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New approaches to total synthesis of quinoid antitumor agents: Cystodytins and discorhabdins

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Rice University, 1991
RICE UNIVERSITY

NEW APPROACHES TO TOTAL SYNTHESIS
OF QUINOID ANTITUMOR AGENTS:
CYSTODYTINS AND DISCORHABDINS

by

NORMAN EDWARD BYRNE

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

APPROVED, THESIS COMMITTEE

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May, 1991
Abstract

New Approaches to Total Synthesis of Quinoid Antitumor Agents: Cystodytins and Discorhabdins

By
Norman E. Byrne

A new pyridine synthesis is described. The key step involves a modified Knoevenagel-Stobbe reaction in which the treatment of an alkoxy-dihydropyran with hydroxylamine hydrochloride generates highly substituted pyridine ring systems. Approaches to efficient syntheses of important natural products in including aza-analogs of polynuclear aromatic hydrocarbons, Eupolauramine, and Streptonigrin are explored.

Antitumor agents Cystodytin A and B were synthesized in 13 steps from 4-hydroxyethyl cyclohexanone in an overall yield of 7%. This efficient total synthesis involves the new pyridine reaction and a photochemical nitrene insertion as crucial steps.

Various approaches are explored toward the total synthesis of antitumor agent Discorhabdin C. The first synthetically useful Paterno-Büchi reaction between benzoquinone and an olefin was discovered. Various applications of this reaction are described, including its use for the synthesis of Discorhabdin C.
ACKNOWLEDGEMENTS

First and foremost, I would like to thank my wonderful wife, Kelly, for her undying support and encouragement. This work truly would not have been possible without her. Thanks for hanging in there.

I would like to extend a special thank you to my advisor, Dr. Marco Ciufolini. His excellent guidance and unfailing support has been a tremendous influence and I will be forever indebted.

To my great friend and colleague, Mike Bishop, your friendship and warped sense of humor has made this otherwise trying time we call graduate school really fly by. I will miss the comraderie as well as the practical jokes.

I also owe a big thankyou to all of my former and present lab mates, Toshio, Cindy, Margaret, George, Angélica, Sandy, Hongbo and Melissa, and, to all of my good friends here at Rice, for friends make life worth living.

To Jane, thank you for all the help and the late night typing. Without her wizardry on the keyboard, this work would not have been possible. Thanks.

Finally, I would like to thank my parents, my brother and my sister for simply being a great family, providing continued support and for making all of this possible.
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</tbody>
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INTRODUCTION
Introduction

Marine natural sources have recently yielded several new cytotoxic alkaloids that share a structural motif in the form of an unusual polycyclic heteroaromatic or quinonoid nucleus. These substances form a small, but well-defined, family of natural products, examples of which include cystodytins,\(^1\) diplamine,\(^2\) the veramines,\(^3\) the shermilamines,\(^4\) dercitine,\(^5\) segoline and isosegoline.\(^6\) (Figure 1)

![Chemical structures of various alkaloids](image)

**Figure 1**

---

A key feature of the ring systems found in 1 - 9 is the presence of a highly substituted pyridine nucleus fused to additional cyclic subunits.

Many of the new compounds exhibit potent antitumor activity, sometimes with ID_{50} of 20 - 50 ng / ml towards the usual tumor lines, and are of interest as potential chemotherapeutic agents and/or as lead compounds for future generations of antineoplastic drugs.\(^1\)-\(^6\) Interest in the new substances is reinforced by recent reports suggesting that heterocyclic quinones possessing structures similar to 1 - 3 may exhibit marked inhibitory activity towards reverse transcriptase.\(^7\) Questions concerning possible antiretroviral activity of these natural products therefore arise.

The new alkaloids tend to be rare substances. It appears that the only practical way to secure sufficient samples of such compounds for further pharmacological evaluation is by total synthesis. However, an approach relying purely on established methods would be expected to run into serious difficulties. Clearly, efficient plans of attack may be formulated only if new methodology for the creation of highly condensed aromatic systems were available. The synthesis of amphimedin by the late J. K. Stille nicely underscores this point.\(^8\)

Careful retrosynthetic analysis led to the identification of an important strategic principle: syntheses of 1 - 9 might be greatly simplified if it were possible to assemble a pyridine subunit around a carbonyl template, as shown in Figure 2.

\[ R^2 \quad \xrightarrow{?} \quad R^3 \]

\[ R^2 \quad R^3 \]

---


An interesting method for the preparation of pyridines, patterned along these lines, entails treatment of a 1,5-dicarbonyl compound with a hydroxylamine salt, a process originally developed by Knoevenagel and Stobbe (Scheme 1).\(^9\)

![Diagram of chemical reaction](image)

Scheme 1

The Knoevenagel-Stobbe pyridine synthesis is not widely used, but sporadic applications, even in total synthesis, have been described.\(^10\) This chemistry lacks popularity for two main reasons. First, 1,5-dicarbonyl compounds are usually prepared by Michael reactions (cf. 12+13 → 14a). Unfortunately, conjugate additions are normally reversible, and an initially formed adduct 14a might (and a number of times does)\(^11\) revert to a new enolate / enone pair (cf. 15 and 16, Scheme 2). The newly formed substances undergo further reaction to provide a mixture of products that may not be easy to separate.

![Diagram of chemical reaction](image)

Scheme 2

Additional problems may be anticipated if the enolate components of the conjugate addition

---


were to be derived from aldehydes. Clearly, sequences involving such reactive, ill-behaved nucleophiles in expressed form would be fraught with severe difficulties, whereas the use of synthetic equivalents of such enolates inevitably adds several steps to a planned sequence. Second, 1,5-dicarbonyls rarely give good yields of pyridines when treated with hydroxylamine, because intra- and intermolecular condensations may consume much starting material into secondary reactions.

It was surmised that the requisite 1,5-dicarbonyl substrate might be introduced into the reaction in protected form. Protected 1,5-dicarbonyls should be unable to participate in secondary condensations: their sole permissible fate would be conversion into pyridines. An appealing feature of this plan is that heterocycloaddition of an α,β-unsaturated carbonyl substrate with a vinyl ether should provide ideal substrates for the planned studies. Reactions of the latter type have recently elicited renewed interest, following Danishesfky's discovery of the strong catalytic action that particular lanthanide complexes exert on them. The advantages of such modus operandi actually transcend the direct preparation of protected 1,5-dicarbonyls. Michael additions would be completely dispensed with, immediately nullifying the problems of Scheme 2, as well as removing the


need for preparing and handling carbonyl enolates (strong bases, inert atmospheres, anhydrous conditions, etc.). Vinyl ethers would be used as synthetic equivalent of the latter reagents. Vinyl ethers are of more practical use than enolates, they are less expensive, less sensitive, they are storable for a long period of time, and they lend themselves more readily to reaction scale-up, to the benefit of process chemistry. Moreover, ethyl vinyl ether and congeners would serve as readily available (and well-behaved) equivalents of aldehyde enolates. A feasibility-level plan was therefore formulated as shown in Scheme 3.

\[
\begin{align*}
\text{17} & \quad \text{cat. Yb(fod)3} \\
\text{18} & \quad \text{dichloroethane reflux} \\
\text{19} & \quad \text{HONH2 HCl} \\
\phantom{18} & \quad \text{CH3CN reflux} \\
\end{align*}
\]

Scheme 3

Enalns participate readily in the cycloaddition step of Scheme 3, however, analogous reactions of ordinary aliphatic enones (cf. 17, R1, R2, R3=alkyl) reportedly fail.\textsuperscript{15, 16} Such claims were readily substantiated. Molecular orbital considerations suggest that the carbonyl component probably participates in the reaction with its LUMO, while the vinyl ether contributes its HOMO. Obviously, the HOMO\textsubscript{ether} - LUMO\textsubscript{carbonyl} energy gap for reactions involving aliphatic enones must be excessively large to permit ready overlap / electron delocalization. It seemed reasonable that if the carbonyl component were conjugated with an aromatic structure, the energy of its LUMO might diminish to an extent sufficient to permit combination with vinyl ethers. Indeed, it was discovered that traces of lanthanide ions facilitate enormously the previously known cycloadditions of chalcones with vinyl ethers, reactions usually run at high temperatures and pressures.\textsuperscript{14} This key
observation provided the starting point for the development of a highly efficient pyridine synthesis.
CHAPTER ONE

DEVELOPMENT AND APPLICATIONS OF
A NEW PYRIDINE SYNTHESIS
Trivalent lanthanide ions in the form of shift reagents, especially Yb(fod)$_3$, were found to catalyze very strongly heterocycloaddition of any enone bearing an aryl group in conjugation with the carbonyl, either directly or in a vinylogous sense, with vinyl ethers$^{17}$ The aryl group need not be phenyl: furan, quinoline, and other subunits may be employed. This chemistry lends itself nicely to large scale manipulation without complications. In many cases, large quantities ($>30$ g) of the required enones are prepared in excellent yield ($>90\%$) and purity by condensation of a suitable ketone-aromatic aldehyde pair in aqueous/ethanolic medium.$^{18}$ Whenever the practicalities of the chemistry so dictate, Wittig or Wadsworth-Emmons reactions may be used quite effectively for the preparation of the substrates.

Cycloadditions of enones, but not of enals, are essentially irreversible at temperatures below 100-120° C. However, even a reversible reaction could only regenerate the same starting enone/ether combination. The problems of Scheme 2 are thus eliminated.

A wide range of enol ethers may be used in the cycloaddition, including highly substituted ones such as 2-ethoxy-2-butene and 1-methoxycyclohexene. Curiously, however, cyclic enol ethers like dihydropyran and dihydrofuran failed to combine with enones, as did alkynyl ethers.

\[
\begin{align*}
\text{NO REACTION} \\
\end{align*}
\]


Yields of cycloadducts are equally high when any (reactive) vinyl ether is used in the chemistry of Scheme 3. However, α-substituted enol ethers such as 2-methoxy-propene react considerably slower than any other class of ethers examined so far, while other 2-alkoxy-1-alkenes were found to isomerize to the more thermodynamically stable internal isomers faster than they would react with the substrate enones. For instance, 2-ethoxy-1-butene provided only products formally arising from 2-ethoxy-2-butene (Scheme 5). An NMR experiment indicated that isomerization of 21a to 21b takes place at 45-50° C in the presence of Yb(fod)₃.

![Scheme 5](image)

Adventitious water activated by the shift reagent is probably responsible for the observed phenomenon, which therefore may be regarded as an acid-mediated reaction, rather than a transition metal-promoted isomerization. Far from representing a limitation of the method, this is an important advantage. Enol ethers are made by acid-catalyzed decomposition of acetals. Such reactions furnish mixtures of kinetic (cf. 21a) and thermodynamic (cf. 21b) products. The mixtures are very difficult to resolve into individual components; moreover, the kinetic product is often dominant. Yet, the phenomena discussed above render the use of such mixtures inconsequential for the purpose at hand.

Two interesting observations were made in the course of investigations on the new heterocycloaddition. It was observed that enones conjugated to only one aromatic group react about 10 times slower with vinyl ethers than their more highly conjugated analogues,
even though yields of pyrans 19 are excellent in either case. This appears to be in complete agreement with the considerations of molecular orbital theory proposed above. More highly conjugated enones should have less energetic LUMO's, which should overlap more readily with HOMO's associated with vinyl ethers, thus increasing reaction rates. Second, it was found that when ethyl vinyl ether (23) is used, the reaction provides only cycloadducts which result from an endo type addition of the vinyl ether to the enone (24). The $^1$H NMR data from the resulting cycloadducts supports these assertions. An endo addition of the vinyl ether (Figure 3) should give an adduct 25 in which $H_A$ and $H_D$ are syn to each other. Therefore, the trans-diaxial coupling between $H_A$ and $H_B$ as well as the coupling between $H_D$ and $H_B$ should be in the range of 8-10 Hz, much larger than the coupling constants for equatorial-axial couplings ($J_{ax-eq} = 2-4$ Hz). Indeed, the coupling constants of $J_{H_A-H_B} = 9.1$ Hz, $J_{H_A-H_C} = 1.9$ Hz, $J_{H_B-H_D} = 10.7$ Hz, and $J_{H_D-H_C} = 6.7$ Hz indicate that the vinyl ether in fact took an endo approach during the reaction.

![Figure 3](image)

Dienones participate normally in the cycloaddition step (Scheme 6). No regioselectivity was found in the reaction of unsymmetrical aromatic dienones with vinyl ethers. For instance, 1-(4-nitrophenyl)-5-(2-furyl)-1,4-pentadien-3-one afforded 1:1 ratios of cycloadducts. However, unsymmetrical dienones of the type 34 react with complete regioselectivity at the less substituted double bond (Scheme 7). Reactions of the latter type are extraordinarily fast: complete conversion is achieved in only 15 - 20 minutes.
Crude dihydropyrans 19 react with moist hydroxylamine hydrochloride at ca. 80 °C to furnish pyridines 11 directly (85-95% yield). The latter frequently require no further purification. The choice of solvent and conditions for this reaction appears to be important. Initial experiments were run in homogeneous ethanolic solutions at reflux. Yields of
pyridines were not uniformly satisfactory, and in some instances they were rather poor. Rough characterization of byproducts obtained from unsatisfactory reactions indicated that materials believed to be bis-oximes were present. Presumably, these arose upon unraveling of the pyran ring and reaction of the 1,5-dicarbonyl compound thus obtained with two molecules of hydroxylamine. Considerable improvements were registered by carrying out the reaction in a heterogeneous system, wherein the effective concentration of hydroxylamine hydrochloride is low, and best results were observed upon refluxing the dihydropyran in a suspension of moist HONH$_2$·HCl in acetonitrile. This very polar solvent (ε = 39) presumably stabilizes very effectively the charged intermediates arising transiently in the course of the reaction.

Tables 1 - 4 demonstrate the wide range of pyridines which are available through this new reaction. Pyridocycloalkanes are useful intermediates$^{19}$ whose preparation involves procedures that are easily implemented in an industrial setting, but that are not practical in a synthetic laboratory (gas phase reactions, supported catalysts, high temperatures and pressures, etc.). Syntheses of these compounds are now facile (Scheme 8).

---

### Table 1: Pyridines Prepared by the New Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Vinyl Ether</th>
<th>Yield % of Cycloadduct</th>
<th>Pyridine</th>
<th>Yield %</th>
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<td>88</td>
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Table 2: Pyridines Prepared by the New Reaction

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<th>Entry</th>
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<th>Yield % of Cycloadduct</th>
<th>Pyridine</th>
<th>Yield %</th>
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### Table 3: Pyridines Prepared by the New Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Cycloadduct</th>
<th>Reaction Conditions</th>
<th>Secondary Adduct</th>
<th>Yield %</th>
<th>Pyridine</th>
<th>Yield %</th>
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<td><img src="image" alt="Pyridine" /></td>
<td>36</td>
</tr>
<tr>
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<td>57</td>
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<tr>
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<td>57</td>
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<td>90</td>
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</tbody>
</table>
Table 4: Pyridines Prepared by the New Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Vinyl Ether</th>
<th>Yield % of Cycloadduct</th>
<th>Pyridine</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="enone_a.png" alt="Image" /></td>
<td><img src="vinyl_ether_a.png" alt="Image" /></td>
<td>87</td>
<td><img src="pyridine_a.png" alt="Image" /></td>
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<tr>
<td>b</td>
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<td><img src="vinyl_ether_b.png" alt="Image" /></td>
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<td><img src="pyridine_b.png" alt="Image" /></td>
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<td><img src="vinyl_ether_c.png" alt="Image" /></td>
<td>78</td>
<td><img src="pyridine_c.png" alt="Image" /></td>
<td>56</td>
</tr>
</tbody>
</table>

Adducts from dienones afford alkenylpyridines (Scheme 6), useful synthetic intermediates of demonstrated value. These substances may also undergo ozonolysis of the olefinic linkage to afford pyrido cycloalkanones (Scheme 9, 70 - 85 % yield).
The vinyl ether-enone adducts are polyfunctional entities in their own right which lend themselves to chemical manipulations prior to pyridine formation. For instance, cycloadducts from acyclic dienones are now recognized as electron rich diene systems which may participate in normal Diels-Alder reactions. Dienophiles such as chloroacrylonitrile and methyl acrylate react readily to give the adducts 39a and 39b, which are noted to maintain the correct oxidation state of the dihydropyran ring system. Products of such "double cycloadditions" are easily converted into annulated pyridines 40a - 40b (Scheme 10).

Adducts from chalcones, e.g. 25, afford bromoacetals when treated with NBS in methanol (Scheme 11). The expected 3-bromopyridine 42 is readily obtained from 41. These systems are quite useful as synthetic building blocks for many natural products containing highly substituted pyridine rings. For instance, Heck reactions\(^\text{20}\) and related transformations might be applied to manipulate simple structure 42 into more complex systems.

Appropriate nucleophiles may displace bromide ion from 41, providing access to even greater ranges of pyridine end-products. The preparation of 3-aminopyridines has been of special interest in these laboratories, in connection with various synthetic studies. Therefore, access to those structures was investigated via intermediate 44. Treatment with sodium azide provided 43, from which azidopyridine 44 was obtained in excellent yield. Not only is it possible to introduce nitrogen in the protected azide form, but chemistry has been developed also to incorporate a primary amine directly. The primary cycloadduct 25 undergoes Leblanc cycloaddition21 with diethyl azodicarboxylate in hexane to give compound 45. A fascinating reaction occurs upon treatment of 45 with hydroxylamine hydrochloride: \textit{aminopyridine 46 is formed directly} (Scheme 11). Although no mechanistic studies were undertaken on this reaction, the formation of the free amine could

---

conceivably result from intermediates shown in Scheme 12. These various transformations demonstrate that this is a general reaction and that it offers a number of advantages even over more recent pyridine syntheses.\textsuperscript{22}

\begin{center}
\begin{tikzpicture}
    \node (n1) [label=above:HONH$_2$] at (0,0) {
        \begin{tikzpicture}
            \node (n2) [label=above:EtO$_2$C] at (0,0) {};
            \node (n3) [label=above:N] at (n2-|n2) {};
            \node (n4) [label=above:Ar] at (n3) {};
            \node (n5) [label=above:N] at (n4) {};
            \node (n6) [label=above:H] at (n5) {};
            \node (n7) [label=above:OEt] at (n6) {};
        \end{tikzpicture}
    };
    \node (n8) [label=above:[H$^+$ transfer]] at (n1) {};
    \node (n9) [label=above:EtO$_2$CNHNOH] at (1,0) {};
    \node (n10) [label=above:EtO$_2$CH, H$_2$O, N$_2$] at (2,0) {};
    \node (n11) [label=above:47] at (0,-1) {};
    \node (n12) [label=above:HONH$_2$] at (1,-1) {};
    \node (n13) [label=above:EtO$_2$CNHOH + 46] at (2,-1) {};
\end{tikzpicture}
\end{center}

Scheme 12

**Synthetic Applications**

It was felt, even at such an early stage of development, that the new pyridine-forming reaction offered indeed a number of important advantages over existing methods. Accordingly, research on possible synthetic applications was undertaken. Targets of opportunity were readily identified among several biologically active substances, as discussed below.

Many higher polynuclear aromatic hydrocarbons (PAH's) exhibit potent carcinogenicity.\textsuperscript{23} Examples include chrysene, 48, benzanthracene, 49, benz[a]pyrene, 50, etc. Replacement of a CH unit in these molecules with a nitrogen atom creates a family of aza analogs of PAH's. Aza-PAH's are often found to be even more potent carcinogens than their carbocyclic parents.\textsuperscript{24} These substances are widespread environmental


pollutants.\textsuperscript{25} The threat to public health that they pose has recently generated a great deal of interest in studying their interaction with life processes and their metabolic activation / fate. However, isolation of aza-PAH's from natural / environmental sources may not be practical, and biochemical studies have had to rely on synthetic materials.

![Chemical structures](image)

Figure 4

Syntheses of aza-PAH's tend not to be particularly efficient.\textsuperscript{26} Moreover, their condensed polyaromatic structures render their chemical modification or manipulation rather difficult. Fortunately, the synthesis of many aza-PAH's is greatly facilitated using the new method of pyridine formation. Aza-phanthrenes and the aza-chrysene were initially identified as representative (and important) synthetic targets.


The synthesis of aza-phenanthrenes started with commercially available α-tetralone (Scheme 13). A valuable precursor to unsubstituted 1-azaphenanthrene was prepared from 57, easily made using Mannich chemistry, followed by elimination of the quaternized trimethyl ammonium group. Cycloaddition of 57 with ethyl vinyl ether was very fast and the usual treatment with hydroxylamine hydrochloride gave dihydro-aza-phenanthrene in 63% overall yield from 57. In a like fashion, condensation of α-tetralone with benzaldehyde gave enone 60 in 88% yield. The now familiar two-step sequence provided 4-phenyl-dihydroazaphenanthrene 61 in 85% yield (Scheme 14). Actual dehydrogenation of the final intermediates to the fully aromatic compounds was not performed in order to avoid exposure to these extremely hazardous substances.

Scheme 13

Scheme 14

Furly dihydroazachrysene was synthesized starting from commercially available tetrahydrophenanthren-4-one (62). Condensation with furfural gave enone 63, as a yellow solid, m.p. 118-119° C. Combination with ethyl vinyl ether was smooth to give the cycloadduct, which, upon exposure to hydroxylamine hydrochloride, gave the furyldihydroazachrysene 64 directly (Scheme 15). These few examples illustrate just a fraction of the functionality which may be incorporated into these classes of molecules.

\[ 
\text{Scheme 15}
\]

Structural features analogous to those found in the aza-PAH's are observed also among particular natural products. One such compound is the interesting plant alkaloid, eupolauramine, 65.\(^{28}\) This unusual azaphenanthrene alkaloid was isolated in 1972 from the bark of *Eupomatia laurentiana* (family Eupomatiaceae), a small tree found along the eastern coasts of Australia and New Guinea, but its structure was determined only in 1976, by X-ray crystallography.\(^{29}\)

\[ 
\text{Figure 5}
\]

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The structure of the alkaloid proved sufficiently unique that it could not be solved by chemical and spectral methods on the very small quantity of material available. Low concentrations in natural sources has stimulated interest in a concise synthesis of the compound in order to determine biological activity, if any. A number of total syntheses have been reported to date,\textsuperscript{30} the most efficient of which relies on compound 66 as the key advanced intermediate.\textsuperscript{30a} (Figure 5) Preparation of 66 thus amounts to a formal total synthesis of eupolauramine.

Condensation of $\alpha$-tetralone with furfural gave enone 67. Cycloaddition with ethyl vinyl ether followed by treatment with hydroxylamine hydrochloride gave the furanodihydroazaphenantrrene (68) in excellent yield. The furan subunit is converted to the free carboxylic acid via ozonolysis in MeOH. Subsequent treatment of the very polar crude acid with diazomethane in CH$_2$Cl$_2$ gave compound 66 in 40% yield from 55 (Scheme 15a).

![Scheme 15a](image)

\textsuperscript{30} (a) Levin, J. I.; Weinreb, M. J. Org. Chem. 1984, 49, 4325; (b) Kikugawa, Y.; Kawase, M.; Miyake, Y.; Sakamoto, T.; Shimada, M. Tetrahedron Lett. 1988, 29, 4297; (c) Karuso, P.; Taylor, W. C. Aust. J. Chem. 1984, 37, 1271; (d) We would like to thank Prof. M. Weinreb for kindly providing spectra of the natural product as well as several important intermediates.
This intermediate was synthesized most effectively by Weinreb,\textsuperscript{30a} through a sequence requiring 6 steps and proceeding in 24\% overall yield. The new pyridine-forming reaction now affords the same compound in just 5 steps and in 40\% yield from $\alpha$-tetralone.

Another important natural product that continues to generate interest is Streptonigrin (70).\textsuperscript{31} This molecule, isolated in 1960 from \textit{Streptomyces flocculus}, is a potent antitumor agent and recently has been shown to be quite effective in inhibiting reverse transcriptase of the human immunodeficiency virus (HIV), the presumed causative agent of AIDS.\textsuperscript{7} Streptonigrin is known to cause single strand breaks in DNA\textsuperscript{32} and depletion of cellular ATP.\textsuperscript{31b} Because of the importance, yet scarcity of this compound, synthetic materials are clearly needed.

![Figure 6](image_url)

Consequently, several syntheses have been reported over the years.\textsuperscript{31,33} Though admirable efforts and great contributions to the science, these syntheses have not produced enough synthetic streptonigrin to perform the necessary biological testing. The main


reason for this lies in the difficulty of synthesizing the central pyridine ring C with all the 
necessary substitution. Our method should allow facile construction of that pyridine ring. 
A model system was investigated to determine the feasibility of such an approach.

The target model was of the structure 71a,b where R could be H or CH₃. With R = 
CH₃, the required carboxylic acid could easily be introduced by oxidation chemistry. 
Readily available 2-acetylquinoline and 2,3,4-tri(methoxy)benzaldehyde were condensed in 
the usual manner to give a bright yellow solid enone 74, m.p. 117-118° C, in 92% yield. 
Subjection of the enone to ethyl vinyl ether with Yb(fod)₃ gave the cycloadduct in near 
quantitative crude yield. Treatment of the enone with 2-methoxypropene yielded the 
corresponding cycloadduct in 99% crude yield. To our dismay, conversion of the 
cycloadducts to the corresponding pyridines 71a and 71b occurred in only 25-30% 
chromatographed yields. Unfortunately, at the time of these investigations, the pyridine 
forming reactions were conducted in EtOH. Only later was it found that acetonitrile was a 
far superior solvent for the pyridine reaction, consequently raising the yields of 71a and 
71b to 43% and 33%, respectively. Although the improvement in yields is modest, 
current work on the total synthesis of Streptonigrin in our laboratories demonstrates that 
considerably more complex systems proceed in far better yields (80-85%).

Scheme 16
Conclusions

The new technique of pyridine formation provides extremely efficient access to a wide range of substituted pyridines. This should greatly facilitate the preparation of other natural products incorporating such ring systems. The synthesis of the azaphenanthenes, the azachrysenes, eupolauramine and the streptonigrinoids are just a few examples illustrating the effectiveness of this reaction. Not only are the pyridines easily made, but the starting materials used to create the enones and enol ethers are usually quite inexpensive, another attractive feature to the synthetic chemist. This, coupled with the high yields of the cycloaddition and the pyridine formation render this method quite valuable for the creation of highly substituted heterocyclic frameworks.
CHAPTER TWO

THE TOTAL SYNTHESIS OF CYSTODYTINS
Background

Cystodytins A, 75, and B, 76, are cytotoxic agents which were isolated from the Okinawan tunicate, *Cystodytes dellechiajei* (Della Valle), by Kobayashi and coworkers in 1987 as an inseparable 3.5 : 1 mixture.\(^1\) Cystodytin C, 77, was also obtained from the same source in smaller quantities, but was found to be almost devoid of biological activity. The mixture of cystodytins A and B strongly inhibited L1210 murine leukemia (IC\(_{50}\) of 0.24 \(\mu\)g/ml), and showed powerful Ca-releasing activity in the sarcoplasmic reticulum, 36 times greater than caffeine.\(^34\)

![Figure 7](image_url)

**Figure 7**

Cystodytins are extremely rare substances.\(^35\) The quantities of 75 - 77 isolated from natural sources have been sufficient only for preliminary screens, while further evaluation of their potential therapeutic value has been hampered by lack of material. In addition, questions of possible differences in biological potency, toxicity, or mechanism of action for cystodytins A or B could not be resolved in any case, because of difficulties encountered in the separation of the two substances. Bioassay and analogue work clearly require totally synthetic cystodytins.


\(^{35}\) Personal communication from Dr. Jun'ichi Kobayashi of Mitsubishi-Kasei Institute of Life Sciences.
A plan of attack based on the new pyridine-forming reaction illustrates the considerable degree of simplification that may be achieved in the synthesis of compounds such as 75 - 77 using the new methodology. Disconnection of the imine linkage led to recognition of compound 78 as a key advanced intermediate. The substituent X in this molecule should allow one to effect cyclization of the future ring C, but its precise nature would be determined later. Symmetrization further simplified the molecular framework, and identified 80 as the starting material. Not only will the dienone give the same product irrespective of the side of the enone participating in the reaction, but also the remaining benzyldiene group will provide the seeds for the required carbonyl function via a future ozonolysis (Scheme 17).
Model Studies and Initial Approaches

It should be pointed out that at the onset of these investigations, the scope and limitations of the new pyridine-forming reaction had not been explored. A model study was therefore undertaken in order to determine the feasibility of the planned approach. Ketone 38 appeared to be a good target for this study. Condensation of cyclohexanone with benzaldehyde in aqueous medium produced dienone 29 as bright yellow crystals, m.p. 101-102 °C, in 91% yield. The cycloaddition with ethyl vinyl ether proceeded without event to give the adduct 30, which was then subjected to pyridine formation with hydroxylamine hydrochloride in refluxing acetonitrile. Pyridine 31 was thus obtained in 86% overall yield from 29. Ozonolysis at -78 °C in MeOH cleaved the benzylidene group to give the target compound in 75% yield (Scheme 18). The success of this sequence induced us to launch a full effort directed towards the total synthesis of cystodytins.

![Scheme 18](image-url)
It will be recalled that the nature of group X in dienone 80 was undecided, so several possibilities were considered. Originally, X = NO₂ seemed to be the most straightforward choice. It was reasoned that the pyridine ketone 81 could be fully aromatized and then oxidized to the para quinone 83 at a later stage of the synthesis. Upon reduction of the nitro group, the resulting amine would then condense with the upper carbonyl and complete the ring system (Scheme 19).

Scheme 19

Unexpected difficulties materialized upon attempted condensation of o-nitrobenzaldehyde with cyclohexanone under the usual conditions. Addition of basic reagents to a mixture of the carbonyl components, or addition of the latter to a basic solution, caused an immediate, vigorous exothermic reaction which caused darkening and fuming of the solution, but produced no identifiable products. While the reasons for this behaviour were not investigated further, it is possible that decarbonylation of the aldehyde might have occurred, as described by Forbes.\textsuperscript{36} Independent work in these laboratories suggested that the problem might have been corrected by engaging a Wittig reagent in the condensation step. However, serious difficulties of a different nature would have been incurred in its (multistep) preparation, resulting in considerable erosion of overall synthetic efficiency. This result forced us to consider another possibility for the X group.

Instead of using ring D as the carrier of the nitrogen functionality and ring B as the acceptor, their roles could be reversed. So, if X were bromine, and ring B had an amino

\textsuperscript{36} Forbes, E.J.; Gregory, M.J. \textit{J. Chem. Soc. (B)} \textbf{1968}, \textit{205}.
substituent appropriately located, it might be possible to cyclize ring C under catalysis by Pd(PPh₃)₄, by analogy with Boger's synthesis of lavendamycin.³⁷ (Scheme 20)

\[
\begin{align*}
&\text{AcO} & \text{Br} & \text{H₃N} & \text{OR} \\
&\text{85} \quad \xrightarrow{\text{Pd(PPh₃)₄}} \quad ? \\
&\text{HN} & \text{OR} \\
&\text{86}
\end{align*}
\]

Scheme 20

In contrast to o-nitrobenzaldehyde, o-bromobenzaldehyde condensed smoothly with ketone 87 and was acetylated (pyridine, Ac₂O) to give dienone 88, m.p. 92-94°C. The enone reacted with ethyl vinyl ether in the expected fashion to give the dihydropyran, which was then converted to the pyridine (89) with hydroxylamine hydrochloride in refluxing acetonitrile. Ozonolysis of 89 cleaved the bromo benzylidene group to yield the desired pyridine ketone 90 (Scheme 21). It is noted that the bromo benzaldehyde released during the ozonolysis may be recycled for use in the original condensation, thus conserving reagents.

\[
\begin{align*}
&\text{OH} & \xrightarrow{1.2 \text{ eq.}} & \text{CHO} & \xrightarrow{\text{EtOH/H₂O}} & \text{Br} & \xrightarrow{\text{EtOCH=CH₂, cat. Yb(iod)₃}} & \text{OAc} & \xrightarrow{\text{DCE, reflux}} & \text{Br} \\
&\text{87} & & \text{88} & & \xrightarrow{1. \text{HO₃H₂, HCl, CH₃CN, reflux}} & \text{Br} & & \text{89} \\
&\text{OAc} & \text{Br} & \text{Br} & \text{Br} & \text{89} & & \text{O₃} & \xrightarrow{\text{MeOH, -78°C}} & \text{OAc} & \text{Br} & \text{Br} & \text{89} & & \text{O₃} & \xrightarrow{\text{MeOH, -78°C}} & \text{OAc} & \text{Br} & \text{Br} & \text{89}
\end{align*}
\]

Scheme 21

In order to effect the final ring closure, it was necessary to first aromatize ring B. Treatment of 90 with isopropenyl acetate followed by brief treatment with DDQ gave fully aromatic quinoline 91 (Scheme 22).

![Chemical diagram](image)

Scheme 22

According to the literature, many quinolines will become nitrated at both positions 5 and 8, unless one of them is blocked. It was hoped that since the acetoxy group occupied position 8, nitration should occur exclusively at the desired position 5. However, repeated attempts at nitration using a variety of methods gave disturbing results. Apparently, steric congestion and/or electronic effects prevent position 5 from becoming nitrated. Mild conditions (HNO₃ / AcOH / Ac₂O / 0 °C) induced selective nitration of the bromo phenyl ring, giving mononitro derivative 93 (Scheme 23).

![Chemical diagram](image)

Scheme 23

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More forcing conditions delivered dinitro derivative 94. Finally, nitration by the mixed acids method delivered trinitro derivative 95. Obviously, the order of reactivity of available sites for nitration is bromophenyl C-5' (fastest), quinoline C-7, then position C-5 thereof (slowest).

This unfortunate turn of events redirected our attention to creating a substrate in which substituent X is already a nitrogen functionality. Compound 91 resisted displacement of bromine with phthalimide under catalysis by copper salts (Scheme 24), so a return to the original idea of incorporating nitrogen functionality into ring D from the beginning proved to be the key to the synthesis.

Fortunately, an azido group proved to be quite satisfactory for our purposes. Ketone 87 underwent smooth condensation with o-azido benzaldehyde\textsuperscript{39} in ethanolic aqueous base, and the intermediate alcohol was acetylated (pyridine, Ac\textsubscript{2}O) to give diene 96, m.p. 98.5-100\(^\circ\) C, as a yellow crystalline solid. Treatment of 96 with ethyl vinyl ether produced the dihydropyran, which was then transformed into pyridine 97. Ozonolysis of 97 yielded the desired pyridine ketone 98 in 56% yield from 96 (Scheme 25).\textsuperscript{40} It is remarkable that the azido group survived all these manipulations. With 98 in hand, the

\textsuperscript{39} The o-azidobenzaldehyde was prepared using a method provided by Prof. Tohru Fukuyama of this department. The Fukuyama procedure is similar to the protocol described by Arakani, M. A.; Smalley, R. K.; Smith, R. H. \textit{J. Chem. Soc., Perkin Trans. 1} 1986, 261, 4139, but results in better yields. Details are provided in the experimental section.

\textsuperscript{40} Ciufolini, M. A.; Byrne, N. E. \textit{Tetrahedron Lett.} 1989, 30, 5559.
stage for completion of the crucial ring C had been set.

Formation of Ring C

A number of key transformations could conceivably produce an advanced tetracyclic structure from the versatile intermediate 98, but an intramolecular aza-Wittig reaction from p-quinone 99, a cycloaddition between a $\Delta^5$ olefin (quinoline numbering) and the azide in a structure such as 101,\(^{41}\) or a direct insertion of a nitrene, arising through deazoniation of the azide, into the neighboring C-H bond\(^{42}\) seemed to offer particularly good opportunities for success. Such general strategies may be described as a nucleophilic, a pericyclic, and an electrophilic mode of cyclization (Scheme 26).

Exploration of the nucleophilic mode of cyclization required the intermediacy of quinone 99. Ring B was aromatized to the 8-hydroxyquinoline by first forming the enol acetate of the ketone using isopropenyl acetate and a trace of triflic acid. Subsequent treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene

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dehydrogenated 104 to 105 in just 10 minutes. Oxidation of ring B to the quinone first required selective removal of the phenolic acetate, a potentially difficult step. However, the selective cleavage occurred remarkably smoothly upon treatment with aqueous sodium bicarbonate in THF to give hydroxy quinoline 106 as a white solid, m.p. 97-100 °C (Scheme 27).

In contrast, oxidation of 106 to the quinone proved to be quite troublesome. Substitution at position 4 of 8-hydroxyquinolines generally precludes formation of the para quinone, and our case was no exception. As a result of this, a variety of oxidants either
gave complex mixtures (DDQ/aq. acetone; CAN/aq. CH₃CN) or did not react at all (O₂/salcombe). Successful oxidation was eventually achieved using Fremy's salt, which produced only the ortho quinone 107 as an orange solid (m.p. 174-177 °C) and none of the para isomer.⁴⁰ (Scheme 28) Although the regioselectivity of this reaction is not unprecedented in the literature, it prevented implementation of the nucleophilic approach.

The structure of 107 was unequivocally determined by its gated-decoupled $^{13}$C NMR spectrum. The $^{13}$C resonances of the carbonyl carbons in this molecule appear at 179.4 and 178.5 ppm under broadband decoupling conditions. In the gated-decoupled mode, the

178.5 ppm resonance remained as a sharp singlet, but the 179.4 ppm signal became a doublet of triplets (J_1=11 Hz, J_2=J_3=J_4=3.8 Hz). The ortho, but not the para quinoid structure is consistent with these results. The splitting pattern may only be explained based on 3J coupling of the C-7 carbon (quinoline numbering) to the protons on the neighboring side-chain methylene (J = 3.8 Hz) and to the olefinic hydrogen at C-5 (J = 11Hz). The C-8 carbon experiences only 4J interactions with those protons (J ~ 0 Hz), therefore it appears as a singlet. The para isomer would still show one of the carbonyls as a doublet of triplets, but the other signal would be split into a doublet, because of 2J coupling between the C-8 carbon and the C-7 proton.\textsuperscript{44}

Although the Fremy oxidation produced the undesired regioisomer of the quinone, the compound was a perfect candidate for the pericyclic approach to the ring closure. To our delight, thermolysis of 107 in refluxing toluene produced directly the hydroxy-cystodytin congeners 110 as a bright orange solid (dec. 204 °C), which precipitated from the reaction solution.\textsuperscript{40} Although the mechanism of this transformation is unclear, an initial step may involve a 1,3-dipolar cycloaddition of the azide with the olefin to produce the intermediate triazoline, which then extrudes molecular nitrogen and rearranges to the final quinonimine.\textsuperscript{45} (Scheme 29) Unusual quinone-azide reactions of this type will undoubtedly be useful for the synthesis of other heterocyclic polycyclic aromatic compounds.

Compound 110 has the entire ring system of the Cystodytins, but it incorporates an extra hydroxy functionality. As shown in Scheme 30, the hydroxy group is particularly amenable to derivatization to either its acetate, 111 (Ac_2O, pyridine), or its triflate, 112 (Tf_2O, Hunig base). Theoretically, the triflate derivative is a perfect candidate for Ortar


\textsuperscript{45} Reactions of this type are well precededented. For example, see: (a) Pearson, W. H.; Lin, K.-C. \textit{Tetrahedron Lett}. 1990, 31, 7531; (b) Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. \textit{J. Am. Chem. Soc}. 1989, 111, 2580.
deoxygcnation. However, all attempts to reductively cleave the oxygen functionality resulted initially in rapid reduction of the quinone ring to the hydroquinone, followed by a slower cleavage of the trifluoromethanesulfonyl group. In all cases, none of the desired reduced compound was obtained and the hydroxy quinone was obtained in quantitative yield (Scheme 31).

Scheme 29

Scheme 30

This series of failures was broken by the results of parallel investigations of the electrophilic method of ring closure. The electrophilic approach relies on the ability of the azide to produce a nitrene or a nitrenoid, upon deazoniation. The (formal) insertion of a nitrene, or a nitrenoid, into a C-H bond represents a very unusual mode of reactivity. Reports of successful reactions of this type are scant in the literature.\textsuperscript{47} Moreover, controversy exists concerning the precise mechanism of such processes, particularly in regard to the spin state of the nitrene.\textsuperscript{48} The easiest way to generate a nitrene from an azide is through thermal activation. Initial investigations into this mode of reactivity involved therefore thermolysis of compound 98.

Prolonged heating of 98 in refluxing toluene produced no reaction and only starting ketone was recovered. However, heating the ketone in degassed solution of o-dichlorobenzene at 200 °C rapidly produced carboline 113, dec. 260-265 °C, in 80% yield (Scheme 32). Unfortunately, none of the desired cystodytin-like product was formed. Likewise, thermolysis of compound 106 under identical conditions produced the carboline 115 as by far the major product, even though a proton NMR spectrum of a chromatographic fraction obtained during the purification of 115 exhibited signals not inconsistent with structure 114 (Scheme 33). Preferential formation of the carbolines may

\textsuperscript{47} McRobbie, I. M.; Meth-Cohn, O.; Suschitzky, H. \textit{J. Chem. Research} 1977, 17.
be rationalized by the formation of a singlet nitrene.\footnote{Smith, P. A. S.; Hall, J. H. \textit{J. Am. Chem. Soc.} \textbf{1962}, \textit{84}, 480.} Cycloaddition to the $\pi$ system and rearrangement of the intermediate aziridine will lead to the observed products. Furthermore, experimental results indicate that even though compound 106 should produce some of the desired tetracyclic product, the kinetic preference for 5- versus 6-member ring closure is dominant and favors formation of the carboline.

A search of the literature revealed an excellent investigation by Meth-Cohn in 1967 dealing with the intramolecular reactivity of singlet versus triplet nitrenes.\footnote{Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzky, H. \textit{J. Chem. Soc., Perkin Trans. 1} \textbf{1977}, \textit{2194}.} Results described in that paper suggested that if a triplet nitrene were to result from deazonation of
the azide, a cystodytin-like end product might result, via hydrogen abstraction of the more weakly bound benzylic methylene hydrogen atom, followed by radical pair recombination. This mode of reactivity was initially explored using pyridine ketone 98. Triplet-sensitized photolysis of 98 under Meth-Cohn conditions (10% acetophenone in chlorobenzene, 110°C, 250 W Sylvania sunlamp) indeed produced a mixture of diastereomeric lumiproducts 116 (Scheme 34). Column chromatography allows isolation of the mixture of these compounds as a thick, intensely purple oil. Undoubtedly, these substances are responsible for a remarkable color change of the reaction solution, from initially clear and colorless to a very deep purple, during photolysis.

![Chemical Structures](image)

Initial Route

Scheme 34

A key observation was made that the material is slowly air oxidized to 100, especially in the presence of silica gel; however, other products are also formed. It was reasoned that a much cleaner method of oxidation would be effected by treating the chromatographed 116 with DDQ, but a substantially more convenient protocol involved titration of the crude photolysis mixture with DDQ at room temperature. Indeed, treatment of the crude mixture with DDQ converted the lumiproduct to bright yellow quinonimine 100, m.p. 157-160 °C, in 31% yield after column chromatography. This modification not only avoids isolation of the sensitive intermediate 116, but also eliminates a chromatographic step, thereby adding to overall efficiency. It was also discovered that photolysis may be carried out by
irradiating 98 in a plain solution of o-dichlorobenzene in a pyrex flask maintained at 110° C. Evidently, the pyridyl ketone possesses chromophoric properties similar to acetophenone so that internal triplet sensitization was possible. Moreover, omission of the acetophenone greatly simplifies the workup and ensuing chromatography. Titration of the crude photolyzed mixture with DDQ again provided 100 in yields identical with those of the externally sensitized reaction. In summary, the best conditions consisted of degassing a dilute solution of the ketone 98 in chlorobenzene and then photolyzing the heated (110° C) solution until all starting material vanished by TLC. Then, the solution was titrated with DDQ until the primary lumiprodust (purple spot) was completely converted to 100. After chromatography, quinonimine 100 was isolated in 32% yield as a bright yellow solid (m.p. 157-159° C). (Scheme 35)

With the entire ring system complete, all that remained was elaboration of the side chain to complete the synthesis. However, all attempts to hydrolyze the acetate group resulted in decomposition of the sensitive quinonimine within minutes. It became obvious that formation of the sensitive quinonimine ring system should be performed last, after appropriate modifications of the side chain have been completed. Since the calculated51 UV absorptions of the unsaturated amide subunits of compounds 75 and 76 do not overlap

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with the photochemically reactive n-π* transition of the pyridyl ketone, it was anticipated that photolysis of those substrates should produce the cystodytins.

Synthesis of Cystodytins A and B

Ketone 98 was protected as the ethylene ketal. Hydrolysis of the acetate (K₂CO₃/MeOH) uneventfully gave the alcohol 117. The alcohol was converted to the amine using standard Gabriel chemistry. The alcohol was activated as the mesylate and then converted to the phthalimide derivative (potassium phthalimide, DMF). The phthalimide was easily cleaved with hydrazine in MeOH to give amine 118 in 80% overall yield from 117 (Scheme 36).

The amine intermediate 118 represents the point at which the syntheses of cystodytins A and B diverge. Completion of cystodytin A involved treatment of the amine with β,β-dimethylacryloyl chloride, which cleanly furnished the dimethylacrylamide. Acid hydrolysis of the ketal gave the key intermediate azido ketone 119 (67% yield from 118) ready for the crucial photolytic ring closure. It was truly delightful to observe that irradiation of compound 119 in chlorobenzene, followed by treatment with DDQ, provided fully synthetic cystodytin A (75) as yellow crystals, mp 182-184 °C, in 30% yield after chromatography (Scheme 37).
Likewise, formation of cystodytin B commenced with treatment of 118 with tigloyl chloride, followed by ketal hydrolysis to give azido ketone 120 in 72% yield from 118. Again, irradiation of ketone 119 followed by DDQ workup and chromatography gave cystodytin B (76) as yellow crystals, m.p. 180 - 182 °C, in 31% yield (Scheme 38). In addition, it known that Cystodytin C may be produced by hydration of the acrylamide subunit of cystodytin A by treatment with 6N aq. HCl. Therefore, the synthesis of cystodytin A amounts to a formal synthesis of cystodytin C. The cystodytins had been conquered.
Conclusions

This work represents the first total synthesis of both Cystodytins A and B, both proceeding in 8% overall yield from enone 96. Although it was not possible to secure authentic samples of the cystodytins, the spectral data of the synthetic material are in complete agreement with the literature.\textsuperscript{1} The minor discrepancy between the melting points of the natural and synthetic cystodytins is understandable in that the literature m.p. refers to an inseparable 3.5:1 mixture of 75 and 76. Such a mixture was prepared and its melting point was measured as 180-183°C, identical to that reported for the mixture. With the availability of the 7-hydroxy congeners of 110 as well as the natural products themselves, further pharmacological evaluation should become possible. Moreover, materials similar to 110, but possessing side chains such as those found in 75 - 76 could be derivatized to furnish cystodytin analogues. Alternatively, unique side chains could easily be incorporated onto the true cystodytin ring system to furnish compounds which would be difficult - or even impossible - to prepare from the natural products, since the latter do not lend themselves readily to chemical modification.

From a chemical standpoint, this synthesis demonstrates the usefulness of our pyridine-forming reaction, and the value of thermal as well as photochemical transformations of azides in the construction of complex polycyclic heteroaromatic frameworks. The principles demonstrated will assuredly facilitate the preparation of many other members of the family of natural products to which the cystodytins belong.

On a final note, even though additional research may unveil a viable method to remove the undesired 7-hydroxy group from 110 to provide the natural products, such a route would add at least seven steps to the synthesis already described, and probably eleven, including protection / deprotection of two sensitive intermediates. Thus, the moderate yields of the final photochemical step are entirely acceptable.
CHAPTER THREE

A SYNTHETIC APPROACH TO DISCORHABDIN C
Background

Blunt and Munro have recently described the isolation of highly cytotoxic pigments from various New Zealand sponges of the genus *Latrunculia*. The new compounds were named Discorhabdins A, B, C, and D.\(^{52}\) It is interesting to note that researchers in Japan independently isolated identical compounds from the Okinawan sponge, *Prianos melanos*, and subsequently named them Prianosins A, B, C, and D.\(^{53}\) Discorhabdin E was isolated later as a very minor fraction of the New Zealand sponge.\(^{54}\) (Figure 8)

![Chemical structures](image-url)

Figure 8


The molecular framework of these compounds represents a new class of ring system. The pyrrolo[1,7]phenanthroline skeleton of the iminoquinone chromophore is previously unreported, and the C$_{18}$N$_{3}$ fused pentacyclic framework has only been reported from four phyla of marine animals: a tunicate, a sponge, an ascidian and a sea anemone.$^{1,55}$ Compounds 121 - 125 all exhibit potent cytotoxicity and antimicrobial activity, both in vitro (IC$_{50}$ values against the P388 cell line in the range 0.03-0.01 µg/ml), and in vivo, but only Discorhabdin D was considered to have significant in vivo P388 activity (T/C 132% at 20 mg/kg; 120% is considered significant). Notably, the cystodytins$^{1}$ and amphimedine$^{55a}$ (isolated from a tunicate and a sponge, respectively) are also active against the P388 cells (ED$_{50}$ at 2.8 µg/ml).

![Diagram](image)

**Figure 9**

Perhaps the most interesting aspect of these compounds is the presence of the unique fused spirocyclic ring system. Examples in the literature to create such systems are sparse. Due to the interesting biological activity of the Discorhabdins, their extremely low concentration in natural sources, and the difficulties associated with chemical modification of the natural products, totally synthetic materials are needed for further pharmacological

evaluation. Therefore, we embarked on research directed towards their total synthesis. The goal that we selected for a feasibility-level investigation was the simplest of the new products: discorhabdin C.

Retrosynthetic Considerations

Prudence advocates that in planning an attack on a molecule of this complexity, potentially difficult steps be performed early, in order to avoid the possibility that an insurmountable roadblock may be encountered well into the synthesis. The spirocyclic ring, with its quaternary carbon joined to an aromatic / quinoid nucleus, constitutes undoubtedly the most problematic subunit of the molecule. Installation of the spirocycle was thus identified as our first priority.

Scheme 39

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Retrosynthetic analysis of Discorhabdin C envisioned introduction of the future ring A as a plain 4,4-disubstituted cyclohexanone, later to be advanced to the dibromodieneone stage. Further simplification may be achieved by disconnection of the quinonimine, because an indoloquinone such as 127 may arise through oxidation of 128, wherein the indole segment may be installed starting, for example, with a Claisen rearrangement of 129. A logical precursor to 129 is 130, which we defined as the primary subtarget of the synthesis (Scheme 39).

Intermediate 130 is recognized as a 4-aryl-4-alkylcyclohexanone. Structures of this type are also found in Amaryllidaceae\textsuperscript{57} and Sceletium \textsuperscript{58} alkaloids and in a number of psychoactive drugs of great pharmacological importance.\textsuperscript{59} On the other hand, existing methods for the construction of these structures are not particularly efficient, as evident from reviews dealing with the subject.\textsuperscript{60} The development of new chemistry by which synthetically challenging quaternary carbon centers could be generated may thus have important ramifications beyond the discorhabdin problem.

An observation that underscored the need for new technology in this general area was made during initial attempts to obtain 132 by Claisen rearrangement of 131 (Scheme 40). It has long been known that \(\beta,\beta\)-disubstituted allylic ethers such as 131 rearrange with great difficulty and only under extreme conditions, presumably because of steric problems.\textsuperscript{61} Thus, it was not entirely surprising that 131 was recovered unchanged after


\textsuperscript{61} Tarbell, D. S. \textit{Org. React.} 1944, 2, 1.
20 hrs at reflux in N,N-diethylaniline. Recent Claisen procedures\textsuperscript{62} involving Lewis acidic catalysts\textsuperscript{63} also gave disappointing results. The synthesis of 132 was in jeopardy because of a limitation of a very old reaction. Certainly, alternative retrosynthetic schemes could be devised, and indeed a recent model study by Confalone\textsuperscript{56b} proposes a different approach. However, it was felt that the logic of Scheme 38 might offer a number of advantages. Radically different chemistry for the construction of structures of the type 130 was thus developed.

New Photochemical Methodology for the Synthesis of 4-Aryl-4-Alkyl Cyclohexanones

Paterno-Büchi reactions of benzoquinones with olefins were first described in the 1960's.\textsuperscript{64} Simple olefins were found to react reasonably efficiently with 1,4-benzoquinone, providing structures 136a - 136b in acceptable yield (Scheme 41). The light source used for such reactions was a common Hanovia lamp. The photoprocess leading to 136a - 136b is believed to involve an initial $n$-$\pi^*$ transition of the quinone ($\lambda_{\text{max}} = 435$ nm), which, now in its excited state, behaves as a synthon for the hypothetical zwitterion 134b (Figure 10).\textsuperscript{65}

\textsuperscript{62} For a review, see Lutz, R. P. \textit{Chem. Rev.} 1984, 84, 218.


Unfortunately, this chemistry is affected by two limitations that have prevented its use in synthetic endeavors. First, unsymmetrical olefins react with photoexcited quinones to furnish adducts in a non-regioselective manner. We verified such claims, and we further observed that even isopropenyl acetate gave a 1:1 mixture of adducts 137a and 137b (Scheme 42).
Second, the common photochemical sources have limited power output in useful regions of the spectrum, making these reactions rather slow and difficult to scale up. A quantum improvement introduced by M. Wilson in 1982\(^{66}\) was the use of an argon ion laser as the photosource, a refinement that rendered these reactions considerably more efficient. In spite of this, no further work in this area has apparently been done, nor have synthetic application of such processes ever been reported.

We discovered alkyldiene cyclohexanes such as \textbf{138} do indeed participate in the phocycloaddition with substantial to virtually complete regioselectivity. This key observation increases enormously the usefulness of the photoreaction for synthetic purposes, and made possible the development of a protocol for the preparation of \textbf{130}.

Olefin \textbf{140} was easily synthesized as shown in Scheme 43. Cycloaddition with benzoquinone occurred readily upon irradiation in benzene solution with light from an argon ion laser running with all lines,\(^{67}\) and emitting 7 W of power (Scheme 44).

\begin{align*}
\text{138} & \xrightarrow{(\text{MeO})_2\text{P(O)CH}_2\text{CO}_2\text{Et}, \text{t-BuOK, DME}} \text{139} & \xrightarrow{1. \text{LAH, Et}_2\text{O}, 2. \text{pyridine, Ac}_2\text{O}} \text{140}
\end{align*}

Scheme 43

Careful scrutiny of the proton NMR spectrum of the crude reaction mixture showed clearly


\(^{67}\) Emission at 514.5, 501.7, 496.5, 488.0, 476.5, and 457.9 nm is observable in the multimode configuration. The power output of the laser was attenuated to 7W in order to prevent vaporization of the solution and/or damage to the reaction vessel. Equally good results are obtained if the laser is operated in a tunable mode at \(\lambda = 457.5\) nm (ca. 1W) or \(\lambda = 476.5\) nm (ca. 2W).
the presence of the desired photoadduct 141a, recognizable from the resonance of the oxetane methine proton, observed as a triplet around 4.70 ppm, but failed to reveal any evidence that regioisomer 141b was present. The oxetane methine proton of compound 141b would be seen as a triplet at around 3.30 ppm, based on the $^1$H NMR spectra of related systems that gave regioisomeric mixtures. The structural assignment is further supported by the $^{13}$C NMR spectrum of 141a. The oxetane quaternary carbon resonates at 53 ppm, excluding the possibility that it may be connected to an oxygen atom. Pure compound 141a was obtained in 58% yield (75% based on recovered starting material) by a simple filtration chromatography, which separated it ($R_f = 0.42$) from unreacted olefin and quinone ($R_f = 0.60$).

\[
\begin{align*}
\text{133} &+ \text{140} \xrightarrow{hv, benzene, 58\%} \text{141a} &\text{ONLY} \\
\delta = 4.70 \text{ ppm} &\text{141b} &\text{NONE} \\
\delta = 3.30 \text{ ppm} &
\end{align*}
\]

Scheme 44

Photoreactions of this type are experimentally very simple to carry out. A benzene solution of quinone and olefin is prepared in an Erlenmeyer flask, which is sealed with an adapter constructed from a bored septum, the perforation of which is sealed with a snugly fitting, inexpensive glass diverging lens (focal length = 5 cm, see Figure 11). The solution is thoroughly degassed by bubbling argon through it, the entire apparatus is placed
in an ice bath, and irradiation is commenced. The diverging lens flares out the extremely intense, concentrated laser beam (diameter = 2 mm) and prevents damage to the apparatus. Batches as large as 20 g of material may be processed in this fashion. The solution tends to darken during the reaction. Photolysis is allowed to proceed until darkening occurs, then the reaction is worked up, and the recovered quinone-olefin mixture is resubmitted to irradiation. Yields of cycloadduct thus increase to an overall 70 -80 % after a single recycling.

![Diagram](Image)

Figure 11

The reasons behind the high margin of regioselectivity observed in these reactions are not clear. An excessively simplistic explanation may be formulated based on the fact that a triplet excited state of the benzoquinone carbonyl is involved in the cycloaddition. In the triplet state, which is produced by fast intersystem crossing from the initially singlet excited state, the electrophilic character of the carbonyl carbon (conventionally held for ground state carbonyls) is effectively transferred to the oxygen atom. It is also known that many of these reactions may go through "preoxetane biradicals" or excited EDA (CT) complexes (in the extreme, an ion pair). Given the reversal in the polarity of the carbonyl, this pre-bond pairing could explain the regiochemical outcome of this particular reaction. Major
problems arise when the following results are taken into account:

i. photocycloaddition of compound 142 to benzoquinone forms adducts 143a and 143b in a modest 2:1 ratio

\[
\begin{align*}
\text{133} & \quad + \quad \text{142} \\
& \quad \xrightarrow{\text{hv}} \quad \text{benzene} \\
& \quad \xrightarrow{\text{143a}} \quad \text{143b}
\end{align*}
\]

Scheme 45

ii. photocycloaddition of compound 144 to benzoquinone forms adducts 145a and 145b in a 1:3 ratio.

\[
\begin{align*}
\text{133} & \quad + \quad \text{144} \\
& \quad \xrightarrow{\text{hv}} \quad \text{benzene} \\
& \quad \xrightarrow{\text{145a}} \quad \text{145b}
\end{align*}
\]

Scheme 46

Clearly, some very special properties of alkylidene cyclohexanes must be responsible for the observed selectivity. While the nature of these remains obscure, they resulted in the first example of a regioselective reaction of this type which can be synthetically useful.

It is recognized that relative to 130, compound 141a exhibits an incorrect connectivity.

\[\text{68 This observation was recently made by M. Angélica Rivera-Fortín of these laboratories.}\]
of the cyclohexane ring. The problem was smoothly corrected by a dienone-phenol rearrangement, which was carried out in CH₂Cl₂ with catalytic BF₃·OEt₂ to give dihydrobenzofuran 146 in 95% yield, fortunately leaving the ethylene ketal intact. The required olefin 149 was easily reached by reductive cleavage of the cyclic ether. To that end, the phenol was protected as the methyl ether using dimethylsulfate and K₂CO₃ in acetone. During the workup of the methylation reaction, the acetate was conveniently removed to give directly alcohol 147 in 95% overall yield from 146. The primary bromide 148 was best prepared using a two-step, one-pot procedure involving first mesylation of the alcohol followed by treatment with solid LiBr in refluxing THF (92% yield from 147). The more direct Hooz reaction⁶⁹ was not satisfactory in this system, because of difficulties in separation of the resulting triphenylphosphine debris from the bromide product.

![Scheme 47]

Among several methods that could reductively cleave 148 to the phenol 149, we sought one that would permit survival of the acid-sensitive functionality present in the molecule. An excellent procedure involved treatment of 148 with 10 eq. of Zn dust and solid NH₄Cl in refluxing dry EtOH to give 149 in 93% yield (Scheme 47).⁷⁰

It should be mentioned that structures similar to 150 - 151 may be obtained by alternative treatments of photocycloadduct 141a. For instance, hydrogenation over Pd(C) induces conversion into 150 (70-75% yield), while reduction with Li in ammonia provides compound 151 in quantitative yield.⁷¹ (Scheme 48)

A future leaving group at the terminal carbon of the vinyl substituent was introduced at this point. This required initial protection of the phenol as its benzyl ether (NaH, benzyl bromide, DMF). Hydroboration with 9-BBN in THF, followed by oxidation with hydrogen peroxide, afforded primary alcohol 152, which was protected as a methoxymethyl ether (MOMCl, Hunig base). The benzyl group was removed using standard Birch conditions to give phenol 153 in 77% overall yield from 149. The stage had been set for a study of the Claisen chemistry of 153. (Scheme 49).

⁷¹ These observations were recently made by Hongbo Qi of these laboratories.
Failure of The Claisen Approach

Phenol 153 was converted into ether 154 using NaH and allyl bromide in DMF, in 96% yield. Claisen rearrangement of 154 in N,N-dimethylaniline at 200 °C smoothly produced phenol 155 in 94% yield. Acetylation (Ac₂O, pyridine, 0.1 eq DMAP) followed by nitration (HNO₃, Ac₂O, Hg(OAc)₂, AcOH)⁷² gave a mixture of 156a and 156b in a ratio of 3 to 1 with no evidence of di-nitratated product. 156a was easily separated from 156b by column chromatography. Interestingly, the spectral results indicated that during the nitration the ethylene ketal was lost, releasing the ketone, yet the methoxymethyl ether remained intact. The nitro group was reduced to the primary amine using Zn dust in conc. HCl. This treatment caused the methoxymethyl group as well as some of the phenolic acetate to be hydrolytically cleaved. Therefore, this crude mixture of the sensitive amine intermediates was immediately subjected to acetylation conditions to furnish the tri-acetylated compound 157. Formation of the indole was effected by ozonolysis of the olefin 157 in MeOH to form the aldehyde, which was intercepted in situ by the acetamide. Treatment of the hemiaminal with 10% aq. H₂SO₄ during the workup caused dehydration to furnish indole 158 directly (Scheme 50).

Considering these encouraging results, efforts were made to employ a more complex olefin, which would provide the skeletal carbons for ring E after the Claisen rearrangement. Olefin 163 was deemed to be the most logical and viable candidate for this transformation. Compound 162 was synthesized beginning with Elie reduction of the benzylidene acetal of 1,3-propane-diol. The unsaturated ester was incorporated using Ireland conditions \([\text{COCl}_2, \text{TEA}, \text{DMSO}],\) followed by treatment \textit{in situ} with the (carbethoxymethylidene)-triphenylphosphorane reagent. DIBAL reduction of the ester provided the allylic

---

alcohol, which was then easily converted to the allylic bromide (162) with PBr₃ in 59% overall yield from 159 (Scheme 51). Subsequent O-alkylation of the phenol 153 with 162 (NaH, DMF) gave cleanly the pre-Claisen compound 163 in 95% yield.

Scheme 50

156a

1. Ac₂O, pyridine
   cat. DMAP
2. HNO₃, Ac₂O,
   AcOH, Hg(OAc)₂

156a

156b

3 : 1

We were dismayed to observe that rearrangement of 163 in refluxing N,N-dimethylaniline at 200 °C gave the desired rearranged product 164a as the minor component of a 30 : 70 mixture with another compound of structure 164b (Scheme 52). The structure of 164b was confirmed by spectral means and appears to be the result of an "abnormal Claisen rearrangement." This well-known problem may occur if an enol-ene reaction of the primary Claisen product takes place at a rate comparable to that of the rearrangement, as shown in Scheme 53.

![Diagrams](image)

Scheme 53

Several conditions were employed in order to coax the rearrangement into stopping at the desired product, but to no avail. With extended reaction times or with higher reaction temperatures, the ratio of the products increased in favor of 164b. A final problem that added insult to injury emerged during chromatographic separation of the "regular" and "abnormal" products. The desired isomer was difficult to obtain in pure form, while fractions containing very pure 164b were easily obtained. These setbacks induced us to formulate a different strategy for completion of the indole ring.

---

The Quinone Ketal Approach

Monomethyl ethers of hydroquinones may be readily oxidized to quinone monoketals through a particularly effective protocol developed by Büchi.\textsuperscript{76} This interesting transformation effectively converts a moderately nucleophilic aromatic ring into a highly electrophilic system. This alteration of the polarity of the ring would enable nucleophiles to enter in a conjugate (Michael) sense.\textsuperscript{77} If our intermediate 153 could be advanced to 166, it would now be possible to introduce the nitrogen and carbon atoms of the future indole through the reactions shown in Scheme 54.

![Scheme 54]

Implicit in this proposed mode of reactivity are a number of key issues. The most direct format in which the new chemistry could be implemented necessitates Michael addition of a primary amine into 166, without attendant imine formation. Furthermore, the conjugate addition should occur regioselectively as shown. An additional advantage of this approach is that the piperidine ring might also be introduced in a similar fashion, through an intramolecular variant of the first reaction.

Investigations into this mode of reactivity commenced with subjection of 153 to Büchi conditions (DDQ, MeOH, $p$-nitrophenol), a treatment that indeed produced quinone monoketal 166 in 87% yield. Similar compounds were obtained by an analogous


oxidation of 169a-c in equally good yields. Initial forays directed towards completion of
the piperidine ring produced disappointing results: all attempts to induce cyclization of
amides 169a-c under basic conditions were unsuccessful, yielding only the unreacted
starting materials (Scheme 56). More promising observations were made in connection
with a study of bimolecular reactions of 166.

Scheme 55

Surprisingly little is known about conjugate additions of heteroatomic nucleophiles
into quinone monoketals. However, a report in the literature was uncovered which
indicated that morpholine would add in the desired sense to a simple benzoquinone monoketal. This claim was substantiated by repeating the very same reaction in neat morpholine using our more elaborate system. Not only did the morpholine add in the conjugate sense, but also it added only once and to the desired side required for creation of the indole (Scheme 57). This may be easily understood if one considers the steric congestion caused by the alkyl cyclohexyl group, which is effectively larger than a t-butyl group, as well as its electron-donating ability, which reduces significantly the reactivity of the other double bond of 166.

Encouraged by these results, we proceeded to investigate analogous reactions with

other amines. Dissolution of 166 in neat allylamine caused complete consumption of the starting material, in less than five minutes, to give a product (99% yield) in which the allylamine had added exclusively to the dienone, in the same sense as the morpholine. Spectral data indicate that the allylamine added only one time and that none of the possible imine product was formed (Scheme 58).

It is recognized that the success of this new approach does not require the lengthy manipulations of the vinyl group of 149, which involve an unattractive protection / deprotection sequence of the phenol. Thus, efforts were made to ascertain whether the vinyl phenol 149 could be engaged in the newly developed sequence. This proved to be the case. Phenol 149 was easily oxidized to the quinone mono-ketal 172 (DDQ, MeOH, p-nitrophenol) in 96 % yield. Again, treatment of the compound with allylamine gave consistent results: Michael addition occurred only once, and the amine added to the "correct" side of 172, giving compound 173 in 99% yield (Scheme 59). This pleasing result indicates that completion of the indole segment of the molecule may be achieved without having to perform lengthy manipulations of the vinyl group present on the other side of the molecule.
Future Considerations

The success of the Michael approach suggests that a nucleophile more elaborate than allylamine could conceivably be used to complete the indole system. It may even be possible to complete the indole ring in one step, if the amine contained an α,β-unsaturated ester, thereby setting the stage for a double Michael ring closure. The amine (174) would attack as in the allylamine case, and then the incipient enolate intermediate (175) would attack the α,β-unsaturated ester to complete the desired heterocycle (Scheme 60). The feasibility of this transformation is implicit in the work of Barco,79 who recently described an analogous transformation of 174 into 176 (Scheme 61). Work is currently in progress in our labs to complete this important sequence.

Scheme 60

Scheme 61

---

Results obtained during this work clearly define the general lines of the final plan of attack on discorhabdin. Future transformations invariably will involve rearomatization of the C ring using either protonic or Lewis-acidic conditions. Nitration of the last available ring position, and reduction of the nitro group to an amine, would set the stage for closure of the piperidine B ring (182), which would be accomplished by hydroboration and oxidation of the vinyl group, followed by activation of the resulting alcohol as a leaving group.

![Chemical structures](image)

Scheme 62

Formation of the dibromo dienone, a transformation that is well precedented in the literature, would be followed by aromatization of the indole and oxidation of the ring C to the corresponding quinone. This event may be anticipated to result in rapid closure of ring E, completing the synthesis of Discorhabdin C (Scheme 62).

---

The approach to discorhabdin C presented herein illustrates an important new synthetic method in the form of the regioselective photocycloaddition of quinones with olefins. We already have accumulated evidence that the new reaction is likely to facilitate the synthesis of other natural products incorporating synthetically challenging features. In addition, our synthetic plan is flexible enough to allow access to the sulfur-bridged prianosins (121, 122, 124) with only minor modifications. Proper manipulation of the vinyl group of one of the previous intermediates at an appropriate time would permit incorporation of the required sulfide. The directness of this approach coupled with the ease with which the spiro-cyclohexyl group is created provides for a promising completion of the Discorhabdin family of compounds.\textsuperscript{81}

\textsuperscript{81} We would like to thank Prof. Tohru Fukuyama of this department for many helpful discussions concerning his current synthetic efforts toward the total synthesis of the Prianosins.
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TECHNICAL NOTES

Melting points (mp), determined on a Fisher-Johns hot stage melting point apparatus, are uncorrected.

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

$^1$H NMR (250 MHz) and $^{13}$C NMR (62.5 MHz) spectra were measured in CDCl$_3$ solutions and were determined on a Bruker AC-250 instrument unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane ($\delta = 0$) as the internal standard, and coupling constants are in Hertz. The following abbreviations are used for spin multiplicity: br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole mass spectrometer at 70 eV, unless otherwise noted, using direct probe insertion at temperatures of 150-300$^\circ$ C. High resolution mass spectra (HRMS) were obtained under similar conditions using a CEC 21-110B instrument.

Analytical thin layer chromatography (TLC) and preparative TLC were performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F$_{254}$.

Column chromatography was performed on grade 62 silica gel, 60-200 mesh, 150 A.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions:

- Dichloromethane distilled over calcium hydride
- Tetrahydrofuran distilled from sodium benzophenone ketyl
- Ethyl acetate distilled
Methanol dried over 4 Angstrom molecular sieves

All moisture or oxygen sensitive reactions were conducted under an argon atmosphere.
Below are general procedures for the synthesis of typical enones, and for the formation of cycloadducts and the corresponding pyridines. Individual procedures which follow the same recipe will refer to these general procedures.

**A. General Procedure For Synthesis of Enones**

10 mmol of the ketone and 10 mmol of the aldehyde are dissolved in 10 ml of absolute EtOH in a 125 ml Erlenmeyer flask. Water is added until the solution almost becomes heterogeneous. Then 4 ml of 20% aq. NaOH solution is added. The solution is stirred at room temperature for half an hour, during which time a precipitate forms. The reaction is followed by TLC and when all starting material vanishes, the solution is filtered and the precipitate is washed well with water. The enone is generally analytically pure at this stage, but usually the precipitate is dissolved in a small amount of CH₂Cl₂ and then passed over a short plug of silica gel (eluting with CH₂Cl₂) to prepare it for the cycloaddition reaction. Yields range from 80-95%.

**B. General Procedure For The Cycloaddition Reaction**

10 mmol of the enone is dissolved in 10 ml of 1,2-dichloroethane and 7 ml of the vinyl ether in a 50 ml round bottom flask equipped with a condenser and a drying tube. Then 0.2 mmol of Yb(fod)₃ is added and the solution is warmed at 60-70 °C for 1-3 days. The reaction is followed by TLC (10-20% EtOAc/hexanes) and then the solvent is evaporated. The residue is dissolved in 15 ml of CH₂Cl₂ and is then washed once with water. The organic phase is dried over Na₂SO₄. The solvents are evaporated to dryness. Generally, the crude cycloadducts are obtained in near quantitative yield and are used as is for ensuing reactions.
C. General Procedure For The Pyridine Formation Reaction

10 mmol of crude cycloadduct is dissolved in 40 ml (0.25 M in cycloadduct) in a 100 ml round bottom flask. Then, 50 wt % (in cycloadduct) of hydroxylamine hydrochloride is added. The reaction is refluxed maintained at a hard reflux for about 1 hour, then the heat is reduced to maintain a gentle reflux overnight. The length of time is critical to ensure good yields and clean products. The solvents are evaporated in vacuo and the residue is dissolved in 15 ml of CH₂Cl₂. The organic phase is washed with 10% aq. Na₂CO₃ and then it is passed over a short plug of silica gel. Yields are generally 80-95%.
Cycloadduct 25

Procedure B.

1.34 g (99%) $R_f$ (30% EtOAc/hexam) 0.86.

$^1$H NMR: 7.20 - 8.10 (m, 10H), 5.45 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 1.2$ Hz), 5.26 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 1.9$ Hz), 4.17 (dq, 1H, $J_1 = 9.5$ Hz, $J_2 = 7.1$ Hz), 3.78 (cm, 2H), 2.38 (ddt, 1H, $J_1 = 13.1$ Hz, $J_2 = 6.7$ Hz, $J_3 = 1.2$ Hz), 1.99 (ddd, 1H, $J_1 = 9.1$ Hz, $J_2 = 13.1$ Hz, $J_3 = 10.7$ Hz), 1.34 (t, 3H, $J = 7.1$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz).

$^{13}$C NMR: 149.87, 144.68, 135.27, 129.72, 128.86, 128.51, 128.13, 127.40, 126.53, 125.51, 124.59, 101.33, 100.29, 64.50, 38.69, 37.32, 15.26.

IR: 3063, 3032, 2975, 2868, 1648, 1604, 1496, 1450, 1377, 1284, 1171, 1044, 932, 852, 766, 692.

MS: 280 ($M^+$), 234, 209, 208, 179, 155, 131, 105, 103, 102, 77 (100%), 51.

HRMS: expected 280.1463, observed 280.1466.
Pyridine 1a

Procedure C.

114.0 mg (95%) Rf (20% EtOAc/hexanes) .36.

$^1$H NMR: 8.76 (dd, 1H, J$_1$ = 5.1 Hz, J$_2$ = .7 Hz), 8.08 (m, 2H), 7.95 (dd, 1H, J$_1$ = 1.7 Hz, J$_2$ = .7 Hz), 7.71 (m, 2H), 7.50 (cm, 7H).

$^{13}$C NMR: 158.03, 150.04, 149.21, 139.44, 138.46, 129.05, 128.97, 128.21, 127.00, 120.19, 118.69.

IR: 3065, 3029, 1595, 1539, 1476, 1391, 765, 702.

MS: 232 (M$^+$+ 1), 231 (M$^+$, 100%), 230, 202, 154, 132.

HRMS: expected 231.1047, observed 231.1045.
Cycloadduct 1b

Procedure B.

3.47 g (99%) R$_f$ (20% EtOAc/hexanes) .65.

$^1$H NMR: 7.70 (m, 2H), 7.32 (cm, 8H), [minor diast. - 5.58 (br.s); major diast. - 5.50 (br.d, J = 2.8 Hz), 1H], [minor diast. - 3.86 (ddd, J$_1$ = 12.2 Hz, J$_2$ = 6.2 Hz, J$_3$ = 2.2 Hz); major diast. - 3.72 (dt, J$_1$ = 8.0 Hz, J$_2$ = 2.9 Hz), 1H], [major diast. - 3.44 (s); minor diast. - 3.42 (s), 3H], [minor diast - 2.29 (ddd, J$_1$ = 13.2 Hz, J$_2$ = 6.2 Hz, J$_3$ = 1.3 Hz); major diast - 2.12 (d, J$_1$ = 8 Hz), 1H], 1.80 (app.t, 1H, J = 12.5 Hz), [minor diast. - 1.62 (s); major diast. - 1.59 (s), 3H].

IR: 3070, 3023, 2944, 1650, 1597, 1491, 1453, 1376, 1286, 1157, 1072, 1038, 10123, 867, 755, 700.

MS: 280 (M$^+$), 248, 209, 208, 207 (100%), 161, 131, 105, 72.

HRMS: expected 280.1463, observed 280.1463.
**Pyridine 1b**

Procedure C.

408 mg (93%) R_f (20% EtOAc/hexanes) .33.

\[ \text{^1H NMR:} \quad 8.02 \text{ (m, 2H), 7.25 - 7.73 (m, 11H), 6.80 (m, 1H), 2.71 (s, 3H).} \]

\[ \text{^13C NMR:} \quad 158.85, 157.75, 149.54, 139.47, 136.15, 134.84, 129.17, 129.01, 128.85, 128.69, 128.41, 127.48, 127.22, 127.07, 119.85, 117.10, 116.28, 24.90. \]

\[ \text{IR:} \quad 3063, 3030, 2924, 1663, 1606, 1552, 1449, 1401, 1214, 1075, 1031, 869, 761, 736, 695. \]

\[ \text{MS:} \quad 246 (M^+ + 1), 245 (M^+, 100%), 244, 230, 202. \]

\[ \text{HRMS:} \quad \text{expected 245.1204, observed 245.1207.} \]
**Cycloadduct 1c**

Procedure B.

6.85 g (97%) \( R_f (20\% \text{ EtOAc/hexanes}) \) 0.83.

Compound exists as a mixture of diastereomers in a 3:2 ratio.

\[ ^1H \text{NMR:} \]
7.69 (m, 2H), 7.33 (cm, 8H), [major diast. - 5.51 (dd, \( J_1 = 2.7 \text{ Hz}, J_2 = 7.9 \text{ Hz} \)), minor diast. - 5.39 (d, \( J = 2.6 \text{ Hz} \)), 1H], [major diast. - 5.28 (d, \( J = 1.8 \text{ Hz} \)), minor diast. - 4.89 (d, \( J = 8.3 \text{ Hz} \)), 1H], 4.17 (cm, 1H), 4.05 (dd, 1H, \( J_1 = 6.5 \text{ Hz}, J_2 = 2.7 \text{ Hz} \)), 3.77 (cm, 1H), 3.28 (dd, 1H, \( J_1 = 9.9 \text{ Hz}, J_2 = 2.6 \text{ Hz} \)), 2.35 (br. quinlet, 1H, \( J = 7.0 \text{ Hz} \)), 2.01 (cm, 1H), [major diast. - 1.35 (t, \( J = 7.0 \text{ Hz} \)), minor diast. - 1.36 (t, \( J = 7.0 \text{ Hz} \)), 3H], [major diast. - .76 (d, \( J = 7.0 \text{ Hz} \)), minor diast. - 1.03 (d, \( J = 6.6 \text{ Hz} \)), 1H].

\[ ^{13}C \text{NMR:} \]
135.32, 135.19, 128.75, 128.40, 128.31, 128.17, 128.12, 128.08, 127.94, 126.62, 126.32, 124.55, 104.90, 103.00, 102.20, 99.80, 65.10, 47.70, 43.10, 40.60, 36.70, 15.40, 14.80, 9.00.

IR:
3057, 2984, 2924, 2877, 1650, 1602, 1496, 1448, 1381, 1292, 1165, 1096, 1058, 1024, 894, 762, 701.

MS:
294 \((\text{M}^+)\), 248, 233, 209, 175, 131, 105, 86 \((100\%)\), 77, 58.

HRMS:
expected 294.1619, observed 294.1619.
**Pyridine 1c**

Procedure C.

358 mg (89%) $R_f$ (10% EtOAc/hexanes) 0.28.

$^1$H NMR: 8.57 (br.s, 1H), 7.99 (m, 2H), 7.58 (br.s, 1H), 7.33 - 7.47 (cm, 10H), 2.27 (s, 3H).

$^{13}$C NMR: 155.17, 151.08, 149.87, 139.29, 139.18, 129.11, 128.61, 128.48, 128.39, 127.90, 126.66, 120.91, 16.90.

IR: 3062, 3031, 2927, 2853, 1696, 1596, 1476, 1450, 1377, 885, 772, 746, 692.

MS: 246 (M$^+$ + 1), 245 (M$^+$, 100%), 244, 243, 202, 166, 139, 115.

HRMS: expected 245.1204, observed 245.1205.
Cycloadduct 22a

Procedure B

139.5 mg (93%) \( R_f \) (20% EtOAc/hexanes) .82.

\(^1\)H NMR 7.68 (m, 2H), 7.30 (m, 8H), \{major diast. - 5.53 (d, \( J = 3.5 \) Hz); minor diast. - 5.30 (d, \( J = 2.4 \) Hz), 1H\}, 3.77 (m, 3H), 2.22 (quintlet, 1H, \( J = 7.0 \) Hz), \{major diast. - 1.57 (s); minor diast - 1.52 (s), 3H\}, \{minor diast. - 1.24 (t, \( J = 7.0 \) Hz); major diast. - 1.17 (t, \( J = 7.0 \) Hz), 3H\}, \{minor diast. - .90 (d, \( J = 6.9 \) Hz); major diast. - .79 (d, \( J = 6.9 \) Hz), 3H\}.

IR: 3054, 3023, 2977, 2888, 1655, 1599, 1496, 1450, 1377, 1330, 1157, 1051, 1018, 878, 766, 692.

MS: 308 (\( M^+ \)), 262 (100%), 261, 247, 209, 207, 206.

HRMS: expected 308.1776, observed 308.1776.

Spectral results indicate that only the adduct 22a was formed.
**Pyridine 1d**

Procedure C

103.7 mg (88%) $R_f$ (10% EtOAc/hexanes) .69.

$^1$H NMR: 7.90 (m, 2H), 7.29 (m, 1H), 2.57 (s, 3H), 2.12 (s, 3H).

$^{13}$C NMR: 157.66, 153.60, 140.21, 139.61, 128.74, 128.57, 128.34, 128.28, 127.63, 127.28, 126.72, 119.26, 23.67, 16.00.

IR: 3062, 3029, 2952, 2919, 1588, 1546, 1494, 1447, 1388, 885, 773, 697.

MS: 259 ($M^+$), 258 (100%), 243, 215, 202.

HRMS: expected 259.1360, observed 259.1361.
Bromoacetal 41

144.6 mg (.51 mmol) of cycloadduct 25 was dissolved in 10 ml of dry MeOH. Then, 20 mg of solid K₂CO₃ was added, followed by 100.7 mg (.57 mmol) of N-bromosuccinimide (NBS). After 5 minutes the reaction was finished. Excess NBS was destroyed by adding 10 ml of a 10% aq. NaHSO₃ solution. The MeOH was evaporated and then the aqueous solution was extracted twice with CH₂Cl₂. The combined extracts were passed over a short plug of silica gel with CH₂Cl₂. 232 mg (86%) Rf (10% EtOAc/hexanes) .24.

¹H NMR: 8.05 (app. br.d, 1H, J = 7.7 Hz), 7.80 (app. br.d, 1H, J = 7.7 Hz), 7.10 - 7.65 (m, 8H), [5.40 (major diast. - d, J = 10.4 Hz), 1H], 4.11 (major & minor diast., m, 1H), 3.66 (major & minor diast., m, 1H), 3.37 (major & minor diast., m, 1H), [3.23 (major diast., s); 3.14 (minor diast., s), 3H], 2.73 (major & minor diast., cm, 1H), 1.97 (major & minor diast., cm, 1H), [1.23 (major diast., t, J = 7.0 Hz); 1.17 (minor diast., t, J = 7.0 Hz), 3H].

IR: 3030, 2984, 2831, 1688, 1593, 1451, 1264, 1126, 1054, 952, 701, 687.

MS: 392 (M⁺, 81 Br), 390 (M⁺, 79 Br), 361, 359, 311, 279, 233, 161, 147, 105, 89 (100%), 77, 61.

HRMS: expected 390.0830, observed 390.0833.
Bromopyridine 42

104 mg (.266 mmol) of bromoacetal 41 was dissolved in 10 ml of CH$_3$CN. Then 52 mg (.75 mmol) of hydroxylamine hydrochloride was added. The solution was refluxed overnight with a drying tube atop the condenser. The solvent was then evaporated and the residue was taken up in CH$_2$Cl$_2$. The solution was washed once with 10% aq. Na$_2$CO$_3$ solution and once with water. The organic layer was then passed over a short plug of silica gel and the solvents were evaporated. 29.7 mg (36%) $R_f$ (10% EtOAc/hexanes) .18.

$^1$H NMR: 8.75 (d, 1H, J = 5.1 Hz), 8.06 (m, 2H), 7.95 (m, 1H), 7.70 (cm, 2H), 7.50 (br.m, 8H).

$^{13}$C NMR: 151.04, 130.16, 129.92, 129.82, 129.57, 128.50, 128.35, 127.84, 127.33, 121.01, 119.52.

IR: 3057, 2361, 2340, 1588, 1539, 1448, 1391, 765, 702.

MS: 311 (M$^+$, 81Br), 309 (M$^+$, 79Br), 264, 263, 262, 246, 231 (100%), 230, 229, 202, 154, 127.

HRMS: expected 309.0153, observed 309.0155.
Azidoacetal 43

116 mg (.297 mmol) of bromoacetal 43 was dissolved in 2 ml of DMF. Then 29 mg (.445 mmol) of NaN₃ was added. The solution was stirred for 1 hour and then the reaction mixture was diluted with 25 ml of water. The mixture was extracted twice with ether and then the combined extracts were dried over Na₂SO₄ and then the solvent was evaporated. 97.5 mg (93% crude); 58.7 mg (56% chrom. - adduct may not be entirely stable to exposure to silica gel chromatography) Rᵣ (20% EtOAc/hexanes) .35.

The compound exists as a mixture of 3 diastereomers in equal ratios.

¹H NMR: 7.15 - 8.0 (m, 10H) [4.99 (d, J = 7.4 Hz), 4.75 (d, J = 8.0 Hz), 4.53 (dd, J₁ = 6.7 Hz, J₂ = 5.0 Hz), 1H], [4.22 (dd, J₁ = 7.2 Hz, J₂ = 4.1 Hz), 4.14 (dd, J₁ = 8.4 Hz, J₂ = 3.5 Hz), 3.94 (dd, J₁ = 9.2 Hz, J₂ = 6.6 Hz), 1H], 3.20 - 3.71 (cm, 3H), [3.39 (s), 3.22 (s), 3.20 (s), 3H], 1.90 - 2.40 (cm, 2H), [1.23 (t, J = 7.2 Hz), 1.17 (t, J = 7.2 Hz), 1.12 (t, J = 7.2 Hz), 3H].

IR: 3066, 3028, 2978, 2104, 1686, 1604, 1450, 1241, 1128, 1064, 757, 697.

MS: 280 (M⁺ - 73), 221, 135, 120, 104 (100%), 76.

HRMS: expected 353.1739, observed 353.1742.
Azidopyridine 44

50 mg (.142 mmol) of azidoacetal 43 was dissolved in 2 ml of CH$_3$CN. Then 25 mg (.36 mmol) of hydroxylamine hydrochloride was added. The solution was refluxed overnight with a drying tube atop the condenser. The solvent was then evaporated and the residue was taken up in CH$_2$Cl$_2$. The solution was washed once with 10% aq. Na$_2$CO$_3$ solution and once with water. The organic layer was then passed over a short plug of silica gel and the solvents were evaporated. 22 mg (57%) R$_f$ (10% EtOAc/hexanes) .20.

$^1$H NMR: 8.54 (d, 1H, J = 4.9 Hz), 7.77 (m, 2H), 7.51 (cm, 8H), 7.22 (d, J = 4.9 Hz).

$^{13}$C NMR: 146.20, 144.10, 137.90, 135.95, 129.18, 128.92, 128.677, 128.39, 124.15.

IR: 3055, 2927, 2847, 2106, 1573, 1396, 1303, 752, 692.

MS: 272 (M$^+$), 245, 244 (100%), 243, 141, 140, 114.

HRMS: expected 272.1061, observed 272.1061.
Cycloadduct 45

A mixture of 289 mg (1.03 mmol) of cycloadduct 25 and 898 mg (5.16 mmol) of diethyl azodicarboxylate (DEAD) was dissolved in 18 ml of hexane in a 25 ml round bottom flask equipped with a condenser. 20 drops of CH₂Cl₂ were added to maintain solubility and the solution was degassed for 20 minutes with argon. Irradiation was carried out with a 250 W Sylvania sunlamp for 36 hours. After TLC indicated that the starting material was gone, the solvent was evaporated and the residue was chromatographed directly on a flash silica gel column with 15% EtOAc/hexanes. 335 mg (75%) Rf (30% EtOAc/hexanes).33.

$^1$H NMR: 7.20 - 7.90 (m, 10H), 5.45 - 6.25 (M, 1H), 3.55 - 4.34 (cm, 7H), 2.68 (br.t, J = 8 Hz, 1H), 1.29 (cm, 11H).


MS: 455 (M⁺ + 1), 454 (M⁺), 407, 348, 309, 278 (100%), 233, 205, 104.

HRMS: expected 466.2103, observed 466.2105.
Aminopyridine 46

305 mg (.672 mmol) of photoadduct 45 was dissolved in 13 ml of CH$_3$CN. Then 454 mg (6.53 mmol) of hydroxylamine hydrochloride was added. The solution was refluxed overnight with a drying tube atop the condenser. The solvent was then evaporated and the residue was taken up in CH$_2$Cl$_2$. The solution was washed once with 10% aq. Na$_2$CO$_3$ solution and once with water. During the reaction, two pyridine products were formed: the desired aminopyridine and a pyridine in which the hydrazo linkage and the carbamate linkage were not reduced to the amine. They were separated by column chromatography. Aminopyridine 89 mg (57%) R$_f$ (50% EtOAc/hexanes) .05.

$^1$H NMR: 8.36 (d, 1H, J = 6.8 Hz), 7.86 (m, 2H), 7.41 - 7.64 (cm, 9H).

$^{13}$C NMR: 148.94, 140.30, 138.25, 136.30, 132.60, 129.50, 129.07, 129.00, 128.93, 128.23, 126.30, 124.90, 122.07.

IR: 3388, 3050, 1532, 1461, 1440, 1412, 1243, 857, 758, 695, 596.

MS: 247 (M$^+$ + 1), 246 (M$^+$, 100%), 245, 231, 230, 218, 217, 193.

HRMS: expected 246.1156, observed 246.1156.
Cycloadduct 27

Procedure B

2.26 g (98%) Rf (10% EtOAc/hexanes) .49.

$^1$H NMR:
7.21 - 7.45 (m, 10H), 6.94 (d, 1H, $J = 15.9$ Hz), 6.50 (d, 1H, $J = 15.9$ Hz), 5.16 (dd, 1H, $J_1 = 8.9$ Hz, $J_2 = 1.9$ Hz), 4.98 (br.d, 1H, $J = 2.3$ Hz), 4.12 (dq, 1H, $J_1 = 9.5$ Hz, $J_2 = 7.1$ Hz), 3.74 (cm, 2H), 2.31 (ddt, 1H, $J_1 = 13.2$ Hz, $J_2 = 6.7$ Hz, $J_3 = 1.3$ Hz), 1.

$^{13}$C NMR:
149.44, 144.39, 136.89, 128.53, 127.61, 127.52, 126.55, 123.54, 107.41, 100.00, 64.53, 38.81, 37.29, 15.28.

IR:
3055, 3023, 2974, 2928, 2861, 1642, 1617, 1489, 1450, 1370, 1323, 1131, 1025, 951, 759, 692.

MS:
306 ($M^+$), 260, 234, 233, 215, 161, 131 (100%), 115, 103, 91, 72.

HRMS:
expected 306.1619, observed 306.1621.
Pyridine 28

Procedure C
183 mg (90%) R_f (20% EtOAc/hexanes) .28.

^1H NMR: 8.63 (d, 1H, J = 5.1 Hz), 7.69 (d, 1H, J = 16.1 Hz), 7.20 - 7.73 (cm, 12H), 7.23 (d, 1H, J = 16.1 Hz).

^13C NMR: 156.02, 149.99, 148.96, 138.20, 136.56, 132.90, 129.02, 128.68, 128.31, 127.90, 127.08, 126.93, 120.14, 120.07.

IR: 3050, 3010, 1638, 1580, 1540, 1498, 1465, 1451, 1400, 1198, 970, 900, 850, 760, 735, 695, 620.

MS: 257(M^+), 256 (100%), 160, 128, 127, 77.

HRMS: expected 257.1204, observed 257.1204.
Cycloadduct 39a

100 mg (.327 mmol) of diene 27 and 37.1 mg (.425 mmol) of chloroacrylonitrile were dissolved in 7 ml of toluene. The solution was refluxed for 3 days. During this time, additional chloroacrylonitrile had to be added due to evaporation losses. The solvents were then evaporated and the crude residue was chromatographed on silica gel with 10% EtOAc/hexanes. 76.2 mg (60% chromatographed yield) R_f (20% EtOAc/hexanes) .59.

$^1$H NMR: 7.35 (m, 10H), 5.10 (cm, 2H), 3.92 (cm, 1H), 3.24 - 3.69 (cm, 3H), 1.93 - 2.92 (cm, 5H), 1.27 (m, 3H).

IR: 3064, 3030, 2976, 2936, 2106, 1596, 1496, 1456, 1383, 1134, 1098, 1053, 871, 761.

MS: 395 (M⁺, $^{37}$Cl), 393 (M⁺, $^{35}$Cl), 349, 348, 347, 322, 321, 320, 182, 151 (100%), 115, 91, 72.

HRMS: expected 393.1495, observed 393.1498.
Pyridine 40a

Procedure C

White crystalline solid. (m.p. 178-180°C) 35.5 mg (90%) Rf (10% EtOAc/hexanes). .19.

$^{1}H$ NMR: 8.57 (d, 1H, $J = 4.9$ Hz), 7.46 (m, 8H), 7.28 (m, 2H), 7.14 (d, 1H, $J = 4.9$ Hz), 3.59 - 3.74 (m, 3H), AB system [$V_A = 3.58$, $V_B = 3.45$, $J_{AB} = 17.0$ Hz, 2H].

$^{13}C$ NMR: 154.19, 150.04, 148.59, 137.69, 137.53, 128.83, 128.62, 128.49, 128.28, 123.79, 122.93, 117.61, 58.85, 50.25, 41.76, 37.34.

IR: 3064, 3029, 2924, 2200, 1581, 1546, 1489, 1461, 1405, 759, 702.

MS: 346 (M$^+$, $^{37}$Cl), 345, 344 (M$^+$, $^{35}$Cl), 343, 310, 309 (100%), 308, 307, 306, 231, 153, 149, 91, 77.

HRMS: expected 344.1080, observed 344.1104.
**Cycloaduct 39h**

106 mg (.379 mmol) of diene 27 and 65 mg (.758 mmol) of methyl acrylate were dissolved in 5 ml of toluene. The solution was refluxed for 7 days. During this time, additional methyl acrylate had to be added due to evaporation losses. After this time, the reaction was only 50% complete. Due to time considerations, the reaction was stopped and worked up. The solvent was evaporated and the starting material was separated from the cycloaduct via flash chromatography using 5% EtOAc/hexanes. 40.1 mg (58% based on recovered starting material - the low yield may be attributable to the extended reaction time) The diastereomers which formed produced 2 unique spots by TLC: Rf (20% EtOAc/hexanes) .48; .52.

\[ ^1H \text{ NMR:} \]
7.28 (m, 10H), 5.32 (dd, 1H, J1 = 5.3 Hz, J2 = 1.42 Hz), [4.80 (dd, J1 = 7.4 Hz, J2 = 4.4 Hz); 4.79 (dd, J1 = 8.5 Hz, J2 = 4.5 Hz), 1H], 4.03 (cm, 2H), 3.67 (m, 1H), [3.63 (s); 3.40 (s), 3H], 2.40 - 2.95 (m, 2H), 1.93 - 2.20 (br.m, 2H), 1.43 - 1.78 (br.m, 1H), 1.28 (t, 3H, J = 7.1 Hz).

**IR:**
3050, 2945, 2868, 1736, 1454, 1138, 1060, 702.

**MS:**
392 (M\(^+\)), 351, 160 (100%), 133, 115, 103, 91, 77.

**HRMS:** expected 392.1978, observed 392.1988.
**Pyridine 40b**

Procedure C

White solid (m.p. 178-180°C) 35.5 mg (90%) diastereomers: $R_f$ (10% EtOAc/hexanes) .09; .15.

$^1$H NMR: [8.51 (d, $J = 4.9$ Hz); 8.47 (d, $J = 4.9$ Hz), 1H], 7.02 - 7.47 (m, 11H), [3.83 (m); 3.42 (m), 1H], [3.58 (s), 3.36 (s), 3H], 3.54 (br.d, 1H, $J = 5.5$ Hz), 2.80 - 3.29 (cm, 3H).

$^{13}$C NMR: 173.50, 156.29, 156.10, 149.75, 149.58, 147.18, 142.52, 141.27, 138.64, 128.45, 128.00, 127.60, 127.32, 126.99, 126.91, 122.43, 122.35, 51.46, 46.78, 44.27, 43.37, 40.34, 40.07, 37.27, 30.60, 25.86.

IR: 3060, 2952, 1736, 1580, 1470, 1435, 1389, 1170, 775, 738, 706.

MS: 344 (M$^+$ + 1), 343 (M$^+$), 342, 284 (100%), 283, 282, 256, 206, 193, 179, 152, 114, 91, 77.

HRMS: expected 343.1572, observed 343.1572.
Enone 74

Procedure A

Yellow solid 2.057 g (92%) Rf (20% EtOAc/hexanes) .27.

\[
\begin{align*}
\text{\textsuperscript{1}H NMR:} & \quad 8.48 \text{ (d, 1H, J = 16.2 Hz), 8.27 \text{ (m, 4H), 7.65 - 7.92}} \\
& \quad \text{ (cm, 3H), 7.63 \text{ (d, 1H, J = 8.8 Hz), 6.78 \text{ (d, 1H,}} \\
& \quad \text{ J = 8.8 Hz), 4.03 \text{ (s, 3H), 3.93 \text{ (s, 3H), 3.92 \text{ (s, 3H).}}} \\
\text{\textsuperscript{13}C NMR:} & \quad 189.77, 155.87, 154.25, 153.99, 147.13, 142.34, 139.69, \\
& \quad 136.98, 130.51, 129.88, 129.41, 128.37, 127.66, 123.65, \\
& \quad 122.42, 119.96, 119.18, 107.59, 61.67, 60.95, 56.07. \\
\text{IR:} & \quad 3040, 2905, 2800, 1675, 1580, 1500, 1460, 1420, 1335, \\
& \quad 1285, 1190, 1050, 856, 810. \\
\text{MS:} & \quad 350 (M^{+} + 1), 349, 318, 290, 196, 191, 163, 129, 128 \\
& \quad (100\%), 101, 77. \\
\text{HRMS:} & \quad \text{expected 349.1314, observed 349.1323.}
\end{align*}
\]
Cycloadduct 2e

Procedure B

474 mg (92%) R_f (20% EtOAc/hexanes) .35.

^1H NMR: 8.18 (d, 1H, J = 8.5 Hz), 8.04 (br.d, 1H, J = 8.5 Hz), 7.81 (cm, 2H), 7.68 (app.dt, 1H, J = 7.7 Hz, J = 1.5 Hz), 7.49 (app.dt, 1H, J = 7.5 Hz, J = 1.2 Hz), 7.02 (d, 1H, J = 8.6 Hz), 6.64 (d, 1H, J = 8.7 Hz), 6.33 (dd, 1H, J = 2.7 Hz, J = 1.0 Hz), 5.34 (dd, 1H, J = 8.8 Hz, J = 1.9 Hz), 4.23 (cm, 1H), 4.18 (dq, 1H, J = 9.5 Hz, J = 7.1 Hz), 3.93 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.78 (dq, 1H, J = 9.5 Hz, J = 7.1 Hz), 2.40 (app.ddt, 1H, J = 13.1 Hz, J = 6.7 Hz, J = 1.6 Hz), 1.96 (cm, 1H), 1.34 (t, 3H, J = 7.1 Hz).

IR: 2970, 2937, 1634, 1597, 1494, 1463, 1347, 1288, 1230, 1100, 1039, 911, 831, 795, 757.

MS: 421 (M^+), 393, 375, 349, 318, 196, 119, 118 (100%).

HRMS: expected 421.1889, observed 421.1896.
Pyridine 71a

Procedure C

44.2 mg (43%) Rf (50% EtOAc/hexanes) .58.

\[ \text{H NMR:} \quad 8.36 (dd, 1H, J_1 = 1.8 \text{ Hz}, J_2 = .7 \text{ Hz}), 8.32 (d, 1H, J = 5.2 \text{ Hz}), 8.17 (d, 1H, J = 8.7 \text{ Hz}), 7.87 (d, 1H, J = 8.6 \text{ Hz}), 7.76 (d, 1H, J = 8.0 \text{ Hz}), 7.09 - 7.46 \text{ (m, 4H)}, 6.82 (d, 1H, J = 8.6 \text{ Hz}), 6.78 (d, 1H, J = 8.7 \text{ Hz}), 3.53 (s, 3H), 3.50 (s, 3H), 3.33 (s, 3H).\]

\[ \text{C NMR:} \quad 156.38, 154.30, 148.92, 147.50, 146.80, 136.73, 129.84, 129.47, 128.23, 127.59, 126.66, 124.28, 124.40, 121.86, 119.13, 107.73, 61.25, 61.04.\]


MS: 372 (M\(^+\)), 371, 357, 242, 128, 82, 69, 57, 44, 31 (100%).

HRMS: expected 372.1474, observed 372.1479.
Cycloadduct 2f

Procedure B

451 mg (100%) R_f (20% EtOAc/hexanes) .32.

^1H NMR:
8.20 (br.d, 1H, J = 8.7 Hz), 8.06 (br.d, 1H, J = 8.5 Hz),
7.89 (d, 1H, J = 8.6 Hz), 7.80 (m, 1H), 7.69 (app.dt, 1H,
J_1 = 7.7 Hz, J_2 = 1.5 Hz), 7.50 (app.dt, 1H, J_1 = 7.5 Hz,
J_2 = 1.1 Hz), [major diast. - 7.04 (d, J = 8.7 Hz); minor
diast. - 7.01 (d, J = 8.7 Hz), 1H], [minor diast - 6.66 (d,
J = 8.7 Hz); major diast. - 6.64 (d, J = 8.7 Hz), 1H], 6.40
(br.s, 1H), 4.0 - 4.25 (cm, 1H), 3.96 (s, 3H), 3.90 (s,
3H), 3.85 (s, 3H), [major diast. - 3.44 (s); minor diast. -
3.37 (s), 3H], 2.03 - 2.36 (m, 2H), [minor diast. - 1.64 (s);
major diast. - 1.62 (s), 3H].

IR:
3055, 2939, 2839, 1621, 1596, 1496, 1466, 1286, 1231,
1105, 1040, 832, 757.

MS:
422 (M^+ + 1), 421 (M^+), 390, 389, 388, 378, 350, 349
(100%), 318, 251, 196, 129, 128, 101.

HRMS:
expected 421.1889, observed 421.1896.
Pyridine 71b

Procedure C

44.7 mg (33%) R_f (50% EtOAc/hexanes) .57.

^1H NMR: 8.55 (d, 1H, J = 5.7 Hz), 8.49 (dd, 1H, J_1 = 1.4 Hz, J_2 = .4 Hz), 8.20 (app.d, 1H, J = 8.6 Hz), 8.10 (app.d, 1H, J = 8.7 Hz), 7.35 - 8.20 (m, 4H), 7.15 (d, 1H, J = 8.6 Hz), 6.71 (d, 1H, J = 8.7 Hz), 3.89 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 2.66 (s, 3H).

^13C NMR: 157.67, 156.72, 155.80, 154.12, 151.68, 147.94, 147.16, 136.60, 129.81, 129.35, 128.16, 127.55, 126.50, 126.26, 124.78, 123.89, 119.34, 119.15, 107.62, 61.25, 61.03, 56.05, 24.72.

IR: 2930, 2857, 1599, 1546, 1497, 1467, 1291, 1089, 1015, 839, 804, 763.

MS: 387 (M^+ + 1), 386 (M^+, 100%), 385, 360, 355, 348, 325, 207, 128.

HRMS: expected 386.1630, observed 386.1631.
Enone 67

Procedure A

8.31 g (83%) \( R_f \) (20% EtOAc/hexanes) .52.

\(^1\)H NMR: 8.08 (d, 1H, \( J = 7.7 \) Hz), 7.58 (s, 1H), 7.48 (s, 1H), 7.39 (app.t, 1H, \( J = 7.4 \) Hz), 7.27 (app.t, 1H, \( J = 7.5 \) Hz), 7.17 (d, 1H, \( J = 7.4 \) Hz), 6.62 (d, 1H, \( J = 3.4 \) Hz), 6.43 (dd, 1H, \( J_1 = 3.0 \) Hz, \( J_2 = 1.87 \) Hz), 3.22 (t, 2H, \( J = 6.5 \) Hz), 2.89 (t, 2H, \( J = 6.5 \) Hz).

\(^13\)C NMR: 151.89, 143.95, 142.97, 133.00, 132.58, 131.32, 127.71, 127.51, 126.39, 122.28, 116.09, 111.64, 27.73, 26.18.

IR: 3113, 2939, 2906, 2835, 1664, 1600, 1468, 1307, 1236, 1028, 961, 741.

MS: 225 (M\(^+\) + 1), 226 (M\(^+\) + 100%), 206, 195, 181, 170, 165, 152, 118, 115, 90, 89.

HRMS: expected 224.0837, observed 224.0836.
Cycloadduct 2b

Procedure B

2.61 g (61% chromatographed yield - 89% based on recovered starting material) Rf (20% EtOAc/hexanes) .68.

$^1$H NMR:

7.54 (br.d, 1H, J = 7.1 Hz), 7.30 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = .9$ Hz), 7.14 (cm, 3H), 6.28 (dd, 1H, $J_1 = 3.1$ Hz, $J_2 = 1.9$ Hz), 6.12 (d, 1H, $J = 3.1$ Hz), 5.16 (t, 1H, $J = 4.8$ Hz), 4.05 (dq, 1H, $J_1 = 9.5$ Hz, $J_2 = 7.1$ Hz), 3.76 (t, 1H, $J = 7.8$ Hz), 3.66 (dq, 1H, $J_1 = 9.5$ Hz, $J_2 = 7.1$ Hz), 2.75 (br.t, 2H, $J = 8.1$ Hz), 2.30 (dd, 2H, $J_1 = 7.9$ Hz, $J_2 = 5$ Hz), 2.14 (br.t, 2H, $J = 8.1$ Hz), 1.26 (t, 3H, $J = 7.1$ Hz).

$^{13}$C NMR:

156.09, 143.08, 140.98, 136.06, 131.44, 127.18, 126.88, 126.13, 121.09, 110.09, 108.43, 106.04, 98.51, 64.15, 35.36, 33.96, 28.06, 24.92, 15.21.

IR:

2972, 2932, 2889, 1651, 1489, 1370, 1307, 1145, 1096, 1053, 772, 730.

MS:

297 (M$^+$ + 1), 296 (M$^+$), 250, 224, 206, 195, 170, 167, 165 (100%), 152, 151, 118, 115.

HRMS:

expected 296.1412, observed 296.1415.
**Pyridine 68**

Procedure C

1.94 g (89%) $R_f$ (20% EtOAc/hexanes) .45.

$^1$H NMR: 8.51 (d, 1H, $J = 5.2$ Hz), 8.30 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 1.6$ Hz), 7.50 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = .6$ Hz), 7.40 (d, 1H, $J = 5.2$ Hz), 7.13 - 7.39 (cm, 3H), 6.59 (dd, 1H, $J_1 = 3.6$ Hz, $J_2 = .5$ Hz), 6.47 (dd, 1H, $J_1 = 3.4$ Hz, $J_2 = 1.8$ Hz), 3.10 (br.t, 2H, $J = 6.7$ Hz), 2.84 (br.t, 2H, $J = 6.7$ Hz).

$^{13}$C NMR: 153.11, 150.61, 147.09, 143.02, 137.49, 136.24, 134.56, 128.89, 127.41, 127.21, 126.91, 125.27, 119.62, 111.57, 27.70, 25.45.

IR: 3128, 3050, 2945, 2896, 2832, 1595, 1567, 1447, 1398, 1236, 1201, 1011, 920, 744, 646.

MS: 248 ($M^+ + 1$), 247 ($M^+$, 100%), 246, 218, 217, 216, 204, 192, 189, 151.

HRMS: expected 247.0997, observed 247.0992.
Dihydroazaphenanthrene acid from pyridine 68

1.323 g (5.357 mmol) of furyl dihydroazaphenanthrene 68 was dissolved in 20 ml of dry MeOH. The solution was cooled to -78°C and then ozone was bubbled through the solution for 1.5 hours. After purging the solution with argon, 5 ml of dimethyl sulfide was added. The solution was allowed to come to room temperature and was stirred for one additional hour. The solvents were evaporated and the residue was passed over a short plug of silica gel. 1.145 g (95%) Rf (70% EtOAc/hexanes) 0.07.

^1H NMR: 8.57 (d, 1H, J = 5.7 Hz), 8.18 (m, 2H), 7.11 - 7.62 (M, 3H), 2.50 - 3.50 (m, 4H).

IR: 3402, 2945, 2839, 1700, 1605, 1397, 1023, 751.

MS: 226 (M^+ + 1), 225 (M^+), 224 (100%), 198, 197, 179, 177, 148.

HRMS: expected 225.0789, observed 225.0789.
90 MHz $^1$H NMR
**Methyl Ester 66**

250 mg (1.11 mmol) of the crude acid was dissolved in 20 ml of CH₂Cl₂. To this solution was added an ethereal solution containing diazomethane (prepared by distillation of an alkaline solution of Diazald). Addition was continued until all starting material was consumed. The solvents were then evaporated. 263 mg (99%).

\[ \text{H NMR:} \quad 8.62 \text{ (d, 1H, } J = 4.9 \text{ Hz)}, \ 8.29 \text{ (m, 1H), 7.54 \text{ (d, 1H, } J = 4.9 \text{ Hz)}, \ 7.21 - 7.41 \text{ (cm, 3H), 3.95 \text{ (s, 3H), 3.29 (t, 2H, } J = 6.9 \text{ Hz)}, \ 2.90 \text{ (t, 2H, } J = 6.9 \text{ Hz).} \]

\[ \text{C NMR:} \quad 166.96, 154.19, 147.52, 138.14, 136.70, 134.10, 131.76, 129.50, 127.52, 127.16, 125.47, 121.76, 52.47, 27.39, 24.93. \]

\[ \text{IR:} \quad 2952, 1729, 1560, 1433, 1391, 1271, 1159, 1110, 793, 744. \]

\[ \text{MS:} \quad 240 \text{ (M⁺ + 1), 239 (M⁺, 100%), 224, 207, 180, 179, 178, 152, 151, 150.} \]

\[ \text{HRMS:} \quad \text{expected 239.0946, observed 239.0944.} \]
Enone 63

Procedure A

256 mg (74%) \( R_f \) 20% EtOAc/hexanes .48.

\(^1\text{H NMR}:\) 8.22 (d, 1H, \( J = 8.7 \text{ Hz} \)), 8.12 (m, 1H), 7.85 (m, 1H), 7.78 (d, 1H, \( J = 8.7 \text{ Hz} \)), 7.58 (cm, 4H), 6.71 (d, 1H, \( J = 3.4 \text{ Hz} \)), 6.53 (dd, 1H, \( J_1 = 3.4 \text{ Hz}, J_2 = 1.8 \text{ Hz} \)), 3.41 (cm, 4H).

\(^{13}\text{C NMR}:\) 187.40, 152.50, 144.20, 142.00, 136.60, 131.40, 131.00, 128.80, 128.20, 127.70, 126.50, 124.80, 123.7, 122.00, 117.20, 112.60, 27.00, 23.95.

\(\text{IR}:\) 2920, 1662, 1596, 1469, 1423, 1330, 1282, 1237, 1178, 1022, 905, 833, 762.

\(\text{MS}:\) 275 (\( M^+ + 1 \)), 274 (\( M^+ \), 100%), 256, 220, 202, 196, 168, 165, 140, 139.

\(\text{HRMS}:\) expected 274.0993, observed 274.0996.
Cycloadduct 2d

Procedure B

pale yellow stars (m.p. 83-84.5 °C). 141.7 mg (64% chromatographed yield) Rf (20\% EtOAc/hexanes) .72.

\(^1\)H NMR: 7.87 (d, 1H, J = 8.3 Hz), 7.63 (M, 3H), 7.20 - 7.38 (m, 3H), 6.19 (dd, 1H, J\(_1\) = 3.1 Hz, J\(_2\) = 1.7 Hz), 6.03 (d, 1H, J = 3.0 Hz), 5.07 (t, 1H, J = 4.9 Hz), 3.97 (dq, 1H, J\(_1\) = 9.5 Hz, J\(_2\) = 7.0 Hz), 4.44 (t, 1H, J = 7.8 Hz), 3.56 (dq, 1H, J\(_1\) = 9.5 Hz, J\(_2\) = 7.0 Hz), 3.06 (cm, 2H), 2.18 (m, 4H), 1.16 (t, 3H, J = 7.0 Hz).

\(^{13}\)C NMR: 156.01, 143.27, 141.03, 133.08, 131.28, 130.90, 128.60, 128.50, 126.04, 125.79, 125.02, 123.45, 119.94, 110.09, 107.55, 106.05, 98.68, 64.19, 35.27, 33.96, 24.53, 23.17, 15.21.

IR: 3063, 2970, 2877, 1660, 1599, 1511, 1442, 1379, 1309, 1160, 1054, 960, 924, 818, 743.

MS: 347 (M\(^+\) + 1), 346 (M\(^+\)), 300, 274 (100%), 220, 202, 151.

HRMS: expected 346.1568, observed 346.1569.
Pyridine 64

Procedure C

62.3 mg (99%) $R_f$ (20% EtOAc/hexanes) .45.

$^1$H NMR: 8.62 (d, 1H, $J = 5.2$ Hz), 8.53 (d, 1H, $J = 8.7$ Hz), 8.13 (cm, 1H), 7.89 (m, 2H), 7.62 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = .7$ Hz), 7.53 (cm, 3H), 6.75 (dd, 1H, $J_1 = 3.4$ Hz, $J_2 = .6$ Hz) 6.60 (dd, 1H, $J_1 = 3.4$ Hz, $J_2 = 1.8$ Hz), 3.34 (br.s, 4H).

$^{13}$C NMR: 153.90, 151.00, 147.10, 143.10, 137.20, 134.20, 132.00, 131.10, 128.70, 127.60, 126.40, 124.00, 123.50, 120.00, 111.80, 111.70, 25.20, 22.80.

IR: 3061, 2934, 1594, 1436, 1396, 1018, 825, 739.

MS: 298 ($M^+$), 297 (100%), 296, 267, 266, 139, 134, 133.

HRMS: expected 297.1153, observed 297.1153.
**Dienone 32**

Procedure A, using p-nitrobenzaldehyde and methyl furylidene ketone.

25 mg (82%) Rf 20% EtOAc/ hexanes .27.

$^1$H NMR: 8.25 (d, 1H, $J = 8.9$ Hz), 7.73 (d, 1H, $J = 8.5$ Hz), 7.71 (d, 1H, $J = 16.2$ Hz), 7.54 (br.s, 1H), 7.52 (d, 1H, $J = 16.2$ Hz), 7.10 (d, 1H, $J = 16.0$ Hz) 6.97 (d, 1H, $J = 16.0$ Hz), 6.74 (d, 1H, $J = 3.5$ Hz), 6.52 (dd, 1H, $J_1 = 3.4$ Hz, $J_2 = 1.8$ Hz).

IR: 2924, 1708, 1653, 1611, 1513, 1337, 1021, 753.

MS: 270 (M$^+$ + 1), 269 (M$^+$), 194, 176 (100%), 166, 165, 152, 121, 102, 65.

HRMS: expected 341.1262, observed 341.1263.
**Cycloadducts 33a + 33b**

Procedure B

24 mg (99% yield) By $^1$H NMR, two cycloadducts (corresponding to reaction with both sides of the diene) were formed in a 1:1 ratio. By TLC, the two spots were visible: $R_f$ (20% EtOAc/hexanes) .47; .55.

1:1 mixture of positional isomers reported as a total of 38 H's:

$^1$H NMR: 8.18 (cm, total of 4H), 7.54 (d, 2H, $J = 8.8$ Hz), 7.42 (d, 2H, $J = 8.7$ Hz), 7.38 (cm, 2H), 6.93 (A part of AB system, 1H, $J_{AB} = 15.8$ Hz), 6.75 (A part of AB system, 1H, $J_{AB} = 15.8$ Hz), 6.62 (B part of AB system, 1H, $J_{AB} = 15.8$ Hz), 6.46 (B part of AB system, 1H, $J_{AB} = 15.7$ Hz), 6.41 (m, 1H), 6.22 (m, 2H), 6.08 (br.d, 1H, $J = 3.2$ Hz), 5.20 (m, 2H), 5.18 (br.t, 1H, $J = 1.5$ Hz), 4.98 (d, 1H, $J = 3.2$ Hz), 4.06 (cm, 2H), 3.84 (cm, 2H), 3.50 - 3.75 (m, 2H), 2.35 (m, 2H), 1.88 - 2.14 (m, 2H), 1.30 (t, 3H, $J = 7.0$ Hz), 1.23 (t, 3H, $J = 7.0$ Hz).

IR: 2970, 2924, 2877, 1595, 1513, 1341, 1144, 1038, 952, 833, 740.

MS: 341 (M$^+$), 295, 269, 267, 206, 176 (100%), 165, 151, 121.

HRMS: expected 341.1343, observed 341.1345.
Dienone 34

$^1$H NMR: 8.08 (d, 1H, $J = 15.9$ Hz), 8.07 (d, 1H, $J = 8.1$ Hz), 7.68 (br.d, 2H, $J = 4.2$ Hz), 7.58 (cm, 1H), 6.85 (d, 1H, $J = 15.9$ Hz), 6.76 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = 10.7$ Hz), 6.42 (dd, 1H, $J_1 = 17.4$ Hz, $J_2 = .9$ Hz), 5.96 (dd, 1H, $J_1 = 10.7$ Hz, $J_2 = 1$ Hz).

$^{13}$C NMR: 189.50, 139.12, 134.41, 133.56, 130.97, 130.40, 129.67, 129.17, 129.10, 125.02.

IR: 3082, 2926, 2846, 1662, 1601, 1524, 1399, 1346, 1202, 1101, 980, 864, 787, 736.

MS: 157 (M$^+$, 100%), 148, 130, 120, 102, 55.

HRMS: expected 203.0582, observed 203.0583.
**Cycloadduct 35**

Procedure B

By $^1$H NMR, only one cycloadduct (corresponding to reaction with only the unsubstituted side of the diene) was formed. 66 mg (98% yield) $R_f$ (50% EtOAc/hexanes) .81.

$^1$H NMR: 7.90 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 1.2$ Hz), 7.50 - 7.65 (cm, 2H), 7.34 (cm, 1H), 7.27 (d, 1H, $J = 15.6$ Hz), 6.44 (d, 1H, $J = 15.6$ Hz), 5.21 (t, 1H, $J = 3.0$ Hz), 5.12 (brt, 1H, $J = 4.7$ Hz), 3.93 (dq, 1H, $J_1 = 9.9$ Hz, $J_2 = 7.1$ Hz), 3.68 (dq, 1H, $J_1 = 9.9$ Hz, $J_2 = 7.1$ Hz), 2.33 (cm, 1H), 2.11 (cm, 1H), 1.89 (cm, 2H), 1.25 (t, 3H, $J = 7.1$ Hz).

IR: 2983, 2924, 1649, 1606, 1526, 1349, 1119, 1039, 960, 778, 745.

MS: 275 (M$^+$), 230, 212, 184, 156, 130, 115 (100%), 97, 72.

HRMS: expected 275.1157, observed 275.1158.
Cycloadduct 36

Procedure B.

27.2 mg. (78%, based on recovered starting material) R\textsubscript{f} (10% EtOAc/hexanes) 0.57.

\textbf{\textsuperscript{1}H NMR:} 7.62 (m, 2H), 7.28 (m, 8H), 5.55 (d, 1H, J = 4.0 Hz), 3.39 (t, 1H, J = 4.0 Hz), [minor diast. - 3.23 (s); major diast. - 3.18 (s), 3H], 2.06-2.25 (m, 2H), 1.38-1.75 (m, 7H).

\textbf{IR:} 3010, 2965, 2845, 1650, 1485, 1450, 1099, 1050, 920, 765, 700.

\textbf{MS:} 320 (M\textsuperscript{+}), 288, 209, 112 (100%), 111, 110.

\textbf{HRMS:} expected 320.1176, observed 320.1177.
Pyridine 37

Procedure C

13 mg. (56%) Rf (10% EtOAc/hexanes) 0.46.

$^1$H NMR: 8.00 (m, 2H), 7.43 (m, 9H), 3.10 (t, 2H, J = 6.4 Hz), 2.66 (t, 2H, J = 6.3 Hz), 1.95 (cm, 2H), 1.76 (cm, 2H).

$^{13}$C NMR: 157.64, 154.33, 150.22, 139.74, 128.61, 128.55, 128.53, 128.42, 128.31, 127.72, 126.86, 119.07, 33.26, 27.28, 23.11, 23.05.

IR: 3050, 2930, 1580, 1540, 1475, 1440, 1370, 760, 700.

MS: 285 (M$^+$), 184 (100%), 283, 256.

HRMS: expected 285.1517, observed 285.1518.
Cycloadduct 4a

Procedure B

118.5 mg (87%) \( R_f (10\% \text{ EtOAc/hexanes}) .64. \)

\(^1\text{H NMR:}\) 
7.60 (m, 2H), 7.31 (cm, 3H), 5.32 (dd, 1H, \( J_1 = 2.4 \text{ Hz,} \) \( J_2 = 1.2 \text{ Hz,} \) 5.07 (dd, 1H, \( J_1 = 9.3 \text{ Hz,} \) \( J_2 = 1.9 \text{ Hz,} \) 4.15 (dq, 1H, \( J_1 = 9.5 \text{ Hz,} \) \( J_2 = 7.1 \text{ Hz,} \) 3.71 (dq, 1H, \( J_1 = 9.5 \text{ Hz,} \) \( J_2 = 7.1 \text{ Hz,} \) 2.39 (cm, 1H), 2.03 (ddt, 1H, \( J_1 = 12.7 \text{ Hz,} \) \( J_2 = 6.5 \text{ Hz,} \) \( J_3 = 1.5 \text{ Hz,} \) 1.60 - 1.88 (m, 6H), 1.33 (t, 3H, \( J = 7.1 \text{ Hz,} \) .98 - 1.45 (br.m, 6H).

\(^{13}\text{C NMR:}\) 
149.17, 135.65, 128.04, 127.79, 124.46, 100.96, 64.49, 42.25, 37.92, 31.66, 30.38, 29.69, 26.63, 26.53, 15.32.

\text{IR:}\) 
3063, 2917, 2857, 1644, 1496, 1448, 1279, 1160, 1050, 915, 757, 691.

\text{MS:}\) 
276 (\( M^+ \)), 240, 214, 203 (100%), 105.

\text{HRMS:}\) 
expected 268.9825, observed 268.1933.
Pyridine 4a

Procedure C

20 mg (84%) $R_f$ (10% EtOAc/hexanes) .38.

$^{13}$C NMR: 157.48, 157.35, 149.53, 136.80, 128.70, 128.63, 126.96, 122.05, 120.86, 120.55, 119.40, 44.10, 33.57, 26.54, 25.93.

IR: 3063, 2930, 2857, 1596, 1557, 1472, 1447, 1407, 836, 776, 746, 694.

MS: 237 ($M^+$), 208, 196, 194, 187 (100%), 185, 169, 155, 77, 41.

HRMS: expected 237.1517, observed 237.1517.
**Cycloadduct 4b**

Procedure B

36.1 mg (99%) R_f (10% EtOAc/hexanes) .48.

**1H NMR:**

7.58 (m, 2H), 7.30 (m, 3H), 5.28 (dd, 1H, J_1 = 1.9 Hz, J_2 = .7 Hz), 5.09 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2 Hz), 4.12 (dq, 1H, J_1 = 9.7 Hz, J_2 = 7.1 Hz), 3.70 (dq, 1H, J_1 = 9.7 Hz, J_2 = 7.1 Hz), 2.48 (br.m, 1H), 2.10 (cm, 1H), 1.57 (cm, 1H), 1.31 (t, 3H, J = 7.1 Hz) 1.25 - 1.45 (m, 19H).

**IR:**

2922, 2858, 1648, 1443, 1370, 1227, 1171, 1044, 752, 692.

**MS:**

330 (M^+), 284, 203, 105 (100%), 73, 62.

**HRMS:**

expected 330.2558, observed 330.2564.
Pyridine 4h

Procedure C

26.6 mg (86%) \( R_f \) (20% EtOAc/hexanes) .68.

\(^1\)H NMR:  
8.57 (br.d, 1H, J = 4.7 Hz), 7.98 (cm, 2H), 7.38 - 7.54 (cm, 5H), 7.06 (br.dd, 1H, \( J_1 = 4.8 \) Hz, \( J_2 = 1.5 \) Hz), 2.66 (t, 2H, \( J = 7.5 \) Hz), 1.67 (cm, 2H), 1.32 (br.m, 12H), .90 (t, 3H, \( J = 7 \) Hz).

\(^{13}\)C NMR:  
157.39, 152.50, 149.44, 139.63, 128.73, 128.63, 126.93, 122.39, 120.83, 35.48, 31.83, 30.41, 29.46, 29.40, 29.26, 29.21, 22.63, 14.07.

IR:  
2930, 2851, 1599, 1557, 1472, 1407, 777, 737, 695.

MS:  
271 (\( M^+ \)), 248, 183, 182 (100%), 169.

HRMS:  
expected 281.2143, observed 281.2144.
Enone 60

Procedure A

5.2 g (91%) R_f (10% EtOAc/hexanes) .43.

$^{1}H$ NMR: 8.15 (br.d, 1H, J = 7.8 Hz), 7.89 (br.s, 1H), 7.22 - 7.53 (cm, 8H), 3.13 (M, 2H), 2.92 (m, 2H).

$^{13}C$ NMR: 187.79, 143.14, 136.54, 135.72, 135.36, 133.38, 133.19, 128.58, 128.46, 128.36, 128.10, 126.92, 28.76, 27.08.

IR: 2946, 2838, 1669, 1589, 1294, 1224, 1136, 948, 756, 739, 699.

MS: 235 (M$^{+}$ + 1), 234 (M$^{+}$, 100%), 233, 232, 202, 188, 128, 115, 91, 89.

HRMS: expected 234.1044, observed 234.1046.
Cycloadduct 2c

Procedure B

784 mg (100%) R_f (10% EtOAc/hexanes) .57.

^1H NMR: 7.61 (m, 2H), 7.27 (m, 7H), 5.17 (dd, 1H, J_1 = 8.3 Hz, J_2 = 2.0 Hz), 4.14 (dq, 1H, J_1 = 9.5 Hz, J_2 = 7.2 Hz), 3.70 (cm, 2H), 2.74 (t, 2H, J = 7.6 Hz), 2.41 ( ddd, 1H, J_1 = 13.4 Hz, J_2 = 7.3 Hz, J_3 = 2.0 Hz), 2.07 (cm, 3H), 1.31 (s, 3H).


MS: 306 (M^+), 260, 234, 233 (100%), 161, 91, 84.

HRMS: expected 306.1620, observed 306.1619.
Pyridine 61

Procedure C

559 mg (85%) R_f (10% EtOAc/hexanes) .34.

\(^1\)H NMR:

8.61 (d, 1H, J = 4.9 Hz), 8.40 (dd, 1H, J\(_1\) = 7.5 Hz, 
J\(_2\) = 1.3 Hz), 7.20 - 7.51 (m, 8H), 7.14 (d, 1H, 
J = 4.9 Hz), 2.83 (cm, 4H).

\(^13\)C NMR:

152.88, 148.42, 147.07, 138.74, 137.99, 134.77, 129.32, 
128.99, 128.65, 128.31, 127.91, 127.39, 127.04, 125.35, 
123.20, 28.10, 25.50.

IR:

3060, 3029, 2936, 2895, 2842, 1587, 1554, 1450, 1390, 
1217, 746, 699.

MS:

258 (M\(^+\) + 1), 257 (M\(^+\), 100%), 256, 226, 178, 151, 127.

HRMS:

expected 257.1204, observed 257.1204.
Enone 57

Procedure A

1.63 g (95%) \( R_f \) (10% EtOAc/hexanes) .41.

IR: \quad 3067, 2940, 2830, 1680, 1599, 1456, 1297, 1230, 1151, 746.

MS: \quad 158 (M\(^+\)), 130, 129, 128, 115, 84 (100%), 66.

HRMS: \quad \text{expected 158.0731, observed 158.0730.}
Cycloadduct 58

Procedure B

882 mg (87%) Rf (10% EtOAc/hexanes) .56.

$^1$H NMR: 7.07 - 7.47 (cm, 4H), 5.20 (t, 1H, J = 3.2 Hz), 3.94 (dq, 1H, $J_1$ = 9.8 Hz, $J_2$ = 7.8 Hz), 3.67 (dq, 1H, $J_1$ = 9.8 Hz, $J_2$ = 7.8 Hz), 2.82 (t, 2H, J = 7.8 Hz), 1.9 - 2.45 (cm, 5H), 1.23 (t, 3H, J = 7.8 Hz).

IR: 3050, 2977, 2937, 2831, 1666, 1488, 1377, 1142, 1109, 1081, 1054, 958, 764.

MS: 230 ($M^+$), 186, 130, 129, 128, 115, 84, 61 (100%).

HRMS: expected 230.1357, observed 230.1358.
Pyridine 59

Procedure C

502.4 mg (72%) Rf (10% EtOAc/hexanes) .47.

$^1$H NMR: 8.55 (dd, 1H, J$_1$ = 4.8 Hz, J$_2$ = 1.7 Hz), 8.32 (m, 1H), 7.51 (dd, 1H, J$_1$ = 7.6 Hz, J$_2$ = 1.7 Hz), 7.22 - 7.42 (cm, 3H), 7.13 (dd, 1H, J$_1$ = 7.5 Hz, J$_2$ = 4.8 Hz), 2.95 (s, 4H).

$^{13}$C NMR: 142.5, 147.9, 138.3, 135.6, 132.1, 129.3, 128.2, 126.2, 125.1, 122.3, 28.0.

IR: 3050, 2937, 2891, 2831, 1580, 1564, 1450, 1431, 1418, 796, 746.

MS: 181 (M$^+$), 180 (100%), 152.

HRMS: expected 181.0891, observed 181.08924.
Ester 139

To a flame-dried 3-neck 1 liter flask equipped with an overhead stirrer was added 21.5 g of KOTBu (.192 mol, 1.5 eq.) and 350 ml of distilled dimethoxyethane (DME). The solution was cooled to 0°C and then 32.3 g (.192 mol, 1.5 eq.) of the phosphonate (2) was added via syringe. The mixture soon became a very thick white suspension and was warmed to room temperature. With good stirring, a solution of 20 g (.128 mol) of cyclohexanedione mono-ethylene ketal in 60 ml of DME was rapidly added. The suspension became homogeneous and then a gooey precipitate formed on the sides of the flask. The reaction was over instantly as indicated by TLC. The DME was evaporated off by rotary evaporator and then the residue was dissolved in 200 ml of water. The solution was extracted twice with ether, and the combined extracts were dried over Na₂SO₄. The solvent was removed in vacuo to yield a clear, colorless liquid. 27.55 g (95%) Rf (30% EtOAc/hexanes) .55.

\[ \text{H NMR:} \]
5.59 (br.s, 1H), 4.06 (q, 2H, \( J = 7.1 \text{Hz} \)), 3.9 (s, 4H), 2.93 (t, 2H, \( J = 6.5 \text{ Hz} \)), 2.30 (t, 2H, \( J = 6.4 \text{ Hz} \)), 1.69 (q,4H, \( J = 6.4 \text{ Hz} \)), 1.2 (t, 3H, \( J = 7.1 \text{ Hz} \)).

\[ \text{C NMR:} \]
166.39, 160.07, 114.18, 107.82, 64.32, 59.47, 35.63, 34.85, 34.46, 25.88, 14.16.
IR: 2950, 2880, 1720, 1657, 1450, 1383, 1201, 1175, 1140, 1091, 1043, 950, 910, 870, 700.

MS: 226 (M^+), 197, 171, 170, 153 (100%), 135, 107.

HRMS: expected 226.1205, observed 226.1204.
Saturated Ester from 139

19.0 g (84.1 mmol) of the unsaturated ester 139 was dissolved in 150 ml of absolute EtOH and transferred to a stainless steel Parr bomb equipped with a stir bar. Then 4.45 g (4.2 mmol) Pd on carbon catalyst was added and the bomb was pressurized with H₂ to 2100 psi. The solution was stirred for 20 minutes at which time the reaction was finished as indicated by TLC. The Pd catalyst was removed by passing the reaction mixture over a pad of celite in a glass fritted funnel with low vacuum. The celite was washed with EtOAc and then the solvents were removed from the combined washes to yield a clear, colorless liquid.; 19.1 g (100%); Rᶠ (30% EtOAc/hexanes) .50.

^1^H NMR: 4.12 (q, 2H, J = 7.1 Hz), 3.93 (s, 4H), 2.21 (br.d, 2H, J = 6.8 Hz), 1.75 (br.m, 5H), 1.56 (br.t, 2H, J = 12.3 Hz), 1.31 (br.t, 2H, J = 12.3 Hz), 1.24 (t, 3H, J = 7.1 Hz).

^1^3^C NMR: 173.9, 109.3, 64.6, 60.6, 41.2, 34.5, 33.6, 30.1, 14.4.

IR: 2940, 2860, 1715, 1441, 1380, 1260, 1140, 1100, 1020, 953.

MS: 228 (M⁺), 183, 141, 140, 99 (100%).

HRMS: expected 228.1361, observed 228.1364.
Reduction of Ester

To an oven-dried 1 liter round bottom flask equipped with a stir bar was charged 5.2 g of LAH (.137 mmol) and 350 ml of anhydrous ethyl ether. The suspension was cooled to -20º C (dry ice/ethylene glycol) and then a solution of 21.3 g (.935 mol) of the ester in 50 ml of ether was added slowly via syringe. The reaction was finished immediately as indicated by TLC. The reaction was worked up by carefully adding 5.2 ml of water, then 5.2 ml of 20% aqueous NaOH solution, followed by 15.6 ml of water. Stirring was continued for 30 minutes and a white precipitate formed. The solution was filtered over a bed of celite, which was then washed with EtOAc. The solvents were removed from the filtrate in vacuo to give a clear, colorless liquid.; 17.2 g (90%); Rf (.40% EtOAc/ hexanes) .20.

^1H NMR: 3.90 (s, 4H), 3.63 (t, 2H, J = 6.6 Hz), 2.01 (s, 1H), 1.70 (AB system, 4H), 1.46 (m, 5H), 1.24 (m, 2H).

^13C NMR: 108.96, 64.08, 60.63, 38.97, 34.36, 32.72, 30.06.

IR: 3400, 2929, 2865, 1447, 1375, 1107, 1088, 1005, 940.

MS: 186 (M^+), 157, 141, 99 (100%), 86.

HRMS: expected 186.1256, observed 186.1253.
Alcohol 87

17.2 g (92.5 mmol) of ketal was dissolved in a mixture of 50 ml of THF and 75 ml of water. Then, 50 ml of 4N HCl was added and the reaction mixture was stirred overnight. Then the THF was removed by rotary evaporator and the remaining aqueous solution was extracted 14 times with 50 ml of CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and the solvent then removed in vacuo to give a colorless liquid. 13.02 g (99%); R_f (70% EtOAc/ hexanes) .33.

¹H NMR: 3.75 (t, 2H, J = 6.5 Hz), 2.38 (m, 4H), 1.85 - 2.15 (m, 3H), 1.60 (q, 2H, J = 6.5 Hz), 1.48 (m, 2H).

¹³C NMR: 214.2, 61.2, 41.3, 38.5, 33.0.

IR: 3409, 2931, 2860, 1709, 1448, 1421, 1334, 1168, 1055.

MS: 142 (M⁺), 99 (100%), 98, 86.

HRMS: 142.0994, observed 142.0995.
Enone Alcohol from 87

12.45 g (87.7 mmol) of ketone 87 and 25.78 g (175 mmol) of azidobenzaldehyde were dissolved in 80 ml of ethanol. Enough water (~30 ml) was then added to almost make the solution cloudy. 15 ml of 20% aqueous NaOH was added and the solution warmed and became opaque. The solution was stirred at room temperature for 30 minutes and a voluminous yellow precipitate formed. The precipitate was filtered off and washed well with water. The wet solid was dissolved in 50 ml of CH₂Cl₂ and was passed over a short plug of silica gel. The solvent was evaporated to give yellow crystals. mp 129-131°C; 31.0 g (88%); Rf (.40% EtOAc/ hexanes) .28.

¹H NMR:

7.84 (br. s, 2H), 7.12 - 7.42 (complex m., 8H), 3.58 (t, 2H, J = 6.5 Hz), 2.94 (dd, 2H, J₁ = 15.5 Hz, J₂ = 3.5 Hz), 2.46 (ddd, 2H, J₁ = 15.6 Hz, J₂ = 10.5 Hz, J₃ = 2.4 Hz), 1.93 (complex m., 1H), 1.58 (q, 2H, J = 6.5 Hz).

¹³C NMR:

189.44, 139.59, 136.07, 132.87, 130.38, 129.85, 127.42, 124.20, 118.48, 60.26, 38.02, 34.24, 30.83.

IR:

3421, 3061, 2927, 2125, 1668, 1606, 1570, 1481, 1446, 1292, 1145, 754.

MS:

373 (M⁺ - N₂), 359, 196, 168, 156, 143 (100%), 130, 129, 119.

HRMS:

expected 400.1647, observed 400.1638.
Dienone 96

30.9 g (77.2 mmol) of the alcohol was dissolved in 80 ml of pyridine. Then 23.6 g (.231 mol) of acetic anhydride was added and the flask was stoppered. The solution was stirred overnight at room temperature. After the reaction finished, 350 ml of 10% aqueous H₂SO₄ was added. The solution was extracted 3 times with CH₂Cl₂. The combined extracts were washed with saturated NaHCO₃ solution, then CuSO₄, and finally with water. The organic phase was passed over a short plug of silica gel and the solvent evaporated to yield a yellow orange solid. (mp 98.5 - 100° C); 33.8 g (99%); Rf (.40% EtOAc/ hexanes) .72.

¹H NMR: 7.78 (br.s, 2H), 7.05 - 7.35 (complex m, 8H), 3.93 (t, 2H, J = 6.4 Hz), 2.87 (dd, 2H, J₁ = 15.5, J₂ = 3.4 Hz), 2.40 (ddd, 2H, J₁ = 15.7 Hz, J₂ = 10.5 Hz, J₃ = 2.3 Hz), 1.84 (s, 3H), 1.65 - 1.85 (complex m, 1H), 1.58 (q, 2H, J = 6.6 Hz).

¹³C NMR: 188.9, 170.8, 139.5, 133.0, 130.3, 129.9, 127.3, 124.2, 118.4, 62.2, 34.1, 34.0, 31.5, 20.7.

IR: 2931, 2124, 1735, 1676, 1594, 1482, 1447, 1288, 1238, 1043, 752.

MS: 400 (M⁺ - 42), 372, 312, 297, 269, 180, 168, 130 (100%), 129.

HRMS: expected 442.1753, observed 442.1760.
Cycloadduct from 96

4.32 g (9.77 mmol) of the enone 96 was dissolved in a mixture of 20 ml of dichloroethane and 20 ml of ethyl vinyl ether. 517 mg (5 mole %) Yb(fod)$_3$ catalyst was added and the solution was heated to a gentle reflux for 24 hours. The solvents were evaporated and the residue was dissolved in 30 ml of CH$_2$Cl$_2$ and washed one time with water. The organic layer was dried over Na$_2$SO$_4$ and the solvents were evaporated to give a dark yellow-brown oil. 5.0 g (99%, crude) of the material was used as is for the pyridine forming reaction; R$_f$ (20% EtOAc/hexanes) .48; Thick oil, 1:1 mixture of two isomers. The molecule contains 30 protons, so the $^1$H NMR spectrum is reported as a total of 60 protons. 24 mg (99% yield) By $^1$H NMR, two cycloadducts (corresponding to reaction with both sides of the diene) were formed in a 1:1 ratio. By TLC, the two spots were visible: R$_f$ (20% EtOAc/hexanes) .47; .55

1:1 mixture of positional isomers reported as a total of 38 H's:

$^1$H NMR: 7.32 - 7.03 (compl. m, 16 H), 6.97 (br.s, 1H), 6.95 (br.s, 1H), 5.13 (dd, 1H, J$_1$ = 5.2 Hz, J$_2$ = 2.4 Hz), 5.09 (dd, 1H, J$_1$ = 8.4 Hz, J$_2$ = 1.9 Hz), 4.16 - 3.90 (compl. m, 7H), 3.79 - 3.59 (compl. m, 3H), 2.76 (br.s, 1H), 2.70 (br.s.; 1H), 2.35 - 2.25 (compl. m., 3H), 2.22 - 1.47 (compl. m., 13H), 2.01 (s, 3H), 2.00 (s, 3H), 1.29 (t, 3H, J = 7.0 Hz), 1.20 (t, 3H, J = 7.0 Hz).

$^{13}$C NMR: 170.59, 144.8, 144.3, 138.24, 137.89, 134.5, 134.1, 133.05, 132.43, 130.56, 130.01, 129.57, 129.47, 127.88,
127.77, 127.57, 124.92, 124.55, 124.18, 118.26, 117.95, 117.63, 117.20, 113.19, 112.26, 99.13, 98.09, 64.49, 64.01, 62.75, 62.51, 36.82, 35.10, 34.54, 34.11, 33.58, 33.32, 31.75, 31.08, 20.96, 15.31.

IR:
3050, 2931, 2123, 1738, 1635, 1580, 1484, 1448, 1286, 1240, 1141, 1046, 910, 753, 733.

MS:
487 [(M+1) - N₂], 413, 399, 269, 256, 168, 158, 130 (100%).

HRMS:
expected 514.2328, observed 514.2327.
Pyridine 97

5.0 g (9.77 mmol) of the crude cycloadduct was dissolved in 42 ml of CH$_3$CN (.25 M solution in cycloadduct) and then 2.5 g (36 mmol, 50 wt. %) of hydroxylamine hydrochloride was added. The solution was stirred well and refluxed overnight; the color changed from a clear, deep orange-brown to a dark brown-black. The solvents were removed in vacuo and the residue was dissolved in CH$_2$Cl$_2$. The solution was washed with saturated NaHCO$_3$ and the organic layer was passed over a short plug of silica gel. The solvent was evaporated to give a thick oil. 2.51 g, (56%); R$_f$ (50% EtOAc/ hexanes) .29; 1:1 mixture of atropisomers.

$^1$H NMR: 8.47 (d, 1H, J = 4.8 Hz), 7.95 (br.s, 1H), 7.39 (dt, 1H, app. $J_1 = 7.42$ Hz, $J_2 = 0.5$ Hz), 7.30 - 7.05 (compl. m, 7H), 6.90 (d, 0.5H, $J = 4.8$ Hz) and 6.88 (d, 0.5H, $J = 4.8$ Hz), 3.92 (t, 2H, $J = 6.6$ Hz), 2.89 (dt, 1H, $J_1 = 14.9$ Hz, $J_2 = 1.5$ Hz), 2.64 - 2.14 (compl. m, 4H), 1.82 (s) and 1.81 (s), 3H total, 1.55 (m, 2H).

$^{13}$C NMR: 171.0, 152.10, 146.90, 146.70, 139.0, 137.50, 136.01, 130.50, 130.26, 130.01, 129.60, 128.35, 124.97, 124.85, 124.19, 123.76, 123.58, 118.41, 118.31, 118.30, 62.39, 34.19, 33.98, 33.82, 33.64, 33.33, 33.09, 31.02, 30.91, 20.78.

IR: 3056, 2926, 2124, 1738, 1600, 1575, 1493, 1443, 1291, 1240, 1046, 910, 754, 732.

MS: 438 [(M + 1) - N$_2$], 410, 409, 219, 205, 130, 43 (100%).
HRMS: expected 465.1913, observed 465.1913.
Ketone 98

8.4 g (18.06 mmol) of the pyridine 97 was dissolved in 150 ml of dry methanol in a 250 ml 3-neck flask equipped with a glass stopper, a drying tube and a tube for bubbling ozone. The solution was cooled to -78°C and ozone was bubbled gently through the solution for one hour and 15 minutes. Workup involved addition of 5 ml of dimethyl sulfide and then the solution was warmed to room temperature over a period of one and a half hours. The solvent was evaporated and then residue was dissolved in CH₂Cl₂. The CH₂Cl₂ solution was loaded onto a column of silica gel and the azidobenzoaldehyde that was produced in the reaction was collected using CH₂Cl₂ as the eluent. The pyridine ketone was recovered by flushing the column with EtOAc. The solvent was evaporated to give a thick oil. 4.87 g (77%); R₇ (100% EtOAc) 0.55.

¹H NMR: 8.67 (d, 1H, J = 4.7 Hz), 7.46 (br.t, 1H, J = 7.29 Hz), 7.08 - 7.26 (compl. m, 4H), 4.01 (t, 2H, J = 6.3 Hz), 2.94 - 2.15 (compl. m, 5H), 1.89 (s) and 1.88 (s), 3H total, 1.74 - 1.62 (m, 2H).

¹³C NMR: 195.8, 170.80, 148.50, 148.30, 147.80, 147.65, 138.5, 138.2, 137.8, 137.3, 130.23, 130.24, 129.1, 128.9, 128.18, 127.87, 125.13, 125.00, 118.59, 118.33, 61.67, 45.20, 34.04, 33.90, 32.81, 32.63, 31.72, 20.72.

IR: 3056, 2955, 2126, 1733, 1700, 1601, 1579, 1493, 1441, 1366, 1293, 1238, 1036, 758, 730.

MS: 350 (M⁺), 322, 270, 262, 235, 207, 206, 180, 179, 43
(100%).

HRMS: expected 350.1379, observed 350.1380.
Ketal from 98

450 mg (1.29 mmol) of ketone 98 was dissolved in a mixture of 10 ml of ethylene glycol and 1 ml of triethylorthoformate. 50 mg of camphorsulfonic acid was added and the solution was heated at 60°C for 3 days. The solution was diluted with 50 ml of saturated NaHCO₃ solution and was extracted 3 times with CHCl₃. The combined extracts were washed once with water and then dried over Na₂SO₄. The solvents were removed to give a tan solid (mp 102-103°C); 456 mg (90%); Rf (70% EtOAc/hexanes) .57.

**1H NMR:**

8.53 (d, 1H, J = 4.8 Hz) 7.44 (AB, ¹H), 7.03 - 7.28 (complex m, 3H), [6.98 and 6.97 (d, 1H, J = 4.8 Hz)], 4.55 - 4.67 (complex m, 1H), 4.32 - 4.43 (complex m, 1H), 4.17 - 4.27 (complex m, 1H), 4.02 - 4.12 (complex m, 3H).

**13C NMR:**

171.0, 156.2, 155.8, 147.4, 147.3, 146.5, 146.2, 137.7, 137.3, 130.8, 130.6, 130.4, 130.2, 130.1, 129.7, 125.0, 124.8, 124.5, 124.3, 118.6, 118.3, 106.3, 106.2, 66.9, 66.8, 65.3, 65.2, 62.2, 62.1, 41.1, 34.7, 33.3, 32.7, 29.5, 20.9.

**IR:**

2956, 2894, 2125, 1737, 1577, 1495, 1442, 1292, 1239, 1083, 1051, 950, 758, 734.

**MS:**

395 (M⁺ + 1), 394 (M⁺), 351 (100%), 323, 263, 235, 179, 125.

**HRMS:**

expected 394.1641, observed 394.1643.
Alcohol 117

450 mg (1.14 mmol) of the acetate was dissolved in 4 ml of dry methanol and then 50 mg of solid K₂CO₃ was added. The suspension was stirred for one and a half hours and then the solvent was removed. The residue was dissolved in 10 ml of water and then extracted twice with methylene chloride to give a thick oil. 397 mg (99%); Rf (70% EtOAc/hexanes) .23.

\[ \text{^1H NMR:} \]
8.53 (d, 1H, J = 4.8 Hz), 7.45 (AB, 1H), 7.05 - 7.29 (complex m, 3H), [6.98 and 6.99 (d, 1H, J = 4.8 Hz)], 4.57 - 4.68 (complex m, 1H), 4.32 - 4.44 (complex m, 1H), 4.04 - 4.28 (complex m, 2H), 3.62 - 3.7 (complex m, 2H), 1.80 - 2.60 (complex m, 5H), 1.55 - 1.75 (complex m, 2H).

\[ \text{^13C NMR:} \]
156.1, 155.8, 147.2, 147.1, 146.5, 146.1, 137.7, 137.2, 131.0, 130.7, 130.6, 130.3, 130.1, 129.6, 124.9, 124.7, 124.5, 124.2, 118.5, 118.3, 106.4, 66.9, 65.2, 60.2, 60.1, 41.0, 38.8, 38.7, 33.7, 32.9, 29.0, 28.9.

IR:
3386, 3055, 2927, 2124, 1577, 1495, 1443, 1291, 1182, 1084, 950, 736.

MS:
353 (M⁺ + 1), 352 (M⁺), 324, 309 (100%), 281, 235, 207, 179.

HRMS:
expected 352.1535, observed 352.1537.
Mesylate from alcohol 117

To a dry 10 ml round bottom flask was charged 1.34 g (3.80 mmol) of the alcohol 117 and 15 ml of CH₂Cl₂. The solution was cooled to 0°C and then 500 mg (4.96 mmol) of triethylamine was added, followed by 524 mg (4.58 mmol) of methanesulfonyl chloride. The reaction was finished immediately and the solution was warmed to room temperature and worked up. The reaction mixture was added to a mixture of 100 ml of 1/2 saturated brine. The resulting mixture was extracted twice with CH₂Cl₂ and the combined extracts were washed once with brine, once with water and finally dried over Na₂SO₄ to give a thick tan oil. 1.63 g (100%); R_f (70% EtOAc/hexanes) .54.

¹H NMR: 8.56 (d, 1H, J = 4.8 Hz), 7.47 (AB, 1H), 7.05 - 7.30 (complex m, 3H), [7.00 and 7.01 (d, 1H, J = 4.8 Hz)], 4.58 - 4.68 (complex m, 1H), 4.33 - 4.44 (complex m, 1H), 4.18 - 4.29 (complex m, 3H), 4.05 - 4.15 (complex m, 1H), [2.93 and 2.95 (s, 3H)], 1.77 - 2.66 (complex m, 7H).

¹³C NMR: 156.0, 155.7, 147.5, 147.4, 146.5, 146.3, 137.7, 137.3, 130.4, 130.2, 130.0, 129.7, 125.0, 124.8, 124.5, 124.3, 118.6, 118.3, 106.1, 67.3, 67.1, 66.9, 66.8, 65.3, 40.7, 37.3, 34.8, 33.1, 32.5, 29.0, 28.9.

IR: 3404, 3056, 2939, 2896, 2126, 1577, 1495, 1443, 1352, 1292, 1175, 1051, 951, 735.

MS: 431 (M⁺ + 1), 430 (M⁺), 387, 263 (100%), 125.

HRMS: expected 430.1311, observed 430.1314.
Phthalimide derivative of alcohol 117

To a dry 25 ml round bottom flask was charged 1.64 g (3.8 mmol) of the mesylate and 10 ml of DMF. Then 809 mg (4.37 mmol) of potassium phthalimide was added and the solution was heated at 50° C for 18 hours. The reaction mixture was then diluted with 75 ml of 10% aqueous Na₂CO₃, twice with water, then once with brine and then dried over Na₂SO₄. The solvents were evaporated to give a creamy yellow colored solid (mp 180-181° C). 1.65 g (90%); Rf (80% EtOAc/hexanes) .52.

¹H NMR: 8.55 (d, 1H, J = 4.8 Hz), 7.81 (complex m, 2H), 7.70 (complex m, 2H), 7.46 (br.t, 1H, J = 7.6 Hz), 7.05 - 7.32 (complex m, 3H), 6.99 (br.d, 1H, J = 4.8 Hz), 4.55 - 4.65 (complex m, 1H), 4.20 - 4.40 (complex m, 2H), 4.11 (br.q, 1H, J = 6.0 Hz), 3.71 (br.t, 2H, J = 6.8 Hz), 1.68 - 2.75 (complex m, 7H).

¹³C NMR: 168.2, 155.9, 155.7, 147.4, 147.3, 146.5, 146.4, 137.6, 137.4, 133.8, 132.0, 130.9, 130.6, 130.4, 130.2, 130.1, 129.6, 124.9, 124.7, 124.4, 124.3, 123.1, 118.5, 118.3, 106.3, 106.2, 66.9, 66.8, 65.2, 65.2, 40.7, 40.5, 35.4, 35.3, 34.3, 32.9, 32.5, 29.6, 29.4.

IR: 2943, 2360, 2124, 1771, 1709, 1575, 1495, 1397, 1291, 1176, 1082, 720.

MS: 453 (M⁺), 439, 438, 411, 410 (100%), 235, 207, 179, 160, 125.

HRMS: expected 481.1750, observed 481.1748.
**Amine 118**

1.60 g (3.33 mmol) of the phthalimide was dissolved in 13 ml of MeOH and then 400 mg (8 mmol) of hydrazine hydrate was added. The solution was warmed to 45° C for 3 hours. The solvents were evaporated and the residue was dissolved in 20 ml of CHCl₃ and washed once with 10% aqueous NaOH. The organic layer was dried over Na₂SO₄ and the solvent was evaporated to yield a thick tan oil. 1.05 g (90%); R₉ (70% EtOAc/hexanes) baseline.

**¹H NMR:**

8.51 (d, 1H, J = 4.8 Hz), 7.43 (br.t, app. J = 7.4 Hz) and 7.42 (br.t, app. J = 7.4 Hz), 1H total; 7.22 - 7.15 (m, 2H), 7.06 (br.t, app. J = 7.5 Hz) and 7.05 (br.t, app., J = 7.5 Hz), 1H total; 6.96 (d, J = 4.8 Hz) and 6.95 (d, J = 4.8 Hz), 1H total; 4.64 - 4.55 (m, 1H); 4.40 - 4.30 (m, 1H); 4.24 - 4.15 (m, 1H); 4.11 - 4.02 (m, 1H); 2.73 - 2.60 (m, 2H); 2.53 - 2.20 (m, 1H), 2.15 - 2.01 (m, 2H); 2.00 - 1.70 (m, 1H); 1.65 - 1.35 (m, 3H).

**¹³C NMR:**

156.26, 155.88, 147.22, 147.11, 146.40, 146.04, 137.66, 137.14, 139.99, 130.57, 130.65, 130.27, 130.07, 129.56, 124.88, 124.74, 124.41, 124.18, 118.48, 118.27, 106.39, 66.84, 65.16, 41.15, 40.05, 39.32, 33.62, 32.86, 29.78, 29.69.

**IR:**

3365, 3055, 2923, 2124, 1601, 1577, 1494, 1442, 1291, 1183, 1083, 1050, 950, 757, 731.
MS: 351 (M+), 308, 290 (100%), 264, 263, 262, 235, 207, 179.

HRMS: expected 351.1695, observed 351.1690.
Dimethylacrylamide from amine 118

584 mg (1.66 mmol) of the amine 118 was dissolved in 10 ml of THF and 748 mg (7.41 mmol) of triethylamine was added and this solution was cooled to 0° C. In a separate flask, 570 mg (5.7 mmol) of 3,3-dimethyl acryloyl chloride was dissolved in 1.5 ml of THF. The acid chloride solution was added to the chilled amine solution and then the reaction mixture was warmed to room temperature. The solvent was evaporated and the residue was dissolved in CHCl₃. This was washed once with 10% aqueous Na₂CO₃, once with water, once with brine and finally dried over Na₂SO₄. The solvent was evaporated to give a tan oil. 503 mg (70%); Rf (70% EtOAc/hexanes) .29.

**¹H NMR:**

8.48 (d, 1H, J = 4.8 Hz), 7.39 (br.t, 1H, J = 7 Hz), 6.96 - 7.23 (complex m, 3H), [6.92 and 6.93 (d, 1H, J = 4.8 Hz)], 5.41 (br.s, 1H), 5.29 (br.s, 1H - NH), 3.98 - 4.60 (complex m, 4H), 3.22 (br.m, 2H), 2.0 - 2.50 (complex m, 4H), 2.05 (s, 3H), 1.71 - 1.89 (br.m, 1H), 1.74 (s, 3H), 1.49 (br.m, 2H).

**¹³C NMR:**

166.9, 150.8, 147.4, 147.3, 130.9, 130.5, 130.2, 130.1, 129.7, 124.8, 124.6, 124.3, 123.3, 118.6, 118.3, 106.4, 66.9, 65.2, 40.9, 36.7, 36.6, 35.8, 35.7, 33.4, 32.8, 30.0, 27.1, 19.7.

**IR:**

3303, 3055, 2936, 2124, 1669, 1636, 1540, 1442, 1291, 1181, 1083, 1050, 757, 731.

**MS:**

390 (M⁺ - 43), 279, 262; 235, 217, 179, 125, 83 (100%).

**HRMS:**

expected 433.2114, observed 433.2118.
This section of the text describes the preparation and characteristics of a chemical compound. It contains several paragraphs that detail the experimental procedure and the results of various spectroscopic analyses. The text includes a table with NMR and IR data, as well as mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) results. The chemical structure is also depicted in the text. The text is rich with technical details and is typical of scientific literature.
Ketone 119

500 mg (1.15 mmol) of the ketal was dissolved in 5 ml of THF. Then 1 ml of 2N aq.
HCl was added and the solution was heated to 60°C for 24 hours. The reaction mixture
was neutralized with 10% aqueous NaHCO₃ and then extracted twice with CHCl₃. The
combined extracts were dried over Na₂SO₄ and the solvent was evaporated to give pale
yellow crystals (mp 154-156°C). 426 mg (95%); Rₕ (100% EtOAc) 0.32.

¹H NMR: 8.72 (d, 1H, J = 4.65 Hz), 7.52 (br.t, 1H, app.
J = 7.7 Hz), 7.34 - 7.21 (m, 3H), 7.17 (br.t, 1H, app.
J = 7.7 Hz), 5.80 - 5.60 (m, 1H), 5.50 (br.s, 1H), 3.38 -
3.20 (m, 2H), 3.01 - 2.18 (compl. m., 5H), 2.12 (br.s,
3H), 1.80 (br.s, 3H), 1.79 - 1.50 (m, 2H).

¹³C NMR: 196.44, 196.32, 167.04, 150.68, 148.21, 148.11, 147.74,
147.42, 138.54, 138.05, 137.68, 137.20, 130.16, 129.00,
128.68, 128.21, 127.87, 125.10, 124.91, 118.58, 118.29,
118.22, 45.03, 36.26, 35.22, 34.95, 32.97, 32.69, 31.98,

IR: 3311, 3060, 2933, 2126, 1701, 1668, 1635, 1540, 1442,
1293, 757, 731.

MS: 390 (M⁺ + 1), 389 (M⁺), 360, 280, 261, 247, 235 (100%).

HRMS: expected 389.1851, observed 389.1849.
Ketone 120

540 mg (1.25 mmol) of the ketal was dissolved in 5 ml of THF. Then 1 ml of 2N aq. HCl was added and the solution was heated at 60°C for 24 hours. The reaction mixture was neutralized with 10% aqueous NaHCO₃ and then extracted twice with CHCl₃. The combined extracts were dried over Na₂SO₄ and the solvent was evaporated to give pale yellow crystals (mp 154-155°C). 449 mg (94%); Rᶠ (100% EtOAc) 0.33.

¹H NMR: 8.72 (d, 1H, J = 4.6 Hz), 7.52 (br.t, 1H, app. J = 8.0 Hz), 7.34 - 7.21 (m, 3H), 7.18 (br.t, 1H, app. J = 8.0 Hz), 6.39 (br.q, 1H, J = 6.9 Hz), 6.02 (br.m, 1H), 3.38 - 3.20 (m, 2H), 3.01 - 2.20 (compl. m, 5H), 1.8 - 1.56 (compl. m, 2H), 1.79 (br.s, 3H), 1.71 (br.d, 3H, J = 6.9 Hz).

¹³C NMR: 196.24, 169.34, 148.38, 148.29, 148.00, 147.74, 147.45, 138.39, 137.95, 137.73, 137.29, 131.44, 130.64, 130.20, 129.08, 128.78, 128.22, 127.91, 125.16, 124.97, 118.62, 118.35, 45.19, 45.09, 36.94, 35.28, 34.96, 32.91, 32.69, 32.13, 13.77, 12.22.

IR: 3340, 3055, 2928, 2126, 1700, 1663, 1617, 1533, 1493, 1441, 1293, 758, 733.

MS: 390 (M⁺ + 1), 389 (M⁺), 361, 360, 261, 249, 235 (100%).

HRMS: expected 389.1851, observed 389.1849.
Cystodytin A  \textit{75}

50 mg (0.128 mmol) of ketone 119 was dissolved in 15 ml of chlorobenzene in a 100 ml round bottom flask equipped with a straight condenser. The solution was degassed with Argon for 25 minutes, and then kept under an Ar atmosphere with a balloon. The solution was heated to 110\(^{\circ}\)C (bath temperature) and the sunlamp was turned on. The bath temperature was monitored so the temperature stayed at 110\(^{\circ}\)C. Photolysis was continued for 10 hours and then the reaction was worked up. At this point, two major products indicated by TLC were the product spot and an intensely purple spot corresponding to the primary photoadduct. Small portions of DDQ were added until all of the purple material was converted to the product. The solvent was evaporated and the material was chromatographed by preparative TLC using 5% MeOH/CHCl\(_3\) as the eluent to give Cystodytin A as bright yellow crystals from CHCl\(_3\) (mp 182-184\(^{\circ}\)C). 14.2 mg (31%); \(R_f\) (5% MeOH/CHCl\(_3\)) purple spot .06, product .26.

\(^1\text{H NMR (CDCl}_3\):\n
9.12 (d, 1H, J = 5.5 Hz), 8.53 (dd, 1H, app. \(J_1 = 8.0\) Hz, \(J_2 = 1.2\) Hz), 8.43 (d, 1H, J = 5.5 Hz), 8.31 (dd, 1H, app. \(J_1 = 8.0\) Hz, \(J_2 = 1.0\) Hz), 7.95 (dt, 1H, app. \(J_1 = 7.2\) Hz, \(J_2 = 1.2\) Hz), 7.86 (dt, 1H, app. \(J_1 = 7.2\) Hz, \(J_2 = 1.2\) Hz), 6.91 (s, 1H), 6.11 (br.m, 1H), 5.57 (br.s, 1H), 3.82 (dt, 2H, \(J_1 = 6.6\) Hz, \(J_2 = 5.7\) Hz), 3.30 (t, 2H, \(J = 6.1\) Hz), 2.12 (d, 3H, J = 0.9 Hz), 1.80 (d, 3H,
$J = 0.9 \text{ Hz}$.

$^1\text{H NMR (CD}_3\text{OD/CDCl}_3$: Note: chemical shifts proved to be extremely sensitive to the precise ratio of CD$_3$OD to CDCl$_3$: 9.07 (d, 1H, $J = 5.5 \text{ Hz}$), 8.58 (m, 2H), 8.29 (dd, 1H, app. $J_1 = 8.0 \text{ Hz}$, $J_2 = 1.0 \text{ Hz}$), 7.96 (dt, 1H, app. $J_1 = 7.0 \text{ Hz}$, $J_2 = 1.2 \text{ Hz}$), 7.86 (dt, 1H, app. $J_1 = 7.0 \text{ Hz}$, $J_2 = 1.2 \text{ Hz}$), 6.88 (s, 1H), 5.66 (br.s, 1H), 3.75 (t, 2H, $J = 6.6 \text{ Hz}$), 3.30 (t, 2H, $J = 6.6 \text{ Hz}$), 2.07 (d, 3H, $J = 1.1 \text{ Hz}$), 1.82 (d, 3H, $J = 1.1 \text{ Hz}$).

$^{13}\text{C NMR:}$

(2:1 CD$_3$OD/CDCl$_3$) 183.32, 167.94, 152.56, 150.57, 149.66, 148.94, 145.85, 145.04, 137.04, 131.76, 131.51, 131.50, 131.40, 129.68, 122.79, 121.33, 119.64, 117.88, 117.65, 117.58, 38.31, 31.14, 26.42, 19.08.

IR: 3437, 3060, 2919, 1658, 1616, 1587, 1465, 1384, 1185, 862, 773.

MS: 359 (M$^+$ + 2), 357 (M$^+$), 329, 328, 274, 273, 260, 248, 247 (100%), 218, 83.

HRMS: expected 357.1477, observed 357.1482.
Cystodytin A - CDCl₃
Cystodytin A - 2:1 CDCl₃/CD₂OD
Cystodytin B 76

50.5 mg (0.130 mmol) of ketone 120 was dissolved in 15 ml of chlorobenzene in a 100 ml round bottom flask equipped with a straight condenser. The solution was degassed with Argon for 25 minutes, and then kept under an Ar atmosphere with a balloon. The solution was heated and maintained at 110° C (bath temperature) and the sunlamp was turned on. Photolysis was carried on for 10 hours and was worked up. As in the workup of Cystodytin A, the reaction mixture was "titrated" with small portions of DDQ until the purple material was gone. The solvent was evaporated and the material was chromatographed by preparative TLC using 5% MeOH/CHCl₃ as the eluent to give Cystodytin B as bright yellow crystals from CHCl₃ (mp 180-182° C). 14.8 mg (32%); Rf (5% MeOH/CHCl₃) product 0.27, purple spot 0.06.

\[ ^1H \text{ NMR (CDCl}_3): \]
9.20 (d, 1H, \( J = 5.5 \) Hz), 8.57 (dd, 1H, app. \( J_1 = 7.4 \) Hz, \( J_2 = 1.2 \) Hz), 8.52 (d, 1H, \( J = 5.5 \) Hz), 8.29 (dd, 1H, app. \( J_1 = 8.1 \) Hz, \( J_2 = 1.4 \) Hz), 7.94 (dt, 1H, app. \( J_1 = 7.4 \) Hz, \( J_2 = 1.4 \) Hz), 7.83 (dt, 1H, app. \( J_1 = 7.4 \) Hz, \( J_2 = 1.4 \) Hz), 6.91 (s, 1H), 6.35 (br.s, 1H), 6.31 (dq, 1H, \( J_1 = 6.9 \) Hz, \( J_2 = 1.4 \) Hz), 3.81 (dt, 2H, \( J_1 = 6.5 \) Hz, \( J_2 = 5.8 \) Hz), 3.32 (t, 2H, \( J = 6.5 \) Hz), 1.74 (br.t, 3H, app. \( J = 1.1 \) Hz) 1.65 (br.dd, \( J_1 = 6.9 \) Hz, \( J_2 = 1.1 \) Hz).

\[ ^1H \text{ NMR:} \]
(2:1 CD₃OD/CDCl₃) Note: chemical shifts proved to be extremely sensitive to the precise ratio of CD₃OD to CDCl₃: 9.16 (d, 1H, \( J = 5.5 \) Hz), 8.68 (d, 1H, \( J = 5.5 \) Hz), 8.66 (dd, 1H, \( J_1 = 1 \) Hz, 1.74 (br.s, 1H, app. \( J = 1.1 \) Hz).
$J_2 = 8.2 \text{ Hz}$, 8.31 (dd, 1H, $J_1 = 1 \text{ Hz}$, $J_2 = 7.0 \text{ Hz}$), 7.97 (dt, 1H, $J_1 = 1 \text{ Hz}$, $J_2 = 7.0 \text{ Hz}$), 7.88 (dt, 1H, $J_1 = 1 \text{ Hz}$, $J_2 = 7.0 \text{ Hz}$), 6.92 (s, 1H), 6.33 (dq, 1H, $J_1 = 1.4 \text{ Hz}$, $J_2 = 7.0 \text{ Hz}$), 3.78 (t, 2H, $J = 6.7 \text{ Hz}$), 3.35 (t, 2H, $J = 6.7 \text{ Hz}$), 1.75 (t, 3H, $J = 1.2 \text{ Hz}$), 1.69 (dd, 1H, $J_1 = 1 \text{ Hz}$, $J_2 = 7.0 \text{ Hz}$).

$^{13}$C NMR: 183.37, 170.49, 152.70, 149.92, 149.11, 145.99, 145.04, 127.17, 131.89, 131.54, 131.45, 131.09, 130.76, 129.74, 122.85, 121.44, 119.75, 117.73, 39.20, 30.79, 13.18, 11.59.

IR: 3467, 3060, 2931, 1654, 1612, 1588, 1540, 1465, 1384, 1185, 862, 774.

MS: 359 (M$^+$ + 2); 357 (M$^+$), 272, 260, 247 (100%), 218.

HRMS expected 357.1477, observed 357.1482.

3.5:1 Mixture of Synthetic 1 and 2. Yellow crystals from CHCl$_3$, m.p. 180-183° C (uncorr.; lit. 181 - 183° C)
Cystodytin B - CDCl₃
Cystodytin B - 2:1 CDCl₃/CD₃OD
Enol acetate 104

4.12 g (11.77 mmol) of ketone 98 was dissolved in 50 ml of isopropenyl acetate and then 12 drops of triflic acid were added. To the flask was attached a vigreaux column and the solution was refluxed so that the acetone that was produced was distilled off. After 12 hours the solvents were evaporated to give a black oil. 4.12 g (89% crude yield); R_f (50% EtOAc/hexanes) .40. The very crude material was used as is for the DDQ oxidation.

Quinoline 105

4.12 g (10.5 mmol) of the crude enol acetate was dissolved in 80 ml of toluene and then 2.67 g (10.5 mmol) of DDQ was added. The solution turned cherry red and was refluxed for 30 minutes. The reaction mixture turned brown and the reaction was finished. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and loaded onto a dry column of silica gel. Elution with 50% EtOAc/hexanes left the reduced DDQ behind. The solvent was evaporated to give a brownish-yellow oil. 2.93 g (71% crude yield); R_f (50% EtOAc/hexanes) .37. The crude material was used as is for the hydrolysis.

IR: 2911, 2223, 2123, 1746, 1704, 1659, 1414, 1245, 1035, 893.

MS: 390 (M^+), 348, 260, 259, 247, 233, 218, 205, 166 (100%), 151.

HRMS: expected 390.1328, observed 390.1332.
Phenol 106

2.90g (7.4 mmol) of acetate 105 was dissolved in 70 ml of MeOH and then 50 ml of saturated aqueous NaHCO₃ was added. The reaction mixture was stirred overnight. The MeOH was evaporated and the aqueous solution was neutralized to pH = 7 using a saturated aqueous NH₄Cl solution. The product was extracted with EtOAc and the extracts were passed over a short plug of silica gel. The solvent was evaporated to yield a cream-colored solid. 1.61 g (40% overall yield from ketone 98); R_f (70% EtOAc/hexanes) .38 streaky.

^1H NMR:  8.78 (d, 1H, J = 4.4 Hz), 7.56 (m, 1H), 7.25 - 7.37 (complex m, 4H), 7.09 (d, 1H, J = 1.7 Hz), 6.83 (d, 1H, J = 1.7 Hz), 4.28 (t, 2H, J = 6.9 Hz), 2.98 (t, 2H, J = 6.9 Hz), 2.02 (s, 3H).

IR:  2122, 1744, 1501, 1235.

MS:  348 (M^+), 260 (100%), 259, 247, 233, 218, 205, 43.

HRMS:  expected 348.1222, observed 348.1224.
Quinone 107

1.10 g (2.86 mmol) of phenol 106 was dissolved in 260 ml of MeOH and was charged to a 1 liter flask. In a separate flask, 5.12 g (19.1 mmol) of potassium nitrosodisulfonate (Fremy’s salt) was dissolved in 275 ml of a .5 M KH$_2$PO$_4$ buffer. The solution of Fremy’s salt was then added to the well-stirred solution of the phenol. The resulting mixture was stirred at room temperature for 3 1/2 hours. The solvents were evaporated. The residue was diluted with 300 ml of water and was extracted with CH$_2$Cl$_2$. The extracts were dried over Na$_2$SO$_4$ and the solvent evaporated to yield an orange-yellow solid (mp 174-177° C). 579 g (56%); R$_f$ (70% EtOAc/hexanes) .42.

$^1$H NMR: 8.79 (d, 1H, J = 5.7 Hz), 7.59 (br.t, 1H, J = 7.5 Hz), 7.21 - 7.40 (br.m, 3H), 7.03 (s, 1H), 4.18 (q, 2H J = 7.2 Hz), 2.73 (t, 2H, J = 7.2 Hz), 1.92 (s, 3H).

$^{13}$C NMR: 179.4, 178.5, 170.6, 150.4, 146.7, 146.2, 138.0, 137.8, 137.4, 131.2, 130.8, 130.6, 130.0, 126.8, 125.4, 118.8, 62.2, 29.0, 21.4, 20.7.

IR: 2921, 2843, 2134, 1735, 1584, 1238, 1045, 758.

MS: 364 (M$^+$ + 2), 293, 276, 275 (100%), 263, 221, 205, 180, 179, 43.

HRMS: expected 362.1014, observed 362.1016.
Hydroxy-quinone 110

To a dry 500 ml round bottom flask was charged 578 mg (1.60 mmol) of orthoquinone 107 and 250 ml of toluene. The solution was degassed with argon for 25 minutes. The deep orange-red solution was refluxed 10 hours. Upon cooling, a fine orange precipitate formed. The solvents were evaporated to give an orange solid (mp 204° C (dec.)). 426 mg (80%); Rf (80% EtOAc/hexanes) .12.

$^1$H NMR:  
9.23 (d, 1H, J = 5.5 Hz), 8.59 (d, 1H, J = 5.5 Hz), 8.52 (br.d, 1H, J = 7.2 Hz), 8.24 (dd, 1H, J₁ = 8.2 Hz, J₂ = 0.9 Hz), 7.88 (dt, 1H, J₁ = 7.8 Hz, J₂ = 1.4 Hz), 4.53 (t, 2H, J = 6.6 Hz), 3.50 (t, 2H, J = 6.6 Hz), 2.00 (s, 3H).

$^{13}$C NMR:  
(CDC$_3$/DMSO d6) 178.8, 170.4, 151.7, 150.4, 149.1, 145.4, 144.9, 136.3, 130.9, 130.4, 127.9, 123.1, 122.4, 120.2, 119.7, 62.2, 23.0, 20.4.

IR:  
3265, 2923, 2852, 1733, 1646, 1380, 1229, 1111, 775, 733.

MS:  
336 (M$^+$ + 2), 334 (M$^+$), 292, 276, 275 (100%), 274, 264, 233, 218, 205.

HRMS:  
expected 334.0953, observed 334.0955.
Acetate 111

21.0 mg (.063 mmol) of enol 110 was dissolved in 1.5 ml of pyridine and then 19.3 mg (.189 mmol) of acetic anhydride was added. The solution was stirred for 3 hours and then all volatiles were removed using a high vacuum rotovap and moderate heat to yield a bright yellow solid (mp 150-154° C). 23 mg (99%); Rf (100% EtOAc) .24.

^1H NMR: 9.26 (d, 1H, J = 5.5 Hz), 8.57 (m, 2H), 8.28 (br.d, 1H, J = 8.0 Hz), 7.92 (br.t, 1H, J = 8.0 Hz), 7.83 (br.t, 1H, J = 7.3 Hz), 4.52 (t, 2H, J = 6.5 Hz) 3.46 (t, 2H, J = 6.5 Hz), 2.48 (s, 3H), 2.02 (s, 3H).

^13C NMR: 176.4, 171.1, 166.2, 150.1, 149.0, 148.6, 146.1, 145.5, 138.6, 137.0, 131.8, 129.8, 122.6, 121.4, 119.6, 117.2, 63.0, 42.9, 25.0, 21.0, 20.5.

IR: 2925, 2853, 1777, 1738, 1666, 1377, 1237, 1184, 1104, 1044, 766.

MS: 378 (M^+ + 2), 336, 334, 292, 275 (100%), 274, 264, 233, 218, 43.

HRMS: expected 376.1059, observed 376.1066.
Triflate 112

To a dry 25 ml round bottom flask was charged 62.2 mg (.186 mmol) of alcohol 110 and 8 ml of CH₂Cl₂. This solution was cooled to O°C and then 33.7 mg (.26 mmol) of diisopropyl ethylamine was added, followed by 63.0 mg (.22 mmol) of triflic anhydride. After 10 minutes, the solution was warmed to room temperature and the solvent was evaporated yield a green-brown solid. The material was chromatographed (70% EtOAc/hexanes) to give a bright yellow solid (mp 145-155°C (dec.)). 78 mg (90%); R₇ (100% EtOAc) .74.

¹H NMR: 9.33 (d, 1H, J = 5.5 Hz), 8.67 (d, 1H, J = 5.5 Hz), 8.64 (dd, 1H, J₁ = 10.1 Hz, J₂ = 1.3 Hz), 8.34 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.3 Hz), 7.87 - 8.02 (AB, 2H), 4.62 (t, 2H, J = 6.1 Hz), 3.63 (t, 2H, J = 6.1 Hz), 2.02 (s, 3H).

¹³C NMR: 175.2, 170.8, 150.4, 147.3, 148.1, 145.2, 141.6, 137.1, 132.0, 130.6, 128.5, 122.8, 121.5, 120.5, 120.1, 117.1, 117.9, 62.5, 25.5, 20.5.

IR: 1745, 1670, 1422, 1219, 1137, 1094, 1036, 973.

MS: 424 (M⁺ - 42), 334, 291 (100%), 275, 264, 263, 233, 218.

HRMS: expected 466.0446, observed 466.0446.
Carboline 113

40.6 mg (.116 mmol) of ketone 98 was dissolved in 15 ml of o-dichlorobenzene in a 50 ml 3-neck flask equipped with a condenser and rubber stoppers. The solution was degassed with Ar for 20 minutes and then the solution was heated to 200°C (bath temperature). After 1 1/2 hours the reaction was finished. The reaction mixture was passed over a short column of silica gel and the solvent was removed by eluting with hexane. The very polar product was flushed out using 50% MeOH/CHCl₃. 30.0 mg (80%); Rf (5% MeOH/CHCl₃).10 (streaky).

¹H NMR: 12.10 (br.s, 1H (NH)), 9.18 (s, 1H), 8.17 (d, 1H, J = 8.2 Hz), 7.94 (d, 1H, J = 8.2 Hz), 7.61 (t, 1H, J = 7.1 Hz), 7.32 (t, 1H, J = 7.1 Hz), 4.30 (m, 2H), 3.47 (br.d, 1H, J = 14 Hz), 2.97 (br.d, 1H, J = 14 Hz), 2.40 - 2.79 (m, 3H), 2.10 (s, 3H), 1.90 (m, 2H).

IR: 3192, 2935, 1742, 1682, 1562, 1346, 1264, 1035, 740.

MS: 322 (M⁺), 235 (100%), 206, 180, 179.

HRMS: expected 322.1317, observed 322.1318.
Carbolines 114, 115

26.2 mg (.075 mmol) of phenol 106 was dissolved in 4 ml of o-dichlorobenzene in a dry 25 ml 3-neck flask equipped with a condenser. The solution was degassed for 20 minutes with Ar and then was heated to 200 ºC (bath temperature) for 30 minutes. The reaction mixture was passed over a short plug of silica gel and the reaction solvent was washed away with hexane. The product was recovered using 10% MeOH/CHCl₃. 21.7 mg (86%); Rf (50% EtOAc/hexanes) .09.

H NMR: 10.47 (br.s, 1H), 8.88 (s, 1H), 8.35 (d, 1H, J = 8.1 Hz), 7.80 (s, 1H), 7.49 (d, 1H, J = 8.1 Hz), 7.37 (t, 1H, J = 7.2 Hz), 7.19 (t, 1H, J = 7.2 Hz), 6.82 (s, 1H), 4.27 (t, 2H, J = 7.0 Hz), 3.02 (t, 2H, J = 7.0 Hz), 1.86 (s, 3H).

C NMR: 170.1, 152.7, 141.1, 139.2, 138.1, 134.9, 133.4, 131.1, 128.6, 126.5, 124.5, 122.7, 120.2, 113.1, 111.9, 107.7, 64.2, 36.5, 21.7.

IR: 3336, 2939, 2841, 1738, 1501, 1398, 1241, 1057, 1033, 741.

MS: 320 (M⁺), 277, 260 (100%), 219.

HRMS: expected 320.1161, observed 320.1156.
Dienone 29

2 g (20.4 mmol) of cyclohexanone and 4.33 g (40.8 mmol) of benzaldehyde were dissolved in 20 ml of EtOH. Water was added until the solution just became cloudy. Then 5 ml of 20% aqueous NaOH was added. The solution became warm and a yellow precipitate formed. The mixture was stirred for 30 minutes and then the solid was filtered off and washed well with water. The solid was dissolved in some CH₂Cl₂ and then passed over a short plug of silica gel. The solvent was evaporated to yield a yellow solid (mp 101-102°C), 5.09 g (91%); Rf (10% EtOAc/hexanes) .40.

$^1$H NMR: 7.89 (br.s, 2H0, 7.31 - 7.61 (m, 10H), 3.55 (dt, 2H, $J_1 = 6.0$ Hz, $J_2 = 1.9$ Hz), 2.17 (quintet, $J = 6.0$ Hz).

$^{13}$C NMR: 190.1, 136.8, 136.0, 135.8, 130.2, 128.5, 128.2, 28.3, 22.8.

IR: 3054, 2933, 2863, 1667, 1607, 1580, 1574, 1445, 1273, 1164, 1144, 772, 695.

MS: 274 (M⁺, 100%), 273, 246, 245, 217, 186, 141, 129, 128, 115.

HRMS: expected 274.1358, observed 274.1362.
Cycloadduct 30

4.75 g (17.3 mmol) of enone 29 was dissolved in a mixture of 50 ml of dichloroethane and 20 ml of ethyl vinyl ether. 933 mg (.86 mmol) of Yb(fod)3 was added and the solution was refluxed for 2 days. The solvents were evaporated and the residue was dissolved in CH2Cl2 and then washed with water. The extracts were dried over NaSO4 and the solvent was evaporated to give a fluorescent green oil. 5.95 g (100% crude yield); Rf (10% EtOAc/hexanes) .53.

1H NMR:

7.01 - 7.25 (m, 10H), 6.90 (s, 1H), 4.92, 4.93 (d, 1H, J = 8.7 Hz), 3.96, 3.98 (q, 1H, J = 7.1 Hz), 3.52, 3.55 (q, 1H, J = 7.1 Hz), 3.41 (br.t, 1H, J = 8.3 Hz), 2.65, 2.70 (t, 1H, J = 4.5 Hz), 2.19 - 2.40 (m, 2H), 1.35 - 1.98 (m, 5H), 1.17 (t, 3H, J = 7.1 Hz).

13C NMR:

144.4, 143.5, 137.9, 132.4, 129.2, 128.3, 128.1, 127.9, 126.3, 126.0, 121.2, 114.5, 99.0, 64.2, 43.9, 38.5, 27.6, 27.2, 22.8, 15.2.

IR:

3024, 2930, 1630, 1601, 1492, 1443, 1373, 1140, 1071, 972, 704.

MS:

346 (M+), 300, 273, 258, 212, 186 (100%), 185, 161, 115.

HRMS:

expected 346.1933, observed 346.1928.
Pyridine 97

3.09 g (8.94 mmol) of cycloadduct 30 was dissolved in 36 ml of CH$_3$CN and then 1.55 g (22.46 mmol) of NH$_2$OH HCL was added. The reaction mixture was gently refluxed overnight. The solvents were evaporated and the residue was taken up in CH$_2$Cl$_2$. This was washed with 10% aqueous Na$_2$CO$_3$ and then was passed over a short plug of silica gel. The solvent was evaporated to yield a tan solid (mp 128-130$^\circ$ C). 2.27 g (86%); $R_f$ (80% EtOAc/hexanes) .73.

$^1$H NMR: 8.52 (d, 1H, J = 4.8 Hz), 8.04 (s, 1H), 7.22 - 7.49 (complex m, 10H), 7.04 (d, 1H, J = 4.8 Hz), 2.92 (dt, 2H, J$^1$ = 6.1 Hz, J$^2$ = 1.8 Hz), 2.73 (t, 2H, J = 6.1 Hz), 1.74 (quintet, J = 6.1 Hz).

$^{13}$C NMR: 153.3, 149.7, 146.7, 139.2, 138.0, 135.8, 130.4, 129.7, 128.6, 128.3, 128.0, 127.8, 127.5, 126.7, 122.8, 28.0, 22.9.

IR: 3050, 2940, 2896, 1575, 1550, 1500, 1460, 1450, 1400, 900, 840, 775, 705.

MS: 297 (M$^+$), 296, 280, 209, 208, 115, 84.

HRMS: expected 297.1517, observed 297.1516.
Ketone 98

225 mg (.76 mmol) of pyridine 97 was dissolved in a mixture of 50 ml of MeOH and 7 ml of CH$_2$Cl$_2$ in a 100 ml 3-neck round bottom flask equipped with a bubbling tube. The solution was cooled to -78$^\circ$C and then ozone was bubbled through the solution for 30 minutes. The solution was purged with Argon and then 2 ml of dimethyl sulfide were added. The solution was allowed to warm to room temperature over 2 hours. The solvents were removed and the residue was chromatographed directly with 80% EtOAc/hexanes. The solvent was evaporated to give cream-colored stars (mp. 131 - 132$^\circ$C). 127 mg (75%); R$_f$ (80% EtOAc/hexanes) .17.

$^1$H NMR: 8.62 (d, 1H, J = 4.7 Hz), 7.22 - 7.43 (complex m, 6H), 2.84 (t, 2H, J = 6.1 Hz), 2.70 (t, 2H, J = 6.0 Hz), 1.98 (quintet, 2H, J = 6.0 Hz).


IR: 3059, 2947, 2862, 1702, 1576, 1337, 1230, 1144, 905, 772, 706.

MS: 223 (M$^+$), 222, 194, 168, 167 (100%), 166, 140, 139.

HRMS: expected 223.0997, observed 223.1006.
Acetate 100

To a 50 ml round bottom flask was added 70 mg (.2 mmol) of azido ketone 98 and 15 ml of chlorobenzene. The solution was degassed with argon and then it was warmed to 110° C in a sandbath. The solution was then irradiated with a sunlamp until the starting material disappeared by TLC. A major purple spot as well as the product spot had appeared. The photolysis and heating were stopped and then DDQ was added to the crude reaction mixture in portions until the purple spot was converted into the product. The solvent was then evaporated and the residue was chromatographed by preparative TLC using 5% MeOH/CHCl₃ as the eluent to give bright yellow crystals (mp 157-159° C). 19.0 mg (31%); Rₚ (5% MeOH/CHCl₃) purple spot .10, product .43.

¹H NMR: 9.24 (d, 1H, J = 5.5 Hz), 8.59 (dd, 1H, J₁ = 6.6 Hz, J₂ = 1.2 Hz), 8.58 (d, 1H, J = 5.5 Hz), 8.29 (dd, 1H, J₁ = 8.2 Hz, J₂ = 1.2 Hz), 7.93 (dt, 1H, J₁ = 7.2 Hz, J₂ = 1.5 Hz), 7.83 (dt, 1H, J₁ = 7.4 Hz, J₂ = 1.4 Hz), 6.97 (s, 1H), 4.57 (t, 2H, J = 6.3 Hz), 3.44 (t, 2H, J = 6.3 Hz), 2.02 (s, 3H).

IR: 1737, 1660, 1588, 1324, 1234, 1040, 861, 771.

MS: 276 (M⁺ - 42), 259, 247, 217 (100 %), 216, 164, 115.

HRMS: expected 318.1004, observed 318.1000.
Alcohol from ester 139 reduction

To a dry 500 ml 1 neck round bottom flask was charged 5.0 g (133.4 mmol) of LAH and 250 ml of anhydrous ether. The solution was cooled to -20°C and then a solution consisting of 20.1 g (88.94 mmol) of ester 139 dissolved in 25 ml of ether was slowly added. The reaction was complete upon total addition of starting material. Workup consisted of adding 5 ml of water to the reaction mixture, followed by 5 ml of 20% aq. NaOH, then 15 ml of water. The solution was stirred and a voluminous white precipitate was formed. The precipitate was filtered off over a bed of celite and was washed with EtOAc. The solvents were evaporated to yield a clear liquid. 15.6 g (95%) R_f (40% EtOAc/hexanes) 0.09.

$^1$H NMR: 5.32 (t, 1H, J = 7.0 Hz), 4.04 (d, 2H, J = 7.0 Hz), 3.88 (s, 4H), 2.65 (br.s, 1H), 2.21 (m, 4H), 1.63 (m, 4H).

$^{13}$C NMR: 140.4, 121.9, 108.5, 64.1, 63.9, 58.3, 35.7, 35.1, 33.3, 25.0.

IR: 3411, 2951, 2880, 1449, 1122, 1030, 944, 907.

MS: 184 (M$^+$), 153, 99, 87 (100%), 86.

HRMS: expected 184.1099, observed 184.1099.
**Acetate 140**

15.6 g (84.78 mmol) of the alcohol was dissolved in 80 ml of pyridine and then 25.94 g (254.3 mmol) of acetic anhydride was added via syringe. After four hours, the volatiles were removed by high vacuum rotary evaporator. The residue was dissolved in CH₂Cl₂ and was washed once with 20% aqueous CuSO₄, then with saturated NaHCO₃, water and finally brine. The organic extract was dried over Na₂SO₄ and then the solvents were removed to yield a clear, colorless liquid. 18.78 g (98%) Rᵢ (40% EtOAc/hexanes) .59.

**¹H NMR:**

5.24 (br.t, 1H, J = 7.1 Hz), 4.46 (d, 2H, J = 7.2 Hz), 3.84 (s, 4H), 2.22 (m, 4H), 1.96 (s, 3H), 1.62 (m, 4H).

**¹³C NMR:**

170.6, 143.5, 116.5, 108.2, 64.1, 60.3, 35.6, 35.0, 33.2, 25.1, 20.7.

**IR:**

2957, 2881, 1734, 1443, 1237, 1121, 1038, 946, 905.

**MS:**

167 (M⁺ - OAc), 166 (M⁺ - HOAc), 137, 99, 86 (100%).

**HRMS:**

expected 226.1205, observed 226.1202.
**Oxetane 141a**

To a 125 ml Erlenmeyer flask was added 10.67 g (47.22 mmol) of olefin 140 and 3.4 g (31.48 mmol) of freshly sublimed benzoquinone. 30 ml of benzene was added and then the solution was degassed with argon for 20 minutes. A simple concave lens was affixed atop the flask to permit light to pass straight down into the flask. Irradiation of the solution was performed with an argon laser using light at a power of 7 W. Lasing was continued for 6 hours at which time the solution had darkened so that no light was able to pass through. Although the starting materials still remained, the reaction was worked up. The benzene was evaporated and then the residue was loaded onto a flash silica gel column in the neat form. The starting materials were eluted using 20% EtOAc/hexanes and the photoadduct was recovered by flushing the column with 60% EtOAc/hexanes. The solvents were evaporated to give a yellow-tan oil. 6.1 g (58% chromatographed yield) R_f (50% EtOAc/hexanes) .30.

**1H NMR:**

7.34 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.9 Hz), 7.18 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.9 Hz), 6.22 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.9 Hz), 6.20 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.9 Hz), 4.70 (t, 1H, J = 6.0 Hz), 4.36 (d, 2H, J = 6.0 Hz), 3.88 (s, 4H), 2.11 (s, 3H), 1.98 (m, 4H), 1.57 (m, 4H).

**13C NMR:**

183.6, 169.8, 147.1, 146.7, 128.8, 128.3, 106.5, 82.6, 80.2, 63.6, 63.4, 50.1, 31.0, 30.6, 25.2, 20.1.
IR: 2957, 2893, 1742, 1665, 1628, 1510, 1451, 1246, 1117, 1040, 928, 855, 734.

MS: 334 (M^+), 274, 246, 233, 232, 225, 203, 188, 166 (100%), 99, 86.

HRMS: expected 334.1416, observed 334.1419.
Phenol 146

To a dry 250 ml round bottom flask was added 6.05 g (18.11 mmol) of dienone 141a and 70 ml CH₂Cl₂. Then 51.4 µl (.362 mmol) of BF₃OEt₂ was added. The solution was stirred at room temperature for 5 hours. Then, 25 ml of saturated aq. NaHCO₃ solution was added to the stirring reaction mixture. The layers were separated and the aqueous later was extracted once with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and then the solvent was evaporated to give a thick oil. 5.77 g (95%) R₁ (60% EtOAc/hexanes) .51.

**¹H NMR:**

6.55 - 6.78 (cm, 3H), 4.55 (dd, 1H, J₁ = 8.8 Hz, J₂ = 2.7 Hz), 4.36 (dd, 1H, J₁ = 11.8 Hz, J₂ = 2.7 Hz), 4.12 (dd, 1H, J₁ = 11.8 Hz, J₂ = 8.8 Hz), 3.95 (s, 4H), 2.08 (s, 3H), 1.6 - 2.0 (cm, 8H).

**¹³C NMR:**

171.30, 151.30, 150.28, 135.49, 114.58, 111.10, 110.20, 107.95, 86.92, 64.28, 64.20, 63.49, 46.44, 34.43, 31.5, 27.39, 20.80.

**IR:**

3395, 2948, 2841, 1736, 1490, 1463, 1370, 1248, 1099, 1038, 949, 785, 736.

**MS:**

335 (M⁺ + 1), 334, 274, 225, 165, 150, 147, 101, 99 (100%).

**HRMS:**

expected 334.1416, observed 334.1419.
Aryl methyl ether 147

2.56 g (7.66 mmol) of phenol 146 was dissolved in 32 ml of dry acetone. 7.93 g (57.4 mmol) of K₂CO₃ was added, followed by 2.41 g (19.2 mmol) of dimethyl sulfate. The solution was stirred at room temperature for 2.5 hours. The acetone was evaporated and 35 ml of MeOH was added. Then 25 ml of a 50:50 mixture of 10% aq. NaOH and conc. NH₄OH was added to destroy the excess dimethyl sulfate as well as hydrolyze the acetate. The MeOH was evaporated off and the aqueous mixture was extracted twice with CH₂Cl₂. The extracts were passed over a short plug of silica gel and then the solvents were evaporated to give a tan, mushy solid. (m.p. 48-50°C) 2.34 g (95%) Rₛ (40% EtOAc/hexanes) .50.

¹H NMR: 6.55 - 6.80 (m, 3H), 4.50 (dd, 1H, J₁ = 6.8 Hz, J₂ = 5.0 Hz), 3.91 (s, 3H), 3.68 (br.s, 5H), 1.52 - 2.34 (br.m, 8H).

¹³C NMR: 154.32, 151.36, 136.25, 117.05, 114.45, 112.95, 109.97, 109.77, 107.82, 89.73, 64.31, 64.26, 61.78, 55.94, 46.22, 35.25, 32.23, 31.56, 27.16.

IR: 3459, 2952, 2885, 1485, 1204, 1093, 1037, 948.

MS: 307 (M⁺ + 1), 306 (M⁺), 275, 262, 231, 192, 175, 161 (100%), 101, 99.

HRMS: expected 306.1467, observed 306.1472.
Bromide 148

2.97 g (9.72 mmol) of alcohol 147 was dissolved in 30 ml of THF in a 100 ml round bottom flask under an argon atmosphere. The solution was cooled to 0°C and then 1.28 g (12.64 mmol) of triethylamine was added, followed by 1.34 g (11.64 mmol) of methanesulfonyl chloride. The mesylation was over instantly. The solution was warmed to room temperature and 4.2 g (48.6 mmol) of LiBr was added to the reaction mixture. The solution was refluxed for 7 hours and then the THF was evaporated. The residue was added to 50 ml of half-saturated aq. NaCl solution. The aqueous solution was extracted twice with CH₂Cl₂ and then the combined extracts were passed over a short plug of silica gel to yield a thick oil. 3.3 g (92%); Rf (60% EtOAc/hexanes) .77.

¹H NMR: 6.45 - 6.83 (m, 3H), 4.66 (dd, 1H, J₁ = 9.7 Hz, J₂ = 2.8 Hz), 3.99 (s, 3H), 3.76 (s, 3H), 3.54 (m, 2H), 1.60-2.00 (m, 8H).

¹³C NMR: 154.42, 151.26, 135.31, 113.04, 110.51, 110.26, 107.63, 89.15, 64.29, 64.21, 56.04, 48.11, 34.73, 31.86, 31.78, 31.68, 27.34.

IR: 2953, 2885, 1479, 1195, 1036.

MS: 370, 368 (M⁺), 326, 324, 256, 254, 187, 175, 174, 151, 115, 99, 91, 77, 57 (100%).

HRMS: expected 368.0623, observed 368.0614.
Phenol 149

9.1 g (28.0 mmol) of bromide 148 was dissolved in 112 ml of absolute EtOH. Then 18.2 g (280 mmol) of Zn dust and 14.98 g (280 mmol) of NH₄Cl were added. The mixture was refluxed for 2 hours and then the solids were filtered off over a bed of celite. The Zn was washed 4 times with boiling CH₂Cl₂. The filtrate was evaporated down and the residue was dissolved in CH₂Cl₂ and passed over a short plug of silica gel. The solvents were evaporated to give a pale yellow thick oil. 6.35 g (92%); Rf (30% EtOAc/hexanes) .41.

¹H NMR: 6.68 - 6.93 (m, 3H), 6.12 (dd, 1H, J₁ = 17.8 Hz, J₂ = 10.7 Hz), 5.32 (dd, 1H, J₁ = 10.7 Hz, J₂ = 1.0 Hz), 5.19 (dd, 1H, J₁ = 17.8 Hz, J₂ = 1.0 Hz), 3.96 (s, 4H), 3.77 (s, 3H), 2.02 - 2.30 (cm, 4H), 1.75 (m, 4H).

¹³C NMR: 153.75, 148.23, 144.32, 118.80, 115.98, 115.05, 114.78, 114.14, 112.06, 108.53, 64.24, 64.17, 55.65, 43.15, 31.93, 31.32.

IR: 3381, 2942, 2886, 1509, 1416, 1209, 1107, 1041, 954.

MS: 291 (M⁺ + 1), 290 (M⁺), 228, 176, 175, 151 (100%), 99.

HRMS: expected 290.1518, observed 290.1510.
**Benzyl ether from phenol 149**

To a flame-dried 250 ml round bottom flask was charged 1.61 g (50 wt % - 33.56 mmol) of NaH. The NaH was washed twice with hexane to remove the oil and then 20 ml of DMF was added. Then, to this suspension was added a solution of 8.11 g (27.97 mmol) of phenol 149 dissolved in 15 ml of DMF, followed by 5.02 g (29.36 mmol) of benzyl bromide. The reaction finished immediately and was quenched by adding 2 ml of water. The reaction mixture was diluted with 200 ml of water and was extracted 3 times with EtOAc. The combined extracts were washed 3 times with water, once with brine and finally dried over Na₂SO₄. The solvents were evaporated to give a thick oil. 10.28 g (97%); Rᵥ (40% EtOAc/hexanes) .73.

**¹H NMR:**

7.39 (m, 5H), 6.97 (d, 1H, J = 3.0 Hz), 6.85 (d, 1H, J = 8.8 Hz), 6.68 (dd, 1H, J₁ = 8.8 Hz, J₂ = 3.0 Hz), 6.21 (dd, 1H, J₁ = 17.6 Hz, J₂ = 10.7 Hz), 5.04 (dd, 1H, J₁ = 10.7 Hz, J₂ = 1.2 Hz), 5.02 (s, 2H), 4.87 (dd, 1H, J₁ = 17.6 Hz, J₂ = 1.2 Hz), 3.93 (br.s, 4H), 3.77 (s, 3H), 2.08 - 2.40 (m, 4H), 1.72 (br.m, 4H).

**¹³C NMR:**

153.49, 151.63, 144.75, 137.61, 128.38, 127.54, 127.18, 115.18, 114.09, 112.88, 110.51, 108.86, 70.91, 64.10, 55.57, 43.46, 32.45, 31.57.

**IR:**

3057, 2950, 2877, 2837, 1584, 1494, 1459, 1377, 1288, 1220, 1103, 1034, 949, 913, 878, 800, 743, 695.

**MS:**

380 (M⁺), 289, 245, 228, 227, 175, 99, 91 (100%).
HRMS:

Alcohol 152

9.81 g (25.8 mmol) of the olefin was dissolved in 20 ml of dry THF in a flame-dried 100 ml round bottom flask. Then 3.44 g (28.39 mmol) of 9-BBN [reagent existed as a .5 M solution in THF from Aldrich - therefore an equivalent of 56.8 ml] was added via syringe. The solution was stirred for 4 hours and then 25 ml of 10% aq. NaOH was added, followed by carefully adding 10 ml of 30% aq. H₂O₂. This solution was stirred overnight at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc. The solvents of the combined organic fractions were removed and the residue was dissolved in CH₂Cl₂ and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed using a flash silica gel column (40% EtOAc/hexanes). 8.10 g (80%); Rₖ (40% EtOAc/hexanes) .23.

¹H NMR: 7.4 (m, 5H), 6.87 (d, 1H, J = 8.9 Hz), 6.86 (d, 1H, J = 3.0 Hz), 6.69 (dd, 1H, J₁ = 8.9 Hz, J₂ = 3.0 Hz), 5.04 (3, 2H), 3.92 (m, 4H), 3.76 (s, 3H), 3.41 (t, 2H, J = 7.1 Hz), 2.50 (br.m, 2H), 2.10 (m, 2H), 1.55 - 1.84 (m, 6H).

¹³C NMR: 153.44, 152.01, 137.21, 133.4, 128.48, 127.71, 127.25, 116.68, 113.69, 110.51, 108.91, 70.80, 64.05, 60.065, 55.47, 41.31, 40.32, 36.21, 33.29, 31.50, 28.15, 20.52.

IR: 3442, 2949, 2885, 1509, 1216, 1103, 1048, 945, 737.

MS: 399 (M⁺ + 1), 398, 307, 176, 167, 123, 99, 91 (100%).
HRMS: expected 398.2093, observed 398.2095.
Methoxymethyl ether from alcohol 152

In a dry 100 ml round bottom flask was dissolved 2.71 g (6.82 mmol) of alcohol 152 in 30 ml of CH₂Cl₂. 1.762 g (13.6 mmol) of freshly distilled diisopropyl ethylamine (Hunig base) was added, followed by 823 mg (10.2 mmol) of methoxymethyl chloride. After one hour, the reaction mixture was poured into 60 ml of saturated aq. NaHCO₃ solution. The layers were separated and the aqueous layer was extracted once with CH₂Cl₂. The combined organic phases were washed once with water, once with brine, and then dried over Na₂SO₄. The solvents were removed to give a thick oil. 2.98 g (99%); R_f (30% EtOAc/hexanes) .37.

¹H NMR: 7.49 (m, 5H), 6.85 (d, 1H, J = 3.0 Hz), 6.84 (d, 1H, J = 8.8 Hz), 6.67 (dd, 1H, J₁ = 8.8 Hz, J₂ = 3.0 Hz), 5.04 (s, 2H), 4.45 (s, 3H), 3.91 (m, 4H), 3.75 (s, 3H), 3.24 (s, 3H), 3.23 (t, 2H, J = 7.6 Hz), 2.42 (br m, 2H), 2.15 (br t, 2H, J = 7.5 Hz), 1.87 (cm, 2H), 1.67 (m, 4H).

¹³C NMR: 153.38, 152.06, 137.43, 133.60, 128.51, 127.67, 127.18, 116.86, 113.57, 110.46, 108.99, 96.25, 70.75, 65.17, 64.08, 55.53, 54.97, 40.23, 33.23, 31.56.

IR: 2944, 2884, 1585, 1495, 1218, 1107, 1030, 738.

MS: 443 (M⁺ + 1), 442 (M⁺), 319, 291, 290, 227, 167, 99, 91 (100%).

HRMS: expected 442.2355, observed 442.2365.
**Phenol 153**

1.08 g (2.45 mmol) of the benzyl ether was dissolved in 3 ml of THF in a 25 ml round bottom flask. 10 ml of NH₃ was condensed into the flask and was allowed to reflux. Small bits of Na metal were added until a deep blue color persisted. Solid NH₄Cl was then added until the blue color vanished. Extra NH₄Cl was added to ensure protonation of the phenol. The NH₃ was boiled off and the residue was dissolved in 50 ml of water. This was extracted twice with EtOAc and then the combined extracts were passed over a short plug of silica gel. The solvents were removed to yield a thick oil. 777 mg (90%); R_f (30% EtOAc/hexanes).60.

**¹H NMR:**

6.78 (m, 1H), 6.59 (m, 2H), 4.48 (s, 2H), 3.94 (AB m, 4H), 3.74 (s, 3H), 3.28 (t, 2H, J = 7.5 Hz), 3.26 (s, 3H), 2.42 (br.m, 2H), 2.12 (br.t, 2H, J = 7.4 Hz), 1.87 (br.m, 2H), 1.66 (m, 4H).

**¹³C NMR:**

153.47, 148.61, 131.34, 126.79, 117.47, 116.33, 111.21, 109.02, 96.26, 65.23, 64.16, 64.09, 55.64, 55.11, 40.08, 33.13, 31.54.

**IR:**

3356, 2937, 2890, 1512, 1423, 1293, 1207, 1103, 1040.

**Mass Spectrum:**

353 (M⁺ + 1), 352 (M⁺), 320, 290 (100%), 206, 188, 176, 151, 99.

**HRMS:**

expected 352.1886, observed 352.1883.
Allyl ether 154

To a dry 25 ml round bottom flask was charged 104.8 mg (50% suspension by weight - 2.18 mmol) of NaH. The oil was washed away with 2 hexane rinses and then 7 ml of DMF was added. Then a solution of 640 mg (1.82 mmol) of phenol 153 dissolved in 3 ml of DMF was added, followed by 242 mg (2.0 mmol) of allyl bromide. The reaction was quenched with 1 ml of water and then further diluted with water. The aqueous mixture was extracted three times with EtOAc and then the combined extracts were washed three times with water and once with brine. The solvents were evaporated to give a thick oil. 685 mg (96%); Rf (50% EtOAc/hexanes) .64.

$^1$H NMR: 6.63 - 6.84 (m, 3H), 6.04 (ddt, 1H, $J_1 = 17.3$ Hz, $J_2 = 10.4$ Hz, $J_3 = 5.1$ Hz), 5.39 (dq, 1H, $J_1 = 17.3$ Hz, $J_2 = 1.5$ Hz), 5.25 (dq, 1H, $J_1 = 10.5$ Hz, $J_2 = 1.5$ Hz), 4.50 (dt, 2H, $J_1 = 5.1$ Hz, $J_2 = 1.5$ Hz), 4.45 (s, 2H), 3.93 (m, 4H), 3.75 (s, 3H), 3.24 (s, 3H), 3.21 (t, 2H, $J = 7.7$ Hz), 2.43 (br.m, 2H), 2.18 (br.t, 2H, $J = 7.7$ Hz), 1.55 - 1.96 (m, 6H).

$^{13}$C NMR: 153.35, 151.91, 133.70, 130.10, 116.97, 116.67, 113.71, 110.47, 108.98, 96.23, 69.59, 65.15, 64.14, 64.07, 55.53, 54.95, 40.12, 37.26, 33.18, 31.53.

IR: 2944, 2884, 1589, 1492, 1287, 1215, 1106, 1038, 929, 883, 799.

MS: 393 (M$^+$ + 1), 392 (M$^+$, 100%), 319, 179, 167, 151, 99.
HRMS: expected 392.2198, observed 392.2206.
Phenol 155

680 mg (1.73 mmol) of allyl phenol 154 was dissolved in 4 ml of N,N-diethylaniline. The solution was degassed with argon for 20 minutes and then refluxed for 2 hours. The solvent was removed using a high vacuum rotovap. The residue was taken up in a small amount of CH$_2$Cl$_2$ and loaded onto a short plug of silica gel. Traces of the reaction solvent were removed by elution with hexane and then the product was recovered by elution with 60% EtOAc/hexanes. The solvents were evaporated to give a thick oil. 641 mg (94%); R$_f$ (30% EtOAc/hexanes) .33.

$^1$H NMR:

6.71 (d, 1H, J = 3.0 Hz), 6.54 (d, 1H, J = 3.0 Hz), 5.99 (ddt, 1H, J, 1 = 17.0 Hz, J, 2 = 10.2 Hz, J, 3 = 6.0 Hz), 5.18 (dd, 1H, J, 1 = 10.0 Hz, J, 2 = 1.5 Hz), 5.04 (m, 1H), 4.45 (s, 2H), 3.92 (m, 4H), 3.73 (s, 3H), 3.36 (br.d, 2H, J = 5.8 Hz), 3.26 (t, 2H, J = 7.5 Hz), 3.24 (s, 3H), 2.40 (br.m, 2H), 2.12 (br.t, 2H, J = 7.5 Hz), 1.86 (m, 2H), 1.69 (m, 4H).

$^{13}$C NMR:

153.02, 147.46, 135.90, 132.27, 126.32, 116.90, 114.54, 112.91, 108.95, 96.20, 65.22, 64.10, 64.05, 55.50, 55.00, 40.19, 37.54, 36.30, 33.30, 31.53.

IR:

3444, 2939, 2877, 1602, 1469, 1204, 1111, 1031, 918.

MS:

393 (M$^+$ + 1), 392 (M$^+$), 360, 331, 330 (100%), 246, 223, 216, 201, 99.

HRMS:

expected 392.2199, observed 392.2206.
Acetate from phenol 155

640 mg (1.63 mmol) of phenol 155 was dissolved in 3 ml of pyridine and then 500 mg (4.9 mmol) of acetic anhydride was added, followed by 99 mg (.82 mmol) of dimethylaminopyridine (DMAP). After 24 hours, the solvents were evaporated and the residue was flash chromatographed on silica gel using 20% EtOAc/hexanes. The solvents were evaporated to give a thick oil. 673 mg (95%); Rf (50% EtOAc/hexanes) .57.

$^1$H NMR: 6.75 (d, 1H, J = 3.0 Hz), 6.65 (d, 1H, J = 3.0 Hz), 5.87 (ddt, 1H, $J_1 = 16.0$ Hz, $J_2 = 10.6$ Hz, $J_3 = 6.7$ Hz), 5.09 (m, 2H), 4.46 (s, 2H), 3.91 (m, 4H), 3.76 (s, 3H), 3.27 (s, 3H), 3.18 (br.m, 2H), 2.15 - 2.49 (br.m, 2H), 2.29 (s, 3H), 1.55 - 2.06 (br.m, 8H).

$^{13}$C NMR: 169.25, 156.69, 141.54, 136.41, 135.66, 134.48, 116.73, 114.66, 112.39, 108.64, 102.44, 96.32, 64.63, 64.12, 55.29, 55.01, 40.36, 38.93, 35.17, 33.75, 31.49, 21.29.

IR: 2945, 2887, 1760, 1596, 1456, 1377, 1171, 1098, 1038, 912.

MS: 435(M$^+$ + 1), 434 (M$^+$), 392, 350, 320 (100%), 236, 228, 216, 201, 99.

HRMS: expected 434.2304, observed 434.2306.
Nitration product 156a

256 mg (.59 mmol) of the acetate was dissolved in 2.97 ml of acetic anhydride and then chilled to 0°C. In a separate flask, 18.7 mg (.059 mmol) of Hg(OAc)$_2$ was dissolved in 1.48 ml acetic acid. This solution was added to the chilled acetic anhydride solution of the acetate. Then 74.3 mg (1.179 mmol) of nitric acid (54.5 μl of a 90% wt HNO$_3$ solution) was carefully added. Additional HNO$_3$ was added after 10 minutes to bring the total amount of nitric acid added to 10 equivalents. The mixture was neutralized with saturated aq. NaHCO$_3$ solution and then the acetic anhydride was removed using a high vacuum rotovap. Several spots were evident by TLC, so the compound was chromatographed with 20% EtOAc/hexanes on silica gel. The identified products and yields are as follows: mono-nitrated para to the allyl group, 18.9 mg; 1:1 mixture of desired mono-nitrated (ortho to the allyl group) and starting material which had lost the ketal, 90.1 mg; the desired mono-nitrated which had lost the ketal, 77 mg (30%); $R_f$ (50% EtOAc/hexanes) .28.

$^1$H NMR:

6.97 (s, 1H), 5.75 (ddt, 1H, $J_1 = 16.7$ Hz, $J_2 = 10.4$ Hz, $J_3 = 6.3$ Hz), 5.05 (dq, 1H, $J_1 = 10.4$ Hz, $J_2 = 1.5$ Hz), 5.03 (dq, 1H, $J_1 = 16.7$ Hz, $J_2 = 1.5$ Hz), 4.49 (s, 2H), 3.90 (s, 2H), 3.29 (s, 3H), 3.14 - 3.32 (m, 2H), 2.32 (s, 3H), 1.95 - 2.7 (br.m, 10H).

IR:

2930, 1754, 1719, 1598, 1540, 1472, 1369, 1191, 1110, 1036, 913.
MS: 375 (M+ - 60), 99 (100%), 86, 45, 43.

HRMS: expected 435.1893, observed 435.1896.
Acetamide 157

60 mg (.174 mmol) of 156a was dissolved in 3 ml of MeOH and then 3 ml of conc. HCl was added. Then 113 mg (1.74 mmol) of activated Zn dust was added in portions until the color of the solution bleached. The Zn was filtered off over a bed of celite and was washed first with MeOH, then CH₂Cl₂. The filtrate was diluted with 50 ml of EtOAc and then 50 ml of saturated aq. NaHCO₃ solution was poured in to precipitate any dissolved Zn dust. The phases were separated and the aqueous phase was extracted once with EtOAc. The combined extracts were washed twice with aq. NaHCO₃ solution, once with brine and then dried over Na₂SO₄. The solvents were evaporated to give a thick film. These treatments caused loss of all of the methoxymethyl protecting group and some of the phenolic acetate. Consequently, the mixture of amines was immediately subjected to acetylation. The crude mixture (56 mg) was dissolved in 2 ml of pyridine and then 124 ml (1.22 mmol) of acetic anhydride was added, followed by 2 mg (.017 mmol) of dimethylaminopyridine. The solution was stirred overnight and then the solvents were evaporated. The residue was chromatographed directly on silica gel using 60% EtOAc/hexanes. 38 mg (51% overall yield); Rf (60% EtOAc/hexanes) .26.

¹H NMR: 7.03 (s, 1H), 5.62 (ddt, 1H, J₁ = 18.0 Hz, J₂ = 10.6 Hz, J₃ = 7.1 Hz), 5.02 (dd, 1H, J₁ = 18.0 Hz, J₂ = 1.5 Hz), 4.98 (dd, 1H, J₁ = 10.6 Hz, J₂ = 1.5 Hz), 3.83 (s, 3H),
3.79 (br.t, 2H, J = 7.2 Hz), 3.31 (s, 3H), 2.85 - 3.14 (br.m, 2H), 2.37 (br.m, 2H), 2.34 (s, 3H), 1.93 - 2.43 (br.m, 8H), 1.90 (s, 3H).

IR: 2943, 1759, 1735, 1718, 1357, 1244, 1191, 1051, 1898.

MS: 446 (M^+ + 1), 445 (M^+), 404, 403, 343, 302, 300, 286, 260, 230, 216, 178, 43 (100%).

HRMS: expected 445.2101, observed 445.2105.
Indole 158

4.8 mg (.011 mmol) of 157 was dissolved in 4 ml of MeOH and was then cooled to -78°C. Ozone was bubbled through the solution in short bursts until the solution turned blue. Excess ozone was purged with argon and then 10 drops of dimethyl sulfide was added and the solution was warmed to room temperature. Then 3 ml of 10% aq. H₂SO₄ were added to the reaction mixture and the solution became warm. After 15 minutes, the mixture was extracted twice with ether. The combined extracts were dried over Na₂SO₄ and the solvent evaporated. 3.5 mg (74%); Rf (50% EtOAc/hexanes) .64.

¹H NMR: 7.59 (d, 1H, J = 3.7 Hz), 6.81 (s, 1H), 6.26 (d, 1H, J = 3.7 Hz), 3.95 (s, 3H), 3.84 (t, 2H, J = 7.7 Hz), 2.68 (s, 3H), 2.40 (s, 3H), 2.20 (br.m, 2H), 2.06 (br.t, 2H, J = 7.8 Hz), 1.89 (s, 3H), 1.60 (br.m, 6H).

IR: 2923, 2858, 1757, 1738, 1726, 1711, 1587, 1368, 1254, 1201, 1118, 1046.

MS: 429 (M⁺), 415, 373 (100%), 313, 255, 278, 176, 151, 89.

HRMS: expected 429.1787, observed 429.1789.
Aryl ether 163

To a dry 50 ml roundbottom flask was added 135 mg (50 wt% - 2.82 mmol) of NaH. The oil was washed away with 2 hexane rinses and then 5 ml of DMF was added. Then a solution of 826 mg (2.35 mmol) of phenol 153 in 5 ml of DMF was added. Then 659 mg (2.58 mmol) of bromide 162 was added. The reaction completed immediately. The reaction was quenched and then diluted with 50 ml water. The aqueous mixture was extracted three times with EtOAc and then the extracts were washed three times with water, once with brine and were finally dried over Na$_2$SO$_4$. The solvent was evaporated to yield a thick oil. 1.17g (95%); R$_f$ (30% EtOAc/hexanes) .58.

$^1$H NMR:

7.38 (m, 5H), 6.50 - 6.82 (cm, 3H), 5.80 (cm, 2H), 4.52 (s, 2H), 4.44 (br.s, 2H), 3.92 (cm, 4H), 3.74 (s, 3H), 3.53 (t, 2H, J = 6.7 Hz), 3.23 (s, 3H), 3.21 (br.m, 4H), 2.42 (br.t, 2H, J = 6.7 Hz), 2.13 (br.m, 2H), 1.90 (br.m, 2H), 1.63 (br.m, 6H).

$^{13}$C NMR:

153.2, 152.0, 141.0, 138.0, 130.6, 128.3, 128.1, 128.0, 127.8, 127.1, 116.8, 114.2, 113.8, 110.9, 110.7, 108.9, 102.4, 96.3, 73.2, 69.7, 67.7, 65.0, 64.1, 55.9, 54.9, 40.2, 38.2, 33.9, 33.6, 32.8, 31.6.

IR:

2951, 2877, 1592, 1476, 1277, 1210, 1104, 918, 739, 692.

MS:

527 (M$^+$ + 1), 526 (M$^+$), 464, 290, 175, 167, 99, 91 (100%).
HRMS: expected 526.2930, observed 526.2919
Phenols 164a, 164b

1.0 g (1.9 mmol) of compound 163 was dissolved in 7 ml of N,N-dimethylaniline. The solution was degassed for 20 minutes and then the mixture was heated at reflux for 2 hours. Progress of the reaction was checked by $^1$H NMR spectroscopy. The solvent was removed by high vacuum rotovap and then the residue was chromatographed on silica gel with 20% EtOAc/Hexanes. Two products were obtained: Desired normal Claisen product 164a, 408 mg (41%); Undesired Abnormal Claisen product 164b, 211 mg (21%); $R_F$ (30% EtOAc/Hexanes) normal .39; abnormal .27.

Normal product 164a:

$^1$H NMR:

7.35 (m, 5H), 6.70 (br.s, 1H), 6.51 (d, 1H, J = 3.1 Hz), 6.05 (ddd, 1H, $J_1 = 17.7$ Hz, $J_2 = 10.2$ Hz, $J_3 = 5.7$ Hz), 5.17 (m, 2H), 4.40 - 4.63 (m, 2H), 4.47 (s, 2H), 3.90 (cm, 4H), 3.72 (s, 3H), 3.52 (cm, 1H), 3.23 (s, 3H), 3.13 - 3.36 (br.m, 4H), 2.48 (br.m, 2H), 2.07 - 2.31 (br.m, 4H), 1.20 - 1.92 (m, 6H).

IR:

3395, 2945, 2876, 1601, 1452, 1374, 1210, 1104, 1039, 919, 741, 715, 700.

MS:

527 (M$^+$ + 1), 526 (M$^+$), 478, 464, 290, 219, 205, 175, 105, 99 (100%), 91.

HRMS:

expected 526.2930, observed 526.2929.
Abnormal product 164b:

$^1$H NMR:

7.33 (m, 5H), 6.71 (d, 1H, $J = 2.5$ Hz), 6.59 (d, 1H, $J = 2.5$ Hz), AB system - A part - 5.92 (dd, 1H, $J_1 = 15.7$ Hz, $J_2 = 5.9$ Hz); B part - 5.69 (ddt, 1H, $J_1 = 15.7$ Hz, $J_2 = 5.8$ Hz, $J_3 = 1.0$ Hz), 5.13 (s, 2H), 4.48 (s, 2H), 4.43 (s, 2H), 3.91 (m, 4H), 3.72 (s, 3H), 3.62 (m, 2H), 3.25 (m, 2H), 3.23 (s, 3H), 2.42 (br.m, 2H), 2.12 (br.m, 2H), 1.87 (br.t, 2H, $J = 7.0$ Hz), 1.66 (br.m, 4H), 1.38 (d, 3H, $J = 7.0$ Hz).

IR:

3448, 2936, 2880, 1599, 1452, 1210, 1107, 1032, 741, 702.

MS:

527 ($M^+ + 1$), 526 ($M^+$), 494, 464, 418, 304, 227, 208, 203, 189, 99, 91 (100%).

HRMS:

expected 526.2930, observed 526.2934.
Quinone monoketal 166

280 mg (.795 mmol) of phenol 153 were dissolved in 10 ml of dry MeOH 1 mg of p-nitrophenol was added, followed by 199 mg (.875 mmol) of DDQ. After the reaction was complete (5 minutes), 25 ml of aqueous saturated NaHCO₃ solution was added. The solution was diluted with water and then extracted twice with CH₂Cl₂. The extracts were passed over a short plug of silica gel and eluted with 60% EtOAc/hexanes. The solvent was evaporated to give a thick oil. 264 mg (87%); Rf (60% EtOAc/hexanes) .52.

**¹H NMR:**

6.53 - 6.80 (m, 2H), 6.19 (d, 1H, J = 10 Hz), 4.46 (s, 2H), 3.91 (m, 4H), 3.34 (s, 3H), 3.33 (m, 2H), 3.26 (s, 3H), 2.08 (br.t, 2H, J = 6.8 Hz), 1.50 - 1.90 (cm, 8H).

**¹³C NMR:**

185.55, 142.56, 141.06, 140.72, 132.06, 108.59, 96.21, 64.49, 64.13, 55.06, 50.40, 39.64, 35.93, 32.25, 31.01.

**IR:**

2946, 2897, 1674, 1635, 1459, 1116, 1041, 960, 924.

**MS:**

382 (M⁺), 351, 350, 319, 289, 175, 161, 100, 99 (100%), 86, 45.

**HRMS:**

Enone 171

102 mg (.267 mmol) of dienone 166 was dissolved in 2 ml of allylamine. After five minutes the solvent was evaporated to give a thick oil. 116 mg (99%); R_f (60% EtOAc/hexanes) .48.

^1^H NMR: 6.36 (d, 1H, J = 2.1 Hz), 5.81 (m, 1H), 5.14 (app.dq, 1H, J_1 = 17.2 Hz, J_2 = 1.5 Hz), 5.06 (app.br.dq, 1H, J_1 = 10.1 Hz, J_2 = 1.1 Hz), 4.48 (s, 2H), 3.91 (s, 4H), 3.33 (cm, 2H), 3.33 (cm, 2H), 3.30 (s, 3H), 3.28 (s, 3H), 3.24 (s, 3H), 3.14 (cm, 1H), AB system - A part - 2.69 (dd, 1H, J_1 = 16.6 Hz, J_2 = 3.2 Hz); B part - 2.57 (dd,1H, J_1 = 16.6 Hz, J_2 = 3.2 Hz), 2.04 (m, 4H), 1.50 - 1.85 (br.m, 8H).

^1^3^C NMR: 197.97, 143.40, 141.93, 136.69, 116.19, 108.82, 102.43, 98.77, 96.15, 64.62, 64.13, 56.16, 55.06, 49.86, 49.56, 47.75, 41.23, 39.57, 36.62, 32.56, 32.42, 31.10.

IR: 2945, 2882, 1681, 1462, 1116, 1040, 921.

MS: 407 (M^+ - MeOH), 356, 311, 99 (100%), 45.

HRMS: expected 439.2570, observed 439.2572.
Quinone monoketal 172

135 mg (0.466 mmol) of phenol 149 was dissolved in 4 ml of dry MeOH. Then 1 mg of p-nitrophenol was added, followed by 111 mg (0.489 mmol) of DDQ. The cherry red solution turned orange and then 25 ml of saturated aqueous NaHCO$_3$ solution was added. The solution was diluted with water and then extracted twice with CH$_2$Cl$_2$. The extracts were passed over a short plug of silica gel and eluted with 60% EtOAc/hexanes. The solvent was evaporated to give a thick oil. 143 mg (96%); R$_f$ (50% EtOAc/hexanes) 0.41.

$^1$H NMR:

6.69 (br.d.d, 1H, $J_1 = 10.2$ Hz, $J_2 = 1.6$ Hz), 6.60 (br.d.d, 1H, $J_1 = J_2 = 1.6$ Hz), 6.16 (d.d, 1H, $J_1 = 10.2$ Hz, $J_2 = 1.6$ Hz), 6.10 (br.d.d, 1H, $J_1 = 10.7$ Hz, $J_2 = 17.7$ Hz), 5.08 (br.d, 1H, $J = 10.7$ Hz), 4.94 (br.d, 1H, $J = 17.7$ Hz), 3.92 (s, 4H), 3.36 (s, 6H), 1.55 - 2.13 (br.m, 8H).

$^{13}$C NMR:

184.70, 145.29, 142.70, 140.78, 138.53, 131.87, 125.70, 126.10, 114.41, 108.50, 93.46, 64.13, 50.37, 42.55, 31.97, 31.12.

IR:

2945, 2898, 1674, 1646, 1119, 1072, 1030, 966.

MS:

320(M$^+$), 289, 227, 203, 183 (100%), 147, 131, 72.

HRMS:

expected 320.1624, observed 320.1615.
Enone 173

12.2 mg (.038 mmol) of dienone 172 was dissolved in 200 ul of allylamine. After 5 minutes, the solvent was evaporated to give a thick oil. 14.1 mg (99%); Rf (50% EtOAC/hexanes) .31.

\[ \text{1H NMR:} \]
6.45 (d, 1H, J = 2 Hz), 6.07 (dd, 1H, J1 = 17.7 Hz, J2 = 10 Hz), 5.80 (cm, 1H), 5.12 (m, 2H), 5.03 (dd, 1H, J1 = 10.0 Hz, J2 = .9 Hz), 4.93 (dd, 1H, J1 = 17.7 Hz, J2 = .9 Hz), 3.92 (s, 3H), 3.30 (s, 3H), 3.26 (s, 3H), 3.14 (m, 1H), AB system - A part - 2.67 (dd, 1H, J1 = 16.7 Hz, J2 = 3.2 Hz); B part - 2.57 (dd, 1H, J1 = 16.7 Hz, J2 = 3.2 Hz), 1.96 (br.t, 2H, J = 6.0 Hz), 1.67 (m, 8H).

\[ \text{13C NMR:} \]
197.00, 145.50, 143.70, 140.01, 136.60, 116.30, 113.98, 108.75, 98.87, 64.20, 56.0, 49.81, 49.75, 48.00, 42.97, 41.30, 32.50, 31.20.

IR:
2943, 2881, 1689, 1456, 1118, 1049, 3346, 3080.

MS:
345 (M⁺ - MeOH), 294, 249, 101, 99 (100%).

HRMS:
expected 377.2202, observed 377.2206.