X-ray crystallographic analysis of the 2,4-dinitrophenylhydrazone derivative 91, figure 1.3, confirmed the structure of 90 and revealed a bicyclic arrangement in which the six- and seven-membered rings have adopted chair and pseudo-boat conformations, respectively.

Figure 1.3: ORTEP Diagram from X-ray Analysis of 91.
Introduction of the requisite oxygen functionality into 90 would require selective enolization of the unsymmetrical ketone towards the bridgehead. Although a search of the literature provided no direct analogy, it has been shown that cis-fused decahydronaphthalen-2-one prefers to undergo deprotonation at C1 rather than C3 (Figure 1.4). This selectivity was attributed to the "reflex effect". This effect postulates that a C2-C3 double bond as in 93 causes the saturated cyclohexane ring to pucker whereas unsaturation at the C1-C2 position as in 92 causes the same ring to flatten. Because the energy of ring flattening is less costly than ring puckering, due to increased ring strain and non-bonded interactions, in the latter case, enolization occurs selectively towards the ring fusion in this system.

![Diagram](image)

**Figure 1.4**: Relative Stability of the Decahydronaphthalen-2-one Enolates.

Encouraged by this observation, molecular mechanics calculations were performed on the two regioisomeric enolates 94 and 95, figure 6, to ascertain whether differences in conformational energy would predict selective enolization. The enolate structures were generated and minimized using the MODEL-MMX87 program based on the Allinger force-field. These calculations led to the prediction that the desired enolate 94 would be thermodynamically favored by approximately 7.9 kcal/mole. The main source of the energy disparity was identified as torsional strain. This was
evident from inspection of output data files for 95 that list the individual energy contributions. Torsional strain imparted by the dihedral angles comprised of C10-1-2-3 and C10-6-5-4, accounted for 31% of the total 19.9 kcal/mole of torsional energy in this arrangement.

**Figure 1.5:** Calculated Minimum Energy Conformations for 94 and 95.

Confirmation of this theory was obtained when thermodynamic deprotonation of 90 using bromomagnesium diisopropylamide, followed by in situ trapping of the magnesium enolate with trimethylsilyl chloride,
afforded exclusively (>99:1) a single silyl enol ether (Scheme 19). That enolization had occurred in the desired sense was supported by the $^1$H-NMR spectrum of 96. Examination of the 400 MHz $^1$H-NMR spectrum revealed a new olefinic signal at $\delta$4.65 ppm appearing as a doublet of doublets ($J$=1,2Hz) which was partially obscured by one of the exo methylene proton signals (doublet) at $\delta$4.62. A $^1$H-COSY spectrum of 96 showed an off-diagonal peak which clearly linked this signal to a broad triplet at $\delta$3.00 ppm. This one-proton resonance was assigned to the C1 bridgehead hydrogen on the basis of its chemical shift, which is considerably downfield (approximately 1ppm) from that typically observed (ca $\delta$2.0 ppm) owing to its bis-allylic nature. An attempt was made to establish a spin-coupling linkage around the 4-carbon bridge of 96 but was blocked by the high signal density in the $\delta$1.6-1.8 ppm region.

Scheme 19

Epoxidation of enol ether 96 according to the procedure of Rubottom$^{87a}$ and Hassner$^{87b}$ with $m$-chloroperbenzoic acid gave a mixture of $\alpha$-siloxy and $\alpha$-hydroxy ketones 97 and 98 (Scheme 19). Since the lability of the trimethylsilyl ether prevented the characterization of 97 in homogeneous form, the mixture was treated directly with mild acid to afford alcohol 98 as a single diastereomer in 74% yield based on recovered 90.
The newly introduced hydroxyl function was assigned the β-configuration based on the observed J_{HaHb}=6Hz coupling in analogy to that of 81.

In a 1965 communication, Lehmann reported moderate yields of butenolides from intramolecular aldol condensation of α-acyloxy ketones with bases in polar aprotic solvents. Following this strategy, α-hydroxy ketone 98 was acylated with acetic anhydride in the presence of 4-(N,N-dimethylamino)pyridine, in preparation for such a ring closure (Scheme 20). Unfortunately, the conditions prescribed by Lehman, as well as those of others, failed to effect ring closure and typically provided 98 and unreacted 85.

Scheme 20
As an alternative to the aldol condensation, the intramolecular Reformatsky reaction\textsuperscript{91} of bromoacetate 99 was investigated (Scheme 20). The latter was prepared by esterification of 98 with \( \alpha \)-bromoacetyl bromide. Reactions of 99 with zinc or combinations of zinc and trimethoxy borate\textsuperscript{92} were disappointing and invariably gave mixtures containing predominantly 85, from reductive debromination and protonation, along with 98. Attempted cyclization of the phosphonate anion derived from 100, prepared by esterification of 98 with dimethylphosphonoacetyl chloride,\textsuperscript{93} was similarly unrewarding. Reactions performed under Rathke's conditions,\textsuperscript{94} using lithium or magnesium halides, triethylamine and elevated temperatures, provided only minor amounts, <8\% as judged by \( ^1 \)H-NMR spectra of crude reaction mixtures, of 84 contaminated with 98. These low conversions thwarted further investigations along these lines.

Cleavage of the \( \alpha \)-acyl groups from 85, 99 and 100 to return 98 during the course of these reactions is interesting. In many instances up to 30\% of 98 was isolated, based on starting ester. It was noted that TLC analysis of the reaction mixtures suggested the presence of 98. This suggested that the acyl groups were not being lost by acidic or basic hydrolysis during workup. A mechanism for the regeneration of 98 which is compatible with this observation is outlined below and parallels the acyl group migrations frequently observed for 1,2-diols. In this proposal, an equilibrium is established between the ketone enolate 101 and ester enolate 102 favoring 101 (\( \Delta pK_a \) ester-ketone = 4-5 units).\textsuperscript{95} Intramolecular O-acylation generates tetrahedral intermediate 103 which decomposes to enol acetate 104. Hydrolysis on silica gel during TLC analysis, or upon mild aqueous workup, would convert this species to 98.
The failure of these reactions to provide the desired butenolide initiated the search for an alternative furan synthesis. Miller, in an extension of earlier work, showed that acetylenic epoxides such as 105 were converted to 3-substituted furans 107 in 65-70% yield upon distillation from dilute sulfuric acid containing a catalytic amount of mercuric sulfate.

Comparable yields of furans were also obtained starting from acetylenic 1,2-diols (106) prepared by acidic hydrolysis of the
corresponding epoxides. From this observation, Miller proposed the intermediacy of 1,2-diols in the reactions of the epoxides. Overall, this transformation involves intramolecular oxymercuration and dehydration as illustrated.

For our purposes, the observed conversion of acetylenic 1,2-diols to furans was significant in that utilization of this method would be compatible with 98. In order to test the feasibility of such a process, the required acetylenic diol 108 was prepared according to scheme 21. Thus, a THF solution of 98 was introduced dropwise to a cold solution of excess lithium trimethylsilylacetylide,98 which after chromatography, afforded 108 as a single diastereomer in 86% yield. Removal of the silicon group by mild basic hydrolysis provided the desired acetylenic 1,2-diol 109 in 94% yield.

![Scheme 21](image-url)
Although the use of trimethylsilyl acetylide, rather than lithium acetylide, necessitated an additional step, this avoided the often troublesome generation of the latter.99 The cis relationship indicated for the 1,2-diol unit was supported by its formation of a cyclic carbonate 110 with triphosgene100 in methylene chloride. An ORTEP representation of 110, generated from an X-ray analysis is shown in figure 1.6, and provided definitive proof of stereochemical assignments.

![Figure 1.6: ORTEP Representation from X-ray Crystal Structure of 110.](image)

The synthesis of dihydropallescensin D (82) was completed using a modification of the Miller protocol. Thus, a solution of 109 in dioxane was treated with a mixture of mercuric sulfate in dilute acid at 35°C and afforded dihydropallescensin D (82) in 62% yield as a fragrant oil. The $^1$H-NMR and
IR spectra of 82 correspond closely to the values reported for pallescensin D itself except for the absence of the olefinic proton signals of the 2,3-double bond in the $^1$H-NMR spectrum.

$$\text{HgSO}_4, 2\text{N H}_2\text{SO}_4$$
dioxane, 32°C (62%)

Scheme 22

The synthesis of dihydropallescensin D was achieved in 10 steps and 10% overall yield starting from commercially available α-ionone (86). A key step in the synthesis was the manganese(III)-mediated oxidative free-radical cyclization of olefinic β-keto ester 79 to construct 81 and thereby gain rapid access to the functionalized bicyclo[4.3.1]decane framework of 82. Problems encountered while manipulating the ester group of 81 were solved by decarboxylation and elaboration of the resultant unsymmetrical ketone 90 which, from molecular mechanics calculations, was predicted to enolize selectively towards the bridgehead. This prediction was then substantiated by experiment. The furan ring of 82 was efficiently installed by intramolecular oxymercuration of acetylenic diol 109.
Experimental

General

Solvents were purified and dried prior to use by distillation from an appropriate drying agent. Diethyl ether, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, dimethyl sulfoxide, pyridine, diisopropylamine and triethylamine were distilled from calcium hydride under an argon atmosphere. Bulk solvents for chromatography and workup of reactions were distilled through glass prior to use. Starting materials were obtained from commercial sources and, unless stated otherwise, used without further purification.

Solvents were removed at water aspirator pressure by rotary evaporation and residual solvent was removed by vacuum pump at less than 1.0 Torr. Glassware and syringes were dried in an oven at 165°C overnight and cooled in a dessicator over CaSO₄ prior to use. Alternatively, flasks were flame-dried under a stream of argon.

Analytical thin layer chromatography (TLC) was performed on E. Merck precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm). Flash chromatography was performed with E. Merck silica gel 60 (230-400 mesh ASTM). Radial chromatography was carried out on individually prepared rotors with layer thicknesses of 1, 2 or 4 mm using a Chromatotron manufactured by Harrisison Research, Palo Alto, California.

Melting points were determined using a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet Model 5DXB FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM300 or AM400 spectrometer,
chemical shifts are expressed as ppm downfield from tetramethylsilane. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High resolution mass spectra (HRMS) were determined on a Kratos MS-50 spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

α,β-Dihydro-α-ionone (87). A flame-dried 3-neck round-bottom flask fitted with a Dry Ice condenser, reflux condenser and pressure-equalizing addition funnel was charged with liquid ammonia (~400 mL) and freshly cut lithium wire (0.72 g, 103.7 mmol) at -78°C under argon. The cooling bath was removed and a solution of 90% α-ionone (86) (5.0 g, 26 mmol) and t-butanol (1.9 g, 26 mmol) in diethyl ether (125 mL) was added dropwise during 30 min. After 15 min. solid ammonium chloride (11 g, 208 mmol) was added portionwise, the condenser was replaced with a sodium hydroxide drying tube, and the ammonia was allowed to evaporate at room temperature. To the mixture was then added water (200 mL) and diethyl ether (200 mL) and the layers were separated. The aqueous layer was saturated with sodium chloride, extracted with diethyl ether (1 X 100 mL) and the combined organic extracts dried over anhydrous magnesium sulfate. Filtration and removal of solvent left 5.2 g of crude product which was purified by chromatography (500 g silica gel 60, ethyl acetate-hexane 1:5) to give 3.32 g (66%, 73% based on 90% α-ionone) of 87 as a colorless oil: IR (neat) 2956, 1717 cm⁻¹; ¹H-NMR (300MHz, CDCl₃) δ 5.34 (bs, 1H), 2.47 (m, 2H), 2.14 (s, 3H), 1.96 (m, 2H), 1.75 (m, 1H), 1.67 (bd, J=2Hz, 3H), 1.62 (m, 1H), 1.41 (m, 2H), 1.14 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H); ¹³C-NMR (75 MHz,
Methyl (±)-3-Oxo-5-(2,6,6-trimethylcyclohexen-2-yl)pentanoate (79). To a flame-dried round-bottom flask containing tetrahydrofuran (23 mL) and diisopropylamine (1.65 g, 16.29 mmol) at 0°C was added a 1.5 M hexane solution of n-butyllithium (11.2 mL, 16.3 mmol) and the mixture was stirred under argon for 30 min. The mixture was then cooled to -78°C, treated with a solution of 87 (2.64 g, 13.6 mmol) in tetrahydrofuran (13 mL) and stirred for 30 min. To this solution was added hexamethylphosphoramide (2.43 g, 13.6 mmol) and methyl cyanoformate (1.39 g, 16.3 mmol). Stirring was continued for 2 h and the mixture was poured into chilled water (60 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (6 X 25 mL). The combined organic extracts were washed with water (3 X 20 mL) and saturated aqueous sodium chloride (3 X 20 mL), then dried over anhydrous magnesium sulfate. Chromatography of the concentrate (400 g silica gel 60, ethyl acetate-hexane 1:10) provided 2.41 g (70%) of 79 as a colorless oil: IR (neat) 2956, 2916, 2869, 1754, 1719, 1437, 1275 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 5.35 (bs, 1H), 3.74, s, 3H), 3.45 (s, 2H), 2.59 (m, 2H), 1.67 (bs, 3H), 0.91 (s, 3H), 0.87 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 202.7, 167.7, 135.4, 121.2, 52.3, 49.1, 48.3, 43.0, 32.6, 31.5, 27.6(2), 24.0, 22.9; MS m/z 252, 234, 219, 136(100); HRMS m/z observed 252.1725 (M⁺), calcd for C₁₅H₂₄O₃ 252.1725.

Methyl (±)-(1α,6α)-7,7-Dimethyl-10-methylene-3-oxabicyclo-[4.3.1]decane-2-carboxylate (81). A suspension of manganese(III)
acetate (241 mg, 0.800 mmol) and copper(II) acetate (180 mg, 0.800 mmol) in degassed glacial acetic acid (10 mL) was warmed to 70°C under argon for 15 min., cooled to room temperature, and added dropwise to a solution of 79 (113 mg, 0.450 mmol) in degassed glacial acetic acid (18 mL) during 1 h. The homogeneous mixture was stirred at room temperature for 2 h, then was concentrated under high vacuum at ambient temperature. The resulting thick sludge was dissolved in ethyl acetate-water 1:1 and the aqueous layer was extracted with ethyl acetate (4 X 20 mL). The combined organic extracts were washed with 5% aqueous potassium carbonate, brine, and dried over anhydrous magnesium sulfate. Concentration of the solution and chromatography (11 g of silica gel 60, ethyl acetate-hexanes 1:10) gave 69 mg (61%) of 81 as a white solid: mp (hexanes) 92-93°C; IR (neat) 2952, 1747, 1712, 1437, 1278, 898 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 4.92 (d, J=2Hz, 1H), 4.75 (d, J=2Hz, 1H), 4.07 (d, J=9Hz, 1H), 3.74 (s, 3H), 3.15 (m, 1H), 2.30 (m, 2H), 2.10 (bt, J=9Hz, 1H), 1.89-1.76 (m, 4H), 1.43 (m, 1H), 1.20 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 206.5, 170.3, 147.2, 114.4, 58.9, 52.3, 51.1, 40.2, 40.0, 34.7, 28.8, 27.6, 27.2, 27.0, 22.1; MS m/z 250 (M⁺, 100%), 235(12), 190 (40), 162 (71), 69 (69); HRMS m/z observed 250.15678 (M⁺), calcd for C₁₅H₂₂O₃ 250.15678. Anal. calcd for C₁₅H₂₂O₃; C, 71.97; H, 8.86. Found; C, 72.22; H, 8.84.

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-3-oxabicyclo[4.3.1]-decane (90). To a solution of 81 (4.40 g, 17.6 mmol) in dimethyl sulfoxide (29 mL) and water (0.3 mL) was added lithium chloride (1.49 g, 35.1 mmol) and the mixture was thoroughly degassed under high vacuum. The flask was fitted with an efficient reflux condenser and warmed to 175°C for 2 h. The mixture was cooled to ambient temperature and poured onto crushed
ice. The aqueous layer was saturated with sodium chloride and extracted with diethyl ether (6 X 80 mL). The combined organic washings were washed with water and dried over anhydrous magnesium sulfate. Chromatography of the concentrate (400 g silica gel 60, diethyl ether-pentane 1:8) afforded 2.77 g (82%) of 90 as a colorless oil: IR (neat) 3070, 2930, 1707, 1649, 1471, 894 cm⁻¹; ¹H-NMR (400MHz, CDCl₃) δ 4.79 (d, J=2Hz, 1H), 4.67 (d, J=2Hz, 1H), 2.89 (dd, J=8,8Hz, 1H), 2.64 (m, 1H), 2.36-2.20 (m, 2H) 2.10 (t, J=9Hz, 1H), 1.94-1.71 (m, 4H), 1.48 (m, 1H), 1.18 (m, 2H) 1.00 (s, 3H), 0.95 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 212.8, 149.4, 112.5, 51.6, 45.4, 40.1, 37.5, 34.7, 28.6, 27.8, 27.7, 27.1, 22.9; MS m/z 192 (M⁺, 100%), 159 (31), 149 (37), 136 (60), 93 (52), 69 (83), 41 (56); HRMS m/z observed 192.15130 (M⁺), calcd for C₁₃H₂₀O 192.15131.

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-3-oxabicyclo[4.3.1]-decane 2,4-Dinitrophenylhydrazone (91). A solution of 2,4-dinitrophenylhydrazine (0.4 g, 2 mmol) in concentrated sulfuric acid (2 mL) was treated with water (3 mL) and 95% ethanol (10 mL) then filtered. To a solution of 90 (14 mg, 0.07 mmol) in 95% ethanol (0.75 mL) was added the 2,4-dinitrophenylhydrazine mixture dropwise and the precipitated 91 was collected by filtration: mp (50% benzene-n-octane) 140°C; ¹H-NMR (400 MHz, CDCl₃) δ 10.98 (s, 1H), 9.13 (d, J=3Hz, 1H), 8.29 (dd, J=3,10Hz, 1H), 7.97 (d, J=10Hz, 1H), 4.75 (d, J=2Hz, 1H), 4.63 (d, J=2Hz, 1H), 2.50 (m, 5H), 2.08 (t, J=9Hz, 1H), 1.92 (m, 4H), 1.20 (m, 1H), 0.97 (s, 3H), 0.94 (s, 3H).

Compound 91 crystallized from 50% benzene-n-octane in a centrosymmetric space group with a=7.534 Å, b=14.802 Å, c=34.310 Å, β=92.00° and z=8. The intensity data were measured on a Rigaku AFC6R diffractometer (Mo Kα radiation). There were 875 observed reflections and
the structure was solved by direct methods with the final discrepancy indices of $R=0.089$ and $R_w=0.101$. The data was collected and the structure solved by Dr. Alan T. Johnson.

$(\pm)-(1\alpha,6\alpha)-7,7$-Dimethyl-10-methylene-3-trimethylsilyloxybicyclo[4.3.1]dec-2-ene (96). A flame-dried round bottom-flask was charged with dry diethyl ether (3.4 mL), freshly distilled diisopropylamine (34 $\mu$L, 0.260 mmol) and a 3.0 M solution of methylmagnesium bromide in diethyl ether (87 $\mu$L, 0.260 mmol) under an argon atmosphere. After stirring for 13 h at 25°C a solution of 90 (56 mg, 0.29 mmol) in diethyl ether (0.80 mL) was introduced dropwise via syringe. The resulting slurry was stirred for 0.25 h and treated with chlorotrimethylsilane (98 $\mu$L, 0.77 mmol, freshly distilled from calcium hydride and precipitated with triethylamine), triethylamine (117 $\mu$L, 0.84 mmol) and HMPA (23 $\mu$L, 0.13 mmol). The mixture was stirred for 19 h at 25°C and treated with a small portion of solid sodium bicarbonate and dry diethyl ether (10 mL). The ethereal solution was extracted with saturated aqueous sodium bicarbonate (1 X 2 mL) and dried over anhydrous sodium sulfate. Removal of solvent gave the crude silyl enol ether 96 which was oxidized directly without purification: $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.80 (d, J=3Hz, 1H), 4.63 (m, 2H), 2.95 (bt, 1H), 2.43 (m, 1H), 2.08 (t, J=8Hz, 1H), 1.72 (m, 4H), 1.42 (m, 1H), 1.15 (m, 1H), 0.93 (m, 1H), 0.87 (s, 6H), 0.16 (s, 9H); $^{13}$C-NMR (75MHz, CDCl$_3$) $\delta$ 154.2, 150.8, 111.2, 111.0, 51.7, 41.2, 34.4, 31.4, 29.0, 28.7, 28.3, 27.6, 27.0, 0.3 (3, Me$_3$Si).

$(\pm)-(1\alpha,6\alpha)-7,7$-Dimethyl-10-methylene-2-hydroxy-3-oxabicyclo[4.3.1]decane (98). To a -20°C solution of crude 96 (63 mg, 0.24 mmol) in dry hexane (1.5 mL) under argon was added $m$-chloroperbenzoic acid (45
mg, 0.26 mmol) and the mixture was stirred for 0.75 h at -20°C then for 2 h at 25°C. The mixture was concentrated, dissolved in THF (2 mL), and treated with 1.5 M aqueous hydrochloric acid (5 drops). After stirring for 0.25 h the mixture was quenched with excess saturated sodium bicarbonate solution and the aqueous layer was extracted with diethyl ether (6 X 2 mL). The combined organic extracts were dried over anhydrous sodium sulfate. Chromatography of the concentrate (6 g silica gel 60, ethyl acetate-hexane 1:8) afforded 30.0 mg (73% based on recovered ketone) of 98 as a colorless solid: mp (hexanes) 76°C; IR (neat) 3462(b), 2950, 2913, 1710, 1649, 1244, 1075, 1062 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 4.77 (d, J=2Hz, 1H), 4.69 (d, J=2Hz, 1H), 4.64 (t, J=6Hz, 1H collapses to d with D₂O exchange of δ 3.71 signal), 3.71 (d, J=6Hz, 1H, exchanges with D₂O), 2.45 (dt, J=19, 4Hz, 1H), 2.29 (m, 1H), 2.06 (t, J=9Hz, 1H), 1.82 (m, 5H), 1.23 (m, 1H), 0.95 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 212.0, 147.2, 112.9, 77.4, 50.8, 50.2, 37.4, 34.7, 29.2, 27.5, 26.9, 26.5, 19.8; MS m/z 208 (M⁺), 190 (32), 179 (62), 161 (31), 81 (61), 79 (90), 69 (100); HRMS m/z observed 208.14623 (M⁺), calcd for C₁₃H₂₀O₂ 208.14623. Anal. calcd for C₁₃H₂₀O₂; C, 74.96; H, 9.68. Found; C, 75.18, H, 9.64.

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-2-acetoxy-3-oxabicyclo-[4.3.1]decane (85). To a solution of 98 (43 mg, 0.21 mmol) in dry toluene (1 mL) was added 4-(N,N-dimethylamino)pyridine (51 mg, 0.42 mmol), pyridine (34 μL, 0.43 mmol) and acetic anhydride (40 μL, 0.42 mmol) under an argon atmosphere. The mixture was warmed to 35°C for 10 h and diluted with diethyl ether (10 mL), and the mixture was washed with saturated aqueous cupric sulfate (2 X 2 mL), saturated aqueous sodium bicarbonate (2 X 2 mL) and saturated aqueous sodium chloride (2 X 2 mL) and then
dried over anhydrous magnesium sulfate. Concentration and chromatography of the residue (5 g silica gel 60, ethyl acetate-hexane 1:8) gave 47 mg (90%) of 85 as a colorless oil: IR (neat) 2941, 2868, 1747, 1729, 1374, 903 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.58 (d, J=7Hz, 1H), 4.86 (d, J=2Hz, 1H), 4.77 (d, J=2Hz, 1H), 2.58 (m, 1H), 2.43 (dt, J=19, 4Hz, 1H), 2.24 (dd, J=14, 4Hz, 1H), 2.14 (s, 3H), 2.09 (m, 1H), 1.84 (m, 4H), 1.65 (bm, 1H), 1.21 (bm, 1H), 0.94 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 205.2, 170.6, 146.2, 114.3, 78.4, 50.8, 43.8, 38.3, 34.8, 29.1, 27.5, 26.9, 25.9, 20.7, 20.5; MS m/z 250(M⁺), 208(100), 177(15); HRMS m/z observed 250.15686 (M⁺), calcd for C₁₅H₂₂O₃ 250.15688.

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-2-bromoacetoxy-3-oxabicyclo[4.3.1]decane (99). A solution of 98 (29 mg, 0.14 mmol), 4-(N,N-dimethylamino)pyridine (18 mg, 0.14 mmol) and pyridine (40 µL, 0.40 mmol) in methylene chloride (1.5 mL) was treated with α-bromoacetyl bromide (18 µL, 0.28 mmol) dropwise under an argon atmosphere. The mixture was stirred for 45 min. at room temperature then diluted with diethyl ether (10 mL) and washed with saturated aqueous cupric sulfate (3 X 2 mL), saturated aqueous sodium bicarbonate (1 X 2 mL) and dried over anhydrous sodium sulfate. Removal of the solvent gave 40 mg (86%) of 99 as a yellow oil. This compound was unstable on silica gel but was homogeneous by proton NMR: IR (neat) 2946, 2867, 1753, 1727, 1467, 1401, 1285, 1164 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 5.62 (d, J=7Hz, 1H), 4.88 (d, J=2Hz, 1H), 4.79 (d, J=2Hz, 1H), 3.96 (s, 1H), 3.95 (s, 1H), 2.63 (bm, 1H), 2.44 (dt, J=4,19Hz, 1H), 2.24 (m, 1H), 2.12 (t, J=9Hz, 1H), 1.82 (m, 4H), 1.65 (bm, 1H), 1.22 (m, 1H), 0.96 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 204.1, 166.9, 145.8, 114.6, 79.9, 50.7, 43.7, 38.1, 34.7, 28.9, 27.4, 26.8, 25.9, 25.4, 20.4.
(±)-(1α,6α)-7,7-Dimethyl-10-methylene-2-dimethylphosphonoacetoxy-3-oxabicyclo[4.3.1]decane (100). A solution of 98 (49 mg, 0.24 mmol), 4-(N,N-dimethylamino)pyridine (29 mg, 0.24 mmol) and pyridine (38 µL, 0.39 mmol) in dry methylene chloride (5.5 mL) was treated with a solution of dimethylphosphonoacetyl chloride (100 mg, 0.54 mmol) in methylene chloride (0.4 mL) dropwise under argon. After stirring for 3 h at ambient temperature the mixture was cooncentrated then dissolved in diethyl ether (15 mL) and washed with saturated aqueous cupric sulfate (3 X 2 mL), saturated aqueous sodium chloride (1 X 2 mL) and dried over anhydrous sodium sulfate. Chromatography of the concentrate (7 g silica gel 60, ethyl acetate-hexane 1:3 to neat ethyl acetate) yielded 67 mg (78%) of 100 as a viscous oil: IR (neat) 3475, 2966, 1745, 1724, 1649, 1307, 1055, 807 cm⁻¹; ¹H-NMR (300MHz, CDCl₃) δ 5.63 (d, J=7Hz, 1H), 4.88 (d, J=2Hz, 1H), 4.79 (d, J=2Hz, 1H), 3.83 (d, J2p=11Hz, 6H), 3.10 (dd, J₉₈=15Hz, 2H), 2.61 (bt, 1H), 2.43 (dt, J=19, 3Hz, 1H), 2.22 (m, 1H), 2.11 (bt, J=9Hz, 1H), 1.85 (m, 4H), 1.69 (m, 1H), 1.25 (bd, J=11Hz), 0.96 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃) δ 204.3, 165.3, 145.9, 114.5, 79.4, 53.3, 53.2, 53.1, 53.0, 50.7, 43.8, 38.2, 34.7, 33.8, 31.9, 29.0, 27.4, 26.9, 25.9, 20.4; MS m/z 358(4), 208(29), 190(21), 151(100), 109(26); HRMS m/z observed 358.15450 (M⁺), calcd for C₁₇H₂₇O₆P 358.15451

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-2,3-dihydroxy-3-(2-trimethylsilylethynyl)bicyclo[4.3.1]decane (108). A solution of trimethylsilyl acetylene (0.51 mL, 3.6 mmol) in THF (4.8 mL) was cooled to 0°C under argon and treated dropwise with a 1.59 M hexane solution of n-butyllithium (2.23 mL, 3.6 mmol). The resulting solution was stirred for 1h at
0°C. To this was added a solution of 98 (125 mg, 0.60 mmol) in dry THF (1 mL) and the cooling bath was removed. The resulting mixture was stirred for 1 h then quenched at -5°C by the addition of saturated aqueous ammonium chloride (1.5 mL) and diethyl ether (5 mL). The layers were separated, the aqueous layer was extracted with diethyl ether (6 X 2.5 mL) and the combined organic extracts were dried over sodium sulfate-magnesium sulfate. Chromatography of the concentrate (20 g silica gel 60, ethyl acetate-hexane 1:5) afforded 158 mg (86%) of 108, and 4 mg of TMS-deprotected 109 as a colorless solid: mp (hexane) 84-85°C; IR (neat) 3422(b), 2955, 2167, 1642, 845 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 4.88 (d, J=2Hz, 1H), 4.76 (d, J=2Hz, 1H), 3.75 (t, J=6Hz, 1H, collapses to d upon D₂O exchange), 2.95 (s, 1H, exchanges with D₂O), 1.82 (m, 8H), 1.05 (b, 1H), 0.89 (s, 3H), 0.86 (s, 3H), 0.16 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃) δ 148.7, 113.8, 108.3, 89.3, 74.0, 51.8, 45.7, 35.9, 34.9, 30.2, 29.7, 27.8, 27.5, 25.9, 22.0, 0.0 (3); MS m/z 306 (m⁺), 291 (7), 270 (8), 194 (19), 165 (19), 73 (100); HRMS m/z observed 306.20113 (M⁺), calcd for C₁₈H₃₀SiO₂ 306.20113.

(±)-(1α,6α)-7,7-Dimethyl-10-methylene-2,3-dihydroxy-3-ethynyl-bicyclo[4.3.1]decane (109). A solution of 108 (15.5 mg, 0.066 mmol) and anhydrous potassium carbonate (21 mg, 0.153 mmol) in methanol (1 mL) was stirred at ambient temperature for 14 h. The mixture was concentrated and the residue was dissolved in diethyl ether (3 mL). Saturated aqueous ammonium chloride (0.25 mL) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (5 X 3 mL) and the combined organic extracts were dried over sodium sulfate-magnesium sulfate. Concentration and chromatography (1 g silica gel 60, ethyl acetate-hexane 1:6) gave 11 mg (94%) of 109 as a colorless solid: mp
(hexanes) 112-112.5°C; IR (KBr), 3369(b), 3309(s), 2932, 2366, 1649, 1011, 878 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.90 (d, J=2Hz, 1H), 4.74 (d, J=2Hz, 1H), 3.82 (bt, 1H), 2.87 (s, 1H), 2.50 (bm, s, 2H), 2.37 (bd, J=4Hz, 1H), 2.22 (m, J=4.5 Hz, 1H), 2.01 (t, J=9Hz, 1H), 1.80 (m, 4H), 1.62 (m, 2H), 1.09 (bm, 1H), 0.89 (s, 3H), 0.87 (s, 3H); \(^1\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) 149.1, 113.4, 87.5, 76.3, 73.7, 72.2, 51.9, 46.7, 36.8, 35.0, 30.1, 27.7, 27.6, 26.5, 21.9; MS m/z 234 (M\(^+\)), 219 (6), 198 (19), 173 (41), 121 (81), 41 (100); HRMS m/z observed 234.16185 (M\(^+\)), calcd for C\(_{15}\)H\(_{22}\)O\(_2\) 234.16185. Anal. calcd for C\(_{15}\)H\(_{22}\)O\(_2\); C, 76.88; H, 9.46. Found; C, 76.62; H, 9.69.

**Cyclic Carbonate 110.** To a solution of 109 (16 mg, 0.068 mmol) in methylene chloride (0.75 mL) was added triethylamine (36 µL, 0.272 mmol) and bis(trichloromethyl)carbonate (40 mg, 0.136 mmol) and the mixture was stirred under argon at ambient temperature for 20 h. The solution was concentrated and the residue was purified by chromatography (silica gel 60, ethyl acetate-hexane 1:5) to give 17.3 mg (98%) of 110 as a colorless glass: mp (hexane) 105°C; IR (neat) 3262, 2944, 2127, 1808, 1213, 1040 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.04 (d, J=2Hz, 1H), 4.88 (d, J=2Hz, 1H), 4.58 (d, J=1Hz, 1H), 2.97 (bd, J=9Hz, 1H), 2.84 (s, 1H), 2.18 (m, 2H), 1.95 (m, 2H), 1.80 (m, 2H), 1.63 (m, 2H), 1.15 (dd, J=13, 8Hz, 1H) 0.95 (s, 3H), 0.89 (s, 3H); \(^1\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.7, 142.7, 117.8, 87.8, 83.0, 50.6, 41.2, 34.1, 32.3, 30.6, 27.7, 27.2, 25.0(2), 21.2; MS m/z 260 (5), 160(14), 130(32), 69(100); HRMS m/z observed 260.14120 (M\(^+\)), calcd for C\(_{16}\)H\(_{20}\)O\(_3\) 260.14119.

Compound 101 crystallized from hexane in space group P2\(_1\)/c with a=8.184(1) Å, b=11.266(3) Å, c=15.735(2) Å, \(\beta\)=93.26(2)°, z=4 and \(d_{calc}\) = 1.19 g/cm\(^3\). The intensity data were measured on a Rigaku AFC6R
diffractometer (Mo Kα radiation). There were 1130 observed reflections [I > 3.00σ(I)] and the structure was solved by direct methods. The final discrepancy indices were R=0.046 and Rw=0.049. The data was collected and the structure solved by Dr. Alan T. Johnson.

(±)-2,3-Dihydropallescensin D (82). To a solution of 109 (19.4 mg, 0.083 mmol) in 1,4-dioxane (0.4 mL) was added mercuric sulfate (20 mg, 0.066 mmol) and 2 N aqueous sulfuric acid (0.32 mL) and the resulting mixture was stirred for 14 h at 32°C. The mixture was then diluted with diethyl ether (4 mL) and neutralized with saturated aqueous sodium bicarbonate. The layers were separated, the aqueous layer was extracted with diethyl ether (5 X 3 mL) and the combined organic extracts were dried over magnesium sulfate. Chromatography of the concentrate (1.5 g silica gel 60, diethyl ether-pentane 1:8) furnished 11 mg (62%) of 82 as a fragrant oil: IR (neat) 3070, 2931, 2874, 1649, 1453, 1164, 1071, 890, 730 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 7.16 (d, J=2Hz, 1H), 6.08 (d, J=2Hz, 1H), 4.90 (d, J=2Hz, 1H), 4.76 (d, J=2Hz, 1H), 3.69 (bt, 1H), 2.45 (m, 2H), 2.24 (t, J=7Hz, 1H), 1.85 (m, 4H), 1.56 (m, 1H), 1.02 (bd, 1H), 0.95 (s, 3H), 0.94 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 151.9, 148.4, 139.1, 121.4, 112.4(2), 51.8, 42.7, 34.4, 30.6, 30.2, 27.9, 27.8, 27.7, 22.4; MS m/z 216 (M⁺) 196 (35), 163 (28), 120 (32), 81 (71), 71 (100); HRMS m/z observed 216.15140 (M⁺), cacld for C₁₅H₂₀O. 216.15140. Anal. calcd for C₁₅H₂₀O: C, 83.28, H, 9.32. Found: C, 82.94; H, 9.34.
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68, 14.

Introduction

The novel sulfur-containing alkaloids prianosins A (1), B (2), C (3), and D (4) were isolated from the Okinawan marine sponge *Prianos melanos* by Kobayashi and co-workers (Figure 2).¹,² Prianosins A, C and D were also reported independently by Blunt and Munro³,⁴ from three sponge species of the genus *Latrunculia* du Bocage and given the names discorhabdin A, 2-hydroxydiscorhabdin D and discorhabdin D, respectively. Discorhabdins B (5) and C (6) were obtained only from the *Latrunculia* species.⁵

![Chemical structures of Prianosins and Discorhabdins](image)

**Figure 2:** The Prianosin and Discorhabdin Alkaloids.
These alkaloids display significant cytotoxicity against several murine cancer cell lines \textit{in vitro} and \textit{in vivo} (Table 1) as well as antimicrobial activity (Table 2). In addition to these properties, 1 and 4 induce Ca\textsuperscript{2+} release from sarcoplasm reticulum, which causes contraction of smooth muscle tissues. They are ten times more potent than caffeine in this assay.\textsuperscript{6} The mode of action of these systems is presently unknown but is under active investigation.\textsuperscript{4}

\textbf{Table 1.} Cytotoxicity profile of the prianosins and discorhabdins.

<table>
<thead>
<tr>
<th>Antiviral activity</th>
<th>P-388 \textit{in vivo} ED\textsubscript{50}</th>
<th>P-388 \textit{in vivo} T/C</th>
<th>L1210 IC\textsubscript{50}</th>
<th>L5178Y IC\textsubscript{50}</th>
<th>Human epiderm. carcinoma KB IC\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>0.05</td>
<td>Toxic</td>
<td>0.037</td>
<td>0.014</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
<td>0.024</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>132%</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>0.1</td>
<td>117%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>0.03</td>
<td>Toxic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textit{In vitro} assays unless indicated otherwise; IC\textsubscript{50} values in \(\mu\text{g/mL}\).

\textbf{Table 2.} Antimicrobial activity of the prianosins and discorhabdins.

<table>
<thead>
<tr>
<th>\textit{Escherichia coli}</th>
<th>\textit{Bacillus subtilis}</th>
<th>\textit{Candida albicans}</th>
<th>\textit{Pseudomonas aeruginosa}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

(+)=Active, (-)=Inactive
The structures of 1 and 6, including the absolute configuration of the former, were secured by single crystal X-ray crystallographic analyses. The crystallographic residue for 1 was 0.039 and the enantiomer was refined to 0.046, and the molecular parameters were also fully consistent with the tautomeric form indicated. The structures of the remaining prianosins and discorhabdins are based on spectroscopic similarities to 1 and 6.

The biogenetic origins of these alkaloids are currently a matter of speculation. It has been suggested that their biogenesis may involve coupling of derivatives of tyramine (7) (C1 to C8, N9) and tryptamine (8) (C-10 to C-21, N-13 and N-18) (Scheme 1). Isolation of 9 from another sponge species lends support to this argument.7

Scheme 1

The prianosin-discorhabdin alkaloids represent the first documented example of the unusual pyrollo[1,7]phenanthroline skeleton in nature. Subsequent to their discovery two additional cytotoxic-antimicrobial pyrolloiminoquinone marine alkaloids have been reported. These are the
isobatzellines (10), from the Caribbean sponge Batzella sp., and wakayin (11) from the ascidian Clavelina sp. Numerous biologically active polycyclic iminoquinone-containing aromatics, of which diplamine (12) from the marine tunicate Diplosoma sp. is representative, have been identified.

The novel molecular frameworks and wide range of biological activities of the prianosins and discorhabdins have kindled significant interest in their synthesis. Although several approaches to these molecules have been reported, only two have culminated in total syntheses thus far. A review of the synthetic literature reveals several strategic parallels in approaches to these molecules (Scheme 2).
All but one research group chose to install the spiroenone moiety (generating rings A and B) via oxidative phenolic coupling of a suitable acyclic precursor such as 15. Confalone and co-workers demonstrated that an alternative strategy employing intramolecular phenolate anion alkylation (13) is synthetically viable. Various approaches to the tricyclic iminoquinone nucleus are discussed in more detail later.

The first total synthesis of a member of the prianosin-discorhabdin family was that of discorhabdin C (6) reported by Yamamura and co-workers. Starting from the differentially protected diaminobenzene derivative 17, prepared in six steps from 16, the indole 19 was generated in good yield utilizing a Bischler indolization protocol with ethyl 4-chloroacetoacetate (Scheme 3). Installation of ring D was then achieved through intramolecular amide formation between the pendant acetate and the arylamino group of 19 in modest yield. Reduction of the lactam carbonyl, followed by oxidation with ceric ammonium nitrate, yielded the unstable quinone imine 22. The phenolic side chain for oxidative coupling was then incorporated by addition of 3,5-dibromotyramine to 22 with elimination of methanol. Anodic oxidation of 24 at a constant current provided N-benzyl discorhabdin C (26) and the ring expanded product 27 in yields of 19 and 9%, respectively. The indole N-benzyl group was found resistant to removal and the natural product was ultimately obtained through a similar sequence employing the N-1 unprotected intermediates (21-25) as indicated.
The dienone-phenol rearranged products 27 and 28 are believed to be an artifact of the slightly acidic conditions of the anodic oxidation and a mechanism describing their formation was proposed (Scheme 4).\textsuperscript{15}
Scheme 4

In this scheme, activation of the dienone carbonyl of 31 by proton transfer initiates intramolecular conjugate addition giving cyclopropane derivative 32. Proton loss and bond reorganization yields the azacycloheptanes 27 and 28. Oxidative coupling studies on a similar system 33 with thallium (III) salts provided comparable yields of dienone and rearranged phenol. It was found that both the trinitrate and trifluoroacetate salts generated greater amounts of the rearranged product and, in the latter case, the ring-expanded material was the only isolated product in 14% yield. The authors suggest that the increased amount of rearranged material may be a reflection of the acidic nature of these reagents.

Similar complications with dienone-phenol rearrangement were encountered by Kita and co-workers during studies of the oxidative
spirocyclization using the hypervalent iodine reagent phenyiodosyl bistrifluoroacetate (PIFA) in 2,2,2-trifluoroethanol (Scheme 5).\textsuperscript{16,17}

They found that oxidation of free phenol 34 gave the desired product 37 only in low yield. Oxidation of methyl ether 35 and trimethylsilyl ether 36 under the same conditions produced the desired dienone 37 in 31% and 86% yields. However, the dienone-phenol rearranged products 38 and 39 were obtained in equal amounts (~26%) along with 37 during the oxidation of 35. These results were rationalized by formation of oxonium ions 42 and 43. \textit{Ipsos} displacement of the R group is believed to occur readily when R= trimethylsilyl (42) to give 37 as the major product, but attack occurs at a much slower rate when R= methyl (43) and consequently the dienone-
phenol rearrangement pathway predominates. Lewis acid-promoted conversion of 37 to 40 was offered in support of such an activated intermediate.

Kita has applied this methodology to a total synthesis of discorhabdin C (6) (Scheme 6).\textsuperscript{13} The indole ring of discorhabdin C was generated using known chemistry of vinyl azides.\textsuperscript{18} The 2-trimethylsilylethoxycarbonyl (TEOC) protected 2-aminoethyl group required for formation of the E-ring was installed in five linear steps, after decarboxylation, to give tryptamine derivative 47. Fremy's salt oxidation yielded indoloquinone 48 which, with the 6-position activated, underwent addition-elimination with dibromotyramine to give the spirocyclization precursor 49. Protection of the latter as its trimethylsilyl ether, followed by oxidation with PIFA, yielded 50 with the ABCD polycyclic structure of the natural product. At this stage, these workers discovered, as did Yamamura,\textsuperscript{15} that the ring building sequence ABCD and finally E is not a viable approach. The failure of the cyclodehydration of 50 to 6 is presumably a consequence of the diminished ketonic nature of the carbonyl which, after addition of the aryl amine, is part of a vinylogous amide function. An alternative construction sequence of CDE then AB was therefore investigated where it was found that the putative indoloquinone imine intermediate 51, from acid-catalyzed intramolecular cyclization, underwent addition of dibromotyramine; rings A and B could now be successfully annealed by the action of the PIFA reagent.
(i) Xylene, reflux; (ii) KOH, EtOH, reflux; (iii) Cu-chromite, quinoline, 215°C; (iv) CH$_2$=N$^+$Me$_2$$^-$, CH$_2$Cl$_2$, rt; (v) Mel, 0°C; (vi) NaCN, H$_2$O, 80°C; (vii) H$_2$, RanNi, NH$_3$, EtOH, 3.3 atm; (viii) p-O$_2$N-C$_6$H$_4$OCO$_2$(CH$_2$)$_2$SiMe$_3$, NaOEt, EtOH, 0°C; (ix) H$_2$, 10%Pd-C, EtOH, 3.3 atm; (x) Fremy's salt, KH$_2$PO$_4$, acetone-H$_2$O; (xi) 3,5-Dibromotyramine HBr, Et$_3$N, EtOH, reflux; (xii) MeCH=CN(OMe)-(OSiMe$_3$)$_2$, CH$_2$Cl$_2$, rt; (xiii) Phl(OCOCF$_3$)$_2$, CF$_3$CH$_2$OH, rt; (xiv) TsCl, t-BuOK, THF; (xv) TsOH, MeCN; (xvi) 3,5-Dibromotyramine, NaHCO$_3$, EtOH, reflux.

Scheme 6
Radically different approaches toward the spirodienone and indole moieties of the discorhabdins have been adopted by Confalone.\textsuperscript{14,19} In the first approach, the highly substituted indole unit was constructed using previously described azidocinnamate\textsuperscript{18} chemistry (Scheme 7). The 5-phenol group required for elaboration into the spiroenone by intramolecular phenolate alkylation (Scheme 2) was installed by the palladium-mediated phenylboronic acid coupling of 54 to 55, described by Suzuki.\textsuperscript{20} Decarboxylation and Vilsmeier reaction effected transposition of the indole 2,3-functionalities giving the indole-3-carboxaldehyde 56 with the functionality needed for eventual formation of the E-ring. Oxidation, deprotection, and tribromination of 56 yielded the bromoquinone 57 which, after reprotaction, underwent addition with ethanolamine. Activation of this intermediate as its mesylate gave the spirocyclization precursor 58. Liberation of the free phenol of 58 and anion formation gave the phenolate alkylation adduct 59 containing the ABCD ring system of discorhabdin C (6) in modest yield. These workers envisage a complete synthesis through a sequence involving reduction of the 2-nitroethyl function of 61 and cyclodehydration as the final step. Selective reduction of the nitro group in the presence of several other, easily reduced functionalities and the fact that this ring closure has been reported to fail\textsuperscript{15,17} are problems to be overcome for a total synthesis of discorhabdin C via this current route.
(i) Xylene, 140°C; (ii) p-MOMOC₆H₄B(OH)₂, Pd(Ph₃P)₄, Na₂CO₃; (iii) NaOH; (iv) Cu, quinoline; (v) POC₃, DMF; (vi) (NH₄)₂Ce(NO₃)₆, MeCN; (vii) 6N HCl; (viii) Pyridine-Br₂-HBr; (ix) MOMCl, CH₂Cl₂; (x) HO(CH₂)₂NH₂, DMF; (xi) MsCl, py, CH₂Cl₂; (xii) 6N HCl, THF, H₂O; (xiii) t-BuOK, DMF; (xiv) MeNO₂, NH₄OAc, reflux; (xv) NaBH₄.

Scheme 7
The second approach described by Confalone\textsuperscript{19} is strategically identical with respect to the use of an intramolecular phenolate alkylation to generate the spirodienone unit. However, it differs by taking an entirely new route to the indole nucleus which involves some novel chemistry of squaric acid.\textsuperscript{21} Coupling of diisopropyl squarate (62) with a protected 4-lithio phenol derivative gave, after rearrangement with trifluoroacetic acid anhydride, the squaric acid derivative 64 (Scheme 8).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {62};
\node at (1.5,0) {63};
\node at (3,0) {64};
\node at (-3,0) {65};
\node at (-4.5,0) {66};
\node at (-6,0) {67};
\end{tikzpicture}
\end{center}

(i) \textit{p-BnOC}_{6}H_{4}Li, THF, -78°C; (ii) NH_{4}Cl, H_{2}O; (iii) CF_{3}CO_{2}O; (iv) 2-lithio-N-tosylpyrrole, THF, -78°C; (v) heat

**Scheme 8**

Attack at the more reactive carbonyl of 64 by 2-lithio-N-tosylpyrrole gave hydroxypyrrole derivative 65, which underwent thermal rearrangement to yield dihydroxyindole 66. A series of transformations similar to those already described (Schemes 6, 7) converted this intermediate to the substituted tryptamine salt 67. This route effectively circumvents any
problems associated with a late stage reduction to create the 2-aminoethyl substituent of the tryptamine. Further elaboration of intermediate 67 requires introduction of the ethanolamine side chain, phenolate alkylation, and cyclodehydration. The sequence in which steps are executed will determine the utility of this intermediate in a total synthesis.

Knölker described the use of a tricarbonyliron-complexed cyclohexadienyl cation in formation of the spiro AB ring system of the prianosins and discorhabdins. This novel method of spiroannelation involves electrophilic aromatic substitution of an arylamine 69 with the iron complexed cation 70, followed by intramolecular N-alkylation (Scheme 9).

\[
\begin{align*}
68 & \xrightarrow{\text{Synthetic Reagents and Conditions}} 69 + 70 \\
71 & + 72 \\
\end{align*}
\]

(i) NaH, Ac₂O; (ii) HNO₃, HOAc; (iii) H₂, Pd-C; (iv) MeCN, -20°C

Scheme 9

This process furnished in good yield the 3- and 1-azaspiro[5.5]undecanes 71 and 72 in a 1.5 to 1 ratio. The choice of an
indoline 69 rather than the indole required for the natural products is curious. The authors failed to discuss this point, nor did they comment on whether any experiments were performed using indole substrates.
Results and Discussion

Outlined in figure 2.1 is a retrosynthetic analysis of prianosin A (1). As others have recognized, it seemed reasonable that the spiroenone moiety of 1 and related alkaloids would be accessible by late-stage intramolecular oxidative phenolic coupling of an aryl amide such as 74 or a similar benzenoid derivative.

![Chemical structures](image)

**Figure 2.1:** Retrosynthetic Analysis of Prianosin A (1).

An expeditious route to the tetrahydrothiophene ring of 1 would invoke conversion of the precursor δ-lactam to thiolactam 73, followed by reduction to a thioaminal and 1,4-addition of the thiol group to the
bromodienone.\textsuperscript{23} As our first synthetic goal we chose to develop an efficient synthesis of the highly functionalized quinolinic indole 75 which, by substitution of the methoxyl group by an amine, or a functional equivalent at the quinone oxidation level would in principle provide access to the entire prianosin family, including the isobatzellines (10) and wakayin (11). In a notable departure from previous approaches to this system, we envisioned a synthesis of 75 which would hinge on oxidative coupling of the two amine functionalities present in 76 to the aromatic nucleus as key steps.

The cyclization of catecholamines to give 5,6-dihydroxyindoles under oxidative conditions is well precedented.\textsuperscript{24} These cyclizations typically proceed through formation of ortho-quinone 78, which undergoes conjugate addition of the pendant amino group followed by a second oxidation to give zwitterion 79 (Scheme 10). Known as aminochromes, species of this type rearrange under reducing conditions to give indoles, eg 80.

\begin{center}
\textbf{Scheme 10}
\end{center}

The scope of this method is limited by the high reactivity of the ortho-quinone intermediates, which often decompose by polymerization before yielding useful products when the cyclization is slow. This is particularly true for primary amines.\textsuperscript{24a} We attempted to extend these observations using hypervalent iodine oxidants, anticipating that a reaction between an iodine(III) reagent and the primary amine would render the nitrogen electrophilic and thus susceptible to attack by the activated aromatic ring.
Using methoxylated aromatics, such a process would produce a new heterocyclic ring without generating highly reactive ortho-quinone intermediates.

Kita and co-workers have reported studies along these lines using phenyliodosyl bistrifluoroacetate (PIFA). It was shown by this group that N-acyltyramines are converted to quinol ethers 82 or cyclohexadienones 83, depending on the reaction solvent (Scheme 11). In nucleophilic solvents, alcohols or acetic acid, the solvent was found to attack the aromatic ring para to the hydroxyl position to give 82. With a less nucleophilic polar solvent such as 2,2,2-trifluoroethanol, cyclization via the amido group occurs to give 83. When N-alkyl-N-benzoyl tyramines 84 (R1=Me,Et) were reacted under the latter conditions, N-heterocycles were obtained. With these substrates, the intermediate spirocyclohexadienones were converted to perhydroindolones 87 upon hydrolysis in approximately 50% yield. A mechanism was proposed for the formation of 87 which involves hydrolysis of 85 to give the nucleophilic secondary amine 86. The latter cyclizes through intramolecular 1,4-addition to the enone moiety.
In order to explore this strategy, a relatively short, efficient synthesis of the appropriately substituted aryl diamine was required. A review of the literature revealed several general approaches towards the synthesis of 1,4-diaminobutanes. Although some of these were potentially applicable to our objective, the unavailability of suitably substituted precursors and consequently the multi-step operations which would be necessary to reach the goal eliminated them. Utilization of succinonitrile derivative 90, reported by Crider and co-workers, in the synthetic plan appeared to be an attractive solution to the problem since reduction of both cyano groups would afford 76 directly. To this end, 90 was prepared by only minor modification to the published procedure (Scheme 13). Thus, commercially available 3,4-dimethoxybenzaldehyde (88) was subjected to a Knoevenagel reaction with ethyl cyanoacetate to afford 89 in excellent yield.
Exposure of 89 to sodium cyanide in a ternary solvent system containing chloroform, ethanol, and water resulted in hydrocyanation and decarboxylation to give 90 in a single operation in 82% yield after purification.

Scheme 13
Protocols for reducing the cyano groups of 90 employing catalytic hydrogenation were initially avoided since the preparative utility of this method is often limited by the production of undesired secondary amines. However, failure to effect this transformation with several hydride reducing agents forced reconsideration of this option. Gould and co-workers described the conversion of adiponitrile to the corresponding diacetamide in quantitative yield by hydrogenation with Raney nickel in acetic anhydride. Presumably, acetylation of the aldimine or amine products is rapid under these conditions and thus prohibits self-condensation and the formation of secondary amines. Encouraged by this report, a mixture of 90 in acetic anhydride was exposed to hydrogen over a palladium catalyst under moderate pressure to give two products which were separated by chromatography. It was clear from the 1H-NMR and IR spectra of the major product, obtained in 76% yield, that the reaction had not proceeded as expected. Instead of the anticipated three sets of methylene signals in the 1H-NMR spectrum, only two sets were apparent. A band at 2246 cm⁻¹ in the IR spectrum indicated that one of the cyano functions had survived the reaction conditions. On the basis of this evidence and single-frequency decoupling experiments, the major product was confidently assigned structure 92. Similar analysis led to the formulation of the minor product as the expected diacetamide 93 in 10% yield. Saturation of the remaining cyano group under the conditions described in scheme 13 was straightforward and afforded 94 in excellent yield. It is likely that the higher rate of reduction observed for the benzylic cyano group may reflect tautomerization to imide 91 prior to the addition of hydrogen. Although incomplete saturation of 90 necessitated a second reduction step, the
unexpected selectivity in hydrogenation provided a convenient means by which the two amino groups of 94 could be differentiated.

With an efficient synthesis of 94 in hand, it was pleasing to find that the first set of conditions investigated for oxidative cyclization, iodobenzene diacetate [PhI(OAc)₂] in 2,2,2-trifluoroethanol, produced a relatively clean reaction (Scheme 15). Other conditions were studied but it was found that replacing 2,2,2-trifluoroethanol with methylene chloride or ethanol resulted in resinous products. Similarly, complex mixtures were obtained from the reaction of 94 with phenyliodosyl bistrifluoroacetate in 2,2,2-trifluoroethanol.

The structure of the oxidation product was not easily assigned from spectroscopic data. The ¹H-NMR and ¹³C-NMR spectra of the product were unexpectedly complex and there was no apparent molecular ion in the mass
spectrum. It seemed reasonable to presume on mechanistic grounds, (Scheme 14), that the oxidation product was the desired tetrahydroquinoline 97 and that the complexity of the NMR spectra was due to acetamide rotamers. However, the product exhibited some uncharacteristic physical properties for this structural assignment. For example, after purification by chromatography, it rapidly decomposed upon standing to give a complex mixture of products. Furthermore, attempts to acylate the aniline nitrogen or

![Scheme 15](image)

Scheme 15

to cleave the N-acetyl group resulted in destruction of the starting material. Finally, the initial oxidation product was treated with lithium aluminum hydride in the belief that reduction of the N-acetyl group to a secondary amine would allow derivatization and conclusive structural assignment. Surprisingly, upon reduction, a product was obtained which had spectral
properties more consistent with the structure 97. It was also found that the same product was obtained from catalytic hydrogenation of the oxidation product. From these results, and the fact that two equivalents of Phl(OAc)$_2$ were required for complete conversion of 94, bicyclic hydrazide 99 was considered to be a possible candidate for the oxidation product. Mechanistically, the requirement for two equivalents of oxidant could be rationalized by formation of a second iodine(III)-nitrogen intermediate 98 which is trapped internally by the acetamide nitrogen. Furthermore, the conversion of 99 to 97 with lithium aluminum hydride and by catalytic hydrogenation accorded well with the known cleavage of nitrogen-nitrogen bonds by reducing agents. However, without direct physical evidence for a nitrogen-nitrogen bond this assignment remained somewhat tenuous. It was a report by Barret and Dauden describing the conversion of sulfonamide 102a to quinone imide ketal 102b by iodine(III) in methanol, (scheme 16), which prompted reconsideration of our structural conclusions. The evidence can now be seen to clearly support 100 as the oxidation product.

The presence of a 2,2,2-trifluoroethoxy group was supported by a complex set of signals at $\delta$ 61.6 ppm in the $^{13}$C-NMR spectrum and, although no molecular ion for 100 was apparent, a fragment corresponding to loss of the 2,2,2-trifluoroethoxy substituent ($m/z$ 264) was visible in the
mass spectrum.\textsuperscript{32} The presence of this group was subsequently confirmed by a signal in the $^{19}$F-NMR (triplet, $J_{FH}=9\text{Hz}$) and allowed confident assignment of the oxidation product derived from 94 as the mixed ketal 100. It follows that the complex NMR spectra are a direct result of epimers at the quinol ether carbon. The identity of the hydrogenation product from 100 was verified as 97 by means of an X-ray crystallographic analysis of the crystalline $p$-toluenesulfonamide 101. An ORTEP plot of 101 is shown in figure 2.2 which confirms the expected regiochemistry of the cyclization and reveals a trans relationship between the acetamidomethyl and $p$-toluenesulfonyl groups.

\textbf{Figure 2.2:} ORTEP Diagram from X-ray Analysis of 101.

A plausible mechanism by which 100 is formed is outlined in scheme 17. The iodine(III) intermediate 95 would be expected to form first since
aminoalkyl groups are known to oxidize faster than methoxy substituted benzene derivatives. Nucleophilic displacement of iodobenzene from 95 by the aromatic ring would give cation 96, which would rearomatize by loss of a proton to yield 97. In a comparatively fast step, a second nitrogen-
iodine(III) intermediate 98 could form which would be followed by oxidation of the aromatic nucleus to an iminoquinone species 103 and trapping with 2,2,2-trifluoroethanol to give 100. The first step in this sequence is believed to be reversible and rate-limiting, with subsequent steps relatively fast. This is supported by the observation that one equivalent of the iodine(III) reagent generates an equimolar mixture of 100 and recovered 94. The conversion of 97 back to 100 upon treatment with one equivalent of iodobenzene diacetate confirms, albeit not directly, the involvement of 97 in this process. Additional credence for the penultimate step in this mechanism is lent by the observations of Barret and Dauden mentioned previously.

The scope of this cyclization was briefly explored using substrates 104 and 76, prepared in the straightforward manner indicated in scheme 18.

![Scheme 18](image)

It was anticipated that the N-benzylamine derivative 104, after cyclization with PhI(OAc)₂, would resist further oxidation and afford directly a
protected tetrahydroquinoline. This compound failed to cyclize, however. It is presumed that this is due to competitive oxidation at the N-α-methylene carbons as indicated by the absence of these proton signals in the $^1$H-NMR spectra of the crude reaction mixture. Experiments using 76 were conducted to test the feasibility of a double annelation process, but these were equally unrewarding and also gave intractable reaction mixtures. Although the inherent regiochemical problems associated with cyclization of 76 were recognized, a successful reaction would have provided 106 and the tricyclic core of the prianosins and discorhabdins in a single operation.

With 96 in hand, methods for effecting closure of the indoline ring of 106 were examined. Encouraged by the initial success with Phl(OAc)$_2$, the acetamide group of 97 was removed by acidic hydrolysis in preparation for attempted cyclization (Scheme 19). Unfortunately, compound 107 failed to cyclize under the conditions studied, apparently due to complications arising from the two reactive functional groups.
Before embarking on laborious protection-deprotection sequences, cyclization at the quinonoid oxidation level, as described earlier (see Schemes 10 and 12) and supported by Boger and co-workers, was explored.\textsuperscript{33} To this end, 97 was converted to the somewhat unstable quinone imine 108 using ceric ammonium nitrate (CAN) in aqueous acetonitrile as prescribed by Yamamura (Scheme 19).\textsuperscript{12} However, 108 did not cyclize by intramolecular addition of the amide nitrogen as hoped. Attempts to increase the nucleophilicity of the amide group by deprotonation resulted in formation of quinoline derivative 109. This compound is most likely produced by an oxidation cascade initiated by abstraction of the γ-proton indicated and terminated by oxidation with molecular oxygen.

In an attempt to overcome the problem of competing deprotonation in 108, the acidity of the amide nitrogen proton was increased by conversion to benzenesulfonamide 110 (Scheme 20). The latter, isolated in 15% yield...
along with 112 (40%) and 113 (39%) from the reaction of 107 with benzenesulfonyl chloride, was cleanly oxidized by CAN, but again underwent enolization and further oxidation to give the quinoline 111 when treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The difficulty in obtaining sufficient amounts of 110 and the proclivity for quinoline formation preempted further investigations along these lines.

![Scheme 20](image)

110 $R_1=H, R_2=SO_2Ph$
112 $R_1=SO_2Ph, R_2=H$
113 $R_1=R_2=SO_2Ph$

**Scheme 20**

As an alternative to augmenting the nucleophilicity of the amide function, a plan was investigated to increase the electrophilicity of the enimine system of 108 by formation of a quaternary salt 114 with methyl chloroformate. However, prolonged (20 hours) exposure of 108 to methyl chloroformate gave, in addition to aromatized material, the chlorinated tetrahydroquinoline derivative 115. Examination of the 300MHz $^1$H-NMR spectrum of 115 revealed only one aromatic signal at $\delta$ 7.33, appearing as a singlet, in addition to the phenol hydrogen signal which appeared as a singlet at $\delta$ 6.00 that was exchangeable with deuterium oxide. A band at 1689cm$^{-1}$ in the IR spectrum indicated a urethane group on nitrogen. The presence of a chlorine atom in 115 was confirmed by its mass spectrum which showed a molecular ion peak ($m/z$ 342, M$^+$) and a $^{37}$chlorine isotope
peak (m/z 344, M+2) that was approximately 30% the intensity of the molecular ion. This result suggests that the enimine system had indeed been activated toward nucleophilic addition but that addition from an external source rather than intramolecular delivery had prevailed. Apparently the favorable geometry of 5-membered ring closure does not overcome the unfavorable stereoelectronic effect predicted for a 5-endo-trig cyclization.\(^{34}\)

![Image of chemical structures](image)

The failure to effect cyclization with tetrahydroquinoline 97 and its congeners mandated changes to the original plan. From a reexamination of our strategy it was concluded that the benzene substitution pattern required for cyclization and further synthetic elaboration would not easily accommodate modifications, and an alternative plan was therefore devised. In particular, a desirable approach to 75 would develop intermediates which would allow further exploration of the iodine(III) cyclization and which would be amenable to modification late in the synthetic sequence. A strategy which appeared to meet these requirements is outlined below in retrosynthetic form (Scheme 21).
A pivotal intermediate along this route would be the substituted indole 117, which we anticipated would allow us to explore several options for closing the tetrahydroquinoline ring of 116. One tactic would entail conversion of the tosylate group of 117 to a primary amine, which would provide the precursor for cyclization with Phl(OAc)$_2$. Conversely, introduction of an amino group at the 4-position of 117 would precede cyclization through direct nucleophilic displacement of the pendant tosylate functionality. It was believed that indole 117 could be obtained from sulfonylation of the tryptophol obtained by Fischer cyclization of hydrazone 118. The functionality present in 118 would obviate the need for lengthy synthetic elaboration at the indole 3-position.$^{35}$

The disubstituted aniline and hydrazine needed for the synthesis of 118 have been reported in the literature. Mauthner prepared 2,3-dimethoxyaniline via a Hoffmann reaction of 2,3-dimethoxybenzamide in less than 40% yield.$^{36}$ Although this intermediate was called for in the early stages of the synthesis, a search for a more efficient route starting from 2,3-dimethoxybenzoic acid (119) was initiated (Scheme 22).
Yamada and co-workers reported excellent conversions of benzoic acids to urethanes in a one-step procedure utilizing diphenylphosphoryl azide.\textsuperscript{37} This modified Curtius reaction\textsuperscript{38} of acyl azides avoids the harsh reaction conditions and multi-step sequences of the Hoffmann and Schmidt protocols. Furthermore, by using \textit{t}-butanol as the solvent, the Yamada method gives directly \textit{t}-butoxycarbonyl (BOC) protected anilines. Conversion of 119 to a \textit{t}-butyl urethane was appealing for the reason that the BOC group would be cleaved by acid in the subsequent diazotization, thus eliminating a separate hydrolytic step. To this end, a solution of 119 in \textit{t}-
butanol was heated at 55°C with diphenylphosphoryl azide in the presence of triethylamine. However, instead of the desired BOC derivative, only urea 123 was obtained which was readily identified by ¹H-NMR and ¹³C-NMR spectroscopy. In particular, no t-butyl group was evident and in the ¹H-NMR spectrum the urea hydrogen was clearly visible as broad singlet at δ 7.30 ppm. The formation of ureas along with the desired amine is known to be a limiting side reaction during direct hydrolysis of isocyanates. Apparently with 119, the steric requirement of the ortho-methoxy group makes addition of t-butanol to the isocyanate 120 slow and allows hydrolysis to a carbamic acid 121. The latter species undergoes decarboxylation to give the aniline 122 which reacts with an isocyanate to produce the urea 123. This problem was readily circumvented by simply replacing t-butanol with ethanol and heating the reaction mixture until nitrogen gas ceased to evolve (Scheme 23). This method afforded urethane 124 in quantitative yield. After appropriate characterization, 124 was used without purification and subjected to basic hydrolysis to give 2,3-dimethoxyaniline (122) in 91% yield.

Scheme 23
yield after purification.

The procedure described above is far superior to the Hoffmann reaction reported by Mauthner, and furnished 122 in multi-gram quantities. With minor modification to the published procedure, 122 was treated with sodium nitrite and the crude diazonium salt was reduced using excess stannous chloride in concentrated hydrochloric acid. Upon neutralization, hydrazine 123 was obtained in 73% yield as a yellow crystalline solid.\textsuperscript{39}

The hydrazone required for Fischer cyclization was next prepared according to Scheme 24. Thus, hydrazine 125 was treated with gaseous hydrogen chloride in methanol, the mixture was concentrated, and the residual solid was reacted with 2,3-dihydrofuran in aqueous tetrahydrofuran\textsuperscript{40} to give 118 and 126 in approximately equal amounts. The two components of the mixture were separated by chromatography, and the more polar constituent was characterized as the hydrazone 118. In addition to satisfactory $^{13}$C-NMR, IR and mass spectral properties, 118 possessed a hydrazone hydrogen, evident in the $^1$H-NMR spectrum as a triplet at $\delta$ 7.20 (J=5Hz) that was coupled to a doublet of triplets at $\delta$ 2.41 (J=5,7Hz). A less polar material, which was slowly converted to 118 on silica gel or on standing at room temperature, was assigned the cyclic aminal structure 126. The $^1$H-NMR spectrum of this material revealed a multiplet at $\delta$ 5.10 ppm for the aminal proton instead of the olefinic signal at $\delta$ 7.20 that was characteristic of 118. Although 118 could be obtained in nearly homogeneous form for characterization purposes, it was found that both components of the mixture of 118 and 126 underwent Fischer cyclization, thereby precluding the need for separation. Thus, when a mixture of 118 and 126 in t-butanol was heated at 82°C with anhydrous zinc chloride, indole 127 was formed as the major product contaminated by
10-15% of 4-methoxy indole 128. The latter was characterized as its derivative 129. The yield and reliability of the Fischer cyclization proved to be somewhat disappointing, typically giving 127 in the 40% range after purification. Unfortunately, attempts to optimize the yield of 127 and suppress the formation of 126 were unrewarding. Tryptophol 127 was found to be unstable and decomposed during purification.

Losses incurred during the indolization step were best minimized by sulfonylating the partially purified mixture of indoles (Scheme 25). Thus, the indole mixture and p-toluenesulfonyl chloride in tetrahydrofuran at 0°C was treated with sodium hydride and then warmed to ambient temperature. This gave 117 in 65% yield after chromatography. In preparation for cyclization, 117 was converted to the tryptamine derivative 131 in 72% overall yield by
displacement of the tosylate group with azide ion in N,N-dimethylformamide, followed by mild reduction of the azide group of 130 with triphenylphosphine in aqueous tetrahydrofuran.\textsuperscript{41}

\[
\begin{align*}
127 + 128 & \xrightarrow{\text{TsCl, THF}} \xrightarrow{\text{NaH, 0° to 25°C}} \text{117} \\
& \quad \xrightarrow{\text{NaN_3, DMF}} \xrightarrow{50°C} \text{130} \\
& \quad \xrightarrow{\text{Ph_3P, H_2O}} \text{131} \\
& \quad \xrightarrow{\text{THF, 25°C}} \text{129}
\end{align*}
\]

Scheme 25

Having successfully implemented the first stage of this new approach, 131 was then subjected to the oxidative cyclization protocol using iodobenzene diacetate. Unfortunately, this reagent produced an intractable reaction mass in which no detectable cyclization product could be identified. Although examination of the crude mixture did not disclose the nature of the oxidation products formed, it is reasonable to assume that the electron-rich indole nucleus of 131 suffered preferential oxidation with the iodine(III) reagent.
An alternative stratagem for constructing the tetrahydroquinoline ring of 116 would entail an intramolecular displacement of the tosylate group by an amino function located at the 4-position of the indole ring. It was believed that the amino substituent required for this plan could be installed by nitration at the 4-position of 117, followed by reduction of the nitro group to an amine. It has been demonstrated by Nakatsuka and co-workers\textsuperscript{42} that acetyl nitrate\textsuperscript{43} can be a useful reagent for selectively nitrating at the 4-position of indoles. However, the reaction of 117 with this reagent in acetic anhydride at low temperature was considerably less selective and gave 4- and 2-nitro indoles 132 and 133 in 45% and 39% yield, respectively, after separation by chromatography (Scheme 26).

Formulation of the major product as 132 was supported by the observation of a 5% nuclear Overhauser enhancement (NOE) between the 5-proton and
6-methoxy group. Attempts to improve the selectivity of the nitration of 117 by changing the temperature, sequence of addition, or the nitrating agent were unsuccessful. TLC analysis of reaction mixtures containing a small amount of nitrating agent, nitric acid or acetyl nitrate, in a solution of 117 at various temperatures revealed the presence of both 132 and 133 indicating that nitration at the two sites of the indole nucleus occurs at comparable rates.

The 4-nitro substituent of 132 was cleanly reduced to an amine by hydrogenation over Adam's catalyst which afforded the 4-aminoindole 134 in excellent yield (Scheme 26). Due to the extreme air sensitivity and poor solubility properties of 134, this material was treated directly with N,N-diisopropylethylamine in refluxing chloroform to give the desired quinolinic indole 116 in 75% yield from 132 after chromatography.

Oxidation of 116 to the quinone imine 51 leads to a substance which is at an intersection of Kita's route to discorhabdin C (6), Scheme 6. Acquisition of 51 would thus represent a formal synthesis of 6.13 Since our eventual goal was a synthesis of prianosin A (1), this strategy could be adapted to activation of the 7-position towards substitution with ammonia which would provide 135 for acylation with a substituted phenylacetic acid derivative for further elaboration (Scheme 27). Accordingly, 116 was oxidized with ceric ammonium nitrate in aqueous acetonitrile and gave 51 as a bright yellow oil. Since 51 had been described by Kita as an unstable species, initial attempts to effect substitution of the 7-methoxy group were performed on crude material. However, the failure to obtain 135 or 136 by substitution at this position with ammonia or phenethylamine was discouraging. More worrisome was our failure to obtain 52, a product reported by Kita to be formed from 51 and 3,5-dibromotyramine. For this
reason, it became necessary to purify 51 and confirm its structure. Purification was accomplished by either preparative layer or radial chromatography and afforded 51 in 60% isolated yield. Compound 51 displayed ¹H-NMR (δ 4.18, t, J=7Hz, C-2 methylene) and ¹³C-NMR (δ 155.5) signals, as well as an IR band (1619 cm⁻¹) characteristic of an imine function in a six-membered ring. Absorptions in the UV spectrum at 240 nm (K-band) and 400 nm (R-band) confirmed the presence of a quinonoid nucleus. Collectively, the data allow confident assignment of structure 51 to the oxidation product. However, even purified 51 failed to undergo a reaction with 3,5-dibromotyramine under the conditions described by Kita.

\[
\begin{align*}
116 & \xrightarrow{(\text{NH}_4)_2\text{Ce(NO}_2)_6} 51 \\
\text{CH}_3\text{CN, H}_2\text{O, 0°C} & \quad (60\%) \\
& \times \quad 135 \text{ R}_1=\text{H, R}_2=\text{Ts} \\
& \quad 136 \text{ R}_1=\text{Ts} \quad \text{R}_2=\text{Ts} \\
& \quad 52 \text{ R}_1=\text{Ts} \quad \text{R}_2=\text{H} \\
& \quad \text{Br} \quad \text{Br} \quad \text{OH}
\end{align*}
\]

Scheme 27

In a different attempt to install a nitrogen substituent at the 7-position, 51 was treated with excess sodium azide. A new compound was isolated (30%, unoptimized) by chromatography (Scheme 28). This was assigned the 2,3-dehydro structure 138, based on its ¹H-NMR and high resolution mass spectra, rather than the desired 7-azido derivative. Particularly
diagnostic signals in the $^1$H-NMR spectrum of 138 were identified with the C-2 and C-3 hydrogens, which appeared as doublets ($J=5\text{Hz}$) at $\delta 8.50$ and $\delta 7.65$ ppm, respectively. The formation of 138 can be explained by a mechanism in which $p$-toluenesulfinic acid is eliminated from 51 to give indolenine derivative 137. Tautomerization of 137 converts this species to the observed product 138. Structurally, compound 138 closely resembles the tricyclic nucleus of prianosin B (2) and isobatzellin D (10). Although the yield from 51 would require optimization, this elimination may prove useful in future investigations directed towards a total synthesis of 2 and 10.

Scheme 28

In summary, there are several features of the chemistry described above that warrant comment. The synthesis of quinone imine ketal 100 from
amine 94 by oxidative cyclization with iodobenzene diacetate has demonstrated a novel application of iodine(III) to organic synthesis. The subsequent elaboration of 100 to tetrahydroquinoline 97 has established a foundation from which further studies aimed at delineating the synthetic utility of this reaction may begin.

A short, reasonably efficient synthesis of the indoloquinone imine nucleus related to the prianosin and discorhabdin alkaloids has been achieved in 11 steps and 3% overall yield starting from commercially available 2,3-dimethoxybenzoic acid (119). Rapid access to the CD ring of these natural products was gained by a Fischer indole synthesis utilizing the functionalized hydrazone 118. This avoided lengthy elaboration of the indole 3-position. Problems encountered during conversion of tryptamine 131 to tricyclic 116 using iodobenzene diacetate were overcome by implementing an alternative mode of cyclization. Nitration at the 4-position of indole 117 and reduction to amine 134 preceded ring closure to 116 through intramolecular displacement of the pendant tosylate group. The viability of this approach in a synthesis of the oxidized tricyclic core of the prianosin and discorhabdin natural products was demonstrated by oxidation of 116 to indoloquinone imine 51 using ceric ammonium nitrate.

Finally, it must be said that our failure to execute substitution of the methoxy group of 51 by 3,5-dibromotyramine raises doubts about the plausibility of Kita’s account of this reaction. While a negative result such as ours must be viewed with appropriate caution, the careful characterization of 51 and the thorough examination given to its reaction with 3,5-dibromotyramine throws into question the reproducibility of Kita’s published synthesis of discorhabdin C. Furthermore, the Yamamura route must also be
regarded as suspect. A resolution of these conflicting results awaits further experimentation.
Experimental

For a general description of experimental methods and apparatus see Part 1. Experimental. The 1% ammoniacal chloroform for chromatography and workup of reactions was prepared by extracting 1 part 30% aqueous ammonium hydroxide with 5 parts chloroform. The chloroform extract was dried over anhydrous potassium carbonate, filtered, and was stored in the dark at 5°C.

Ethyl α-Cyano-β-(3,4-dimethoxyphenyl)acrylate (89). A solution of 88 (10.0 g, 60 mmol), ethyl cyanoacetate (6.8 g, 60 mmol), and piperidine (0.75 mL) in toluene (100 mL) was heated at 110°C with removal of water via a Dean-Stark apparatus. The mixture was cooled, and the solvents were evaporated to yield 14.8 g (94%) of 89 as a pale yellow solid: mp 155-156°C (lit. 156°C); IR (KBr) 3003, 2220, 1715, 1589, 1516, 1264, 1018, 852 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 8.16 (s, 1H), 7.81 (d, J=2Hz, 1H), 7.48 (dd, J=2,8Hz, 1H), 6.95 (d, J=8Hz, 1H), 4.37 (q, J=7Hz, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 1.40 (t, J=7Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 163.0, 154.6, 153.6, 149.2, 127.9, 124.6, 116.3, 111.5, 110.9, 99.3, 62.4, 56.1, 55.9, 14.1; MS m/z 261 (M⁺, 100), 233 (19), 188 (6), 172 (20), 144 (11), 116 (10).

(±)-(3,4-Dimethoxyphenyl)succinonitrile (90). To a mixture of 89 (7.3 g, 28 mmol) in chloroform (83 mL) and ethanol (62 mL) was added a solution of sodium cyanide (1.5 g, 31 mmol) in water (22 mL) dropwise. The mixture was heated at reflux for 15 h, cooled, and acidified with concentrated hydrochloric acid. Evaporation of the solvents under reduced pressure gave a pink solid which was partitioned between water (62 mL) and chloroform (42 mL). The aqueous layer was extracted with chloroform (2 X 42 mL), and
the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Recrystallization from ethanol yielded 4.6 g (77%) of **90**. Chromatography of the mother liquor (silica gel 60, ethyl acetate-methanol-chloroform 1:1:8) provided an additional 0.35 g (5%) of **90**: mp 108°C (lit. 108-110°C); IR (KBr) 2944, 2247, 1596, 1523, 1270, 1237, 1157, 1144, 1018 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.97 (dd, J=12, 4Hz, 1H), 6.92 (d, J=9 Hz, 1H), 6.89 (d, J=2Hz, 1H), 4.11 (t, J=7 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.97 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 149.9, 149.7, 124.3, 119.8, 117.9, 115.3, 111.6, 109.9, 56.0, 55.9, 33.7, 24.9; MS m/z 216 (M⁺), 176 (100), 131 (33), 115 (20), 103 (26), 90 (32), 76 (27).

(±)-4-Acetamido-3-(3,4-dimethoxyphenyl)butyronitrile (**92**). To a Parr reaction vessel was added **90** (235 mg, 1.1 mmol), acetic anhydride (9 mL), sodium acetate (89 mg, 1.1 mmol) and 10% palladium on carbon (125 mg). The mixture was shaken under hydrogen at 46 psi at 25°C for 6 h or until TLC indicated complete reaction. The catalyst was removed by filtration over Celite and the mixture was concentrated under reduced pressure. Chromatography (silica gel 60, ethyl acetate-methanol-chloroform 1:1:8) gave 218 mg (76%) of **92** as an oily wax: IR (neat) 3369, 3296, 2944, 2246, 1655, 1516, 1270, 1137, 1031 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.86 (d, J=8 Hz, 1H), 6.81 (d, J=2Hz, 1H), 6.77 (dd, J= 2,7Hz, 1H), 5.81 (bt, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.73 (m, 1H), 3.39 (m, 1H), 3.18 (m, 1H), 2.66 (m, 2H), 1.95 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 170.5, 149.2, 148.5, 131.4, 119.2, 118.2, 111.5, 110.3, 55.9, 55.8, 43.5, 41.4, 23.0, 22.3; MS m/z 262 (M⁺), 203 (100), 190 (54), 175 (14), 91 (8), 72 (26); HRMS m/z observed 262.13170 (M⁺), calcd for C₁₄H₁₈N₂O₃ 262.13174.
Further elution gave 34 mg (10%) of (±)-1,4-di-N-acetyl-2-(3,4-dimethoxyphenyl)-1,4-diaminobutane (93) as a colorless wax: IR (KBr) 3329, 2964, 1649, 1629, 1529, 1444, 1025 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.82 (d, J=8Hz, 1H), 6.71 (d, J=2Hz, 1H), 6.69 (s, 1H), 6.28 (bt, 1H), 6.02 (bt, 1H), 3.87 (3, 3H), 3.86 (s, 3H), 3.63 (m, 1H), 3.16 (m, 3H), 2.75 (m, 1H), 1.92 (s,3H), 1.91 (s, 3H), 1.77 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 170.4, 170.3, 149.1, 147.9, 134.4, 119.5, 111.3, 110.4, 55.9, 55.8, 44.9, 43.1, 37.8, 33.2, 23.2(2); MS m/z 308 (M⁺), 249( 81), 190( 69), 177 (100); HRMS m/z observed 308.17360 (M⁺), calcd for C₁₆H₂₄N₂O₄ 308.17361.

(±)-1-N-Acetyl-2-(3,4-dimethoxyphenyl)-1,4-diaminobutane (94).
A mixture of 92 (1.0 g, 3.8 mmol), absolute methanol (38 mL), concentrated hydrochloric acid (0.6 mL) and 10% palladium on carbon (0.5 g) was stirred under a hydrogen atmosphere at 25°C for 20 h. The mixture was filtered over Celite and the solvent was removed at reduced pressure to give 1.1 g (96%) of the hydrochloride salt of 94. This was suspended in chloroform, cooled to 0°C, and treated with excess 1% ammoniacal chloroform. The precipitated ammonium chloride was removed by filtration. Chromatography of the concentrate (silica gel 60, 20% methanol in 1% ammoniacal chloroform) afforded 0.89 g (89%) of 94 as a colorless oil: IR (neat) 3296, 2931, 1649, 1516, 1264, 1025 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.84 (d, J= 8Hz, 1H), 6.72 (dd, J= 2,8Hz, 1H), 6.68 (d, J=2Hz, 1H), 5.59 (bt, 1H), 3.87 (s, 6H), 3.69 (m, 1H), 3.17 (m, 1H), 2.81 ( m, 1H), 2.61 (m, 2H), 1.88 (s, 3H), 1.73 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 169.9, 149.1, 147.8, 134.7, 119.6, 111.3, 110.4, 55.8(2 OMe), 45.1, 42.9, 39.9, 37.5, 23.2; MS m/z 266 (M⁺), 207 (100), 178 (87), 165 (49), 91 (29), 77 (27), 73 (53); HRMS m/z observed 266.16300 (M⁺), calcd for C₁₄H₂₂N₂O₄ 266.16300; Anal. Calcd for
C$_{14}$H$_{24}$N$_{2}$O$_{4}$; C, 59.14; H, 8.51; N, 9.85. Found; C, 59.05; H, 8.24; N, 9.57.

(±)-6-(2,2,2-Trifluoroethoxy)-6,7-dimethoxy-4-acetamidomethyl-2,3,4,6-tetrahydroquinoline (100). A solution of 94 (43 mg, 0.16 mmol) in 2,2,2-trifluoroethanol (2.5 mL) was treated with iodobenzene diacetate (103 mg, 0.32 mmol) and the solution was stirred at 25°C under argon for 23 h. The mixture was concentrated and the residue was purified by chromatography (silica gel 60, ethyl acetate-methanol-chloroform 1.5:1.5:7) to yield 42.0 mg (72%) of 100 as an unstable, tan wax: IR (neat) 3289, 2937, 1656, 1630, 1284, 1210, 1164 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$, diastereomeric mixture) δ 5.95, 5.90 (d, 1H), 5.87 (s, 1H), 3.99 (m, 2H), 3.84 (m, 2H), 3.78 (s, 3H), 3.40 (m, 1H), 3.30 (s, 3H), 2.75 (m, 1H), 2.01 (s, 3H), 1.90 (m, 1H), 1.69 (m, 1H); $^{19}$F-NMR (280 MHz, CDCl$_3$) δ -6.45 (t, J=9Hz); $^{13}$C-NMR (75 MHz, CDCl$_3$, diastereomeric mixture) δ 174.8, 170.6, 170.4, 159.5, 159.4, 157.5, 131.6, 131.2, 129.4, 129.0, 121.9, 103.3, 94.8, 94.7, 61.7, 61.6, 61.5, 55.6, 51.5, 51.4, 46.5, 46.3, 41.5, 41.1, 35.6, 35.2, 24.7, 23.2, 23.0, 21.5; MS m/z 332 (-OMe), 264 (-OCH$_2$CF$_3$, 56), 260 (73), 217 (32), 205 (32), 192 (100).

(±)-4-Acetamidomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (97). A mixture of 100 (85 mg, 0.23 mmol) and 10% palladium on carbon (45 mg) in absolute methanol (1.5 mL) was stirred for 6h at 25°C under a hydrogen atmosphere. The catalyst was removed by filtration over Celite and the concentrate was purified by chromatography (silica gel 60, ethyl acetate-methanol-chloroform 1:1:8) to give 45.0 mg (73%) of 97 as a tan wax: IR (neat) 3355, 2930, 1649, 1509, 1370, 1237, 1151, 958, 858, 819
cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.61 (s, 1H), 6.11 (s, 1H), 5.60 (bt, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.48 (t, J=6Hz, 2H), 3.26 (m, 2H), 2.94 (quin., J=6 Hz, 1H), 1.99 (s, 3H), 1.85 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 170.3, 148.8, 141.3, 139.1, 113.3, 112.5, 99.5, 56.8, 55.7, 44.5, 38.6, 34.9, 25.1, 23.4; MS m/z 264 (M⁺), 205 (34), 192 (100), 190 (17), 161 (21); HRMS m/z observed 264.1474 (M⁺), calcd for C₁₄H₂₀N₂O₃ 264.1474.

(±)-4-Acetamidomethyl-6,7-dimethoxy-1-(p-toluenesulfonyl)-1,2,3,4-tetrahydroquinoline (101). To a solution of 97 (18 mg, 0.07 mmol) in dry pyridine (0.3 mL) at 0°C was added a solution of p-toluenesulfonyl chloride (13 mg, 0.07 mmol) in methylene chloride (0.1 mL) under argon and the solution was stirred for 15.5 h at 0°C. The mixture was diluted with chloroform (7 mL) and transferred to ice-cold saturated aqueous sodium bicarbonate (2.5 mL). The aqueous layer was extracted with chloroform (4 X 2.5 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. Removal of the solvent and purification by chromatography (silica gel 60, ethyl acetate-methanol-chloroform 1:1.5:7.5) gave 24.0 mg (84%) of 101 as a tan solid: mp 168°C; IR (KBr) 3396, 3250, 3077, 2938, 1636, 1511, 1443, 1343, 1271, 1224, 1160, 859, 680 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.49 (d, J=8 Hz, 2H), 7.28 (s, 1H), 6.65 (s, 1H), 5.56 (bt, J=6 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (m, 1H), 3.72 (m, 1H), 3.35 (m, 1H), 2.95 (m, 1H), 2.83 (m, 1H), 2.39 (s, 3H), 1.91 (s, 3H) 1.53 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 170.4, 147.5, 146.8, 143.8, 136.0, 130.0, 129.6(2 Ar), 127.3(2 Ar), 122.6, 110.6, 108.7, 55.9, 55.8, 44.4, 44.3, 34.7, 24.1, 23.2, 21.5; MS m/z 418 (M⁺), 264 (11), 207 (19), 204 (19), 195 (80), 190 (28), 178 (100), 164 (22), 152 (30), 91 (40).
Compound 101 crystallized from 5% aqueous methanol in space group Pbca with a=19.929(6) Å, b=23.169(5) Å, c=9.235(4) Å, z=8, and \( d_{\text{calc}} = 1.304 \text{ g/cm}^3 \). The intensity data were measured on a Rigaku AFC6R diffractometer (Mo k\( \alpha \) radiation). Of the 3417 reflections collected, 1587 were considered to be observed \([I > 3.00\sigma(I)]\). The structure was solved by direct methods and the final discrepancy indices were \( R = 0.048 \) and \( R_w = 0.054 \). The data was collected and the structure solved by Frank Stappenbeck.

(±)-2-(3,4-Dimethoxyphenyl)-1,4-diaminobutane (76). A suspension of 90 (100 mg, 0.46 mmol) and 10% palladium on carbon (50 mg) in methanol was treated with concentrated hydrochloric acid (155 μL, 2 mmol) and stirred under an atmosphere of hydrogen for 22 h. The catalyst was removed by filtration over Celite and the solvent was evaporated in vacuo. The solid residue was treated with 1% ammoniacal chloroform at 0°C and the ammonium chloride was removed by filtration. Chromatography of the concentrate (silica gel 60, 20% methanol in 1% ammoniacal chloroform) yielded 24.4 mg (24%) of 76 as a colorless oil: IR (neat) 3356(b), 2937, 1589, 1423, 1257, 1144, 1025 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta 6.82 \) (d, J=8Hz, 1H), 6.74 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.88 (m, 2H), 2.64 (m, 3H), 2.31 (bs, 4H), 1.82 (m, 2H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \( \delta 149.1, 147.8, 134.4, 119.6, 111.4, 110.5, 55.8(2), 48.2, 45.8, 39.1, 35.7; \) MS m/z 224 (M\(^+\)), 207 (13), 195 (82), 178 (100), 152 (22); HRMS m/z observed 224.15249 (M\(^+\)), calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\) 224.15248. There was also obtained 41.5 mg (44%) of (±)-3-(3,4-dimethoxyphenyl)pyrrolidine (105) as a colorless oil: IR (neat) 3402(b), 2950, 1520, 1423, 1257, 1144, 1025 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta 6.80 \) (m, 3H),
3.88 (s, 3H), 3.86 (s, 3H), 3.36 (dd, J=8Hz, 1H), 3.11 (m, 3H), 3.00 (bs, 1H),
2.85 (dd, J=8Hz, 1H), 2.23 (m, 1H), 1.85 (m, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$
$\delta$ 148.8, 147.3, 136.4, 118.8, 111.1, 110.5, 55.8, 55.7, 54.9, 47.1, 45.1, 34.4;
MS $m/z$ 207 (M$^+$, 100), 178 (26), 165 (21), 164 (36), 147 (30); HRMS $m/z$
observed 207.12592 (M$^+$), calcd for C$_{12}$H$_{17}$NO$_2$ 207.12593.

(±)-1-N-Acetyl-4-N-benzyl-2-(3,4-dimethoxyphenyl)-1,4-diaminobutane (104). To a solution of 94 (76 mg, 0.28 mmol) in toluene (1 mL)
was added benzaldehyde (30 mg, 0.28 mmol). The mixture was stirred for
20 h under argon and anhydrous magnesium sulfate (40 mg) was added.
Stirring was continued for 3.5 h and the suspension was filtered and
concentrated to give 111 mg of crude imine as a light yellow oil. To a
solution of this material in methanol (1 mL) was added sodium borohydride
(16 mg, 0.42 mmol) portionwise over 5 min. After stirring for 1 h, the solution
was concentrated, diluted with water (2.5 mL) and extracted with chloroform
(3 X 5 mL) and ethyl acetate (8 X 5 mL). The combined organic extracts were
dried over anhydrous sodium sulfate-magnesium sulfate. Concentration of
the solution and chromatography (silica gel 60, 5% methanol in 1%
ammoniacal chloroform) gave 79 mg (79%) of 104 as a colorless oil: IR
(neat) 3302, 2931, 1649, 1516, 1257, 1144, 1025 cm$^{-1}$; $^1$H-NMR (300 MHz,
CDCl$_3$) $\delta$ 7.29 (m, 5H), 6.81 (d, J=8Hz, 1H), 6.69 (dd, J=2,8Hz, 1H), 6.67 (d,
J=2Hz, 1H), 5.72 (bt, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.68 (s, 2H), 3.63 (m,
1H), 3.17 (m, 1H), 2.79 (m, 1H), 2.54 (t, J=7Hz, 2H), 1.85 (s, 3H) 1.81 (m,
2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 170.0, 149.0, 147.7, 140.0, 134.8, 128.3,
127.9, 127.3, 126.9, 126.8, 119.5, 111.2, 110.4, 64.8, 55.8, 53.9, 47.1, 45.0,
43.2, 34.3, 23.2; MS $m/z$ 356 (M$^+$), 248 (14), 206 (12), 120 (95) 106 (56), 91
(±)-4-Aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (107). A mixture of 96 (20 mg, 0.076 mmol) in ethanol (2 mL) and 3M aqueous hydrochloric acid (3 mL) was heated to reflux for 17 h and concentrated. The tan residue was suspended in chloroform (2 mL) and was treated with an excess of 1% ammoniacal chloroform at 0°C. The resulting ammonium chloride was removed by filtration and the concentrate was purified by chromatography (silica gel 60, 5% methanol in 1% ammoniacal chloroform) which afforded 13 mg (78%) of 107 as a tan oil: IR (neat) 3369, 2931, 1616, 1514, 1463, 1230, 1138, 1031, 859 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.61 (s, 1H), 6.10 (s, 1H), 3.78 (s, 6H), 3.22 (m, 2H), 2.89 (m, 2H), 2.69 (m, 1H), 1.93 (m, 2H), 1.25 (bs, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 148.5, 141.2, 138.9, 113.9, 113.5, 99.4, 56.8, 55.7, 47.7, 38.7, 38.3, 24.7; MS m/z 222 (M⁺), 192 (100), 161 (20) 160 (17); HRMS m/z observed 222.13680 (M⁺), calcd for C₁₂H₁₈N₂O₂ 222.13681.

(±)-7-Methoxy-4-acetamidomethyl-2,3,4,6-tetrahydroquinolin-6-one (108). To a solution of 96 (13 mg, 0.05 mmol) in acetonitrile (0.3 mL) at 0°C was added a solution of ceric ammonium nitrate (57 mg, 0.10 mmol) in water (0.1 mL). After 1 h at 0°C the mixture was diluted with chloroform (1 mL), then carefully treated with saturated aqueous sodium bicarbonate until neutral, and the layers were separated. The aqueous layer was washed with chloroform (7 X 1 mL) and the combined organic extracts were concentrated to give 12.3 mg (~100%) of 108 as a bright yellow oil that was not purified due to its instability: IR (neat) 3309, 1656, 1636, 1556, 1510 cm⁻¹; ¹H-NMR
4-Acetamidomethyl-6-hydroxy-7-methoxyquinoline (109). To a solution of 97 (21 mg, 0.08 mmol) in acetonitrile (0.5 mL) at 0°C was added a solution of ceric ammonium nitrate (177 mg, 0.32 mmol) in water (0.4 mL). The bright yellow mixture was stirred for 2 h and poured into chloroform (3 mL) and was treated with saturated aqueous sodium bicarbonate (35 drops) and water (30 drops). The mixture was extracted with chloroform (4 X 5 mL) and the combined organic washings were passed through a plug of anhydrous sodium sulfate. Removal of the solvent gave 20 mg of a 2:1 mixture of 109 and 108. The crude material was dissolved in chloroform (2.5 mL) and was stirred under an atmosphere of oxygen for 18 h. Concentration and purification by radial chromatography (ChromatotronR, 1mm rotor, 20% methanol-chloroform) afforded 18 mg (90%) of 109 as a tan wax: IR (KBr) 3283, 2930, 1649, 1516, 1483, 1264, 1032, 852 cm⁻¹; ¹H-NMR (300 MHz, CD₃OD) δ 8.49 (d, J=5Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.21 (d, J=5Hz, 1H), 4.70 (s, 2H), 3.99 (s, 3H), 2.04 (s, 3H); ¹³C-NMR (75 MHz, CD₃OD) δ 173.4, 153.4, 149.2, 147.7, 145.3, 144.1, 123.9, 118.8, 107.8, 105.8, 56.4, 41.2, 22.5; MS m/z 246 (M⁺, 96), 203 (67), 176 (100); HRMS m/z observed 246.10040 (M⁺), calcd for C₁₃H₁₄N₂O₃ 246.10043.

(±)-4-Benzzenesulfonamidomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (110). To a flame-dried round-bottom flask containing 107 (19 mg, 0.08 mmol) in dry pyridine (0.3 mL) at 0°C under argon was
added a solution of benzenesulfonyl chloride (14 mg, 0.08 mmol) in dry methylene chloride (0.1 mL) during 20 min. and the solution was stirred for 24 h. The mixture was concentrated and purified by chromatography (silica gel 60, 10% methanol-ammoniacal chloroform) to afford 4.3 mg (15%) of 110 as a tan foam: IR (neat) 3276, 2931, 2851, 1616, 1516, 1450, 1323, 1158. 726 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.84 (m, J=1,2,7Hz, 2H), 7.54 (m, 3H), 6.44 (s, 1H), 6.07 (s, 1H), 4.60 (bt, J=6Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.15 (m, 4H), 2.87 (bm, 1H), 1.91 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 149.2, 141.4, 139.9, 139.3, 132.6, 129.2(2), 126.9(2), 113.2, 111.3, 99.5, 56.8, 55.7, 48.1, 38.3, 35.0, 24.6; MS m/z 362 (M⁺), 192 (100), 161 (7); HRMS m/z observed 362.13000 (M⁺), calcd for C₁₈H₂₂N₂O₄S 362.13002.

There was also obtained 11.5 mg (40%) of (±)-4-aminomethyl-1-N-benzenesulfonyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (112) as a tan foam: IR (neat) 3389, 2937, 1609, 1509, 1450, 1343, 1164 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.56 (m, 3H), 7.40 (m, 3H), 6.60 (s, 1H), 3.97 (m, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.66 (m, 1H), 2.63 (m, 2H), 2.40 (m, 1H), 1.56 (bm, 4H); ¹³C-NMR (75 MHz, CDCl₃) δ 147.5, 146.9, 139.4, 132.8, 130.1, 128.9(2), 127.3(2), 123.3, 110.5, 109.1, 56.0(2-OMe), 46.8, 44.9, 37.9, 23.9; MS m/z 362 (M⁺), 204 (16), 192 (100), 190 (69); HRMS m/z observed 362.13000 (M⁺), calcd for C₁₈H₂₂N₂O₄S 362.13002.

As a third component of the reaction mixture there was obtained 15.3 mg (39%) of (±)-4-benzenesulfonamidomethyl-1-N-benzenesulfonyl-6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (113): IR (neat) 3283, 2937, 1616, 1513, 1330, 1164 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.77 (m, 2H), 7.55 (m, 6H), 7.40 (m, 4H), 6.46 (s, 1H), 4.25 (bt, J=6Hz, 1H), 3.89 (s, 3H), 3.82 (m, 1H), 3.77 (s, 3H), 3.66 (m, 1H), 2.89 (m, 1H), 2.69 (m, 2H), 1.47 (m, 2H); MS
m/z 502 (M⁺), 361 (10), 204 (70), 192 (94), 190 (56), 77 (100); HRMS m/z observed 502.12320 (M⁺), calcd for C₂₄H₂₆N₂O₆S 502.12321.

N-(Ethoxycarbonyl)-3,4-dimethoxyaniline (124). A flame-dried round-bottom flask was fitted with a reflux condenser and charged with 119 (11.0 g, 60.4 mmol) and dry tetrahydrofuran (230 mL) under argon. To this solution was added diphenylphosphoryl azide (16.6 mL, 72.5 mmol), absolute ethanol (35.4 mL, 0.6 mol) and dry triethylamine (10.1 mL, 72.5 mmol). The mixture was stirred for 2h at 55°C, cooled to ambient temperature, diluted with ethyl acetate (600 mL), and washed with saturated aqueous sodium bicarbonate (4 X 100 mL), water (3 X 100 mL) and saturated aqueous sodium chloride (3 X 100 mL). The organic layer was separated and was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 13.5 g (99%) of 124 as a colorless wax. A small sample was purified by chromatography (silica gel 60, 40% ethyl acetate-hexane) for characterization: IR (neat) 3429, 1736, 1602, 1530, 1231, 1052, 779 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 7.73 (d, J=8Hz, 1H), 7.26 (s, 1H), 7.02 (t, J=8Hz, 1H), 6.62 (dd, J=1,8Hz, 1H), 4.24 q, J=7Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.33 (t, J=7Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 153.5, 152.0, 136.9, 132.2, 124.2, 110.9, 106.4, 61.1, 60.6, 55.8, 14.5; MS m/z 225 (M⁺, 100), 138 (28), 95 (10), 92 (15); HRMS m/z observed 225.10010 (M⁺), calcd for C₁₁H₁₅NO₄ 225.10009.

2,3-Dimethoxyaniline (122). To a suspension of potassium hydroxide (18.4 g, 330 mmol) in absolute ethanol (290 mL) was added a solution of crude 124 (7.4 g, 33 mmol) in absolute ethanol (47 mL). The flask was fitted with a reflux condenser and the mixture was stirred at 72°C for 4.5 h, cooled
to room temperature, and filtered over Celite. The filtrate was concentrated and diluted with diethyl ether (200 mL), and the yellow solution was decanted from the brown solid. The insoluble material was rinsed with diethyl ether (4 X 100 mL) and the combined organic solutions were washed with saturated aqueous sodium chloride (3 X 25 mL) and dried over anhydrous sodium sulfate. Removal of the solvent afforded 4.6 g (91%) of 122 as an orange oil that was homogeneous by $^1$H- and $^{13}$C-NMR: IR (neat) 3467, 3370, 2937, 1617, 1496, 1317, 1271, 1131, 1005, 785 cm$^{-1}$; $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.84 (t, J=8Hz, 1H), 6.38 (dd, J=1,8Hz, 1H), 6.33 (dd, J=1,8Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.83 (bs, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 152.9, 140.6, 135.6, 124.1, 108.7, 102.2, 59.7, 55.6; MS m/z 153 (M$,^+$, 100), 138 (14), 95 (32), 84 (41); HRMS m/z observed 153.07897 (M$,^+$), calcd for C$_8$H$_{11}$NO$_2$ 153.07897.

2,3-Dimethoxyphenylhydrazine (125). To a solution of 122 (3.8 g, 24.8 mmol) in 6M aqueous hydrochloric acid (10 mL) at 0°C was added a solution of sodium nitrite (1.9 g, 28.7 mmol) in water (5.4 mL) during 30 min. and the yellow mixture was stirred for 1.5 h. To this mixture was added dropwise a solution of stannous chloride (33.0 g, 146 mmol) in concentrated hydrochloric acid (30.0 mL) during 2 h. After stirring for 1 h the mixture was poured into 10M aqueous sodium hydroxide (80 mL) at 0°C, and the solids were filtered and washed with benzene (5 X 50 mL). The gray solid residue was suspended in water (30 mL) and extracted with diethyl ether (5 X 100 mL), and the combined benzene and diethyl ether extracts were dried over anhydrous sodium sulfate. Filtration and removal of the solvent gave the crude product which was recrystallized from diethyl ether to yield 3.05 g (73%) of 125 as a pale yellow solid: mp 78-81°C (lit. 78-82°C); IR (neat)
3335, 2937, 1603, 1477, 1264, 772 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.00 (t, J=8Hz, 1H), 6.65 (dd, J=1.8Hz, 1H), 6.43 (dd, J=1.8Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 152.3, 145.3, 134.8, 124.4, 140.5, 103.0, 60.0, 55.8; MS m/z 168 (M⁺), 153 (33), 138 (100), 95 (63).

4-Hydroxybutanal 2,3-Dimethoxyphenylhydrazone (118). A stream of hydrogen chloride gas was bubbled through a solution of 125 (1.50 g, 8.9 mmol) in absolute methanol (20 mL) at 0°C for 1 min. and the solution was concentrated. The residual hydrochloride salt was taken up in tetrahydrofuran (22 mL) and water (2.2 mL) at 0°C and to this solution was added dropwise 2,3-dihydrofuran (0.81 mL, 10.7 mmol). After stirring for 18 h at 4°C the mixture was cooled to 0°C and diluted with diethyl ether (40 mL). The layers were separated and the yellow organic layer was washed with saturated aqueous sodium chloride (1 × 5 mL) and dried over anhydrous magnesium sulfate. Concentration of the solution followed by chromatography (silica gel 60, 5% methanol-chloroform) gave 1.80 g (85%) of an approximately 1:1 mixture of 118 and 126 as an amber oil. The following NMR spectral data is for a homogeneous sample of 118 obtained by collection of the more highly retained chromatographic fractions: IR (neat) 3329, 2937, 1603, 1476, 1264, 1125, 773, 732 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.20 (t, J=5Hz, 1H), 6.98 (m, 2H), 6.40 (dd, J=1.8Hz, 1H) 3.84 (s, 3H), 3.82 (s, 3H), 3.72 (t, J=6Hz, 2H), 2.41(td, J=5,7Hz, 2H), 1.84 (quin., J=7Hz, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 152.4, 141.8, 139.1, 133.5, 124.6, 106.1, 102.8, 62.3, 60.2, 55.7, 29.4, 28.9; MS m/z 238 (M⁺), 168 (10), 153 (10), 138 (55), 95 (33), 77 (100); HRMS m/z observed 238.13170 (M⁺), calcd for C₁₂H₁₈N₂O₃ 238.13173.
3-(2-Hydroxyethyl)-6,7-dimethoxyindole (127). A mixture of 118 and 126 (1.0 g, 4.20 mmol) and anhydrous zinc chloride (1.3 g, 9.6 mmol) in t-butanol (9 mL) was thoroughly degassed by evacuating the flask and back-filling with argon (3X). The suspension was stirred at 50°C for 15 min. and heated at 82°C for 8 h. The dark red mixture was concentrated, taken up in ethyl acetate (30 mL) and the suspension was filtered over Celite. The filter pad was washed with ethyl acetate (30 mL) and the combined organic solutions were washed with water (2 X 20 mL) and saturated aqueous sodium chloride (2 X 20 mL), and dried over anhydrous magnesium sulfate. Concentration of the solution and chromatography (silica gel 60, 5% to 20% (5% gradient) methanol-chloroform) gave 362 mg (41%) of 127 as a tan oil: IR (neat) 3409, 2937, 1629, 1510, 1257, 1091, 1038, 792 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 8.25 (bs, 1H), 7.25 (d, J=9Hz, 1H), 6.98 (d, J=2Hz, 1H), 6.85 (d, J=9Hz, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.89 (t, J=6Hz, 2H), 3.98 (td, J=2,6Hz, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 147.2, 134.5, 131.0, 124.2, 122.8, 113.7, 112.5, 108.2, 62.5, 60.8, 57.4, 28.8; MS m/z 221 (M⁺), 206 (12), 190 (68), 160 (100); HRMS m/z observed 221.10520 (M⁺), calcd for C₁₂H₁₅NO₃ 221.10519.

1-N-(p-Toluenesulfonyl)-3-(2-p-toluenesulfonatoethyl)-6,7-dimethoxyindole (117). A flame-dried round-bottom flask was charged with 127 (24 mg, 0.11 mmol), p-toluenesulfonyl chloride (83 mg, 0.43 mmol) and dry tetrahydrofuran (0.3 mL) under argon. The solution was cooled to 0°C, treated with sodium hydride (18 mg, 0.43 mmol, 60% dispersion in mineral oil), and slowly warmed to ambient temperature during 4 h. The mixture was diluted with diethyl ether (5 mL) and water (1 mL), and the aqueous layer was extracted with diethyl ether (6 X 5 mL). The combined organic extracts
were washed with saturated aqueous sodium chloride (2 X 5 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent and chromatography (silica gel 60, 40% ethyl acetate-hexane) gave 38 mg (65%) of 117 as a tan wax. IR (neat) 2937, 1596, 1503, 1357, 1177, 1091, 905, 812 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.74 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H), 7.23 (m, 4H), 7.03 (d, J=9 Hz, 1H), 6.85 (d, J=9 Hz, 1H), 4.26 (t, J=7 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.01 (td, J=1,7 Hz, 2H), 2.41 (s, 3H), 2.35 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 150.7, 144.8, 144.2, 136.7, 132.6, 129.7, 129.6, 129.5, 128.6, 127.6, 127.3, 127.0, 126.4, 125.8, 114.8, 113.6, 109.8, 68.9, 60.5, 56.6, 24.8, 24.5; MS m/z 529 (M⁺), 331 (13), 246 (12), 202 (54), 138 (29), 91 (100); HRMS m/z observed 529.12288 (M⁺), calcd for C₂₆H₂₇S₂N⁰₇ 529.12288.

1-N-(p-Toluenesulfonyl)-3-(2-p-toluenesulfonatoethyl)-4-methoxyindole (129): A solution of 128 (17 mg, 0.09 mmol) and p-toluenesulfonyl chloride (67 mg, 0.35 mmol) in dry tetrahydrofuran (0.5 mL) was cooled to 0°C. To the mixture was added sodium hydride (12 mg, 0.35 mmol, 60% dispersion in mineral oil) and the solution was slowly warmed to room temperature during 2.5 h. The mixture was diluted with diethyl ether (5 mL) and water (0.75 mL), and the aqueous layer was extracted with diethyl ether (5 X 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 X 5 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure followed by chromatography (Chromatotron®, 20 mm rotor, 30% ethyl acetate-hexane) gave 35 mg (78%) of 129 as a tan wax: IR (neat) 2950, 1596, 1503, 1363, 1177, 978, 898, 819 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.73 (d, J=8 Hz, 2H), 7.52 (d, J=8 Hz, 1H), 7.48 (d, J=8 Hz, 2H), 7.24 (d, J=8 Hz, 2H), 7.21 (d,
J=1Hz, 1H), 7.16 (t, J=8Hz, 1H), 7.04 (d, J=8Hz, 2H), 6.50 (d, J=8Hz, 1H),
4.27 (t, J=8Hz, 2H), 3.72 (s, 3H), 3.07 (td, J=1.6Hz, 2H), 2.33 (s, 3H), 2.32 (s,
3H); 13C-NMR (75 MHz, CDCl3) δ 153.9, 144.9, 144.4, 136.7, 135.1, 132.5,
129.9(2), 129.4(2), 127.5(2), 126.2(2), 125.5, 123.3, 119.5, 117.0, 106.6,
103.4, 69.8, 55.1, 26.8, 21.5(2); MS m/z 499 (M+), 327 (23), 172 (100), 91
(81); HRMS m/z observed 499.11230 (M+) calcd for C25H25S2N06
499.11232.

1-N-(p-Toluenesulfonyl)-3-(2-azidoethyl)-6,7-dimethoxyindole
(130). A mixture of 117 (55 mg, 0.104 mmol) and sodium azide (136 mg,
2.08 mmol) in dry N,N-dimethylformamide (0.5 mL) was stirred at 50°C for 45
min. under argon. The mixture was diluted with diethyl ether (20 mL) and
filtered through Celite. The filtrate was washed with water (3 X 3 mL) and
saturated aqueous sodium chloride (1 X 3 mL), and dried over anhydrous magnesiu
m sulfate. Concentration followed by chromatography of the
residual oil (silica gel 60, 40% ethyl acetate-hexane) afforded 34 mg (82%)
of 130 as a tan glass: IR (film) 2938, 2100, 1603, 1503, 1357, 1257, 1091,
806 cm⁻¹; 1H-NMR (300 MHz, CDCl3) δ 7.76 (d, J=8Hz, 2H), 7.59 (s, 1H),
7.22 (d, J=8Hz, 2H), 7.13 (d, J=9Hz, 1H), 6.90 (d, J=9Hz, 1H), 3.85 (s, 3H),
3.83 (s, 3H), 3.58 (t, J=7Hz, 2H), 2.94 (t, J=7Hz, 2H), 2.34 (s, 3H); 13C-NMR
(75 MHz, CDCl3) δ 150.7, 144.0, 136.8, 136.7, 129.5(2),128.8, 127.2(3),
125.6, 116.4, 113.5, 109.9, 60.5, 56.6, 50.6 ,24.7, 21.5; MS m/z 400 (M+, 100), 245 (44), 189 (78), 160 (72), 129 (30), 91 (84); HRMS m/z observed
400.12050 (M+), calcd for C19H20SN4O4 400.12050.

1-N-(p-Toluenesulfonyl)-3-(2-aminoethyl)-6,7-dimethoxyindole
(131). To a solution of 130 (33 mg, 0.082 mmol) in tetrahydrofuran (0.5 mL)
was added triphenylphosphine (24 mg, 0.091 mmol) and water (2 drops) and the mixture was stirred for 17 h at ambient temperature. Concentration followed by chromatography of the residual oil (silica gel 60, 5% methanol-chloroform to 10% methanol-1% ammoniacal chloroform) gave 27 mg (88%) of 131 as a colorless oil: IR (neat) 3370(b), 2944, 1596, 1503, 1350, 1257, 1171, 1091, 806 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.76 (d, J=8 Hz, 2H), 7.75 (s, 1H), 7.21 (d, J=8 Hz, 2H), 7.15 (d, J=9 Hz, 1H), 6.87 (d, J=9 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.05 (t, J=7 Hz, 2H), 2.83 (t, J=7 Hz, 2H), 2.34 (s, 3H), 2.21 (bs, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ 150.6, 144.0, 136.8(2), 129.5(2), 128.8, 127.6, 127.2(2), 125.2, 117.7, 113.9, 109.7, 60.5, 56.6, 41.2, 28.6, 21.5; MS m/z 374 (M⁺), 190 (100); HRMS m/z observed 374.13001 (M⁺), calcd for C₁₉H₂₂SN₂O₄ 374.13001.

1-N-(p-Toluenesulfonyl)-3-(2-p-toluenesulfonatoethyl)-4-nitro-6,7-dimethoxyindole (132): Acetyl nitrate was prepared by adding 70% aqueous nitric acid (1mL) to acetic anhydride (6.6 mL) at -10°C and stirring the mixture for 1 h. A solution of 117 (30 mg, 0.057 mmol) in acetic anhydride (1 mL) was cooled to -45°C, treated with the acetyl nitrate solution (14 drops), and then warmed to -20°C during 2 h. The yellow mixture was diluted with chloroform (5 mL) and washed with saturated aqueous sodium bicarbonate (1 X 2 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by chromatography of the residue (silica gel 60, 40% ethyl acetate-hexane) gave 14.6 mg (45%) of 132 as a yellow solid: IR (neat) 2951, 1510, 1357, 1178, 1104, 978, 905, 812, 666 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.78 (s, 1H), 7.73 (d, J=8 Hz, 2H), 7.64 (d, J=8 Hz, 2H), 7.58 (s, 1H), 7.30 (d, J=8 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 4.21 (t, J=6 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.17 (t, J=6 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H);
\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) 148.2, 144.9, 144.5, 141.3, 136.9, 136.5, 132.7, 132.0, 129.8(2), 129.7(2), 127.9, 127.7(2), 127.1(2), 120.3, 113.3, 107.5, 69.7, 60.8, 56.8, 27.5, 21.6, 21.5; MS m/z 574 (M\(^+\)), 246 (10), 155 (27), 91 (100); HRMS m/z observed 574.1079 (M\(^+\)), calcd for C\(_{26}\)H\(_{26}\)S\(_2\)N\(_2\)O\(_9\) 574.1079; Anal. calcd for C\(_{26}\)H\(_{26}\)S\(_2\)N\(_2\)O\(_9\); C, 54.35; H, 4.56; N, 4.88. Found; C, 54.05; H, 4.58; N, 4.78.

There was also obtained 12.8 mg (39%) of 1-N-(p-toluenesulfonyl)-2-nitro-3-(2-p-toluenesulfonatoethyl)-6,7-dimethoxyindole (133) as a yellow solid: IR (neat) 2951, 1510, 1357, 1178, 1104, 978, 905, 812, 666 cm\(^{-1}\); \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.25 (d, J=8Hz, 2H), 7.62 (d, J=8Hz, 2H), 7.40 (d, J=8Hz, 1H), 7.40 (d, J=8Hz, 2H), 7.26 (d, J=8Hz, 2H), 7.04 (d, J=8Hz, 1H), 4.35 (t, J=6Hz, 2H), 3.95 (s, 3H), 3.56 (s, 3H), 3.25 (t, J=6Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)) \(\delta\) 154.5, 145.1, 142.5, 137.9, 136.5, 132.1, 129.9(2), 129.4(2), 128.4(2), 127.6(2), 126.0, 123.5, 118.2(2), 112.1(2), 68.7, 60.1, 56.5, 25.2, 21.7, 21.6.

6,7-Dimethoxy-5-N'-(p-toluenesulfonyl)-pyrrollo[3,2-d,e]-1,2,3-trihydroquinoline (116). A suspension of platinum(IV) oxide hydrate (40 mg, 0.162 mmol) in absolute ethanol (2 mL) was stirred under an atmosphere of hydrogen for 15 min. and then treated with a solution of 132 (62 mg, 0.108 mmol) in absolute ethanol (10 mL) and tetrahydrofuran (2 mL). The mixture was stirred for 30 min. and the colorless suspension was filtered over a cotton plug and concentrated to give crude 134 as a brown solid. This material was taken up into dry chloroform (18 mL) and N,N-diisopropylethylamine (59 \(\mu\)L, 0.339 mmol), and the solution was heated under argon at 61°C for 8 h and then at 55°C for 9 h. The mixture was cooled to room temperature, diluted with chloroform (30 mL), washed with
saturated aqueous sodium bicarbonate (1 X 10 mL) and dried over anhydrous sodium sulfate. Concentration followed by chromatography of the residual oil (silica gel 60, 2.5% methanol-chloroform) gave 25 mg (75%) of 116 as a tan foam. IR (film) 3389, 2938, 1623, 1509, 1171, 1098, 739, 673 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.86 (d, J=8 Hz, 2H), 7.21 (d, J=8 Hz, 2H), 7.17 (t, J=1 Hz, 1H), 6.10 (s, 1H), 3.85 (bs, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.37 (t, J=6 Hz, 2H), 2.87 (td, J=1,6 Hz, 2H), 2.34 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 152.6, 143.9, 136.7, 136.4, 129.5(2), 127.7(2), 127.1, 127.0, 118.7, 115.3, 114.8, 93.2, 61.1, 56.9, 42.7, 22.5, 21.6; MS m/z 372 (m⁺), 219 (35), 218 (38), 217 (100), 203 (25); HRMS m/z observed 372.11436 (M⁺), calcd for C₁₉H₂₀₅N₂O₄ 372.11437.

7-Methoxy-5-N′-(p-toluenesulfonyl)-pyrrolo[3,2-d,e]-2,3,6-tri-hydroquinolin-6-one (51). A mixture of 116 (8 mg, 0.023 mmol) in acetonitrile (0.35 mL) was cooled to 0°C and treated dropwise with a solution of ceric ammonium nitrate (31 mg, 0.057 mmol) in water (0.23 mL). After stirring for 45 min., the bright yellow mixture was diluted with methylene chloride (5 mL) and neutralized with 0.1M aqueous sodium bicarbonate. The layers were separated, the aqueous layer was extracted with methylene chloride (2 X 5 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The volume was reduced to approximately 1 mL and the solution was chromatographed (Chromatotron®, 1mm rotor, 5% methanol-chloroform) to give 4.7 mg (60%) of 51 as a yellow glass: IR (neat) 2924, 1668, 1619, 1576, 1463, 1377, 1184, 1118, 1005, 812 cm⁻¹; UV-VIS (CHCl₃) 305 (λ_max), 400 (sh) nm; ¹H-NMR (300 MHz, CDCl₃) δ 8.10 (d, J=8 Hz, 2H), 7.52 (s, 1H), 7.31 (d, J=8 Hz, 2H), 6.11 (s, 1H), 4.18 (t, J=7 Hz, 2H), 3.79 (s, 3H), 2.78 (t, J=7 Hz, 2H), 2.41 (s, 3H)
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For bibliographic citations relating to Part 1 see pp. 49-57.


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32. Swenton and co-workers observed similar fragmentation patterns with no apparent molecular ion in the mass spectra of quinone imine dimethyl ketals. (Swenton, J.S.; Shih, C.; Chen, C.-P.; Chou, C.-T. J. Org. Chem. 1990, 55, 2019 and references cited therein).

