INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700  800/521-0600
RICE UNIVERSITY

A NOVEL ENE REACTION:
DEVELOPMENT AND APPLICATIONS TO THE SYNTHESIS OF
(±)-PHYLLANTHOCIN

by

MELISSA VIRGINIA DEATON

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

APPROVED, THESIS COMMITTEE

M. A. Ciufolini
Associate Professor of Chemistry, Chair

T. Fukuyama
Professor of Chemistry

K. Beckingham
Associate Professor of Biochemistry and Cell Biology

Houston, Texas

August, 1995
ABSTRACT

A Novel Ene Reaction:
Development and Applications to the Synthesis of (+)-Phyllanthocin

by
Melissa V. Deaton

A new reaction has been discovered that forms carbon-carbon bonds at room temperature under catalysis by lanthanide reagents. This reaction occurs between vinyl ethers, which have an oxygen functionality located at the central carbon of the allylic system, and aldehydes and is catalyzed by a 1:1 complex of Yb(fod)₃ and AcOH. The primary product, 3, is not observed but becomes protected, in situ, by excess vinyl ether present as the solvent, or co-solvent, to form the observed product 4. This reaction is very general and proceeds to form pure vinyl ether products in excellent yields.

\[
\begin{align*}
\text{R} \cdot \text{H} + \text{OMe} &\rightarrow 0.5 \text{ mol % 1:1 complex} \\
&\text{Yb(fod)₃} \cdot \text{AcOH} \\
&\text{25 °C, 6 - 48 hours} \\
1 &\rightarrow \left\{ \begin{array}{c}
\text{R} \cdot \text{O} \cdot \text{OMe} \\
\text{OH} \cdot \text{OMe}
\end{array} \right\} \rightarrow \text{4}
\end{align*}
\]

The vinyl ether products formed through the use of this novel reaction can be used to quickly piece together more complex functionalities such as furanones, cyclopentanes, bromoketones, and benzazepinones. Approaches to the efficient syntheses of these compounds and others will be discussed.
Phyllanthocin, 5, the aglycon of the potent antitumor agent Phyllanthoside, has been targeted for synthesis using the ene reaction. Furanone formation, using a functionalized vinyl ether formed in the ene reaction, is the primary goal. Applications to the total synthesis of Phyllanthocin will be discussed.
ACKNOWLEDGEMENTS

To my advisor, Dr. Marco Ciufolini, I would like to express my sincerest gratitude. It is you who first directed me to the field of chemistry and it is you who helped me to understand it, love it and challenge it.

To my family and friends, thank you for supporting me in every possible way. I would never have been able to make it without your love and understanding. Your unwavering belief in me these past few years and throughout my life gives me the will to move forward and face any problems that life may bring.

To my co-workers past and present, thanks for making the countless hours in the lab a little easier. Thanks for the advice and the friendship. I’m going to miss our outings to Dolce and Freddo, the softball games and even group meeting. Good luck to you all.

Finally, to Quintin, I cannot express the love and appreciation that I feel for you. I truly owe you for helping me to make it through these years of graduate school. Although we have not been able to be together this past year, you are always with me. Your support and understanding have traveled thousands of miles.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Discussion</td>
<td>10</td>
</tr>
<tr>
<td>Phyllanthocin</td>
<td>32</td>
</tr>
<tr>
<td>Synthetic Studies on Phyllanthocin</td>
<td>47</td>
</tr>
<tr>
<td>Appendices: Experimental</td>
<td>75</td>
</tr>
</tbody>
</table>
To my Mom and Dad.
INTRODUCTION

Formal ene reactions which take place between olefins and aldehydes or ketones as the enophiles have been studied fairly extensively over the past twenty years, and their significance has been amply recognized.\textsuperscript{1} Generally, these reactions require activation of the carbonyl component by at least stoichiometric quantities of Lewis acid catalysts such as AlCl\textsubscript{3} or SnCl\textsubscript{4}, though unusually reactive carbonyl compounds, e.g., 2-ketomalonic esters, have been observed to combine with suitable olefins in a strictly thermal mode. Conversely, multiple equivalents of Lewis acid promoters are needed in numerous other cases.

A troublesome feature of these processes is their limited scope. While some latitude exists in the choice of alkene and carbonyl components, it remains generally true that most common aldehydes, and even modestly functionalized olefins, are not good substrates for ene reactions. In order to highlight the significant aspects of this chemistry, along with its limitations, a brief discussion of the major contributions in the area of Lewis acid catalyzed ene reactions will follow. We must stress that the term “ene reaction” will be used here, and indeed throughout the remainder of this discussion, only to describe the general structure of the products arising from the various reactions. No mechanistic inferences should therefore be drawn from this usage.

Formaldehyde appears to be an outstanding enophile. Excellent yields of ene products can be obtained from BF\textsubscript{3}-Et\textsubscript{2}O– or SnCl\textsubscript{4}-catalyzed reaction with those alkenes that give a stabilized tertiary carbocation as a primary intermediate.\textsuperscript{2} This chemistry has been used to great advantage in efficient syntheses of natural products such as lavandulol 1,\textsuperscript{3} pseudomonic acid A 2,\textsuperscript{4} and the side chain of vitamin D 3 (Figure 1).\textsuperscript{5}

Two major problems affecting this reaction concern the limited usefulness of formaldehyde adducts and the reactivity of the product alcohol in the presence of Lewis acids. Formaldehyde is highly limited in its functionality, and can only be used to form products containing primary alcohols. In order to create more complex structures, carbonyl compounds which already incorporate additional substituents would be highly desirable as enophiles. However, complex mixtures of products, including ene adducts, are often obtained when the carbonyl component is changed from formaldehyde to more highly functionalized aldehydes, even acetaldehyde. This observation is symptomatic of the fact that common aliphatic and aromatic aldehydes are much less reactive than formaldehyde and will, under no circumstances, undergo thermal ene reactions. On a different note, the alcohol-Lewis acid complex formed in the reaction is susceptible to solvolysis; furthermore, it may act as a strong protic acid, which can induce ionic polymerization of unreacted starting materials and products with disastrous consequences. One may alleviate these problems by using Me₂AlCl as the catalyst. Reaction of the Brønsted acidic complex above with this organometallic agent releases CH₄ and consumes protons, preserving ene reactants / products intact. On the other hand, stoichiometric to suprastoichiometric amounts of Me₂AlCl are then required in the reaction.⁶

Alkylaluminum halides are also reasonably competent catalysts in transformations involving simple aliphatic aldehydes as enophiles, a poorly documented mode of ene reactivity. Snider and coworkers have carried out the pioneering work in this area, and have realized moderate yields of ene adducts in reactions catalyzed by stoichiometric amounts of Me₂AlCl. Addition of a methyl group to the aldehyde by the catalyst is a very significant side reaction in all cases. The use of EtAlCl₂ reduces this side reaction, but the desired adducts still emerge in moderate yields. Furthermore, the reaction does not tolerate sterically hindered aldehydes or olefins.

Research directed towards the resolution of at least some of the foregoing difficulties has focused on ways to enhance the reactivity of the aldehyde, of the olefin, or of both, in order to achieve a cleaner overall process. The use of highly electron deficient aldehydes as enophiles has proved to be a particularly successful strategy. These especially electrophilic substrates, e.g., chloral (CCl₃CHO), glyoxalate esters, etc., display substantially enhanced ene reactivity and readily engage in thermal reactions (90-130 °C) with olefins. These aspects of their chemistry have been extensively studied. A general Lewis acid catalyzed (AlCl₃ or SnCl₄) reaction of chloral with olefins is shown in Figure 2. Recent studies by Gill and coworkers have provided great insight into this process. The products always arise from reaction at the less substituted end of the olefinic double bond, giving the trichloromethyl alcohol 5 as the major product. The principal side reactions lead to chloro ketones 6 and Prins type products 7, which are formed in significant amounts. However, the major drawbacks to this chemistry are that the trichloromethyl alcohol

---

products are not particularly useful, and that chloral cannot be substituted even for the slightly less reactive bromal (CBr₃CHO).

![Figure 2]

Glyoxalate esters have also been extensively investigated as enophiles. As shown in the research of Klimova and Arbuzov, SnCl₄ and AlCl₃ promote reactions of glyoxalate esters with a variety of olefins at room temperature. Thermal ene reactions (150 °C) are also viable. More recently, Snider and coworkers have thoroughly reinvestigated thermal ene reactions of methyl glyoxalate, and have found them to be highly endo-selective. Presumably, this is due to the fact that steric interactions are minimized in the endo-transition state (Figure 3). Interestingly, similar Lewis acid catalyzed reactions showed very little diastereoselectivity.

![Figure 3]

---


One intriguing aspect of the chemistry of glyoxalates is that a chiral ester group can be used to obtain asymmetric induction in the ene process. This was first shown by Achmatowicz, who observed only modest enantioselectivities in reactions of (-)-menthyl glyoxalate promoted by a variety of Lewis acids.\(^\text{10}\) Whitesell has since improved greatly on this strategy by using the more sterically hindered 8-phenylmenthyl and \textit{trans}-2-phenylcyclohexyl glyoxylate esters (Figure 4).\(^\text{11}\) Thus, reaction of the Whitesell ester with many alkenes in \(\text{CH}_2\text{Cl}_2\) at \(-78\,^\circ\text{C}\), in the presence one equivalent or greater of \(\text{SnCl}_4\) as the catalyst, furnishes the ene products in yields as high as 90\% and in greater than 97\% enantiomeric excess.

**Figure 4**

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{SnCl}_4 \\
\text{O} & \quad \text{O} & \quad \text{H} & \quad \text{H} & \quad \text{R} \\
\text{Ph} & \quad \text{O} & \quad \text{H} & \quad \text{R} \\
\end{align*}
\]

A most significant development was described even more recently by Mikami and Nakai, who reported excellent chemical yields and good levels of asymmetric induction in ene reactions of achiral glyoxalates with particular olefins promoted by a chiral catalyst.\(^\text{12}\)

**Figure 5**

\[
\begin{align*}
\text{8}
\end{align*}
\]


The Mikami-Nakai catalyst is a titanium-based complex with 2,2′-binapthol as the chiral ligand (Figure 5). Unfortunately, no ene products were formed from mono- or 1,2-disubstituted olefins in the present process.

The seemingly obvious alternative strategy, enhancement of the reactivity of the olefinic component, has not been particularly successful. The reactivity of the alkene may be increased by introducing an electron-releasing heteroatomic group at the central carbon of the allylic system. Thus, alkoxy- or siloxy enol ethers 9, as well as vinyl sulfides 10 would be good candidates for this strategy (Figure 6). Ene products arising from such olefins would retain a vinyl ether/thioether group that renders them readily amenable to further functionalization. A wide range of valuable building blocks could thus be obtained in an expeditious manner. Furthermore, β-hydroxy ketones would be available by mild hydrolysis of the products, making the process fully equivalent to an aldol reaction. This property becomes even more significant if the initial ene reactions could be carried out in a catalytic mode, as there are very few truly catalytic aldol condensations.13

![Figure 6]

until recently, however, ene reactions with olefins 9-10 appeared to be rather unfeasible. Vinyl ethers such as 2-methoxypropene polymerize readily under the influence

of Lewis acids commonly used as ene promoters: with one exception, no reports of sensible products arising from the combination of this ether, or structurally similar substances, with carbonyl compounds appear in the literature. On the other hand, silyl enol ethers normally incur loss of the silicon functionality during reaction with carbonyl receptors promoted by Lewis acids, providing aldol-type adducts. The latter property has been effectively exploited by Mukaiyama as a means to achieve controlled cross-aldol reactions. In 1993, Mikami reported formation of ene-type products in reactions of appropriate TIPS enol ethers with glyoxylate esters. These reactions were shown to proceed in an enantiocontrolled mode with chiral catalysts; moreover, the great reactivity of both ene partners permits the use of truly catalytic amounts of catalyst. Unfortunately, the reaction remains somewhat limited in scope, because it still relies on the use of reactive enophiles that are not highly functionalized.

Kuwajima takes the credit for disclosing the first successful ene-type reaction that works well with ordinary aliphatic and aromatic aldehydes. The key to this chemistry is the use of certain vinyl thioethers as the alkenes. These combine smoothly with aldehydes in CH₂Cl₂ with 1.1 equivalents of Me₂AlCl as the catalyst (Figure 7). Ethers react to furnish threo products highly stereoselectively, while elevated enantioface selectivity at the level of the aldehyde is observed in reactions of optically active thioethers. Similar

---

conditions permit the use of an aldimine as the enophile, resulting in functionalized amine products.\textsuperscript{20} Despite these significant improvements, the requirement for at least stoichiometric quantities of catalyst persists.

Figure 7

\[
\begin{align*}
\text{SR'} \quad \text{OTBS} & + \quad \text{O} \quad \text{H} \quad \xrightarrow{\text{Me}_2\text{AlCl}} \quad \text{OH} \quad \text{SR'} \quad \text{OTBS} \\
\text{11} & \quad \text{12} & \quad \text{13}
\end{align*}
\]

\[
\begin{align*}
\text{SR} \quad \text{OTBS} & + \quad \text{Ph} \quad \text{H} \quad \xrightarrow{\text{Me}_2\text{AlCl}, \text{CH}_2\text{Cl}_2, -40^\circ\text{C}} \quad \text{Ph} \quad \text{OH} \quad \text{SR} \quad \text{OTBS} + \quad \text{Ph} \quad \text{OH} \quad \text{SR} \quad \text{OTBS} \\
\text{14} & \quad \text{15} & \quad \text{16} & \quad \text{17}
\end{align*}
\]

\[
\begin{align*}
\text{SR} \quad \text{OTBS} & + \quad \text{Ph} \quad \text{H} \quad \xrightarrow{\text{Me}_2\text{AlCl}, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}} \quad \text{Ph} \quad \text{OH} \quad \text{SR} \quad \text{OTBS} \quad \text{96\% yield} \quad \text{96\% ee} \\
\text{18} & \quad \text{19} & \quad \text{20}
\end{align*}
\]

The foregoing discussion underscores the main reasons why ene reactions do not yet enjoy the same level of diffusion as other carbonyl addition processes: frequent necessity for equimolar, or larger, quantities of Lewis acid catalysts, poor tolerance of spectator functionality, and consequently modest levels of functionalization of ene products. Yet, ene-like transformations enjoy a number of potential advantages over other types of carbonyl addition processes, especially organometallic ones. A truly catalytic ene reaction of simple execution that works well with ordinary aliphatic and aromatic aldehydes, that accepts vinyl ethers such as 2-methoxy propene and congeners, and that is not particularly sensitive to moisture or oxygen, would be equivalent to a fully catalytic

aldol reaction, yet it would have broader scope, as products normally unavailable from
aldols could be readily made by electrophilic functionalization of ene adducts. The reaction
would not require strong bases or organometallic reagents to achieve C–C bond formation,
minimizing the production of waste. No extreme measures would be needed to exclude
water or oxygen from the reaction, to the benefit of process efficiency. Indeed, the
appearance of such a process would remove most, if not all, of the limitations that have
prevented the widespread acceptance of carbonyl-ene reactions as viable (and valuable)
synthetic transformations.

In 1991, we discovered an ene-like transformation that we believe fulfills these
criteria. Herein, we present an account of how this reaction was found, optimized, and
eventually developed into a preparatively useful tool. Challenges and opportunities offered
by the new reaction will also be illustrated in connection with studies on the synthesis of
the antitumor agent, phyllanthocin. The results of our ensuing studies will follow.


DISCUSSION

The discovery of our ene-type reaction occurred in the Spring of 1991 and was quite serendipitous. In connection with work focusing on a new pyridine synthesis,\textsuperscript{21} we had occasion to examine the reaction of enals with 2-methoxypropene under our standard inverse-electron demand Diels Alder conditions (5 mol % Yb(fod)\textsubscript{3}, excess vinyl ether, 1,2-dichloroethane, 80 °C).\textsuperscript{22} The attempts to form the expected dihydropyrans 21 were wholly unsuccessful, yielding instead complex mixtures comprising small amounts (~7\% of total yield) of the remarkable product 22 (Figure 8).

\begin{center}
\textbf{Figure 8}
\end{center}

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction_diagram.png}
\end{center}

Compound 22 may be regarded as originating through an ene-like reaction of the aldehyde with the vinyl ether to give carbinol 23, which subsequently becomes protected \textit{in situ} by excess vinyl ether present in the reaction medium (Figure 9). Again we note that the term "ene reaction" is used without mechanistic implications, though an outline of


The great potential of this reaction became immediately apparent, as products 24, *inter alia*, are equivalent to aldols (cf. *Introduction*). A problem of immediate significance and concern was that the yield of the ene product was quite low under the conditions of the cycloaddition step. Other issues of pressing urgency concerned the scope of the reaction with respect to the reactants, its applicability to the synthesis of complex natural products, and the feasibility of an enantioselective variant thereof. It was decided to confront such issues in the above order; therefore, we first launched an intensive effort to optimize the novel reaction.\(^{23}\)

Our initial efforts attempted to define an ideal solvent system, and because early experiments indicated that nitrobenzaldehydes were especially reactive, we chose 2-nitrobenzaldehyde (NBA) as our standard substrate. The new transformation was first observed to occur in refluxing dichloroethane (DCE), but it soon became apparent that heat had a deleterious effect on the ene products. Thus, exposure of NBA to excess 2-methoxypropene in DCE in the presence of 5 mol % of Yb(fod)\(_3\) (relative to the NBA) at various temperatures, revealed that better yields of cleaner ene products (\(^{1}\)H NMR) were obtained from reactions run below 50° C. Higher temperatures accelerated the ene process, but they also promoted various side reactions, including polymerization of the reactant vinyl ether and of the product. In the end, we found that best results were obtained in reactions run at room temperature. The lower temperature did not decrease the rate of the

initial ene step to a dramatic extent, but the subsequent protection of alcohol 23 became rather slow. We attempted to circumvent this problem by the use of neat 2-methoxypropene (2-MP) as the reaction medium. This ether, a cheap commodity chemical, is also less toxic than DCE. We were pleased to find that, in almost all cases, this proved to be the solvent of choice.

The major byproduct of these reactions was a polymer of the starting vinyl ether. It so happens that the polymer is practically insoluble in methanol, which, in turn, is an excellent solvent for the ene adduct, so that separation of the product from unwanted material is quite easy. While loss of 2-MP to polymerization is not a serious problem, as the material is cheap and commercially available, it was readily envisioned that minimization of this side reaction could become highly desirable when more complex ethers were used. We reasoned that adventitious protonic acid must be responsible for ether polymerization; therefore, we investigated the use of various bases as preservatives / catalyst dopants. Organic bases such as diisopropylethylamine, triethylamine, 2,6-lutidine, did not have a major effect on the reaction when used in small amounts. Larger quantities thereof seemed to damage the catalyst and inhibit the process. We attributed this to strong coordination to the Yb complex and consequent permanent occupation of catalytically active sites. In retrospect, this is probably not the reason why amines function as inhibitors (vide infra); but at that time it seemed logical to examine insoluble bases that, presumably, would not interact with the catalyst. Bicarbonates (Na or K) had no significant effect, but some interesting observations emerged from experiments carried out with the more basic potassium carbonate. Introduction of a small amount of solid K₂CO₃ into the reaction did, in fact, diminish the extent of polymerization, but more significantly, it repressed MIP protection of the carbinol intermediate. A simple, and potentially useful, technique to arrest the reaction at the stage of the primary product was thus available. However, larger amounts of K₂CO₃ completely inhibited the ene process itself. This knowledge was later
instrumental for the development of conditions suitable for ene reaction of aliphatic aldehydes.

Parallel investigations were designed to optimize catalyst load. A decrease in the amount of Yb(fod)$_3$ in those reactions run at higher temperatures significantly reduced the extent of polymerization of the vinyl ether. Similarly, cleaner ene products were obtained from room temperature reactions run at lower catalyst concentrations. In the end, we established that the best catalyst load was 0.5 mol % of Yb(fod)$_3$ versus the aldehyde. Optimal ene conditions for aromatic aldehydes thus emerged as follows: 1 mol equivalent of aldehyde; 0.5 mol equivalents of Yb(fod)$_3$; 10 mol equivalents of 2-MP; room temperature; 5-24 hrs. We refer to these conditions as the Standard Procedure for the ene reaction. On a final note, we observed that the ene products are very acid sensitive (they are vinyl ethers) and relatively unstable, and therefore do not survive chromatography or distillation. Fortunately, they emerge from the reaction in a state of high homogeneity, precluding the need for further purification. This is fully apparent from the spectra of crude products shown in the Experimental section. Likewise, the TLC traces of ene products that are essentially homogeneous by $^1$H and $^{13}$C NMR display several spots, corresponding to substances arising through various modes of decomposition. As a consequence, the progress of the various reactions was found to be most conveniently followed by $^1$H NMR. Furthermore, the acid sensitivity of the ene products mandated the use of benzene-D6 as an NMR solvent, to avoid exposure to the damaging action of traces of DCl that always contaminate CDCl$_3$.

Translation of these results to the aliphatic series of aldehydes was fraught with several difficulties. Initial attempts with butyraldehyde and cyclohexane carboxaldehyde were quite satisfactory; however, soon we became unable to duplicate the earlier results. Extensive purification (distillation) of both vinyl ether and aldehydes, extensive drying of the Yb complex (Abderhalden), and scrupulous exclusion of air and moisture from our
reactions (argon atmosphere), not only failed to solve reproducibility problems, but actually seemed to exacerbate them. In all cases, there seemed to be an induction period in our reactions, whereupon no product would form for up to several days. Once product formation had begun, however, the reaction would quickly complete.

The above observations, as well as the fact that appropriate amounts of (insoluble) \( \text{K}_2\text{CO}_3 \) inhibited the ene step, strongly implicated the need for some sort of acidic agent as co-catalyst in the overall process. In further support of this surmise, application of the Standard Procedure to carefully vacuum-distilled benzaldehyde, with exclusion of air (argon), induced no reaction until oxygen (air) was admitted to the reaction vessel.

It is well established that unusually interesting catalytic properties are associated with hydroxylic units present within the coordination sphere of highly charged metal ions.\(^{24}\) Therefore, it seemed most likely that catalyst activation resulted through coordination to the Yb complex of either some moisture present in the air, or of small amounts of carboxylic acid arising through air oxidation of the aldehyde. Clearly, purification of butyraldehyde or cyclohexanecarboxaldehyde must have removed the requisite acidic catalyst promoters. Elucidation of the precise nature of these became an urgent priority.

Introduction of small amounts of water (1-10 \( \mu \)L) into mixtures prepared according to the Standard Procedure, containing cyclohexanecarboxaldehyde, maintained under argon, and showing no evidence of ene product formation, had no effect on the system. Introduction of similar amounts of 4 N aqueous \( \text{HCl} \) or 10 \% \( \text{H}_2\text{SO}_4 \) caused only polymerization of the vinyl ether. Yet, when traces of acetic acid were added, product formation began immediately. Reactions wherein acetic acid was added from the beginning no longer exhibited an induction period, and began to rapidly form product at once.

It was earlier mentioned that the progress of the ene reaction is best followed by proton NMR. However, TLC techniques are complementarily useful to monitor

disappearance of the starting aldehyde. A number of times, NMR analysis of mixtures that, by TLC, appeared to have reacted completely after unusually short times, indicated only a modest degree of conversion. Repeated incidents of this type induced us to suspect that silica gel may somehow promote the reaction. This was found to be the case. Addition of chromatographic-grade silica gel to the reacting mixtures had a marked accelerating effect on rates, and resulted in even cleaner products. The optimal amount proved to be equal to ten times the weight of Yb(fod)₃ catalyst, in reactions of both aliphatic and aromatic aldehydes.

The role of silica gel is not fully understood. It probably serves to adsorb adventitious moisture or contaminants that might be present in the mixture and that might coordinate to the Yb³⁺ causing loss of activity, revealed in slower reaction times. It is less clear whether it also acts a general acidic cocatalyst. We must stress, however, that despite its beneficial effect, silica gel is by no means required in the reaction.

Further investigations into the use of acids in conjunction with the ytterbium catalyst strongly suggested an interesting mode of interaction between the two. Briefly, free carboxylic acids do not induce the reaction without Yb(fod)₃, while optimal activity is obtained with a 1:1 molar ratio of carboxylic acid to Yb(fod)₃. If excess acetic acid is added, polymerization of the vinyl ether occurs. These observations are consistent with the intervention of a ternary complex of Yb(fod)₃, aldehyde and acid as the active catalytic species (Figure 10). In this complex, the aldehyde experiences "double activation" through coordination to the Lewis acidic Yb³⁺ and through hydrogen bonding with the acid proton. These interactions would facilitate nucleophilic attack into the aldehyde. A similar activation scheme has been recently described by Yamamoto as Brønsted acid-assisted Lewis acid ("BLA") catalysis. ²⁵ We believe that it is this activation which allows for the ene reaction to occur even with aldehydes that have been previously labeled as unreactive.

Figure 10

A final refinement was necessitated by the propensity of enolizable aliphatic aldehydes to undergo aldol condensation, as an often serious side reaction, in the presence of the Yb catalyst. Because such condensation would be essentially second-order in the aldehyde, a decrease in concentration of carbonyl compound was anticipated to drastically retard the rate of aldolization. It was quickly found that rather than diluting the mixture with further vinyl ether, it was best to introduce the aldehyde as a 10% solution in dichloromethane. This minimized polymer formation.

In summary our initial investigations unveiled optimal conditions for the ene reaction of aldehydes with 2-methoxypropene. Aromatic substrates react best under the following conditions (Procedure A): 1 mol equivalent of aldehyde; 0.5 mol % of Yb(fod)_3 and AcOH; 10-fold weightwise amount of silica gel relative to Yb catalyst; 10 mol equivalents of 2-MP; room temperature. Aliphatic (enolizable) aldehydes are instead best treated as follows (Procedure B): 1 mol equivalent of aldehyde as a 10% weight/volume (= g/mL) CH_2Cl_2 solution; 0.5 mol % of Yb(fod)_3 and AcOH; 10-fold weightwise amount of silica gel relative to Yb catalyst; 10 mol equivalents of 2-MP; room temperature. In all cases, the reactions complete in 6 to 48 hours (NMR). To workup, the silica gel is filtered off under aspirator vacuum and the filtrate is then washed with an aqueous saturated solution of NaHCO_3 to remove Yb(fod)_3. As indicated earlier, no need for further purification exists.
With reliable reaction conditions in hand, we proceeded to explore the scope of the novel ene process in relation to differing aldehydes. We were pleased to observe that the reaction proceeded extremely well with virtually any kind of aldehyde. Table 1 shows some representative examples, along with reaction procedures and crude yields. As can be discerned from such examples, the reaction tolerates most functional groups that are poor ligands for the Yb catalyst, such as nitro, azide, halogen, olefin, cyano, ester and aryl groups. However, aldehydes which incorporate strong alternative coordination sites for the Yb³⁺, especially alkoxy groups (e.g., anisaldehyde), are often poor substrates, probably because Lewis basic substituents effectively compete with the carbonyl group for the Lewis acidic metal ion, and therefore decrease the effective concentration of catalytically active complex. It will be seen later that alkoxy groups are nonetheless tolerated if they are present as carbonyl α-substituents.

The diastereoselectivity of the ene reaction has also been briefly investigated. When pyran carboxaldehyde 26 was reacted with methoxypropene under the conditions of Procedure B, the reaction proceeded with a 4 : 1 selectivity in favor of the Cram-Felkin diastereomer (Figure 11). This stereochemical assignment was made based on comparison of homonuclear vicinal coupling constants between protons A and B in the major and minor isomers of ketols 29 and 30, formed after mild hydrolysis of the vinyl ether products, with the analogous coupling constants of the major and minor isomers of the product of Sakurai reaction of 26. The Sakurai reaction is known to be Cram-Felkin selective in this and related systems.²⁶

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Procedure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph-</td>
<td>A</td>
<td>100%</td>
</tr>
<tr>
<td>b</td>
<td>2-NO₂-C₆H₄-</td>
<td>A</td>
<td>100%</td>
</tr>
<tr>
<td>c</td>
<td>2-I-C₆H₄-</td>
<td>A</td>
<td>99%</td>
</tr>
<tr>
<td>d</td>
<td>2-N₃-C₆H₄-</td>
<td>A</td>
<td>97%</td>
</tr>
<tr>
<td>e</td>
<td>4-NO₂-C₆H₄-</td>
<td>A</td>
<td>90%</td>
</tr>
<tr>
<td>f</td>
<td>2-(5-Me)Furyl-</td>
<td>A</td>
<td>83%</td>
</tr>
<tr>
<td>g</td>
<td>(E)-Ph-CH=CH-</td>
<td>A</td>
<td>83%</td>
</tr>
<tr>
<td>h</td>
<td>n-C₃H₇-</td>
<td>B</td>
<td>71%</td>
</tr>
<tr>
<td>i</td>
<td>cyclo-C₆H₁₁-</td>
<td>B</td>
<td>80%</td>
</tr>
<tr>
<td>j</td>
<td>MeOOCC-CH₂-CH₂-</td>
<td>B</td>
<td>98%</td>
</tr>
<tr>
<td>k</td>
<td>EtOOCC-CH=CH-</td>
<td>A</td>
<td>82%</td>
</tr>
<tr>
<td>l</td>
<td>2-I-3-quinoly-</td>
<td>A</td>
<td>99%</td>
</tr>
<tr>
<td>m</td>
<td>CH₂=CH-C≡</td>
<td>A</td>
<td>100%</td>
</tr>
<tr>
<td>n</td>
<td>Me-CH=C=CH-C≡</td>
<td>A</td>
<td>40%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a) Procedure A: a solution of aldehyde (1 equivalent), 1:1 Yb(fod)<sub>3</sub>: AcOH (0.5 mol %), and silica gel (Merck 60-230 mesh, 100% w/w vs. Yb(fod)<sub>3</sub>) in 10 molar equivalents of 2-methoxypropene was stirred under argon at rt. Procedure B: same as A, except that the aldehyde is introduced as a 10% v/v solution in CH₂Cl₂.

(b) Crude % yields (see text)

(c) Experiments carried out by S. Zhu.

(d) Unoptimized reaction
Some comments are in order here. The low level of Felkin-Anh selectivity may reflect, at least in part, an intrinsic property of 26, as even the Sakurai reaction afforded only a modest 5 : 1 Felkin selectivity with this aldehyde. Considerably greater diastereoselectivities are normally seen with other substrates of this general type. Secondly, and more significantly, the fact that the reaction is Felkin selective, and that therefore chelation-control²⁷ is not favored, further supports the hypothesis of intervention of the Yb based ternary complex. It is well established that Yb(III) favors octacoordination. If six such sites are assumed to be occupied by the diketonate ligands of Yb(fod)₃, the availability of two remaining sites for 26 would probably result in formation of a chelate 31 (Figure 12). Nucleophilic addition to the carbonyl would then occur with

anti-Felkin selectivity. The observed diastereoselectivity is most consistent with the availability of only one coordination site for the aldehyde; the other site being probably occupied by the carboxylic acid as described earlier.

While all of the examples shown to this point use 2-methoxypropene, the reaction proceeds with any vinyl ether which incorporates the oxygen functionality at the central carbon of an allylic system. For instance, 4-nitrobenzaldehyde reacted with 1-methoxycyclohexene 33 to form a 3 : 1 ratio of diastereomeric ene products. The stereochemistry of these was ascertained after bland acid hydrolysis to a 3 : 1 mixture of ketols 36 and 37. The major ketol displayed a diagnostic coupling constant of 8.4 Hz between protons A and B, strongly suggesting anti (= trans-like) relative stereochemistry. In the minor ketol, the coupling constant was 2.9 Hz, consistent with the syn stereochemistry. We thus inferred that the major isomer of the ene product must have been the anti diastereomer (Figure 13).

![Figure 13](image)

Unsymmetrical ethers such as 4,5-dihydro-2-methyl furan 38 can also be used, but one must be mindful that an ether isomerization pathway is at work in the present context (Figure 14). Reaction between the dihydrofuran and 4-nitrobenzaldehyde afforded only ene product 40 as a 1.5 : 1 mixture of unassigned methyl group diastereomers. Seemingly, ether 38 equilibrated with 39, which then reacted with the aldehyde much
faster than the starting 38. The structural assignment of 40 was further corroborated through hydrolysis to 41.

Figure 14

![Chemical reaction diagram]

There can be little doubt that ether isomerization is a proton-catalyzed process. Far from being a drawback, this property removes the need to make regiochemically defined, unsymmetrical ethers, as components for the ene reaction. Because such ethers are often troublesome to make in pure form, our ene process is one of a few in which non-regiospecificity is actually an advantage. It should be noted that similar vinyl ether isomerizations have been effectively exploited in the Bishop/Ciufolini formal synthesis of lavendamycin methyl ester.28

A more interesting observation is that isomer 39 appears to be significantly more reactive than 38. This fact has ramifications into the mechanism of our reaction. MNDO calculations29 support the intuitive fact that isomer 38 (ΔHf = -40 kcal/mol) is more stable than 39 (ΔHf = -39 kcal/mol). Therefore, 38 should be the dominant isomer at thermodynamic equilibrium. Extended Hückel molecular orbital (EHMO) calculations on molecular mechanics (MM+) structures of ether isomers 38 and 39 and of acetaldehyde, a representative aldehyde that is computationally better tractable than more complex congeners, yielded the orbital energies shown in Figure 15. It is apparent from these

---

29 Restricted Hartree-Fock. All computational work was carried out with the Hyperchem® package, available from Hypercube, Inc., Waterloo, Ont.
results that the major frontier orbital interaction during the ene process must be between the HOMO of the ether and the LUMO of the aldehyde.

Figure 15

It is apparent that the greater reactivity of 39 over 38 must be attributed to diminished steric interactions at or near the transition state for the "ene" reaction, and not to ease of orbital overlap, as 39 has a HOMO that is 0.32 eV (7.5 kcal/mol; 1 eV ≈ 23.5 kcal/mol) farther from the aldehyde LUMO compared to isomer 38. This is in complete contrast with the case of vinyl ether-ene cycloadditions, wherein reaction rates are largely a function by HOMO-LUMO gaps.\textsuperscript{30} The "ene" step thus exhibits hallmark properties of a nucleophilic addition reaction, suggesting a most plausible mechanism as shown on the next page (Figure 16). We underscore the fact that positional selectivity for the product vinyl ether probably results from intramolecular proton transfer at the stage of 43.

\textsuperscript{30}Bishop, M. J. Doctoral Dissertation, Rice University, 1993.
Figure 16

We conclude a discussion of the scope of the ene reaction by pointing out that N-sulfonylimines 45 and Ciufolini activated imines 46 furnish small amounts of adducts 47 under the conditions of Procedure B (Figure 17). Notice that these products do not undergo in situ N-protection. Unfortunately, ene reactions of imines are considerably slower and lower-yielding than those of aldehydes. More work is necessary in this area.

The true preparative value of the novel reaction would largely be a function of the structures available from the primary ene products. Exploration of this issue became the next phase of our research. While the extreme reactivity of the newly formed vinyl ethers renders ene products quite delicate substances, it proved to be readily harnessed to obtain a range of useful building blocks. Again we stress the equivalence of our reaction to a fully 

catalytic aldol process, as evident from the fact that hydrolysis or ozonolysis of the vinyl ethers delivered β-hydroxy ketones or β-hydroxy esters: the formal products of an aldol condensation. Some examples of the resultant ketones and esters are shown in Figure 18.

**Figure 18**

\[
\begin{align*}
48 & \quad R = \text{Ph} \\
50 & \quad R = \text{cyclohexyl-} \\
52 & \quad R = \text{n-propyl-} \\
49 & \quad R = \text{Ph} \\
51 & \quad R = \text{cyclohexyl-} \\
53 & \quad R = \text{n-propyl-} \\
54 & \quad R = 2-\text{N}_3\text{-C}_6\text{H}_4\text{-} \\
55 & \quad R = 2-\text{NO}_2\text{-C}_6\text{H}_4\text{-} \\
56 & \quad R = 4-\text{NO}_2\text{-C}_6\text{H}_4\text{-}
\end{align*}
\]

The reactive vinyl ether unit is selectively attacked by various electrophiles even in the presence of other olefinic linkages in the ene product. In particular, methoxybromination gives α-bromo ketals 57/59 (Figure 19). These bromo ketals may, in turn, be hydrolyzed to give α-bromo ketones 58/60. Compounds such as 58/60 are formal aldol products arising from the "unavailable" enolate of bromo acetone. We therefore term products of type 58/60 as "anti-Darzens" compounds. Although the bromo ketals are somewhat unstable, the bromo ketones are remarkably resilient, e. g. showing no inclination to cyclize to furanones even after prolonged standing at room temperature.

**Figure 19**

\[
\begin{align*}
\text{OMIPOMe} & \xrightarrow{\text{NBS, MeOH, CH}_2\text{Cl}_2, K_2\text{CO}_3, 0^\circ \text{C}} \text{MIPOOMe} \\
57 & \quad R = \text{n-Pr} \\
59 & \quad R = \text{Ph} \\
\text{MIPOOMe} & \xrightarrow{1\text{N HCl, CH}_2\text{Cl}_2} \text{H} & \text{O} & \text{O} \\
58 & \quad R = \text{n-Pr} \\
60 & \quad R = \text{Ph}
\end{align*}
\]
Their stability may be attributed to a strong intramolecular hydrogen bond that locks the molecule in conformation 58/60.

However, the bromo ketals can be reacted to give a variety of building blocks that have interesting applications in heterocyclic chemistry; in particular, they can be used to quickly piece together functionalized 3-furanones (Figure 20). First, the MIP group is removed through mild acid treatment (CSA, MeOH) so that the ketal remains intact. Deprotonation of the free alcohol thus formed (NaH) induces cyclization to furan ketals 62/65. Acid hydrolysis will then afford 3-furanones 63/66. This chemistry can be used with a variety of alkyl or aryl groups α to the hydroxyl group and therefore is widely useful.

**Figure 20**

\[
\begin{align*}
57 & \quad R = n-\text{Pr} \\
59 & \quad R = \text{Ph}
\end{align*}
\]

Bromo ketals incorporating additional olefinic functionality may be converted to cycloalkanes under radical conditions. This was demonstrated with the ene product of cinnamaldehyde and 2-methoxypropene 25g (Figure 21). Methoxybromination provided compound 67 exclusively. Radical cyclization was then carried out using Bu$_3$SnH and AIBN in refluxing benzene. The functionalized cyclopentane was obtained in good yield as a 4 : 1 ratio of trans : cis isomers, as determined by NOEDS spectroscopy. Irradiation of H$_a$ in the minor diastereomer caused a significant enhancement in the signal for H$_b$ (minor). As the measurable NOE effect can be expected between protons over a distance of no more than 4 Å, this result suggests that H$_a$ and H$_b$ in the minor diastereomer are cis to one.
another. Conversely, no $H_b$ signal enhancement occurred from irradiation of $H_a$ of the major diastereomer, as the protons are separated by more than 4 Å in the trans diastereomer.\textsuperscript{32}

\textbf{Figure 21}

The observed selectivity is most likely due to stereoelectronic control of the cyclization step\textsuperscript{33}. It is widely accepted that radical additions into olefins involve primarily interaction of the SOMO of the radical agent with the LUMO of the olefin. The transition state leading to the major isomer appears to benefit not only from diminished nonbonding interactions, but also from a beneficial mixing of the $\sigma^*_{C-O}$ and $\pi^*_{C=C}$ orbitals (Figure 22). This interaction would lower the energy of the $\pi$-type antibonding orbital to a level closer to that of the radical SOMO, thus facilitating the reaction.


The cyclized product may be readily hydrolyzed to cyclopentenone 69 under acidic conditions. Similar functionalized cyclopentenones occur in the structures of various prostanoid-type compounds, suggesting that a similar ene / radical cyclization sequence could be effectively used in the synthesis of such compounds. Indeed, a formal synthesis of the antitumor agent, (±) chlorovulone II (Figure 23) has been recently completed in our group by an application of that strategy.34

A variety of alternate electrophiles can also react selectively with the vinyl ether unit in the ene products (Figure 24). Reaction with PhSCl in MeOH produces an α-phenyl sulfonyl ketal 71, while α-hydroxy ketals 70 can be synthesized by oxidation with methanolic mCPBA.

34Zhu, S. Unpublished results from these laboratories
Another notable example of electrophilic reaction is methoxypalladation of the vinyl ether. The ene product is combined with stoichiometric amounts of PdCl$_2$/KOAc in MeOH under a CO atmosphere to produce lactones 74 and 75 (Figure 25).\textsuperscript{35} These lactones, as well as other reaction products, arise from alkyl-Pd species 72/73.

Ene products of aldehydes which incorporate dipolar functionality may undergo intramolecular reactions leading to synthetically important heterocycles. This is the case with the ene product of $o$-azidobenzaldehyde and 2-methoxypropene, 25d (Figure 26). When the ene product is heated in benzene to approximately 80 °C, an intramolecular [2 + 3] dipolar cycloaddition occurs cleanly, quantitatively and stereospecifically to the triazoline, 76. The triazoline is relatively stable at room temperature but will very slowly begin to release N$_2$ and rearrange to give the benzazepinone 77.\textsuperscript{36} We can carry out the rearrangement more quickly and efficiently by simply irradiating the triazoline, as a solution

\textsuperscript{35}This experiment was carried out by Dr. M. A. Ciufolini and is an unoptimized reaction.

\textsuperscript{36}Triazolines are often unstable and will undergo deazoniaiation to an aziridine: Morimoto, Y.; Matsuda, F.; Shirihama, H. Tetrahedron Lett. 1990, 31, 6031.
in benzene, using thioxanthone as a triplet sensitizer.\textsuperscript{37} In our attempts to create the azezipinone directly from the ene product, we tried thermolysis in boiling xylene (140 °C). The final product was the undesired 3-methoxyquinoline 78. The high temperature induced a Huisgens-type retro-[3 + 2] dipolar loss of diazomethane\textsuperscript{38} and aromatization to the quinoline.

Finally, we briefly explored the feasibility of an enantioselective ene process. As mentioned earlier, we believe that a ternary complex between Yb\textsuperscript{3+} ion, carboxylic acid and aldehyde is the catalytically active species in the ene reaction. It seemed logical to introduce asymmetry in this complex, in the hope that a chiral aggregate could induce enantioface selectivity at the level of the aldehyde. There are three obvious ways to test this hypothesis: one could use a lanthanide reagent which contains chiral ligands or a chiral carboxylic acid as co-catalyst, or both in concert.

\textsuperscript{37} Dr. Paul Engel aided us greatly in discerning the necessary conditions for rearrangement.

L-amino acids are probably the most readily available chiral carboxylic acids. We therefore screened N-Tosyl tryptophan, phenylalanine, and proline as substitutes for the acetic acid in our catalytic system, but we observed no enantioselectivity whatsoever. Also, when the reaction was carried out with a combination of (achiral) acetic acid and chiral, camphor-based diketonate, Eu(hfc)₃, we observed only negligible rotations in the products. We additionally observed that europium based catalysts were not as active in the ene process, as the reactions tended to stall.

While we were actively engaged in the above research, an enantioselective variant of our chemistry was reached by Carreira. The Carreira catalyst is a binaphthyl-titanium (IV) complex that produces high ee's and excellent chemical yields with most aliphatic aldehydes, except enals. This, and other problems, detract somewhat from the Carreira technology; therefore, investigations of opportunities in this area continue in our laboratory.

It is apparent from the foregoing discussion that the novel ene reaction has a great deal of potential as a general preparative method, thanks to the wide variety of aldehydes and vinyl ethers that can be employed, the efficiency of the reaction, and the range of important building blocks that can be rapidly obtained from ene adducts.

An especially attractive feature of the ene adducts is their facile conversion into 3-furanones. These substructures are found in a variety of bioactive agents of current interest. Although there have been syntheses of compounds which contain the 3-furanone subunit, there exist few good approaches to this type of system.

Deficiencies have prompted a landmark investigation of 3-furanone synthesis and reactivity by Smith,\textsuperscript{42} who demonstrated that the target heterocycles are generally available through cyclodehydration of 4-hydroxy-1,3-diketones in yields ranging from 20-78\% (Figure 27). In turn, the diketones are prepared through a mixed aldol condensation between an aldehyde and ketone 79, followed by oxidation with the Collins reagent.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure27.png}
\caption{Figure 27}
\end{figure}

A limitation of this procedure is that it can only be used to make furanones that possess disubstitution at the 2-position. Also, the reaction tolerates only limited variability in the starting ketones 79, which are not commercially available and need to be made through multistep sequences. As an initial application of our new chemistry, we elected to exploit our facile 3-furanone preparation in a synthesis of phyllanthocin, 84, the aglycone of the anti-tumor agent, phyllanthoside (Figure 28). The reasons for our selection of 84 as the initial target are apparent from the discussion in the following chapter.

PHYLLANTHOCIN

The *Phyllanthus* genus from the Euphorbiaceae family occurs in tropical climates and includes species purported to treat tubercular ulcers, sores, malaria, ring-worm, jaundice, and diarrhea.\(^{43}\) Also, three species, *P. amblica*, *P. niruri* and *P. urinoria*, have been used in the primitive medical treatment of cancer.\(^{44}\) Such practices were recognized by the U. S. National Cancer Institute and the genus became targeted as part of their exploratory plant evaluation program. Initial species collections were taken in 1974.\(^ {44}\)

Phyllanthoside 83 was initially isolated in 1977 by Kupchan and coworkers from a Costa Rican tree believed to be *Phyllanthus brasiliensis* (Figure 28).\(^ {45}\) The ethanol extract from Kupchan's isolate was found to show significant *in vitro* activity against cells derived from the human carcinoma of the nasopharynx (KB), with a cytotoxicity (ED\(_{50}\)) of 10^{-2} \mu g/ml. It also exhibited activity against the P388 lymphocytic leukemia in mice (PS) with T/C values ranging from 137 to 153 at dose levels from 6 to 24 mg/kg.

---

\(^{45}\) Spjut, R. W.; Perdue, R. E. *Cancer Treatment Reports*, 1976, 60, 979.  
Five years later, in 1982, Pettit and coworkers also isolated phyllanthoside and other related compounds from the roots of the Costa Rican tree *Phyllanthus acuminatus* Vahl. Pettit’s investigations found that phyllanthoside exhibited a curative level of antineoplastic activity against the NCI murine B16 melanoma. At a dose range of 4-16 mg/kg, it induced an average life extension of 62-74%. For this reason, phyllanthoside has come under consideration for human clinical trials for the treatment of breast and colon cancer.

A key step in Kupchan’s structural elucidation of phyllanthoside was a degradative methanolysis, which yielded the crystalline methyl ester of the aglycone. This material, a bisabolane sesquiterpene, was dubbed phyllanthocin, 84, and it was found to exhibit no biological activity. Its structure was solved by single-crystal X-ray diffractometry, but the full structure of phyllanthoside remained unknown until Pettit’s report in 1982.

An observation of major significance for a possible synthetic attack on 84 emerged from structural studies: phyllanthocin had the most thermodynamically stable relative configuration at all stereogenic centers. Suitable epimerizable forerunners should therefore converge to the natural diastereomer upon equilibration. This hypothesis was validated during later synthetic work on 84.

Several total syntheses of phyllanthocin have been described. These have been carried out by the groups of Collum, Williams, Burke, Smith, and Martin. Smith also completed the total synthesis of phyllanthoside. In order to fully appreciate the importance of our furanone formation technique and its utility in the synthesis of phyllanthocin, a discussion of the five previous syntheses will follow.

\[\text{Footnotes:}\]

46 It was later discovered that *Phyllanthus brasiliensis* does not extend into Central America and that, in fact, the original isolation was carried out on *Phyllanthus acuminatus* Vahl.

The Collum Approach

The first total synthesis of (+)-phyllanthocin was reported by Collum in 1982.\textsuperscript{48} His approach involved the formation of the 6,5-bicyclic lactone 85 which would then be merged with the precursor of the spiroketal, compound 86 (Figure 29). The lactone was prepared in eight steps starting from the commercially available, but expensive, (S)-perilla aldehyde 87. The spiroketal precursor, homoallyl alcohol 86, was also synthesized in eight steps starting from (S)-(+)3-hydroxy-2-methyl-propanoic acid 88.

Lactone 85 was synthesized as shown in Figure 30. A key sequence involved stereoselective hydroboration-oxidation of 89 with thexyloborane, followed by a Mitsunobu lactonization that proceeded with clean and complete inversion of configuration at the OH bearing carbon.

Collum’s strategy for the critical connection of the two key intermediates envisioned a nucleophilic attack of a Grignard-type reagent into the lactone carbonyl. The spiroketal precursor was treated with Schlosser’s base to give a dianion, which was then reacted with MgBr$_2$ to give the necessary nucleophile (Figure 31). This agent added to the lactone to

Figure 31

\[ \text{86} \xrightarrow{\text{a}} \left[ \begin{array}{c} \text{Mg} \\ \text{O} \\ \text{HO} \\ \text{OBn} \end{array} \right] \xrightarrow{\text{b}} \text{93} \]

\[ \text{94} \xrightarrow{\text{c}} + \text{95} \]

a. 1) t-BuOK/α-BuLi/hexane 0 °C, 2) MgBr$_2$/THF; b. 85/Et$_2$O -60 °C

\[ \text{a. 1) t-BuOK/α-BuLi/hexane 0 °C, 2) MgBr$_2$/THF; b. 85/Et$_2$O -60 °C} \]

\[ \text{c. ZnCl$_2$/CH$_2$Cl$_2$ -20 °C (69%) } \]
furnish the lactol 93, which was easily induced to spiroketalize by treatment with ZnCl₂. The spiroketalization formed mostly the desired isomer of the ketal, 94, over the undesired, 95, in a ratio of 48 : 1. This elevated level of diastereoselectivity is due to the fact that the desired isomer is also the most thermodynamically stable one.

The completion of the synthesis proceeded as follows (Figure 32). First, the spiro epoxide 96 was formed through sequential debenzylolation, mesylation and DBU treatment. It was then time to unmask the two latent carbonyl moieties through the use of the Sharpless oxidation (RuCl₃/NaIO₄)⁴⁹, which afforded keto acid 97. The acid was esterified with CH₂N₂ followed by reduction of the ketone with Selectride to give, selectively, the desired axial alcohol 98. Cinnamoylation afforded phyllanthocin.

**Figure 32**

![Chemical structures](attachment:image.png)

96 97 98

*The Williams Route*

The Williams synthesis of (+)-phyllanthocin⁵⁰ is similar to Collum's as they both start with pre-functionalized cyclohexane ring systems and anneal the rest of the molecule around it. The retrosynthetic analysis, shown in Figure 33, requires cyclohexane carboxaldehyde 99 and dithiane 100 as the key intermediates. The dithioacetal is masked for effective conversion to an acyl anion equivalent for the crucial connection of the two parts.

---


The dithiane component was made starting with chiral epoxide 101, available from diethyl tartrate (Figure 34). Several functional group manipulations provided 102 with the requisite anti stereochemistry between OH and methyl groups. A critical step involved opening of terminal epoxide 102 by 2-lithio-1,3-dithiane. MEM protection afforded the key dithioacetal intermediate. The entire process requires 11 steps.

The synthesis of the aldehyde component from the known, but racemic, cyclohexenyl alcohol 104\textsuperscript{51} required a crucial epoxidation, which proved to be stereochemically difficult to control (Figure 35). Thus, a 1:1 mixture of α and β isomers 105/106 was obtained after benzylation of the primary alcohol and reaction with MCPBA. The epoxides were advanced through the next two reactions as a mixture. Base treatment provided two diastereomeric allylic alcohols, which were subsequently protected as their silyl ethers 107/108. At this point, the desired axial isomer was separated through column

chromatography, resulting in loss of half of the starting material. Stereoselective hydroboration provided a primary alcohol, which was readily resolved as the camphanate ester. Conversely, a second loss of 50% of the initial material ensued. PCC oxidation of the now stereochemically — and enantiomerically homogeneous alcohol afforded the second key intermediate, 99.

![Figure 35](image)

---

**Figure 35**

104 105 α-Me 107 axial OR
106 β-Me 108 equatorial-OR

a. BnBr, base; b. mCPBA, CH₂Cl₂, 10 °C to r.t. (89%); c. Lithio-2,6-dimethylpiperidide, Et₂O, 50 °C (90%) d. t-BuMe₃SiCl, DMF, DMAP, r.t. (100%); e. Borane, THF, H₂O, NaOH; f. PCC, CH₂Cl₂

Connection of the two key intermediates occured by nucleophilic attack of the deprotonated dithiane into the cyclohexane carboxaldehyde to give a mixture of two diastereomeric adducts 109 in an α:β ratio of 3.5:1 (Figure 36). This relatively poor selectivity was inconsequential, as the new carbinol would be later oxidized to a ketone. The silyl protecting group was then removed with TBAF to give a triol as a mixture of diastereomers. Upon hydrolysis of the dithiane moiety (HgCl₂, HgO), the compound immediately cyclized to afford a 6:1 mixture of spiro ethers. Unfortunately, the major isomer was the undesired one. This obviously kinetic product was isomerized using magnesium trifluoroacetate to give only the naturally occurring, thermodynamically more stable isomer. The remaining secondary alcohol was oxidized to give the furanone as a single diastereomer 110. The ester unit of phyllanthocin was then introduced through sequential debenzylization (Pd/H₂), Jones oxidation and esterification (CH₂N₂). Prior to the
final MEM deprotection and cinnamoylation, the spiro epoxide 111 was formed by condensation of the furanone ketone with excess methyleneoxysulfurane. The sulfur ylide selectively attacked from the less hindered face to give a mixture of α (desired) and β (undesired) epoxides in 30:1 ratio and in almost quantitative yield.

The Burke Approach

The retrosynthetic outline below reveals that Burke’s strategy involves the aldol coupling of an enolate, derived from epoxy ketone 112, and aldehyde 113 (Figure 37). This coupling, termed “Cram-cyclic”, requires that the mixed aldol partners be optically pure. Also, notice that a precursor to the methyl ester unit of phyllanthocin is missing. A hydroformylation reaction will introduce that group in the last stages of the synthesis.

The synthesis of ketone 112 commenced with a Diels-Alder reaction between the known vinyl ketone 114 and butadiene 115 (Figure 38). Wittig olefination followed

---

by acetate hydrolysis afforded racemic alcohol 117 in 61% yield. This compound was subjected to Sharpless asymmetric epoxidation\textsuperscript{53} to give an equimolar mixture of epoxy alcohol diastereomers. Thus, separation by column chromatography, and loss of half of the starting compound as the undesired isomer, is required. The desired isomer was then oxidized under Swern conditions to give aldehyde 118. The ketone participant in the aldol coupling was finally obtained by treatment of the aldehyde with methyllithium, followed by oxidation.

\textbf{Figure 38}

![Chemical structure diagram](image)

114 + 115 → 116 \quad \text{a.b}

116 \quad \text{c.d}

\text{CHO}

118 \quad \text{e.d}

119

\text{p-MeOPh}

\text{a. Ph}_3\text{P}=\text{CH}_2, \text{THF}, -100 \text{ °C}; \text{ b. K}_2\text{CO}_3, \text{MeOH, r.t.; c. t-BuOOH, (+)-DET, Ti(O-t-Bu)}_4, \text{CH}_2\text{Cl}_2, -23 \text{ °C; d. Swern ox.; e. MeLi, THF, -78 °C}.

The aldehyde required for the aldol coupling was available by standard procedures from commercial (R)-(−)-methyl-3-hydroxy-2-methylpropionate. Addition of the enolate of ketone 119 into the aldehyde afforded the secondary alcohol 120 as a 3.6:1 mixture with its C-10 epimer (Figure 39). As this diastereoselectivity follows the Cram rule, it is termed a "Cram-cyclic" coupling. The two epimers were separated and the stereochemically pure alcohol was carried into the next step. Deprotection of the \( p \)-methoxybenzyl group and the

silyl ether, in a two step process, provided the spiroketal 121 with complete stereoselectivity.

The last major problem, the placement of the methyl ester, was solved through the use of hydroformylation technology. A silylated derivative of compound 121 was reacted with CO and H₂ under catalysis by [(COD)RhOAc]₂ to give a 1:1 mixture of the α and β stereoisomers in low yield (20%). The undesired isomer could be equilibrated to give, at best, a 2.3:1 mixture in which the desired epimer 122 predominated. The synthesis was then completed using procedures previously described by Collum and Williams.

**Figure 39**

\[
\begin{align*}
113 + 119 & \xrightarrow{a} 120 \\
& \xrightarrow{b,c} 121 \\
& \xrightarrow{d,e} 122
\end{align*}
\]

a. LDA, THF, -78 °C; b. DDQ, CH₂Cl₂/H₂O; c. 5% HF, CH₃CN; d. TBDMSOTf, lutidine; e. 8 mol % [(COD)RhOAc]₂, PhH, 1:1 CO₂/H₂, 76 °C

Although this was the shortest synthesis to date, the strategy suffers because of the lack of selectivity in several of the reactions.

**The Smith Route**

The strategy presented by Smith permits high levels of stereocontrol, as it takes advantage of the predictable stereochemical bias of the bicyclic system of 84. The key intermediates 123 and 124 will be connected by a nucleophilic attack of a vinyl anion into the optically active aldehyde (Figure 40). The necessary aldehyde can, in turn, be

---


constructed using a stereoselective intramolecular ene reaction. The strategy is well devised as the stereochemistry of aldehyde 123 directs the remaining reactions, affording (+)-phyllanthocin enantioselectively.

**Figure 40**

![Chemical Structure](image)

The chiral aldehyde was synthesized using Evans methodology starting with imide 125, made from the corresponding (+)-oxazolidone (Figure 41). The imide was selectively alkylated with allyl bromide, and reductive removal of the chiral auxiliary with LAH gave a primary alcohol, which was protected as the benzyl ether 126. The ene precursor was then synthesized by ozonolysis followed by Lindlar reduction of the acetylene to the cis olefin 127. Finally, target aldehyde 123 emerged upon intramolecular ene cyclization with Me₂AlCl in CH₂Cl₂ and subsequent MEM protection.

**Figure 41**

![Chemical Structure](image)

Dihydropyran 124 was prepared from commercially available tetrahydropyran-4-one by sequential ketalization, bromination (Pyr-HBr₃) and elimination (tBuOK) in 70% overall yield. Union of the two fragments was realized by addition of the anion of the dihydropyran, formed by treatment with tert-butyllithium, to chiral aldehyde 123 (Figure
The secondary alcohol product was hydrolyzed, in order to remove the neopentyketal, and then oxidized under Swern conditions to give ketone 128. After deprotection of the MEM group to give the free alcohol, cyclization to the furan was induced by treatment with a catalytic amount of camphorsulfonic acid in dry benzene. Formation of furanone 129 occurred with good selectivity, affording only 2% of the undesired epimer. The next step, spiro epoxide formation using Williams' sulfur ylide chemistry, was completely stereoselective.

Figure 42

![Chemical structures](image)

a. ZnBr₂; b. CSA; c. CH₂SO(CH₂)₂d. 1) LDA, 2) TMSCl; e. BnMe₂NF/MεI; f. DBU, THF

The major problem still remaining in the synthesis was the regiocontrolled placement of a methyl group on the spiro pyran, a goal attainable through methylation of a regioselectively generated enolate of the pyranone. Such procedures afforded good positional selectivity, but, at best, produced a 1:5 mixture of methylated compounds with the undesired epimer in majority. Fortunately, this mixture could be equilibrated to the correct stereochemistry with DBU to afford methyl ketone 130 in 60% yield. The remaining steps, formation of the methyl ester and cinnamoylation, are well-documented in previous syntheses. Upon completion of phyllanthocin, Smith investigated the formation of its biologically active parent, phyllanthoside, and is credited with its first total synthesis.¹⁵

The Martin Approach

Martin's enantioselective synthesis of (+)-phyllanthocin features a highly selective dipolar cycloaddition of a nitrile oxide to form an oxazoline 133 (Figure 43). The oxazoline is a masked form of the β-hydroxy ketone 132 needed for furanone/spiroketal formation. Compound 131, which also served as an intermediate in Williams' synthesis, is perceived as the key subgoal.

Figure 43

Cyclohexene 135 was synthesized from the known optically pure carbinol 134 by oxidation to the carboxylic acid followed by iodolactonization and dehydroiodination (Figure 44). The crucial dipolar cycloaddition is then carried out between the cyclohexyl olefin and the nitrile oxide, which is generated in situ from acetylhydroximidoyl chloride, by refluxing in toluene to give the desired isoxazoline ring in 45% yield. The lactone moiety directs the cycloaddition to occur from the less hindered face, hence the observed selectivity. After cycloaddition, the lactone is no longer needed, and it was cleaved by

---

methanolysis. The hydroxyl group present in compound 137 is unnecessary and it was removed under Barton conditions.\(^{58}\)

**Figure 44**

![Chemical structures](image)

134 135 136 137

The carbon framework was completed through merger of 137 with chiral aldehyde 138 (Figure 45). The enolate of the ketone was formed by treatment with LDA followed by addition of 138 to give a 1.2:1 mixture of alcohols 139. Deprotection of the silyl ether with HF caused concomitant cyclization to the methyl glycosides 140/141. At this

**Figure 45**

![Chemical structures](image)

137 + 138 139

140 + 141 131

---

junction, Martin inverted the stereochemistry of the undesired hydroxy compound to give glycoside 140 selectively. The latent 1,2-diketone system was finally unmasked using H₂/Raney Ni, and cyclized to the spiroketal with trifluoromethanesulfonic acid, affording Williams’ intermediate 131 with good selectivity (18:1).

While the various syntheses discussed above differ significantly in overall logic, they all rely on the fact that the relative stereochemistry of phyllanthocin corresponds to the most thermodynamically stable diastereomer.
SYNTHETIC STUDIES ON PHYLLANTHOCIN

Our strategy, shown in Figure 46, also takes advantage of phyllanthocin’s thermodynamic preferences, and it relies on our ability to create functionalized furanones from the ene products. Previous syntheses have indicated that the epoxide can be made selectively from the C(7)-ketone using sulfur ylide chemistry. Also, the C(3)-methyl ester can be masked as a vinyl, aldehyde, benzyloxy methyl, or even an aromatic group. As these reactions are well-documented, we felt that fused bicyclic compound 142 was the key subgoal for our diastereoselective synthesis of phyllanthocin.

Two possibilities were envisioned for the formation of the spiropyran system after completion of the bicyclic unit. The first option was an S_N2 alkylation of the enolate of the furanone with a suitably functionalized carrier of “side chain,” e.g. an allylic bromide. A potential weakness of this approach lies in the unpredictable behavior of α-alkoxy ketones toward enolization.\(^59\) If the desired enolate were difficult to form, or if the compound

preferred enolate formation toward the ring junction, we could possibly activate the desired site with anion-stabilizing groups X (Figure 46) such as phenylthio, ester or formyl. Cyclization to the spiro compound would be carried out after this key alkylation. For example, if the X group were phenylthio, a Pummerer reaction could be used for the spirocyclization. The remaining steps needed for completion of the synthesis have been reported in the previous syntheses.

Our alternate plan, termed the aldol route, involves a mixed aldol reaction between the enolate of the furanone and a suitably functionalized aldehyde. This reaction would provide us with an enone/vinyl ether system which would be cyclized to the spiropyran upon acid treatment. Spiroketal formation should occur with good selectivity, as it is very similar to the cyclization reaction used by Smith (Figure 47). This plan converges with the alkylation route upon release of the dimethyl ketal.

![Figure 47](image)

Whichever of the two routes were to be successful, our primary goal was clearly the synthesis of the fused bicyclic system 142 (Figure 48). However, further synthetic planning required a strategic decision concerning the nature of activating group X and of substituent Z, the precursor to the ultimate ester unit of 84. It was hoped that the
designated $X$ group, if necessary, could be put in place starting with a plain bicyclic system wherein $X = H$. This would minimize the number of additional steps required for introduction and removal of $X$. Of course, the best case scenario was one in which no furanone activation would be necessary.

**Figure 48**

The choice of $Z$ became in large part a function of the overall strategy for the synthesis of the bicyclic core. Our initial plan visualized formation of the 3-furanone first, followed by cyclization of the six-membered ring through either an aldol condensation (Figure 49, cf. 143, $Y = O$), or an intramolecular alkylation ($Y = H$, $I$) occurring from the appropriate furanone enolate. In order to set the stage for these events, we needed an aldehyde such as 144 that already has the precursor to the six-membered ring in place, or one such as 145, which can be suitably functionalized after furanone formation.

**Figure 49**
The search for an aldehyde suitable for the conduct of the planned transformations was a long one. Our initial efforts centered around a substrate of the type 145, and the first aldehyde that we investigated was 146 (Figure 50). Our plan was to execute ene reaction and furanone formation first. Then, a second alkylation of the malonate system would occur as a prelude to six-membered ring formation. The extra ester group would be removed by a Krapcho decarboxylation.\textsuperscript{60}

Small quantities of aldehyde 146 were made by mono-allylation of dimethyl malonate, followed by ozonolysis. We also were able to synthesize aldehyde 147 through a multistep sequence that utilized 146 as an intermediate (Figure 50). However, the mono-allylation of the malonate was inefficient because a competing double allylation forced upon us a problematic separation at the very first stage of the synthesis.

![Figure 50](image)

Unfortunately, 146 and 147 were exceedingly poor substrates for the ene reaction. We believe that the diester system might have strongly chelated the Yb catalyst, preventing coordination of the aldehyde and suppressing ene reactivity. In order to remove the troublesome diester system, our efforts turned to the use of alternative aldehydes. Compound 148 appeared to be an ideal substrate, because the lactone already contains all

\textsuperscript{60}Krapcho, A. P Synthesis, 1982, 893 and references cited therein.
the functionality necessary for introduction of the carboxylic group and for completion of the six-membered ring. However, preliminary observations had led us to erroneously believe that aldehydes incorporating carboxalkoxy groups or lactones may not be well tolerated by the ene reaction. Therefore, we favored substrates that carried the eventual ester unit in latent form. A safe choice appeared to be 151 (Figure 51), which possesses no alternative sites for coordination to Yb³⁺, and wherein the aryl group would be amenable to oxidation to the desired carboxylic acid by catalytic Ru(VIII) under Sharpless conditions.⁴⁸ The X group could be either a hydrogen or an electron-donating substituent such as methoxy, which might aid in aryl group oxidation. In light of the above, we elected to focus on 151. Ironically, aldehyde 148 eventually proved to be the best alternative.

Figure 51

![Chemical structure](image)

149 → 150 → 151

a. allylmagnesium chloride, THF, -78 °C (98%); b. KH, THF, reflux (crude 54%)

Aldehyde 151 was obtained by anionic oxy-Cope rearrangement of the product of allyl magnesium chloride addition to cinnamaldehyde derivative 149 (Figure 51). It became immediately apparent that the oxy-Cope reaction was low yielding and provided products which were rather impure. The ene reaction requires extremely pure starting materials, therefore, extensive purification of the crude aldehyde was necessary. Kugelrohr distillation and extensive chromatography were quite detrimental to overall efficiency. Moreover, the ene reactions of the compound 151 (X = OMe) were very slow, requiring over a week to complete. It will be recalled that this is typical of many aldehydes
incorporating alkoxy groups at sites other than the carbonyl α-position.

Nonetheless, we were able to reach the desired bicyclic furanone from compound 151. The ene reaction of this aldehyde provided an essentially 1:1 mixture of diastereomeric adducts 152 (Figure 52). This would result in formation of the final bicyclic system as a 1:1 mixture of aryl epimers. Because the aryl unit would eventually be converted to an epimerizable ester group, diastereomer formation was not regarded as a cause for concern. The terminal vinyl group survived the methoxybromination step required for furanone formation unscathed, but it was finally ozonolyzed to an aldehyde at the stage of 154. When this aldehyde was treated with 20% NaOH in THF, cyclization occurred, resulting in a mixture of diastereomers of alcohol 156. The choice of base was suggested by the work of Burke, and also by our own observation that alkoxide reagents were less satisfactory. In particular, the isolation of aldol dimers of 156 from reactions conducted with EtONa or tBuOK as the bases presaged a fatal problem that surfaced during later attempts at merging 142 with a forerunner of the spirocyclic segment.

Figure 52

\[
\begin{align*}
152 & \xrightarrow{a,b} 153 & \xrightarrow{c,d} 154 \\
\text{OMe} & \text{OMe} & \text{OMe} \\
\text{OMIP} & \text{OMIP} & \\
\breve{\text{Ar}} & \breve{\text{Ar}} & \\
\text{Ar} & \text{Ar} & \\
\end{align*}
\]

a. NBS, MeOH, CH₂Cl₂, K₂CO₃, 0 °C (94%); b. CSA, MeOH (95%); c. NaH, THF, reflux (50%);
d. 1N HCl, THF (pure 20%); e. O₂, MeOH/CH₂Cl₂, -78 °C; Me₂S (98%); f. 20% NaOH, THF (90%)

The secondary alcohol formed during aldol condensation is not present in phyllanthocin and requires removal. A variety of conditions, including mesylation/DBU treatment and POC13/pyridine, were unable to form conjugated system 157 reliably. Most likely, the strain inherent in the incipient enone system causes polymerization or decomposition immediately upon formation. Barton deoxygenation reactions were also attempted, but the poor results obtained and the increase in overall number of steps discouraged us from undertaking an extensive pursuit of this strategy.

Fortunately, an alternative to the aldol cyclization was available in the form of intramolecular S_N2 alkylation of the furanone enolate. Alcohol 158 formed by NaBH_4 reduction of the aldehyde was transformed into mesylate 159, which was subsequently treated with acid to unmask furan ketone 160 (Figure 53). Yet, all attempts to close the cyclohexane ring under basic conditions met with failure. Disappointing results were similarly obtained with a tosylate, but iodide 161, formed through a Finkelstein-type reaction of the mesylate, closed easily upon treatment with base to give the desired bicyclic

![Figure 53](image)

a. MsCl, TEA, CH_2Cl_2 (98%); b. 1N HCl, THF (90%); c. NaI, acetone, reflux (90%); d. 20% NaOH, THF, reflux (100%)

---

system. Initially, this step was also conducted by the use of 20% aqueous NaOH. It will later be seen that maximal yields were obtained in a similar reaction involving tBuOK as the base, under appropriate conditions. Not unexpectedly, compound 162 emerged exclusively as the thermodynamic, cis fused isomer.

Surprisingly, an analogous cyclization reaction proved to be extremely problematic in substrate 165, wherein an ester unit is present in expressed form. Compound 165 was made starting with aldehyde 164, readily available from butyrolactone (Figure 54). Treatment with potassium tert-butoxide afforded cyclopropane 166 as the major product, with no trace of the desired cyclohexane. Although the ester is less acidic than the ketone, and therefore its enolate should be present in minor amounts relative to the enolate of the ketone under our conditions, three-membered ring formation is extremely fast. Notice that the use of aqueous base was inappropriate in the present context, as rapid hydrolysis of the

---

**Figure 54**

![Chemical structures](image)

---

ester would result in $S_N2$ lactonization and subsequent lactone cleavage. Overall, the product of apparent $S_N2$ displacement of I by OH would result.

The newly completed synthesis of bicyclic furanone 162 validated our general strategic thinking, but it was rather demanding and modestly efficient, requiring too many steps, some of which afforded unsatisfactory yields. With considerable trepidation, we therefore turned our attention back to aldehyde 148. The ene reaction between 148 and 2-methoxypropene (2MP) proceeded extremely well, provided that the aldehyde was rigorously free of DMSO. This contaminant may be present in 148 as a result of the technique employed for its preparation; namely, ozonolysis of 2-allyl-butyrolactone, followed by reduction of peroxides with dimethyl sulfide. The strongly Lewis basic DMSO must be an effective ligand for the Yb(III) present in the catalyst. Even small amounts of DMSO are sufficient to prevent ene reaction, presumably because aldehyde coordination to Yb(fod)$_3$ is no longer possible.

The switch to 148 as an ene substrate resulted in a remarkably concise route to the bicyclic system and greatly improved overall efficiency (Figure 55). Conversely, it

Figure 55

![Chemical structures](image)

148  a  b  c  167  168  169

a. 2MP, CH$_2$Cl$_2$, Yb(fod)$_3$/AcOH, SiO$_2$, r.t.; b. NBS, MeOH, CH$_2$Cl$_2$, K$_2$CO$_3$, 0 °C; c. NaH, t-BuOH, THF, reflux (40% pure)
required us to deal with some new problems. First, optimization of the methoxybromination step was necessary, as α-bromo ketal 168 proved to be quite sensitive and seriously prone to decomposition. This intermediate appeared to slowly release traces of HBr, small accumulations of which would precipitate rapid destruction of the bulk of the material. The following safeguards proved to be essential for survival of the fragile 168. Any excess N-bromosuccinimide (NBS) had to be carefully avoided during the reaction, which was therefore carried out by titrating the ene adduct with a solution of reagent. The end-point of this fast reaction was readily detected by TLC. Quenching (reduction) of whatever slight excess NBS might have been present in the crude reaction mixture was effected by addition of sodium thiosulfate, Na₂S₂O₃ and of some solid K₂CO₃. In this manner, the mixture remained neutral to slightly basic at all times. Also, the crude product must be maintained over K₂CO₃ at all times. Use of the more common sodium hydrogen sulfite, NaHSO₃, instead of Na₂S₂O₃, as a reductant had a deleterious effect on the product, because of its greater acidity, and because of the acidity of its oxidation products.

A second difficulty was encountered with all lactone-containing intermediates in the form of significant water solubility (γ-butyrolactone is water miscible). This caused major losses of material into aqueous phases during extractive workups in the course of initial efforts to scale up the process leading to 169. Fortunately, the crude products of most steps emerged in a state of excellent purity. This allowed us to dispense altogether with aqueous workups during initial phases of the synthesis. For example, the workup of the ene reaction simply involved filtration to remove the silica gel, followed by evaporation of solvent under reduced pressure. The crude oil was advanced directly to the methoxybromination step, workup of which proceeded simply through vacuum-stripping of the solvents and redissolution of the resulting slurry in Et₂O, causing precipitation of
succinimide. Vacuum filtration and concentration provided a crude product, good enough to be put directly into the cyclization step (Figure 55).

Technical problems surfaced also in the course of this latter reaction. Earlier furanone cyclizations had been smoothly accomplished with NaH in refluxing THF. We fully expected that this procedure could be applied verbatim to 168. A possible side reaction was equilibration between lactones 168 and 170 (Figure 56). Of these, 168 can cyclize to a five-membered ring product, while 170 would produce a kinetically highly unfavorable, bridged nine-membered ring. Side reactions could also occur as a result of lactone enolization. Intramolecular alkylation of enolate 168 could result in a six-membered ring which is disfavored by the steric hindrance of the tertiary nucleophile and of the neopentyl-type halide. Cyclization of 170 would be even more troublesome, as a bridged system results. In light of the above, we did not anticipate serious problems with the desired step.

![Figure 56](image)

While furanone formation did in fact proceed without side reactions, the alkoxide (or alkoxides) arising through deprotonation of 168 by NaH were essentially insoluble in THF and other ethers. The use of DMF or DMSO as solvents might have nullified
solubility problems, but major difficulties could then be envisaged during workup and recovery of the water-soluble furan product from mixtures containing those water-miscible substances. The general solubility of metal alkoxides in alcohols suggested the use of alcohols as solvents. Tertiary butanol was examined first, with the expectation that its low acidity and poor nucleophilic reactivity would ensure a large preponderance of the desired alkoxide at thermodynamic equilibrium, and discourage any interaction with the lactone or the bromide units. This represented a fortunate choice, as the reaction became extremely well behaved both in execution and workup.

The cyclization step was the first one to require an extractive workup; however excess water had to be avoided. The reaction was thus quenched with aqueous 4N HCl, which not only destroyed the remaining NaH, but it also released the dimethyl ketal to give furanone 169 directly. Repeated extraction of the water-soluble 169 from the water phase with EtOAc and purification by column chromatography (the first one in the entire synthesis) afforded the desired furanone in 40% overall yield from 148. We were now ready to explore formation of the cyclohexane ring.

As discussed earlier (Figure 54), an expressed ester unit would not be tolerated in the cyclization step. Therefore, the lactonic carbonyl group of 169 had to be masked as a suitable equivalent. In preparation for such manipulations, it seemed desirable to reduce the water solubility of 169, a goal that was readily accomplished by conversion to the minimally water soluble neopentyl ketal 174.

It is apparent from the diagram below that the best ester surrogate is a vinyl group (Figure 57). This unit may be introduced in two steps from 174, and it may be expeditiously converted back to an ester by Ru(VIII) oxidation\textsuperscript{32} followed by diazomethane esterification. Alternative masking schemes would require more steps both for introduction of the ester equivalent and for ester retrieval from it. Compound 175 was smoothly reached through the use of a diisobutylaluminum hydride (DIBAL) reduction of 174,
which formed as a mixture of four diastereomers. Wittig olefination with triphenylphosphonium methyldie yielded 176.

Figure 57

![Chemical structure](image)

169 $\xrightarrow{a}$ 174 $\xrightarrow{b}$ 175 $\xrightarrow{c}$ 176

a. neopentyl glycol, TsOH, CH(OMe)$_3$, benzene, reflux (94%); b. DIBAL, THF, -78 °C (99%); c. Ph$_3$PMe, BuLi, THF, 0 °C to reflux (30% pure)

We were pleased to determine that all subsequent reactions involving the vinyl series of substrates were quite reliable. Thus, the bicyclic system was completed by a procedure similar to the one used in the synthesis of 162. Mesylation and iodination were carried out as previously mentioned (Figure 58), but the deketalization step was best run

Figure 58

![Chemical structure](image)

176 $\xrightarrow{a}$ 177 $\xrightarrow{b}$ 178

179 $\xrightarrow{c}$ 180

a. MsCl, TEA, CH$_2$Cl$_2$ (99%); b. NaI, acetone, reflux (98%); c. 80% AcOH, reflux; d. t-BuOK, THF, 0 °C (54% pure)
in refluxing 80% AcOH, rather than with the aqueous HCl utilized in the aforementioned process. The furanone product, 179, was contaminated with the diacetate of neopentyl glycol. Because the chromatographic mobility of the two substances very nearly coincided, no purification was done at this stage. The crude mixture was directly utilized for the bicyclic ring closure reaction, which was effected cleanly by treatment with a slight excess of potassium tert-butoxide in THF at 0 °C.

The synthesis of the bicyclic system, as proposed, is diastereoselective. Because the configuration of C-5 in 180 can enforce the appropriate relative stereochemistry at the other stereogenic centers including those present on the spirocyclic segment, an enantioselective synthesis of phyllanthocin should be possible if the stereochemistry of C-5 were to be introduced with absolute stereocontrol. This may now be accomplished through the use of the Carreira catalyst. This issue will not be further debated here. Instead, we wish to turn the attention to a discussion of methodology for the attachment of a side chain to 180 as a prelude to spiroketal formation.

Implementation of our alkylation strategy (cf. p. 51) required alkylation of the enolate of 180 with an alkyl bromide. The appropriate bromide was prepared starting with dimethyl acrylic acid (Figure 59). The acid was esterified with trimethyl orthoformate, and the resultant 182 was selectively α-methylated using LDA and MeI. DIBAL reduction of the ester provided alcohol 184, which was subsequently protected as its benzyl ether 185. Oxidation using tert-butyl hydroperoxide and catalytic SeO₂ adsorbed on silica gel⁶⁴ was then employed to transform the terminal allylic site into an aldehyde. NaBH₄ reduction and bromination with PBr₃ provided the desired side chain 188.

In preparation for the crucial connection of 180 to 188, the enolization / alkylation chemistry of the bicyclic system was investigated using readily available allyl bromide as the electrophile. We felt that it was advisable to ascertain the feasibility of the alkylation

Figure 59

\[
\begin{align*}
&\text{181} \quad \xrightarrow{\text{a}} \quad \text{182} \quad \xrightarrow{\text{b}} \quad \text{183} \\
&\quad \xrightarrow{\text{c}} \quad \text{184} \quad \xrightarrow{\text{d}} \quad \text{185} \\
&\text{186} \quad \xrightarrow{\text{f}} \quad \text{187} \quad \xrightarrow{\text{g}} \quad \text{188}
\end{align*}
\]

\text{a. CH(O\text{Me})_3, CSA; b. MeI, LDA, THF, -78 °C; c. DIBAL, THF, -78 °C; d. BnBr, NaH,}
\text{THF, reflux; e. 5% \text{SeO}_2 (supported on silica gel), \text{t-BuOOH, CH}_2\text{Cl}_2, r.t.; f. NaBH}_4, \text{EtOH,}
\text{0 °C to r.t.; g. FBr}_3, \text{Et}_2\text{O, 0 °C (20% from acid-pure)}}

step, before committing 188 to the reaction, because of the aforementioned potential
difficulties with the enolization of \(\alpha\)-alkoxyketones toward the oxygen substituent.\(^\text{59}\) In
retrospect, this was a wise decision.

Treatment of 180 with LDA under standard enolate-forming conditions provided a
multitude of products, among which aldol dimers of 180 as well as the product of carbonyl
reduction were apparent, but virtually no allylated product was discernible. We note that
reduction of non-enolizable, or of difficultly enolizable, ketones by LDA is documented in
the work of Kowalski.\(^\text{65}\) No such reduction products seemed to form during enolization
experiments conducted with lithium bis-trimethylsilyl amide (LiHMDS), the next logical
choice of base, but aldol dimerization consumed virtually all of the substrate. Seemingly,

\(^{65}\)
the desired enolate formed unusually slowly, allowing self condensation of 180 to effectively compete with its deprotonation.

The foregoing observations are in accord with results obtained by Linderman with similar systems.\textsuperscript{66} Linderman went on to devise a moderately successful protocol for intercepting the desired enolate, prepared with LiHMDS, with N-chlorosuccinimide (NCS), resulting in $\alpha$-chlorination of the ketone. Our system, however, resisted all such attempts, either by refusing to react or, under more forcing conditions, by furnishing intractable mixtures of products.

Theoretically, the troublesome properties of 180 could be circumvented by the use of the Corey-Gross protocol for \textit{in situ} trapping of an enolate with TMSCl.\textsuperscript{67} However, 180 underwent no reaction under standard Corey-Gross conditions (-78 °C). A temperature increase to -40 °C resulted indeed in a reaction, but instead of the silyl enol ether, the product was alcohol 192 (Figure 60): reduction by the LDA was now the almost exclusive event. Base switch to LiHMDS gave similarly disappointing results, none of the desired material being evident in crude spectra of the various reaction mixtures.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure60.png}
\caption{Figure 60}
\end{figure}


A similar logic envisaged *in situ* trapping of the desired furanone enolate with a group that would stabilize the anion 189, thus making the enolate thermodynamically favored. A phenylthio group seemed to be an ideal choice, as it could also be used as a handle for the critical spirocyclization reaction. Reaction of 189 with PhS-SPh under the influence of alkoxides gave only complex mixtures containing the now familiar aldol dimers, but the synthetic attractiveness of a sulfonyl intermediate induced us to briefly explore an alternative way of putting that group in place. It was hoped that phenylsulfonylation of the vinyl ether unit in methanol would afford compound 193 (Figure 61), which could in principle advance to furanone ketal 196 via Pummerer reaction. The ene product of *p*-nitrobenzaldehyde was used to examine this new possibility. Phenylsulfonylation occurred normally and proceeded with *in situ* deprotection to give 193. Likewise, oxidation to the sulfoxide was uneventful, but all subsequent attempts to form furan 196 under Pummerer reaction conditions met with failure. We were able indeed to isolate small amounts of lactol 195 from these reactions, but the refusal of 195 to form the desired sulfonyl derivative 196 under various
conditions, including Volante's efficient thiol formation chemistry,\textsuperscript{68} simply added insult to injury.

Activation of the $\alpha$ position with alternate functional groups was also attempted. Attempted condensations of the bicyclic system with ethyl formate, diethyl carbonate, or diethyl oxalate, using $t$-BuOK or NaOEt as base, gave results that were inconclusive.

Parallel studies focused on our aldol strategy. We were pleased to observe that benzaldehyde condensed efficiently with the furanone at the desired position, using 20\% NaOH in THF, to provide enone 197 cleanly and in high yield. By contrast, the use of LDA as the base for this aldol condensation resulted in complex mixtures containing some alcohol 198 (Figure 62).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure62.png}
\caption{Figure 62}
\end{figure}

The success of the condensation reaction suggested that an appropriately substituted aldehyde could well introduce all the requisite functionality for spiroketal formation. This directed us to prepare aldehyde 203 as a plausible carrier of the necessary functionality. This substance was obtained starting with diethyl oxalopropionate, readily available by an \textit{Organic Syntheses} procedure (Figure 63).\textsuperscript{69} The ketone in 199 was protected as dithiane 200, LAH reduction of which provided diol 201. The newly formed hydroxyl group $\alpha$ to the dithiane is poorly nucleophilic due to steric interactions and inductive

effects, allowing for facile selective protection at the other OH as silyl ether 202. Finally, aldehyde 203 was formed by Swern oxidation.

**Figure 63**

a. NaOEt, Et₂O, reflux (80%); b. 1,3-propanediol, BF₃·OEt₂, CH₂Cl₂, r.t. (93%); c. LAH, Et₂O, 0 °C to r.t. (83%); d. thexyldimethylsilyl chloride, TEA, DMAP, CH₂Cl₂ (81%); e. (COCl)₂, DMSO, TEA, CH₂Cl₂, -78 °C (88%)

The critical condensation between the bicyclic core and this aldehyde was attempted using the same procedure that had proved successful in the reaction with benzaldehyde (20% NaOH). However, we witnessed only rapid decarbonylation of the aldehyde to dithiane 206 (Figure 64), and no product formation. The bicyclic system remained intact.

Decarbonylation seems possible because an intermediate 204, formed through addition of a nucleophile (HO⁻ or enolate) to the aldehyde, can fragment with expulsion of a relatively stabilized dithiane anion, 205. Therefore, we synthesized a new form of the requisite aldehyde as the dimethyl ketal, 207, expecting that oxygen substitution would
destabilize the hypothetical anion, suppressing fragmentation. Unfortunately, a new set of problems surfaced with this substrate. The aldol condensation between 180 and 207 afforded mostly dimers of the bicyclic ketone and other poorly characterized byproducts, but only small amounts of alcohol 208 (Figure 65). Changes in base (tBuOK, NaOEt) and temperature only reinforced the conclusion that, in contrast to the case of aromatic aldehydes, the condensation of 180 with aliphatic aldehydes was low-yielding. Some consolation derived from an NMR experiment, wherein spiroketalization of 208 was attempted by treatment with trifluoroacetic acid and trifluoroacetic anhydride. A new product thus formed generated NMR signals consistent with structure 209. In particular,
chemical shifts and coupling constants for the protons present on C(9) matched those of a similar compound synthesized by Smith.55

These setbacks forced us to once again modify our strategy for side chain introduction. We surmised that an aromatic aldehyde that could act as a precursor to the spiroketal may be merged with 180. Inspired by the work of Curran,70 Kozikowski,71 and Kobayashi,72 we decided to explore the use of 214 (Figure 66), wherein the isoxazole unit could fulfill our various requirements. As an aromatic aldehyde, 219 (Figure 67) should condense well with 180. Subsequent reductive cleavage of the isoxazole with Mo(CO)6 would reveal functionality that is fully serviceable for spirocyclization, as evident from the new retrosynthetic plan of Figure 66.

---

Interestingly, isoxazole-5-carboxaldehydes appear to be unknown in the literature. Even so, the synthesis of 219 was straightforward (Figure 67). Potassium tert-butoxide-promoted condensation between acetophenone and ethyl diethoxyacetate afforded diketone 215 cleanly and in quantitative yield. When treated with hydroxylamine hydrochloride under neutral conditions the diketone reacted to give a variable mixture of isoxazole

Figure 67

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_2\text{CH}_2\text{CHO} \quad \text{EtO} \quad \text{OEt} \quad \text{EtO} \quad \text{OEt} \quad \text{EtO} \quad \text{OEt} \\
\text{Ph} & \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\end{align*}
\]

\[\text{a. } \text{t-BuOK, THF, 0 °C (100%); b. NH}_2\text{OHHCl, aq. NaHCO}_3, \text{MeOH (99%); c. TFA, CH}_2\text{Cl}_2 (48\% \text{ pure); d. } 80\% \text{ AcOH, reflux (95%)}}\]

precursor 216 and its regioisomer 217. Although the two isoxazolinols were separable by chromatography, this operation was best postponed to the next step. Upon treatment of the mixture of 216 and 217 with trifluoroacetic acid in CH$_2$Cl$_2$, only 216 underwent dehydration to the desired isoxazole acetal 218. Separation of the isoxazole from the isoxazolinol was then more easily carried out. Finally, the aldehyde was unveiled by acetal hydrolysis in refluxing 80% AcOH for several hours.

The critical connection of the isoxazole aldehyde with the bicyclic system was a complete success. The aldol reaction, promoted by 20% NaOH in EtOH, finished in less than half an hour, providing enone 220 in quantitative yield (Figure 68). Isoxazole degradation could theoretically be carried out at the stage of either 220 or 222, the latter
compound arising through hydration of the vinyl ether subunit of 220. It was quickly determined that 220 was not a good substrate for isoxazole cleavage, attempts at which produced only complex mixtures under standard conditions (Mo(CO)₆, wet CH₃CN, heat). Conceivably, the initially formed β-diketone could have participated in conjugate addition reactions with the surviving enone system, resulting in polymerization of the primary product.

Figure 68

![Chemical structures](image)

Our next efforts focused, therefore, on the acid hydrolysis of the enone/vinyl ether system. Unexpectedly, 3(2H)-furanone 227 was cleanly and quantitatively obtained as the exclusive product upon treatment of 220 with aqueous acid (Figure 69). This rearrangement may be rationalized as proceeding through protonation of the vinyl ether to give oxonium ion 225. Seemingly, capture by water or methanol present in the medium occurs reversibly, allowing equilibration of ion 225 with enol 226. Deprotonation leads to a 3-furanol, which rapidly decays to the final furanone. Alternatively, oxonium ion 225 may be so strongly destabilized by the neighboring carbonyl and electron-deficient isoxazole ring that its formation becomes possible only after acid-promoted enol formation.
It is worthy of note that aldol condensation and rearrangement could even be carried out in a single pot simply by acidifying the reaction mixture (4N HCl) after the condensation has completed and refluxing for approximately one hour. Moreover, reductive opening of the isoxazole in 227 successfully yielded 228.

The unanticipated rearrangement had lowered the oxidation state of C(8) below that of the desired spiroketal, formation of which requires a hydroxyl group at that site. In order to reoxidize this position, we planned to employ a widely used approach for the α-
hydroxylation of ketones: the Rubottom reaction. However, upon completion of this reaction we would still have two olefins in the molecule: the vinyl group, which would later form the methyl ester, and the olefin at the ring fusion. Anticipated difficulties with differentiation of the two alkenes would disappear if the vinyl group were to be oxidized prior to attachment of the isoxazole moiety. The necessary oxidation, already documented in the Collum synthesis of phyllanthocin, occurred smoothly under Katsuki-Sharpless conditions (Figure 70). The free carboxylic acid 229 proved to be an excellent substrate for the one-pot aldol condensation/rearrangement reaction, giving furanone 230 in quantitative yield. The acid was then esterified using ethereal diazomethane. Treatment of the resulting furanone 231 with TBDMS triflate in triethylamine (TEA) afforded us with siloxy furan 232. The Rubottom procedure was completed by oxidizing with m-chloro-

![Figure 70]

229

230 $R = H$

231 $R = Me$

232

233

a. RuCl$_3$(H$_2$O)$_n$, KIO$_4$, CH$_3$CN/H$_2$O, r.t. (56%); b. 219, 20% NaOH, EtOH; 1N HCl reflux (100%); c. CH$_2$N$_2$, Et$_2$O, 0 °C (82%); d. TBDMSOTf, TEA, r.t. (97%); e. mCPBA, hexane, CHCl$_3$, 0 °C to r.t.; 1N HCl

---

peroxybenzoic acid (mCPBA) to provide the α-hydroxy compound 233. This oxidation is the last successful step of our strategy that has been completed in the laboratory.

The last remaining subgoal of our synthetic plan is the preparation of the spiroketal. In order to carry out the key cyclization, the isoxazole must first be opened. Reductive ring cleavage using Mo(CO)₆ will give β-aminoenone 234 (Figure 71). This system can be easily alkylated either with formaldehyde or Eschenmoser’s salt. Reaction with Eschenmoser’s salt would most likely result in methylenation of the diketone-type system. The spiroketalization could then occur in a Michael mode to give spiroketal compound 237. The hydroxymethylation with formaldehyde would give either the same enedione compound as the Eschenmoser’s salt, or the dialkylated compound, 236. Treatment of the dialkylated compound with acid would afford cyclized compound 237.

Figure 71

After formation of the spiroketal is complete, only a few cosmetic changes would be required. Removal of the benzoyl group on the spiroketal could be carried out such that enone system 238 would be provided (Figure 72). Catalytic hydrogenation followed by
epimerization of the methyl group and the methyl ester would afford compound 239. Upon formation of this intermediate, our synthesis converges with the Martin and Williams syntheses and would therefore represent a formal total synthesis of phyllanthocin.

However, we became fully conscious that the various obstacles marring this strategy, and the various detours imposed upon us as a consequence, greatly detract from the elegance of the original plan. In particular, the use of the isoxazole as our spiroketal precursor requires many extra steps for proper functionalization and removal, yet it is mandated by our inability to alkylate the bicyclic system cleanly and in high yield with aliphatic aldehydes. As the latter problem appears to have no easy solution, a very significant change must be made in the synthetic plan. The unalkylated bicyclic system cannot be used as an intermediate. Also, the furan formation step must afford a furanone that already contains functionality α to the carbonyl.

A solution that promises to effectively deal with the foregoing difficulties has recently emerged thanks to a newly found protocol to convert ene adducts into aldehydes of the type 241 through methanolic MCPBA oxidation of the vinyl ether to α-hydroxy ketal 240, followed by Swern oxidation. This new development further highlights the capabilities of the ene reaction, but it results in a different mode of furanone formation (Figure 73). The vinyl ether unit in 167 is stable to bases and reductants; therefore it should remain unaffected during advancement of the lactone moiety to 240 as described

74 This transformation has been studied by our colleague, Kirsten F. Dilzer, and it is thoroughly detailed in her Master's Dissertation, Rice University, 1995.
previously. Substituents “P” in 240 are acid-labile protecting groups. Oxidation of 240 to 241 and delivery of a nucleophilic form of the side chain to the aldehyde would be followed by oxidation to diketone 243. Acidic treatment should afford spiroketal 244. The final six-membered ring would be introduced as demonstrated earlier.

This method would result in a particularly concise route to phyllanthocin, as it affords tricyclic compound 244 in just 11 steps from the lactone aldehyde, 148, while retaining all the desirable features of our earlier plan; including the possibility of an enantioselective synthesis. Investigations of this new strategy are actively being pursued in our laboratory.
APPENDICES
EXPERIMENTAL
Experimental Index

Synthesis of the ene products and their derivatives

General procedures 84
Synthesis of benzaldehyde ene product 25a 86
Synthesis of o-nitrobenzaldehyde ene product 25b 89
Synthesis of o-azidobenzaldehyde ene product 25d 92
Synthesis of p-nitrobenzaldehyde ene product 25e 95
Synthesis of 5-methyl-2-furfural ene product 25f 98
Synthesis of cinnamaldehyde ene product 25g 101
Synthesis of butyraldehyde ene product 25h 104
Synthesis of cyclohexanecarboxaldehyde ene product 25i 107
Synthesis of pyran carboxaldehyde ene product 27/28 110
Synthesis of β-hydroxy ketone 29/30 113
Synthesis of ene product 34/35 116
Synthesis of β-hydroxy ketone 36/37 119
Synthesis of ene product 40 122
Synthesis of enone 41 124
Synthesis of β-hydroxy ketone 48 127
Synthesis of β-hydroxy ester 49 130
Synthesis of β-hydroxy ketone 50 133
Synthesis of β-hydroxy ester 51 136
Synthesis of β-hydroxy ketone 52 139
Synthesis of β-hydroxy ester 53 142
Synthesis of β-hydroxy ester 54 145
Synthesis of β-hydroxy ester 55 148
Synthesis of β-hydroxy ester 56 151
Synthesis of α-bromo ketal 57 154
Synthesis of α-bromo ketone 58 156
Synthesis of α-bromo ketal 59 159
Synthesis of α-bromo ketone 60 162
Synthesis of bromo alcohol 61 165
Synthesis of furan ketal 62 168
Synthesis of furanone 63 171
Synthesis of bromo alcohol 64 174
Synthesis of furan ketal 65 177
Synthesis of furanone 66 180
Synthesis of \( \alpha \)-bromo ketal 67 183
Synthesis of cyclopentane 68 186
Synthesis of cyclopentenone 69 189
Synthesis of triazole 76 192
Synthesis of azepinone 77 195

Synthesis of Phyllanthocin

Synthesis of lactone aldehyde 148 198
Synthesis of ene product 167 201
Synthesis of bromo alcohol 168 204
Synthesis of furanone lactone 169 207
Synthesis of neopentyl ketal 174 210
Synthesis of lactol 175 213
Synthesis of alcohol 176 216
Synthesis of mesylate 177 219
Synthesis of iodide 178 222
Synthesis of furanone 179 225
Synthesis of bicyclic 180 228
Synthesis of \( \beta \)-diketone 215 231
Synthesis of isoxazolinol 216 234
Synthesis of isoxazole acetal 218 237
Synthesis of isoxazole carboxaldehyde 219 240
Synthesis of acid 229 243
Synthesis of furanone 230 246
Synthesis of ester 231 248
Synthesis of siloxy furan 232 251
Synthesis of \( \alpha \)-hydroxy ketone 233 254
TECHNICAL NOTES

Melting points (mp.), determined on a Fisher-Johns 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, c. m = complex multiplet.

Mass spectra (MS) were obtained on a Finnigan 3300 quadrupole mass spectrometer at 70 eV, using direct probe insertion at temperatures of 100-300 °C. High resolution mass spectra (HRMS) were obtained under similar conditions using a Finnigan MAT95. I would like to thank Dr. Terry Marriott and Mr. Frank Roschangar for helping greatly with the HRMS analysis.

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 grade and were used as supplied with the following exceptions:

- Dichloromethane distilled over calcium hydride
- Tetrahydrofuran distilled from sodium benzophenone ketyl
- Ethyl acetate distilled
Methanol  
distilled form magnesium/I₂ solution

2-Methoxypropene  
distilled

All moisture or oxygen sensitive reaction were conducted under an argon atmosphere.
General procedures used in the ene reactions

Procedure A (used with non-enolizable aldehydes):

A solution of the aldehyde (1 equivalent), Yb(fod)_3 catalyst (0.5 mol %), acetic acid (0.5 mol %), and silica gel (Merck 60-230 mesh, 1000% w/w vs Yb(fod)_3) in 20 molar equivalents of vinyl ether was stirred at room temperature. Upon completion (6-72 hrs, followed by TLC and / or NMR), the crude reaction mixture was poured into saturated aqueous NaHCO_3 solution and extracted with methylene chloride. Evaporation yielded the crude product.

Procedure B (used with enolizable aldehydes):

Procedure A is used with two exceptions. First, the vinyl ether is present only in 10 molar equivalents. Second, the aldehyde is introduced as a 10% v/v solution in CH_2Cl_2, present as a co-solvent.

General procedure for the hydrolysis of ene products:

Procedure C:

A round bottom flask is charged with the ene product (1mmol) in a 0.1M solution of CH_2Cl_2 (10ml). A catalytic amount of aqueous 1N HCl (0.5 ml) is then added and the mixture is stirred at room temperature for 5-10 minutes. The crude reaction mixture is neutralized using saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2. Evaporation yields the crude product.
General procedure for the ozonolysis of ene products:

Procedure D:

A dry, three-necked round bottom flask is fitted with a drying tube, an ozone/nitrogen bubbling tube, and a glass stopper. It is then charged with the ene product (one equivalent) in a 0.1M solution of a 4:1 mixture of CH₂Cl₂ and MeOH, respectively. Some solid K₂CO₃ is also added to the reaction mixture. The flask is cooled to -78° C (dry ice / acetone), and ozone is bubbled through the flask until the solution becomes blue. Excess ozone is then purged by bubbling nitrogen through the solution for 10 minutes, followed by the addition of 4 equivalents of dimethyl sulfide and a stir bar. The dry ice bath is removed and the solution is allowed to warm to room temperature while stirring. After approximately one hour, the solution is washed with aqueous saturated sodium bicarbonate and sodium chloride solutions. CH₂Cl₂ extracts are then treated with aqueous 1N HCl to deprotect the unstable MIP protecting group. The crude product is then extracted with CH₂Cl₂ and evaporated down to yield the free β-hydroxy methyl esters.
Synthesis of benzaldehyde ene product 25a

Procedure A using 9.85 mmoles benzaldehyde.

Received 9.87 mmoles product (100%); \( R_f (20\% \text{ EtOAc/hexanes}) \) 0.68.

\( ^1\text{H NMR(C}_6\text{D}_6) \) 7.30-7.19 (c.m, 5H), 4.93 (br. t, 1H, \( J = 6.8 \text{ Hz} \)), 3.80 (d, 1H, B part of AB, \( J = 1.9 \text{ Hz} \)), 3.76 (d, 1H, A part of AB, \( J = 1.9 \text{ Hz} \)), 3.48 (s, 3H), 3.04 (s, 3H), 2.60 (dd, 1H, \( J_1 = 13.7 \text{ Hz}, J_2 = 7.4 \text{ Hz} \)), 2.31 (dd, 1H, \( J_1 = 13.7 \text{ Hz}, J_2 = 6.7 \text{ Hz} \)), 1.37 (s, 3H), 1.11 (s, 3H).

\( ^{13}\text{C NMR(C}_6\text{D}_6) \) 161.0, 144.0, 127.9, 126.7, 126.3, 101.8, 83.1, 71.1, 54.5, 49.0, 45.4, 26.0, 24.9.

IR 3070, 3030, 2984, 2944, 2831, 1656, 1616, 1503, 1450, 1383, 1211, 1144, 1078, 1025, 951, 819, 753, 700.

MS 193 (M$^+$ - MeOC=CH$_2$), 179 (M$^+$ - Me$_2$COMe), 161, 147, 131, 129, 121, 105, 104, 103, 91, 89, 79, 78, 77, 73 (100%), 43.
Benzaldehyde ene product 25a
Benzaldehyde ene product 25a
Synthesis of ortho-nitrobenzaldehyde ene product 25b

Procedure A using 3.512 mmols ortho-nitrobenzaldehyde.

Received 3.587 mmols product (~100%); R_f (20% EtOAc/hexanes) 0.66.

^1H NMR(C6D6) 7.59 (d, 1H, J = 7.9 Hz), 7.43 (d, 1H, J = 8.1 Hz), 7.08 (t, 1H, J = 7.5 Hz), 6.79 (t, 1H, J = 7.4 Hz), 5.94 (t, 1H, J = 6.8 Hz), 3.83 (d, 2H, J = 9.7 Hz), 3.23 (s, 3H), 2.98 (s, 3H), 2.77 (dd, 1H, B part of AB, J1 = 13.6 Hz, J2 = 6.6 Hz) 1.33 (s, 3H), 1.15 (s, 3H).

^13C NMR(C6D6) 160.0, 149.2, 140.1, 132.1, 129.0, 127.5, 123.6, 101.4, 83.6, 66.6, 54.4, 48.9, 45.2, 25.6, 24.8.

IR 2997, 2937, 2831, 1649, 1523, 1350, 1204, 1158, 1071, 1052, 1032, 859.

MS 264 (M+ - OMe), 224, 206, 192, 174, 159, 152, 130, 89, 73 (100%).

HRMS expected 296.1498 (M+ + H); observed 296.1507
o-Nitrobenzaldehyde ene product 25b
o-Nitrobenzaldehyde ene product 25b
Synthesis of ortho-azidobenzaldehyde ene product 25d

Procedure A using 10.556 mmoles ortho-azidobenzaldehyde.

Received 3.2328g product (100%); Rf (20% EtOAc/hexanes) 0.68.

$$\begin{array}{c}
\text{OMe} \\
\text{O} \\
\text{OMe} \\
\text{N}_3 \\
\text{25d}
\end{array}$$

$^1$H NMR(C$_6$D$_6$) 7.50 (app. dd, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 7.26 (app. dt, 1H, $J_1 = 7.2$ Hz, $J_2 = 1.5$ Hz), 7.15-7.07 (c. m, 2H), 5.24 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 5.6$ Hz), 3.85 (d, 1H, B part of AB, $J = 1.8$ Hz), 3.82 (d, 1H, A part of AB, $J = 1.8$ Hz), 3.50 (s, 3H), 3.07 (s, 3H), 2.47 (dd, 1H, B part of AB, $J_1 = 13.8$ Hz, $J_2 = 7.8$ Hz), 2.32 (dd, 1H, A part of AB, $J_1 = 13.8$ Hz, $J_2 = 5.6$ Hz), 1.36 (s, 3H), 1.08 (s, 3H).

$^{13}$C NMR(C$_6$D$_6$) 160.7, 137.4, 136.5, 128.3, 128.2, 124.9, 117.9, 101.0, 83.1, 65.7, 54.3, 48.9, 45.0, 26.0, 25.0.

IR 2997, 2944, 2831, 2134, 1582, 1489, 1450, 1376, 1303, 1204, 1184, 1144, 1071, 1044, 753.

MS 220 (M+ - CH$_2$=C(OMe)CH$_2$), 174, 160, 148, 130, 89, 73 (100%).

HRMS expected 274.1556 (M+ - OH); observed 274.1556
o-Azidobenzaldehyde ene product 25d
O-Azidobenzaldehyde ene product 25d

MVD - 26d
Subtraction Result 01 May 92 11:57:88

[Graph showing infrared spectrum with wave number (cm⁻¹) on the x-axis and intensity on the y-axis]

92114S . MVD 26d
μ 4

[Graph showing Raman spectrum with wave number (cm⁻¹) on the x-axis and intensity on the y-axis]
Synthesis of para-nitrobenzaldehyde ene product 25e

Procedure A using 3.055 mmoles para-nitrobenzaldehyde.

Received 3.137 mmoles product (~100%); Rf (20% EtOAc/hexanes) 0.63.

$^1$H NMR(C$_6$D$_6$) 8.18 (app. d, 2H, J = 8 Hz), 7.46 (app. d, 2H, J = 8 Hz), 5.01 (t, 1H, J = 7.1 Hz), 3.68 (br. s, 1H), 3.10 (s, 3H), 2.90 (s, 3H), 2.61 (dd, 1H, J$_1$ = 13.6 Hz, J$_2$ = 6.8 Hz), 2.22 (dd, 1H, J$_1$ = 13.6 Hz, J$_2$ = 7.4 Hz), 1.27 (s, 3H), 1.00 (s, 3H).

$^{13}$C NMR(C$_6$D$_6$) 157.7, 150.4, 145.2, 125.1 (X2), 121.4 (X2), 99.3, 81.9, 68.3, 52.3, 47.0, 43.4, 24.2, 22.9.

IR 2997, 2944, 2831, 1662, 1603, 1523, 1450, 1350, 1211, 1144, 1085, 1038, 859.

MS 295 (M$^+$), 224 (M$^+$ - MeOCH=CH$_2$), 206 (100%), 174, 152, 128, 115, 104, 74, 73 (100%), 72.

HRMS(Cl) expected 296.1498; observed 296.1479
p-Nitrobenzaldehyde ene product
p-Nitrobenzaldehyde ene product 25e
Synthesis of 5-Methyl-2-furfural ene product 25f

Procedure A using 5.032 mmoles 5-methyl-2-furfural.

Received 5.21 mmoles product (~100%); Rf (20% EtOAc/hexanes) 0.65.

$^1$H NMR(C$_6$D$_6$) 6.05 (d, 1H, $J = 3.0$ Hz), 5.75 (m, 1H, $J = 1.0$ Hz), 4.91 (t, 1H, $J = 7.3$ Hz), 3.96 (d, 1H, $J = 1.8$ Hz), 3.78 (d, 1H, $J = 1.9$ Hz), 3.17 (c.m, 1H, B part of AB), 3.13 (s, 3H), 3.08 (s, 3H), 2.86 (dd, 1H, A part of AB, $J_1 = 7.6$ Hz, $J_2 = 2.9$ Hz), 2.00 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H).

$^{13}$C NMR(C$_6$D$_6$) 160.7, 155.2, 150.9, 107.7, 106.2, 101.2, 83.1, 65.1, 54.3, 49.0, 42.5, 25.6, 25.2, 13.4.

IR 2991, 2938, 2825, 1656, 1609, 1563, 1450, 1377, 1304, 1211, 1178, 1072, 1012, 793.

MS 254 (M$^+$), 183, 165, 151, 133, 125, 109, 108, 107, 105, 74, 73 (100%), 43.
5-Methyl-2-furfural ene product 25f
5-Methyl-2-furfural ene product 25f

[Graph showing infrared spectrum with wavenumber and absorbance axes]

950702 MVD FURFURAL

[Graph showing UV spectrum with wavelength axes]
Synthesis of cinnamaldehyde ene product 25g

Procedure A using 7.94 mmol cinnamaldehyde.

Received 8.55 mmol product (>100%); Rf (20% EtOAc/hexanes) 0.65.

$^1$H NMR(C$_6$D$_6$) 7.42-7.18 (c. m, 5H), 6.50 (d, 1H, $J = 16.0$ Hz), 6.21 (dd, 1H, $J_1 = 16.0$ Hz, $J_2 = 7.3$ Hz), 4.61 (ddd tending to a q, 1H, $J_1 = 7.6$ Hz, $J_2 = 7.3$ Hz, $J_3 = 7.3$ Hz), 3.94 (d, 1H, B part of AB, $J = 1.9$ Hz), 3.92 (d, 1H, A part of AB, $J = 1.9$ Hz), 3.52 (s, 3H), 3.22 (s, 3H), 2.55 (dd, 1H, B part of AB, $J_1 = 13.7$ Hz, $J_2 = 6.45$ Hz), 2.31 (dd, 1H, A part of AB, $J_1 = 13.7$ Hz, $J_2 = 7.6$ Hz), 1.41 (s, 3H), 1.37 (s, 3H).

$^{13}$C NMR(C$_6$D$_6$) 160.2, 137.1, 132.0, 129.0, 128.6, 127.1, 126.1, 100.9, 83.1, 69.8, 54.5, 49.2, 43.1, 25.6, 25.1.

IR 2991, 2944, 2831, 1656, 1622, 1603, 1496, 1450, 1370, 1204, 1184, 1025, 958, 812, 746, 693.

MS 244 (M$^+$ + H$^+$), 254 (M$^+$), 183, 165, 151, 133, 125, 109, 108, 107, 105, 74, 73 (100%), 43.
Cinnamaldehyde ene product 25g
Cinnamaldehyde ene product 25g
Synthesis of butyraldehyde ene product 25h

Procedure B using 45.0 mmoles butyraldehyde.

Received 9.7909 g product (100%); Rf (30% EtOAc/hexanes) 0.63.

\(^1\)H NMR (C\(_6\)D\(_6\)) 4.25 (m, 1H), 3.95 (d, 1H, J = 1.2 Hz), 3.80 (d, 1H, J = 1.5 Hz), 3.20 (s, 3H), 3.15 (s, 3H), 2.6 (dd, 1H, B part of AB, J\(_1\) = 13.7 Hz, J\(_2\) = 5.4 Hz), 2.3 (dd, 1H, A part of AB, J\(_1\) = 13.7 Hz, J\(_2\) = 8.2 Hz), 1.6 (m, 2H), 1.45 (m, 2H), 1.3 (s, 6H), 0.90 (t, 3H, J = 7.2 Hz).

\(^13\)C NMR (C\(_6\)D\(_6\)) 162.7, 101.1, 82.8, 69.6, 54.7, 49.3, 42.3, 38.0, 25.9, 25.8, 18.7, 15.0.

IR 3502, 3123, 2997, 2964, 2878, 2831, 1656, 1463, 1377, 1317, 1271, 1211, 1158, 1072, 1025, 806.

MS 127 (M\(^+\) - OC(OMe)Me\(_2\)), 84, 73 (100%).
Butyraldehyde ene product 25h
Synthesis of cyclohexanecarboxaldehyde ene product 25i

Procedure B using 1.65 mmols cyclohexanecarboxaldehyde.

Received 2.20 mmols product (>100%).

$^{1}H$ NMR($C_{6}D_{6}$) 4.09 (m, 1H, $J_{1} = J_{2} = 6.8$ Hz, $J_{3} = 2.8$ Hz), 4.01 (d, 1H, $J = 1.7$ Hz), 3.86 (d, 1H, $J = 1.7$ Hz), 3.28-3.03 (c. m, 1H), 3.19 (s, 3H), 3.14 (s, 3H), 2.61 (dd, 1H, B part of AB, $J_{1} = 13.8$ Hz, $J_{2} = 6.4$ Hz), 2.42 (dd, 1H, A part of AB, $J_{1} = 13.8$ Hz, $J_{2} = 6.9$ Hz), 1.90-1.50 (c. m, 5H), 1.40-1.00 (c. m, 5H), 1.33 (s, 3H), 1.31 (s, 3H).

$^{13}C$ NMR($C_{6}D_{6}$) 162.5, 100.8, 82.4, 73.5, 73.5, 54.3, 48.9, 42.3, 38.4, 29.2, 28.0, 27.2, 27.1, 26.0, 25.4, 25.2.

IR 2991, 2938, 2851, 1656, 1450, 1377, 1204, 1151, 1072, 1031, 799.

MS 225 (M+ - OMe), 209, 162, 155, 115, 89, 73 (100%), 43.

HRMS expected 257.2117 (M+ + 1); observed 257.2117
Cyclohexanecarboxaldehyde ene product 25i
Cyclohexanecarboxaldehyde ene product 25i

Hiacat 800 02 Jun 92 02:48:03

Wavenumber (cm⁻¹)

MVD CYCLOHEX ENE

>100 x 3
Synthesis of pyran carboxaldehyde ene product 27/28

Procedure B using 6.36 mmoles pyran carboxaldehyde.

Received 5.38 mmoles product (85%).

3 : 1 Mixture of diastereomers

\(^1\)H NMR  
Major & minor: 4.35 (c.m, 1 + 1H), 4.15 (d, 1H, minor, J = 1.4 Hz), 4.08 (d, 1H, major, J = 1.6 Hz), 3.93 (d, 1H, minor, J = 1.5 Hz), 3.90 (d, 1H, J = 1.6 Hz), 3.60 (c.m, 1 + 1H), 3.3 (s, 3H, major), 3.24 (s, 3H, minor), 3.22 (s, 3H, major), 3.17 (s, 3H, minor), 2.95 (dd, 1H, A part of AB, minor, J\(_1\) = 13.7 Hz, J\(_2\) = 4.8 Hz), 2.76 (dd, 1H, A part of AB, major, J\(_1\) = 14.2 Hz, J\(_2\) = 6.2 Hz), 2.55 (dd, 1H, B part of AB, major, J\(_1\) = 14.2 Hz, J\(_2\) = 7 Hz), 2.52 (dd, 1H, B part of AB, minor, J\(_1\) = 13.7 Hz, J\(_2\) = 7.5 Hz), 1.8-1.0 (c.m, 8H), 1.47 (s, 3H, major), 1.43 (s, 3H, major), 1.39 (s, 3H, minor), 1.37 (s, 3H, minor).

\(^{13}\)C NMR  
161.4, 100.9, 82.6, 79.9, 71.7, 68.5, 54.5, 49.2, 36.9, 26.8, 26.2, 25.2, 25.0, 23.6.

IR  
2988, 2943, 2846, 1654, 1448, 1377, 1299, 1261, 1203, 1151, 1087, 1048, 900, 803.

MS  
186 (M+ - OC(OMe)Me\(_2\)), 169, 137, 85, 73 (100%), 72, 55, 43.
Pyran carboxaldehyde ene product 27/28
Pyran carboxaldehyde ene product 27/28
Synthesis of β-hydroxy ketone 29/30

Procedure C using 0.79 mmoles pyran carboxaldehyde ene product 27/28.

Received 0.78 mmoles product (99%); Rf (20% EtOAc/hexanes) 0.35.

3:1 Mixture of ketols

$^1$H NMR  
Major and minor: 3.93 (c. m, 2 + 2H), 3.40 (c. m, 1 + 1H), 3.22 (ddd, 1H, major, $J_1 = 11.7$ Hz, $J_2 = 5.6$ Hz, $J_3 = 2.2$ Hz, CHO), 3.18 (c. m. overlapping with the signal at 3.22, 1H, minor, CHO), 3.09 (d, 1H, major, $J = 4.5$ Hz, CHO), 2.95 (d, 1H, minor, $J = 4.3$ Hz, CHO), 2.75-2.51 (c. AB m, 2 + 2H), 2.20 (s, 3H, minor), 2.19 (s, 3H, major), 2.0-1.1 (c. m, 8 + 8H).

$^{13}$C NMR  
209.7, 79.6, 70.4, 68.5, 45.6, 30.7, 27.3, 26.0, 22.9.

IR  
3442, 2938, 2851, 1709, 1430, 1364, 1284, 1204, 1171, 1091, 1045, 892.

MS  
173 (M$^+$ + 1), 154 (M$^+$ - H$_2$O), 114, 111, 85 (100%), 67, 57, 43.

HRMS  
expected 172.1099; observed 172.1103
$\beta$-hydroxy ketone 29/30
β-hydroxy ketone 29/30

[Diagram of infrared spectrum]

[Diagram of another spectrum]
Synthesis of ene product 34/35

Procedure A using 2.80 mmoles p-nitrobenzaldehyde and 1-methoxycyclohexene as the vinyl ether.

Received 3.19 mmoles product (>100%).

^1H NMR 8.21 (d, 2H, J = 8 Hz), 7.54 (d, 2H, J = 8 Hz), 4.82 (m, 2H), 4.24 (d, 1H, J = 1.3 Hz), 3.65 (s, 3H), 2.50 (q, 1H, J1 = 14.5 Hz, J2 = 8.0 Hz), 2.04 (c.m, 2H), 1.60-1.05 (c.m, 4H).

IR 3449, 2944, 2864, 1696, 1669, 1602, 1516, 1443, 1343, 1204, 1157, 1091, 1045, 852.

MS 296, 278, 263, 246, 239, 191, 151, 112 (100%), 101, 84, 79.
Fm3 product 34/35
Synthesis of β-hydroxy ketone 36/37

Procedure C using 0.56 mmoles ene product 34/35.

Received 0.51 mmoles product (92%).

3:1 Mixture of ketols

1H NMR  
Major and minor: 3.93 (c.m, 2 + 2H), 3.40 (c.m, 1 + 1H), 3.22 (ddd, 1H, major, J₁ = 11.7 Hz, J₂ = 5.6 Hz, J₃ = 2.2 Hz, CHOCH), 3.18 (c.m, overlapping with the signal at 3.22, 1H, minor, CHOCH), 3.09 (d, 1H, major, J = 4.5 Hz, CHOCH), 2.95 (d, 1H, minor, J = 4.3 Hz, CHOCH), 2.75-2.51 (c. ABm, 2 + 2H), 2.20 (s, 3H, minor), 2.19 (s, 3H, major), 2.0-1.1 (c.m, 8 + 8H).

13C NMR  
209.7, 79.6, 70.4, 68.5, 45.6, 30.7, 27.3, 26.0, 22.9.

IR  
3442, 2938, 2851, 1709, 1430, 1364, 1284, 1204, 1171, 1091, 1045, 892.

MS  
173 (M⁺ + 1), 154 (M⁺ - H₂O), 114, 111, 85 (100%), 67, 57, 43, 28.
β-hydroxy ketone 36/37
β-hydroxy ketone 36/37

[Graph of spectral data]

[Graph of another spectral data]
Synthesis of ene product 40

Procedure B using 1.056 mmoles p-nitrobenzaldehyde with 4,5-dihydro-2-methylfuran as the vinyl ether.

Received 1.01 mmoles product (96%); Rf (20% EtOAc/hexanes) 0.52.

$^1$H NMR($\text{C}_5\text{D}_6$) 8.16 (d, 2H, J = 8.8 Hz), 7.46 (d, 2H, J = 8.9 Hz), 5.59 (s, 1H), 4.17 (c.m, 2H), 3.85 (c.m, 2H), 3.46 (c.m, 1H), 2.58 (c.m, 1H), 2.25-1.60 (c.m, 6H), 1.50 (s, 2H), 1.29 (s, 2H).

MS 319 (M+), 260, 235, 218, 217, 128, 115, 86 (100%), 85 (100%), 55, 43.
Enne product 40
Synthesis of enone 41

Procedure C using 0.20 mmoles ene product 40.

Received 0.20 mmoles product (100%); mp. = 97-98 °C.

$^1$H NMR 8.24 (d, 2H, J = 8.8 Hz), 7.67 (d, 2H, J = 8.7 Hz), 7.57 (d, 1H, J = 16.2 Hz), 6.85 (d, 1H, J = 16.2 Hz), 3.71 (t, 2H, J = 6.0 Hz), 2.85 (t, 2H, J = 7.0 Hz), 2.09 (br. s, 1H), 1.95 (t, 2H, J = 6.2 Hz).

$^{13}$C NMR 199.8, 148.5, 140.6, 139.5, 129.4, 128.8 (X2), 124.1 (X2), 62.0, 37.9, 26.6.


MS 235 (M$^+$), 217 (M$^+$ - H$_2$O), 200, 191, 176 (100%), 170, 141, 130, 115, 102, 90, 76.
Enone 41
Synthesis of $\beta$-hydroxy ketone 48

Procedure C using 0.432 mmoles benzaldehyde ene product 25a.

Received 0.0698g product (98%); $R_f$ (20% EtOAc/hexanes) 0.20.

$^1$H NMR 7.23 (c. m, 5H), 5.05 (m, 1H), 3.34 (m, 1H), 2.80 (app. dd, 1H, B part of AB, $J_1 = 17.5$ Hz, $J_2 = 8.7$ Hz), 2.68 (ddd, 1H, A part of AB, $J_1 = 17.4$ Hz, $J_2 = 3.6$ Hz, $J_3 = 1.7$ Hz), 2.08 (s, 3H).

$^{13}$C NMR 208.9, 142.8, 128.4 (X2), 127.6, 125.6 (X2), 69.8, 51.9, 30.7.

IR 3429, 3064, 3030, 2904, 1702, 1364, 1158, 1065, 753, 700.

MS 164 (M$^+$), 146 (M$^+$ - H$_2$O), 131, 107, 105, 91, 79, 77, 58, 51, 43.

HRMS expected 164.0837; observed 164.0835
β-hydroxy ketone 48
β-hydroxy ketone 48
Synthesis of ester 49

Procedure D using 0.420 mmoles bezaldehyde ene product 25a.

Received 0.0937g (89%); Rf (20% EtOAc/hexanes) 0.55.

$^1$H NMR 7.27 (c. m, 5H), 5.13 (app. dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 6.2$ Hz), 3.59 (s, 3H), 2.98 (s, 3H), 2.80 (dd, 1H, B part of AB, $J_1 = 14.6$ Hz, $J_2 = 7.8$ Hz), 2.57 (dd, 1H, A part of AB, $J_1 = 14.6$ Hz, $J_2 = 6.2$ Hz), 1.34 (s, 3H), 1.10 (s, 3H).

$^{13}$C NMR 171.2, 143.8, 128.2 (X2), 127.3, 126.2 (X2), 101.2, 70.3, 51.4, 49.1, 44.5, 25.8, 24.9.

IR 2991, 2951, 2831, 1749, 1457, 1437, 1377, 1257, 1211, 1151, 1078, 1032, 819, 766, 700.

MS 220 (M+ - MeOH), 194, 163, 131, 121, 104, 77, 73 (100%).

HRMS expected 220.1100 (M+ - MeOH); observed 220.1091
Synthesis of β-hydroxy ketone 50

Procedure C using 0.398 mmoles cyclohexanecarboxaldehyde ene product 25i.

Received 0.277 mmoles product (70%); Rf (20% EtOAc/hexanes) 0.27.

$^1$H NMR 3.78 (m, 1H, $J_1 = 8.9$ Hz, $J_2 = 5.8$ Hz, $J_3 = 3.6$ Hz), 2.61 (dd, 1H, B part of AB, $J_1 = 17.7$ Hz, $J_2 = 3.4$ Hz), 2.50 (dd, 1H, A part of AB, $J_1 = 17.7$ Hz, $J_2 = 9.0$ Hz), 2.16 (s, 3H), 1.65 (c. m, 5H), 1.40-0.85 (c. m, 7H).

$^{13}$C NMR 210.3, 71.6, 47.1, 42.9, 30.8, 28.8, 28.2, 26.4, 26.1, 26.0.

IR 3455, 2924, 2851, 1709, 1450, 1357, 1164, 1105, 1058.

MS 87, 85, 51, 49, 47, 43, 37, 35 (100%), 32.

HRMS expected 170.1307; observed 170.1300.
β-hydroxy ketone 50
β-hydroxy ketone 50

Subtraction Result 02 Jun 95 14:37:52

Transmittance

Wavenumber (cm⁻¹)

950000 . MVD HYDROLYSIS

= 1
Synthesis of β-hydroxy ester 51

Procedure D using 0.382 mmole cyclohexanecarboxaldehyde ene product 25i.

Received 0.098g product (100%); Rf (20% EtOAc/hexanes) 0.60.

$^1$H NMR 3.77 (m, 1H), 3.70 (s, 3H), 2.83 (d, 1H, J = 3.7 Hz), 2.53 (dd, 1H, B part of AB, J$_1$ = 16.2 Hz, J$_2$ = 3.2 Hz), 2.41 (dd, 1H, A part of AB, J$_1$ = 16.2 Hz, J$_2$ = 9.2 Hz), 1.90-1.60 (c. m, 5H), 1.45-0.90 (c. m, 6H).

$^{13}$C NMR 173.9, 72.1, 51.7, 43.0, 38.4, 28.7, 28.2, 26.3, 26.1, 26.0.

IR 3489, 2924, 2851, 1736, 1443, 1284, 1164, 1045, 892.

MS 169 (M$^+$ - OH), 168 (M$^+$ - H$_2$O), 136, 103 (100%), 95, 71, 55, 43, 41.

HRMS expected 186.1256; observed 186.1255
$\beta$-hydroxy ester 51
β-hydroxy ester 51
Synthesis of β-hydroxy ketone 52

Procedure C using 0.569 mmole butyraldehyde ene product 25h.

Received 0.0666g product (90%); Rf (20% EtOAc/hexanes) 0.32.

**1H NMR**

4.00 (br. m, 1H), 3.10 (br. s, 1H), 2.57 (dd, 1H, B part of AB, J1 = 17.4 Hz, J2 = 3.6 Hz), 2.47 (dd, 1H, A part of AB, J1 = 17.4 Hz, J2 = 8.3 Hz), 2.13 (s, 3H), 1.50-1.20 (c. m, 4H), 0.87 (t, 3H).

**13C NMR**

209.9, 67.1, 49.9, 38.5, 30.6, 18.5, 13.8.

**IR**

3422, 2964, 2931, 2878, 1709, 1423, 1364, 1171, 1125, 1085, 1025, 992, 846.

**MS**

129 (M+ - 1), 121, 115, 105, 97, 91, 87, 86, 84, 77, 73, 55, 44 (100%), 43, 40.

**HRMS**

expected 115.0759 (M+ - Me); observed 115.0769
β-hydroxy ketone 52
β-hydroxy ketone 52
Synthesis of β-hydroxy ester 53

Procedure D using 0.572 mmoles butyraldehyde ene product 25h.

Received 0.574 mmoles product (100%); Rf (20% EtOAc/hexanes) 0.28.

\[ \text{53} \]

\(^1\)H NMR 3.99 (m, 1H), 3.69 (s, 3H), 2.96 (br. s, 1H), 2.49 (dd, 1H, B part of AB, \( J_1 = 16.3 \text{ Hz} \), \( J_2 = 3.5 \text{ Hz} \)), 2.38 (dd, 1H, A part of AB, \( J_1 = 16.3 \text{ Hz} \), \( J_2 = 8.6 \text{ Hz} \)), 1.55-1.20 (c. m, 4H), 0.91 (t, 3H).

\(^{13}\)C NMR 173.3, 67.5, 51.5, 41.0, 38.5, 18.5, 13.7.

IR 3449, 2957, 2931, 2871, 1736, 1437, 1171, 1025.

MS 145 (M\(^+\) - 1), 129 (M\(^+\) - OH), 115, 113, 105, 103, 97, 84, 74, 73, 71, 69, 61, 55, 43 (100%).

HRMS expected 146.0943; observed 146.0959
β-hydroxy ester 53
β-hydroxy ester 53
Synthesis of β-hydroxy ester 54

Procedure B using 0.681 mmole o-azidobenzaldehyde ene product 25d.

Received 0.654 mmole product (96%); Rf (20% EtOAc/hexanes) 0.28.

**^1H NMR**

7.52 (compl. d, 1H), 7.30 (dt, 1H, J₁ = 7.7 Hz, J₂ = 1.6 Hz), 7.14 (c. m, 2H), 5.29 (dd, 1H, J₁ = 9.3 Hz, J₂ = 2.4 Hz), 3.70 (s, 3H), 2.76 (dd, 1H, B part of AB, J₁ = 16.2 Hz, J₂ = 3.3 Hz), 2.60 (dd, 1H, A part of AB, J₁ = 16.2 Hz, J₂ = 9.3 Hz).

**^13C NMR**

172.6, 136.0, 133.5, 128.6, 126.8, 125.0, 117.8, 65.7, 51.7, 41.6.

**IR**

3469, 2957, 2134, 1735, 1576, 1490, 1443, 1291, 1204, 1164, 1065, 1032, 759.

**MS**

221 (M⁺), 193 (M+ - N₂), 161, 144, 133, 120 (100%), 92, 77, 73, 60.

**HRMS**

expected 221.0800; observed 221.0801
β-hydroxy ester 54
β-hydroxy ester 54
Synthesis of β-hydroxy ester 55

Procedure D using 0.806 mmole o-nitrobenzaldehyde ene product 25b.

Received 0.817 mmole product (100%); Rf (40% EtOAc/hexanes) 0.47.

$^1$H NMR 7.91 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 1.2$ Hz), 7.85 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.3$ Hz), 7.64 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.2$ Hz), 7.41 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.4$ Hz), 5.62 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 2.5$ Hz), 3.90 (br. s, 1H), 3.70 (s, 3H), 2.92 (dd, 1H, B part of AB, $J_1 = 16.6$ Hz, $J_2 = 2.8$ Hz), 2.64 (dd, 1H, A part of AB, $J_1 = 16.6$ Hz, $J_2 = 9.4$ Hz).

$^{13}$C NMR 172.4, 147.2, 138.1, 133.7, 128.3, 128.0, 124.3, 65.8, 51.9, 42.2.

IR 3482, 2957, 1736, 1530, 1443, 1350, 1171, 1065, 1025, 859, 793, 753, 713.

MS 226 (M$^+$ + 1), 207 (M$^+$ - H$_2$O), 177, 162, 152, 148, 135, 134, 121, 104 (100%), 91, 77, 65, 51, 43.

HRMS expected 207.0531 (M$^+$ - H$_2$O); observed 207.0537
\(\beta\)-hydroxy ester 55
β-hydroxy ester 55
Synthesis of β-hydroxy ester 56

Procedure D using 0.757 mmoles p-nitrobenzaldehyde ene product 25e.

Received 0.719 mmoles product (95%); Rf (40% EtOAc/hexanes) 0.41.

$^1$H NMR 8.16 (d, 2H, B part of AB, J = 8.8 Hz), 7.54 (d, 2H, J = 8.8 Hz), 5.21 (t, 1H, J = 6.1 Hz), 3.80 (br. s, 1H), 3.69 (s, 3H), 2.72 (m, 2H).

$^{13}$C NMR 172.2, 149.7, 147.3, 126.4 (X2), 123.6 (X2), 69.2, 52.0, 42.7.

IR 3469, 3117, 3084, 2957, 1729, 1609, 1523, 1437, 1350, 1198, 1171, 1072, 852.

MS 225 (M$^+$), 207 (M$^+$ - H$_2$O), 165, 152, 151, 150, 134, 122, 105, 94, 91, 77, 74 (100%), 51, 43.

HRMS expected 225.0637; observed 225.0637
β-hydroxy ester 56
β-hydroxy ester 56

![Graph 1](image1)

![Graph 2](image2)
Synthesis of α-bromo ketal 57

A 25 ml round bottom flask was charged with 2.0 ml distilled MeOH, N-bromosuccinimide (2.411 mmoles), a small amount of solid K₂CO₃ and 7.0 ml distilled CH₂Cl₂. The flask was cooled to 0° C in an ice water bath. The butyraldehyde ene product 25h (2.165 mmoles) was then added as a solution in 3.0 ml CH₂Cl₂. The mixture was stirred for 30 minutes and the reaction was complete (followed by TLC). The reaction mixture was washed one time each with saturated aqueous solutions of Na₂S₂O₃ and NaHCO₃. The CH₂Cl₂ extracts were then dried and evaporated down to give bromoketal 57 as a colorless oil. 0.6679 g (95%); Rf (20% EtOAc/hexanes) 0.51.

¹H NMR 3.85 (m, 1H, J₁ = 12.0 Hz, J₂ = 8.1 Hz, J₃ = 4.1 Hz), 3.54 (d, 1H, B part of AB, J = 11.2 Hz), 3.42 (dd, 1H, A part of AB, J₁ = 11.2 Hz, J₂ = 1.3 Hz), 3.23 (s, 3H), 3.22 (s, 3H), 3.20 (s, 3H), 2.07 (dd, 1H, B part of AB, J₁ = 15.4 Hz, J₂ = 8.1 Hz), 1.85 (ddd, 1H, J₁ = 15.4 Hz, J₂ = 4.0 Hz, J₃ = 1.2 Hz), 1.70-1.40 (c. m, 4H), 1.39 (s, 3H), 1.35 (s, 3H), 0.91 (t, 3H).

MS 285 (M⁺ - CH₂CH₂CH₃), 249, 247, 245, 239/237, 207/205, 169/167, 153/151, 143, 89, 87, 74 (100%), 73 (100%), 72, 43.
α-bromo ketal 57
Synthesis of α-bromo ketone 58

A 10 ml round bottom flask was charged with α-bromo ketal 57 (0.113 mmoles) and 3.0 ml THF. 0.5 ml aqueous 4N HCl was added and the mixture was stirred at room temperature. After 3 hours, the reaction was found to be complete (followed by TLC). To workup, the solution was washed with saturated aqueous NaCl solution, extracting with EtOAc. The organic extracts were then dried over NaSO₄ and evaporated down to give the crude product as a pale yellow oil. 0.0213 g (91%); Rₕ (20% EtOAc/hexanes) 0.18.

$^1$H NMR 4.15 (s, 2H), 4.12 (br. s, 1H), 2.83-2.15 (c. m, 3H), 1.65-1.25 (c. m, 4H), 0.94 (t, 3H, J = 7Hz).

$^{13}$C NMR 204.0, 67.4, 48.7, 46.5, 38.7, 18.6, 13.9.

IR 3424, 2957, 2931, 2871, 1722, 1463, 1396, 1118, 1065, 1018.

MS 167/165 (M⁺ - CH₂CH₂CH₃), 147, 138, 123/121, 115, 111, 97, 95, 93, 73, 71, 69, 57, 55, 43 (100%).

HRMS (⁷⁹Br) expected 189.9994 (M⁺ - H₂O); observed 189.9992
(⁸¹Br) expected 191.9928 (M⁺ - H₂O); observed 191.9944
α-bromo ketone 58
α-bromo ketone 58
**Synthesis of α-bromo ketal 59**

A 25 ml round bottom flask was charged with 1.0 ml distilled MeOH, N-bromosuccinimide (1.358 mmole), a small amount of solid K₂CO₃ and 3.0 ml distilled CH₂Cl₂. The flask was cooled to 0°C in an ice water bath. The benzaldehyde ene product 25a (1.216 mmole) was then added as a solution in 2.0 ml CH₂Cl₂. The mixture was stirred for 30 minutes and the reaction was complete (followed by TLC). The reaction mixture was washed one time each with saturated aqueous solutions of Na₂S₂O₃ and NaHCO₃. The CH₂Cl₂ extracts were then dried and evaporated down to give bromoketal 59 as a colorless oil. 0.4128 g (94%); Rf (20% EtOAc/hexanes) 0.63.

**¹H NMR**

7.35 (c. m, 5H), 4.76 (t, 1H, J = 6.6 Hz), 3.53 (dd, 1H, B part of AB, J₁ = 11.3 Hz, J₂ = 0.9 Hz), 3.23 (s, 3H), 3.18 (dd, 1H, A part of AB, J₁ = 11.3 Hz, J₂ = 0.7 Hz), 3.07 (s, 3H), 3.02 (s, 3H), 2.39 (ddd, 1H, B part of AB, J₁ = 15.3 Hz, J₂ = 7.0 Hz, J₃ = 0.8 Hz), 2.17 (ddd, 1H, A part of AB, J₁ = 15.3 Hz, J₂ = 6.3 Hz, J₃ = 0.7 Hz), 1.40 (s, 3H), 1.11 (s, 3H).

**¹³C NMR**

144.6, 128.0 (X2), 127.2, 126.9 (X2), 101.2, 100.3, 70.1, 49.3, 48.4, 48.1, 40.1, 32.3, 26.0, 25.0.

**MS**

273/271 (M⁺ - OC(OMe)Me₂), 209, 169/167, 121, 73 (100%), 43.

**HRMS**

expected 360.0936; observed 360.0899.
α-bromo ketal 59
α-bromo ketal 59
Synthesis of α-bromo ketone 60

A 10 ml round bottom flask was charged with α-bromo ketal 59 (0.403 mmoles) and 3.0 ml THF. 1.0 ml aqueous 4N HCl was added and the mixture was stirred at room temperature. After 1 hour, the reaction was found to be complete (followed by TLC). To workup, the solution was washed with saturated aqueous NaCl solution, extracting with EtOAc. The organic extracts were then dried over NaSO₄ and evaporated down to give the crude product as a pale yellow oil. 0.0807 g (83%); Rf (20% EtOAc/hexanes) 0.28.

**1H NMR**
7.32-7.18 (c. m, 5H), 5.06 (dd, 1H, J₁ = 9.1 Hz, J₂ = 3.5 Hz), 3.84 (s, 2H), 3.24 (br. s, 1H), 2.98 (dd, 1H, B part of AB, J₁ = 16.8 Hz, J₂ = 9.1 Hz), 2.85 (dd, 1H, A part of AB, J₁ = 16.8 Hz, J₂ = 3.5 Hz).

**13C NMR**
201.3, 142.4, 128.5, 127.8, 125.5, 70.0, 48.5, 35.0.

**IR**
3437, 3029, 2931, 1721, 1497, 1448, 1391, 1349, 1194, 1068, 1046, 759, 702.

**MS**
163 (M⁺ - Br), 107, 105, 88, 86 (100%), 84, 79, 77, 51.

**HRMS**
expected 243.9923; observed 243.9903
α-bromo ketone 60
α-bromo ketone 60
Synthesis of bromo alcohol 61

A 10 ml round bottom flask was charged with bromo ketal 57 (0.944 mmoles) in 4 ml MeOH. A catalytic amount of camphorsulfonic acid was added and the mixture was stirred at room temperature until complete (30 minutes—followed by TLC). To workup, the reaction mixture was washed twice with saturated aqueous NaHCO₃. The CH₂Cl₂ extracts were the dried over NaSO₄ and evaporated down to give the free secondary alcohol 61 as a colorless oil. 0.2410 g (100%); Rf (20% EtOAc/hexanes) 0.24.

**¹H NMR** 3.82 (c. m, 1H), 3.64 (dd, 1H, B part of AB, J₁ = 11.2 Hz, J₂ = 0.9 Hz), 3.44 (d, 1H, A part of AB, J = 11.2 Hz), 3.28 (s, 3H), 3.25 (s, 3H), 2.88 (d, 1H, J = 2.2 Hz), 1.97 (AB system, 2H), 1.42 (c. m, 4H), 0.93 (br. t, 3H).

**¹³C NMR** 101.6, 67.6, 48.8, 48.5, 40.0, 38.8, 32.6, 18.6, 14.0.

**IR** 3428, 2957, 2871, 2831, 1716, 1463, 1423, 1191, 1085, 1045, 925, 812, 686.

**MS** 195, 177, 169/167, 153, 152, 151, 150, 107/105, 89 (100%), 79, 77, 73, 71, 55, 43, 41, 32.

**HRMS** expected 161.1178 (M⁺ - CH₂Br); observed 161.1199
Bromo alcohol 61
Bromo alcohol 61
**Synthesis of furan ketal 62**

A 50 ml flame-dried round bottom flask was charged with a 60% dispersion of solid NaH (8.02 mmole) using a N₂ glove bag. The mineral oil was removed from the sodium hydride suspension by washing several times with hexanes followed by drying under a stream of argon. 7.0 ml THF was then added and the flask was cooled to 0°C in an ice water bath. Bromo alcohol 61 (0.949 mmole) was added as a solution in 3.0 ml THF to the cold NaH mixture. The mixture was then allowed to warm to room temperature, followed by heating to a gentle reflux for 1 hour. The reaction was followed by TLC and, upon completion, it was quenched with aqueous 1N HCl solution. The crude product was extracted three times with Et₂O. The Et₂O extracts were further washed with a saturated aqueous solution of NaCl. The organic extracts were then dried over NaSO₄ and evaporated to give the crude furan dimethyl ketal 62. 0.1140 g (70%); Rₓ (20% EtOAc/hexanes) 0.58.

**¹H NMR**

3.96 (c. m, 1H), 3.84 (d, 1H, B part of AB, J = 9.3 Hz), 3.67 (d, 1H, A part of AB, J = 9.3 Hz), 3.21 (s, 6H), 2.15 (dd, 1H, B part of AB, J₁ = 12.6 Hz, J₂ = 6.1 Hz), 1.75-1.15 (A part of AB, c. m, 5H), 0.91 (t, 3H, J = 7.1 Hz).

**¹³C NMR**

110.7, 78.7, 72.6, 50.2, 49.7, 41.1, 37.5, 19.1, 14.0.

**IR**

2964, 2931, 2871, 2825, 1463, 1364, 1251, 1151, 1085, 1052, 886, 852.

**MS**

173 (M⁺ - 1), 169, 167, 143, 115, 113, 101 (100%), 88, 55, 43.
Furan ketal 62

HRMS  
expected 174.1255; observed 174.1251
Furan ketal 62
Synthesis of furanone 63

A 10 ml round bottom flask was charged with furan ketal 62 (0.392 mmoles) in 3.0 ml THF. 0.5 ml aqueous 1N HCl was added and the mixture was stirred at room temperature overnight (followed by TLC). To workup, the mixture was washed one time each with saturated aqueous solutions of NaHCO₃ and NaCl. The Et₂O extracts were dried over NaSO₄ and evaporated down to give the crude product. 0.0399 g (80%); Rf (20% EtOAc/hexanes) 0.46.

**1H NMR**

4.24 (m, 1H), 4.04 (d, 1H, B part of AB, J = 16.9 Hz), 3.82 (d, 1H, A part of AB, J = 16.9 Hz), 2.52 (dd, 1H, B part of AB, J₁ = 17.8 Hz, J₂ = 5.9 Hz), 2.15 (ddd, 1H, A part of AB, J₁ = 17.8 Hz, J₂ = 9.4 Hz, J₃ = 1.2 Hz), 1.83-1.30 (c. m, 4H), 0.96 (t, 3H, J = 7.3 Hz).

**13C NMR**

215.3, 78.1, 71.3, 43.0, 37.4, 18.7, 13.9.

**IR**

2964, 2931, 2871, 1762, 1463, 1384, 1164, 1065, 965, 819.

**MS**

128 (M⁺), 86, 84 (100%), 70, 55, 49, 47.

**HRMS**

expected 128.0837; observed 128.0845
Synthesis of bromo alcohol 64

A 50 ml round bottom flask was charged with bromo ketal 59 (0.945 mmoles) in 10 ml MeOH. A catalytic amount of camphorsulfonic acid was added and the mixture was stirred at room temperature until complete (15 minutes—followed by TLC). To workup, the reaction mixture was washed twice with saturated aqueous NaHCO₃. The CH₂Cl₂ extracts were then dried over NaSO₄ and evaporated down to give the free secondary alcohol 64 as a colorless oil. 0.2639 g (96%); Rf (20% EtOAc/hexanes) 0.40.

¹H NMR 7.45-7.20 (c. m, 5H), 4.91 (dd, 1H, J₁ = 9.5 Hz, J₂ = 2.5 Hz), 3.72 (app. dd, 1H, B part of AB, J₁ = 11.2 Hz, J₂ = 0.7 Hz), 3.52 (d, 1H, A part of AB, J = 11.2 Hz), 3.33 (s, 3H), 3.25 (s, 3H), 2.28 (app. ddd, 1H, B part of AB, J₁ = 15.1 Hz, J₂ = 9.6 Hz, J₃ = 0.9 Hz), 2.19 (app. dd, 1H, A part of AB, J₁ = 15.1 Hz, J₂ = 3.1 Hz).

¹³C NMR 144.1, 128.4 (X2), 127.4, 125.5 (X2), 101.3, 70.3, 48.8, 48.6, 41.6, 32.6.

IR 3475, 2944, 2831, 1457, 1423, 1198, 1098, 1045, 700.

MS 195, 172, 169/167, 154/152, 153/151, 107/105, 89, 79, 77 (100%), 61, 43.

HRMS expected 195.1021 (M⁺ - CH₂Br); observed 195.1015.
Bromo alcohol 64
Bromo alcohol 64

![Graph 1](image1)

![Graph 2](image2)
Synthesis of furan ketal 65

A 250 ml flame-dried round bottom flask was charged with a 60% dispersion of solid NaH (13.0 mmole) using a N₂ glove bag. The mineral oil was removed from the sodium hydride suspension by washing several times with hexanes followed by drying under a stream of argon. 40 ml THF was then added and the flask was cooled to 0°C in an ice water bath. Bromo alcohol 64 (2.36 mmole) was added as a solution in 10 ml THF to the cold NaH mixture. The mixture was then allowed to warm to room temperature. The reaction was followed by TLC and, upon completion, it was quenched with saturated aqueous NH₄Cl solution. The crude product was extracted three times with Et₂O. The Et₂O extracts were further washed with saturated aqueous solutions of NaHCO₃ and NaCl. The organic extracts were then dried over NaSO₄ and evaporated to give the crude furan dimethyl ketal 65. 0.4236 g (86%); Rf (20% EtOAc/hexanes) 0.54.

**1H NMR**

7.40-7.26 (c. m, 5H), 5.03 (dd, 1H, J₁ = 9.7 Hz, J₂ = 6.2 Hz), 4.08 (d, 1H, B part of AB, J = 9.5 Hz), 3.92 (d, 1H, A part of AB, J = 9.5 Hz), 3.31 (s, 3H), 3.28 (s, 3H), 2.51 (dd, 1H, J₁ = 12.5 Hz, J₂ = 6.2 Hz), 2.03 (dd, 1H, J₁ = 12.5 Hz, J₂ = 9.7 Hz).

**13C NMR**

141.5, 128.4, 127.6, 125.9, 110.5, 80.3, 73.2, 50.4, 49.7, 43.7.

**IR**

3063, 3037, 2944, 2831, 1496, 1457, 1364, 1251, 1144, 1071, 1045, 759, 700.

**MS**

177 (M⁺ - OCH₃), 121, 105, 77, 73, 71, 57, 55, 51, 43 (100%), 41.

**HRMS**

expected 178.0994 (M⁺ - OCH₂); observed 178.0996
Furan ketal 65
Furan ketal 65
Synthesis of furanone 66

A 5 ml round bottom flask was charged with furan ketal 65 (0.517 mmoles) in 1.0 ml THF. 0.5 ml aqueous 1N HCl was added and the mixture was stirred at room temperature overnight (followed by TLC). To workup, the mixture was washed one time each with saturated aqueous solutions of NaHCO₃ and NaCl. The Et₂O extracts were dried over NaSO₄ and evaporated down to give the crude product. 0.0828 g (95%); Rf (20% EtOAc/hexanes) 0.40.

^1H NMR 7.42-7.33 (c. m, 5H), 5.29 (dd, 1H, Jₑ = 9.5 Hz, J₂ = 6.3 Hz), 4.25 (br. d, 1H, B part of AB, J = 17.0 Hz), 4.01 (d, 1H, A part of AB, J = 17.0 Hz), 2.88 (dd, 1H, B part of AB, J₁ = 17.9 Hz, J₂ = 6.3 Hz), 2.55 (ddd, 1H, A part of AB, J₁ = 17.9 Hz, J₂ = 9.6 Hz, J₃ = 1.1 Hz).

^13C NMR 214.2, 139.9, 128.6 (X2), 128.2, 125.8 (X2), 79.3, 71.7, 44.6.

IR 3509, 3063, 3030, 2918, 1762, 1596, 1496, 1171, 1058, 753, 700.

MS 162 (M⁺), 105, 104 (100%), 78, 77, 51, 28.

HRMS expected 162.0681; observed 162.0681
Furanone 66
Furanone 66

Subtraction Result 02 Apr 98 20:37:10

Wavenumbers (cm⁻¹)

n 15

20 50 100 150 200
Synthesis of α-bromo ketal 67

A 100 ml round bottom flask was charged with cinnamaldehyde ene product 25g (5.426 mmols), 5.0 ml distilled MeOH, and some K₂CO₃ in 30.0 ml distilled CH₂Cl₂. The mixture was cooled to 0 °C. N-bromosuccinimide was then titrated into the reaction mixture, as a solid, in small amounts and followed by TLC; 1) 1.913 mmols was added followed by stirring for 15 min. Reaction incomplete; 2) 1.666 mmols was added followed by stirring for 15 min. Reaction incomplete; 3) 0.990 mmols was added followed by stirring for 15 min. Reaction complete (total added was 0.84 equiv.). The solution was warmed to room temperature then washed one time each with aqueous solutions of Na₂S₂O₃ and NaHCO₃. The CH₂Cl₂ extracts were then dried over Na₂SO₄ and stripped down to give the crude product as a yellow oil. Received 5.988 mmols product (>100%); Rf (20% EtOAc/hexanes) 0.58.

^1H NMR(C₆D₆) 7.32 (c. m, 5H), 5.06 (dd, 1H, J₁ = 9.1 Hz, J₂ = 3.5 Hz), 3.84 (s, 2H), 3.24 (br. s, 1H), 2.98 (dd, 1H, B part of AB, J₁ = 16.8 Hz, J₂ = 9.1 Hz), 2.85 (dd, 1H, A part of AB, J₁ = 16.8 Hz, J₂ = 3.5 Hz).

^13C NMR(C₆D₆) 201.3, 142.4, 128.5, 127.8, 125.5, 70.0, 48.5, 35.0.

IR 2991, 2944, 2831, 1682, 1450, 1377, 1211, 1151, 1058, 972, 746, 693.

MS 163 (M⁺ - Br), 107, 105, 88, 86 (100%), 84, 79, 77, 51.
α-bromo ketal 67
α-bromo ketal 67
Synthesis of cyclopentane 68

A 50 ml round bottom flask was charged with α-bromo ketal 67 (2.09 mmole), tributyltin hydride (2.941 mmole), and a catalytic amount of AIBN in 20 ml of dry benzene. The mixture was purged with argon for 15 minutes and maintained under argon throughout the reaction. The reaction was then heated to reflux for approx. 7 hours (followed by TLC). Upon completion, the mixture was cooled and 15 ml aqueous 10% KF solution was added. Stirred overnight. Extracted two times with Et₂O. The ether extracts were then dried and evaporated down to give the crude product as a colorless oil. Received 2.38 mmoles (>100%).

\[ \text{1H NMR} \]
7.30-7.16 (c.m, 5H), 3.92 (q, 1H, J = 7.5 Hz), 3.25 (s, 3H), 3.21-3.12 (m, 2H), 3.14 (s, 3H), 3.13 (s, 3H), 2.43-2.24 (c.m, 3H), 1.92-1.78 (c.m, 2H).

\[ \text{13C NMR} \]
140.9, 128.7 (X2), 128.2 (X2), 125.8, 108.2, 100.4, 74.4, 67.3, 49.0, 48.8, 45.7, 43.1, 39.4, 37.8, 25.8, 25.1.

\[ \text{IR} \]
3050, 2990, 2944, 2824, 1496, 1450, 1384, 1211, 1144, 1051, 859, 753, 700.

\[ \text{MS} \]
277 (M⁺ - OMe), 219, 218, 187 (100%), 155, 116, 91, 72.
Cyclopentane 68

[Graphical representation of a chemical spectrum or NMR data]
Cyclopentane 68
Synthesis of cyclopentenone 69

A 25 ml round bottom flask was charged with cyclopentyl ketal 68 (0.2 mmole) in 10 ml THF. 10 drops of aqueous 1N HCl was added and the mixture was stirred at room temperature. Upon completion (followed by TLC, 1 day), the reaction mixture was washed one time each with saturated aqueous solutions of NaHCO₃ and NaCl. The CH₂Cl₂ extracts were then dried and evaporated down to give the crude product as a yellow oil. 0.0397 g (100%); Rf (20% EtOAc/hexanes) 0.35.

**¹H NMR**

7.61 (dd, 1H, J₁ = 5.6 Hz, J₂ = 2.5 Hz), 7.40-7.15 (c. m, 5H), 6.20 (dd, 1H, J₁ = 5.6 Hz, J₂ = 2 Hz), 3.26 (c. m, 1H), 2.80 (app. d, 2H, J = 7.8 Hz), 2.52 (dd, 1H, B part of AB, J₁ = 18.9 Hz, J₂ = 6.4 Hz), 2.12 (dd, 1H, A part of AB, J₁ = 18.9 Hz, J₂ = 2.2 Hz).

**¹³C NMR**

209.8, 167.8, 138.7, 133.9, 128.6 (X2), 128.5 (X2), 126.4, 42.8, 40.6, 40.5.

**IR**

3090, 3063, 3030, 2924, 2851, 1709, 1589, 1503, 1456, 1410, 1350, 1251, 1184, 700.

**MS**

172 (M⁺), 129, 128, 115, 92 (100%), 91 (100%), 65

**HRMS**

expected 172.0888; observed 172.0889.
Cyclopentenone 69
Cyclopentenone 69
Synthesis of triazole 76

A 50 ml round bottom flask was charged with o-azidobenzaldehyde ene product 25d (3.200 mmoles) in 17 ml benzene. The reaction mixture was then heated to reflux. The reaction was followed by TLC and after approximately 7 hours, the reaction was complete. To workup, the mixture was simply rotovapped down to give the crude product as a brownish oil. Received 0.8856 g (95 %); Rf (40% EtOAc/ hexanes) 0.46. Upon attempting purification by preparative TLC, the desired triazole reacted with light to begin forming the benzazepinone directly.

$^1$H NMR 7.77 (dd, 1H, J$_1$ = 8.2 Hz, J$_2$ = 1.1 Hz), 7.44 (br. d, 1H), 7.29 (compl. t, 1H), 7.07 (dt, 1H, J$_1$ = 7.6 Hz, J$_2$ = 1.2 Hz), 5.21 (m, 1H, J$_1$ = 11.2 Hz, J$_2$ = 5.8 Hz), 4.53 (d, 1H, B part of AB, J = 18.8 Hz), 3.98 (d, 1H, A part of AB, J = 18.8 Hz), 3.29 (s, 3H), 2.91 (s, 3H), 2.85 (m, 2H, J$_1$ = 12.4 Hz, J$_2$ = 5.8 Hz), 1.54 (s, 3H), 1.49 (s, 3H).

IR 2991, 2944, 2831, 1726, 1607, 1473, 1371, 1204, 1183, 1086, 1049, 1000, 920, 855.

MS 292 (M$^+$ + 1), 259 (M$^+$ - MeOH), 249, 217, 191, 177, 174, 160, 142, 132, 130, 117, 73 (100%), 43.
Triazole 76
Triazole 76

[Graph showing mass spectra with labeled peaks and annotations for mass and intensity.]
Synthesis of azepinone 77

A 10 ml round bottom flask was charged with triazole 76 (0.286 mmole) and a catalytic amount of thioxanthone in 2 ml benzene. The reaction mixture was irradiated with a mercury lamp for approx. 1.5 hours (followed by TLC). Upon completion, the mixture was stripped down to give the crude product as a brownish oil. Received 0.290 mmole (~100%); Rf (40% EtOAc/hexanes) 0.65.

$^1$H NMR 7.22 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 1.5$ Hz), 7.13 (dt, 1H, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 6.82 (dt, 1H, $J_1 = 7.4$ Hz, $J_2 = 0.8$ Hz), 6.69 (br. d, 1H, $J = 8.1$ Hz), 5.04 (d, 1H, $J = 7.1$ Hz), 4.16 (d, 1H, B part of AB, $J = 16.9$ Hz), 3.70 (d, 1H, A part of AB, $J = 14.7$ Hz), 3.24 (d, 1H, B part of AB, $J = 14.7$ Hz), 3.14 (s, 3H), 2.87 (dd, 1H, A part of AB, $J_1 = 14.7$ Hz, $J_2 = 7.2$ Hz), 1.42 (s, 3H), 1.33 (s, 3H).

$^{13}$C NMR 210.2, 147.2, 132.7, 128.7, 125.8, 119.1, 118.0, 101.2, 68.3, 57.2, 49.7, 47.4, 25.5, 25.3.

IR 3389, 2991, 2944, 2831, 2127, 1716, 1603, 1490, 1377, 1317, 1204, 1144, 1065, 1018, 972, 839, 753.

MS 249 ($M^+$), 172, 160, 159, 132, 130, 117, 104, 91, 77, 73 (100%), 43.

HRMS expected 249.1365; observed 249.1365
Azepinone 77
Azepinone 77
Synthesis of lactone aldehyde 148

A dry, 1l three-necked round bottom flask was fitted with a drying tube, an ozone/nitrogen bubbling tube, and a glass stopper. It was then charged with 25 g allylbutyrolactone (0.198 moles) in a 0.5M solution of a 4:1 mixture of CH₂Cl₂ and MeOH. The flask was cooled to -78° C (dry ice/acetone) and then bubbled with ozone until solution became blue (approx. 2.5 hrs). Excess ozone was purged by bubbling with nitrogen for 20 min. 37 ml dimethyl sulfide (0.50 moles) was added and the solution was warmed to room temperature while stirring (approx. 1 hr). The crude reaction mixture was stripped down and was immediately chromatographed using 40% EtOAc/hexanes. Pure aldehyde was obtained as a colorless oil. 16.0137 g (63%); Rf (40% EtOAc/hexanes) 0.15.

1H NMR

9.72 (s, 1H), 4.41 (app. td, 1H, B part of AB, J₁ = 10.9 Hz, J₂ = 9 Hz, J₃ = 1.9 Hz), 4.24 (app. ddd, 1H, A part of AB, J₁ = 9.3 Hz, J₂ = 10.5 Hz, J₃ = 9.3 Hz), 3.11 (dd, 1H, B part of AB, J₁ = 18.5 Hz, J₂ = 3.7 Hz), 2.99 (m, 1H, J₁ = 11.2 Hz, J₂ = 8.6 Hz, J₃ = 2.8 Hz), 2.70 (dd, 1H, A part of AB, J₁ = 18.7 Hz, J₂ = 8.3 Hz), 2.57 (m, 1H, J₁ = 12.4 Hz, J₂ = 8.5 Hz, J₃ = 6.5 Hz, J₄ = 2.0 Hz), 1.94 (c. m, 1H).

13C NMR

199.0, 178.3, 66.6, 43.7, 33.5, 28.3.

IR

3489, 3190, 2997, 2917, 1769, 1384, 1271, 1211, 1164, 1025

MS

129 (M+ + 1), 128 (M+), 100, 55 (100%), 41, 39.

HRMS

expected 128.0473; observed 128.0453
Lactone aldehyde 148
Lactone aldehyde 148

![Graph of lactone aldehyde](image)

- 941061
- MVD 1439
- 100
- >120 x 10
Synthesis of ene product 167

Procedure B using 49.149 mmoles aldehyde 148. Reaction workup is altered, however. Filtered reaction mixture over Celite under reduced pressure. Stripped down filtrate to give the crude product as a light yellow oil. Received 65.81 mmoles product (>100%); Rf (20% EtOAc/hexanes) 0.68.

$^1$H NMR($\text{C}_6\text{D}_6$) 4.3-3.9 (c.m, 1H), 3.92 (d, 1H, J = 1.9 Hz), 3.84 (d, 1H, J = 1.9 Hz), 3.67 (c.m, 1H), 3.46 (c.m, 1H), 3.30-2.90 (c.m, 4H), 3.18 (s, 3H), 3.03 (s, 3H), 2.75-1.2 (c.m, 3H), 1.25 (s, 6H).

$^{13}$C NMR($\text{C}_6\text{D}_6$) There are two diastereomers. Some resonances overlap, others are unique. 179.1, 178.9, 161.5, 161.3, 101.0, 100.8, 83.1, 82.9, 68.0, 68.0, 65.8, 65.7, 54.4, 49.0, 42.0, 41.6, 36.4, 36.0, 35.9, 30.2, 29.9, 25.4, 25.3, 25.2.

IR 2944, 2824, 1769, 1656, 1457, 1377, 1191, 1151, 1078, 1025, 805.

MS 273 (M$^+$ + 1), 241, 226, 225, 209, 201, 183, 169, 153, 145, 137, 129 (100%), 113, 97, 88, 73.

HRMS expected 273.1702 (M$^+$ + H); observed 273.1700
Ene product 167
Ene product 167

Subtraction Result 18 Jul 98 13:24:23

950728 MVD LA ENE

>190 X 3
Synthesis of β-hydroxy ketal 168

A 1l flask was charged with NBS (0.124 moles) and 40 ml distilled MeOH in 300 ml distilled CH₂Cl₂. The reaction was cooled to 0 °C. Ene product 167 in 50 ml CH₂Cl₂ was then added to the cold solution. The reaction was followed by TLC and was shown to be complete after approx. 30 minutes. Warmed to room temperature. Solid Na₂S₂O₅ and K₂CO₃ were added. The solvent was evaporated under reduced pressure. The resulting slurry was redissolved in Et₂O to precipitate out any succinimide. All solids were then filtered off under vacuum. The filtrate was dried over NaSO₄ followed by filtration and evaporation of solvent to give the crude product as a colorless oil. Rf (40% EtOAc/hexanes) 0.20.

\[ \text{1H NMR} \]

4.46 (c.m, 1H), 3.80 (c.m, 2H), 3.57 (dd, 1H, \( J_1 = 11.6 \) Hz, \( J_2 = 2.7 \) Hz), 3.42 (dd, 1H, \( J_1 = 11.6 \) Hz, \( J_2 = 1.4 \) Hz), 3.27 (s, 3H), 3.23 (s, 3H), 2.80 (c.m, 1H), 2.57 (c.m, 1H), 2.37 (dd, 1H, B part of AB, \( J_1 = 15.6 \) Hz, \( J_2 = 8.2 \) Hz), 2.25-1.95 (c.AB m, 4H), 1.90-1.70 (c.m, 2H).

\[ \text{13C NMR} \]

There are two diastereomers. Some resonances overlap; others are unique. 179.1, 100.0, 74.9, 74.7, 60.7, 60.5, 48.7, 48.6, 48.4, 38.7, 37.9, 37.7, 36.6, 36.3, 34.7, 33.2, 32.8, 32.3, 32.2.

\[ \text{IR} \]

3488, 2944, 2838, 1769, 1457, 1423, 1363, 1291, 1171, 1085, 1052, 959, 680.

\[ \text{MS} \]


\[ \text{HRMS} \]

expected 279.0233 (M⁺ - OMe); observed 279.0231
β-hydroxy ketal 168
β-hydroxy ketal 168
Synthesis of furanone lactone 169

A 1 l flame-dried round bottom flask was charged with a 60% dispersion of solid NaH (0.215 moles). The NaH was washed several times with hexane to remove the mineral oil present in the dispersion. 250 ml distilled THF was added and the mixture was cooled to 0° C in an ice water bath. 50 ml distilled tert-butanol was added slowly and the mixture became very viscous. A solution of bromo alcohol 168 (68.27 mmoles) in 40 ml tert-butanol was added causing the new mixture to become much less viscous. The flask was then allowed to warm to room temperature followed by heating to reflux for 30 minutes. Upon completion (followed by TLC), the reaction was quenched by pouring it into 4N HCl/ice solution. The product was extracted many (5 to 7) times using EtOAc. The organic extracts were then washed one time each with saturated aqueous solutions of NaHCO₃ and NaCl. The EtOAC extracts were dried over NaSO₄ and evaporated down to give furanone lactone 169 as an oil. 8.3453 g (66.4%); Rf (40% EtOAc/hexanes) 0.14.

1H NMR 4.50 (m) and 4.35 (c. m; 2H), 4.21 (c. m, 1H), 4.02 (dd, 1H, B part of AB, J₁ = 17.0 Hz, J₂ = 6.4 Hz), 3.81 (d, 1H, A part of AB, J = 17.0 Hz), 2.88 (c. m) and 2.74 (c. m; 1H), 2.68-2.45 (several m, 2H), 2.38-2.18 (several c. m, 2H), 2.18-1.99 (c. m, 1H), 1.81 (c. m, 1H).

13C NMR some resonances overlap, others are unique; 214.1, 214.0, 178.9, 76.8, 76.4, 75.4, 71.0, 66.5, 42.9, 42.7, 36.8, 36.0, 35.9, 35.8, 35.5, 29.4, 28.8.
**Furanone lactone 169**

**IR**
3509, 2918, 2851, 1756, 1377, 1164, 1058, 1018.

**MS**
185 (M+ + 1), 184 (M+), 109, 99, 86 (100%), 67.

**HRMS**
expected 184.0735; observed 184.0738.
Furanone lactone 169

Subtraction Result 01 Nov 94 17:04:07

MVD 1444

>160 X 9
**Synthesis of neopentyl ketal 174**

A 500 ml round bottom flask was fitted with a Dean-Stark trap and a reflux condenser. It was then charged with 9.7290 g of furanone lactone 169 (52.87 mmole), neopentyl glycol (0.108 mmole), and trimethyl orthoformate (80.53 mmole) in 200 ml of benzene. A catalytic amount of p-toluenesulfonic acid was added and the mixture was heated to reflux for approx. 7 hrs (followed by TLC). Workup included washing two times with a 10% NaOH solution followed by two washes with saturated aqueous NaCl solution. The EtOAc extracts were combined and dried over NaSO₄. The solvent was removed by evaporation to give 18.4031 g crude product as a dark oil. Chromatographed using 25% EtOAc/hexanes to give the pure ketal as a colorless oil. 6.5982 g (46 %); Rf (40% EtOAc/hexanes) 0.38.

**1H NMR**

4.35 (c.m, 1H), 4.22-4.0 (c.m, 2H), 3.98 (d, 1H, B part of AB, J = 9.5 Hz), 3.74 (dd, 1H, A part of AB, J₁ = 9.5 Hz, J₂ = 4.4 Hz), 3.48 (several s, 4H), 2.79 and 2.62 (c. m, 2H), 1.74 (c. m, 2H), 1.02 (s, 3H), 0.91 (s, 3H).

**13C NMR**

some resonances overlap, others are unique; 179.3, 108.0, 77.8, 76.2, 75.0, 74.7, 72.9, 72.8, 66.7, 66.6, 40.8, 40.4, 37.6, 36.3, 35.9, 35.3, 30.0, 29.7, 28.9, 22.3, 22.1.

**IR**

2957, 2864, 1775, 1470, 1370, 1158, 1125, 1085, 1025.
Neopentyl ketal 174

MS 270 (M+), 255 (M+ - Me), 171, 155, 142, 127, 79 (100%).

HRMS expected 270.1467; observed 270.1478
Neopentyl ketal 174
Synthesis of lactol 175

A 500 ml flame-dried round bottom flask was charged with lactone 174 (24.44 mmoles) in 180 ml THF and the mixture was cooled to -78°C (dry ice/acetone). Diisobutyl aluminum hydride (DIBAL; 27.0 mmoles) was then added slowly via syringe. The reaction mixture was stirred for 30 minutes and checked by TLC. More DIBAL was added (4.5 mmoles) because the reaction was found to be incomplete. Upon completion, the excess DIBAL was quenched, at -78°C, by the addition of MeOH. The mixture was then warmed to 0°C and acidified using NaHSO₄. The crude product was extracted two times with EtOAc. These extracts were further washed with a saturated aqueous solution of NaCl. The combined organic extracts were then dried over NaSO₄ and evaporated down to give the product as a yellow oil. Received 6.6056 g (99%).

**¹H NMR**

5.34 and 5.20 (m, 1H), 4.15-3.85 (c. m, 3H), 3.85-3.65 (c. m, 2H), 3.55-3.35 (c. m, several s, 4H), 2.37 (m, 1H) 2.19 (c. m, 2H), 2.07-1.92 (c. m, 1H), 1.92-1.45 (c. m, 4H), 0.99 (s, 3H), 0.92 (s, 3H).

**¹³C NMR**

There are 4 diastereomers. Some resonances overlap, others are unique; 108.1, 103.2, 103.0, 99.4, 97.9, 97.3, 77.9, 77.7, 77.6, 77.2, 74.8, 74.7, 72.8, 72.7, 67.1, 67.0, 66.8, 66.6, 43.9, 43.7, 42.1, 41.3, 41.2, 41.1, 37.5, 34.2, 33.8, 30.7, 30.0, 29.2, 28.7, 22.3, 22.1.

**IR**

3416, 2931, 2864, 1769, 1463, 1364, 1277, 1184, 1125, 1078, 1025, 912.
**Lactol 175**

**MS**

272 (M+), 255 (M+ - OH), 241, 197, 185, 171, 155, 141, 69 (100%).
**Synthesis of alcohol 176**

A 1l flame-dried flask was charged with Ph₃P⁺-MeI⁻ (0.110 moles) and 250 ml THF. The mixture was then cooled to 0° C. Butyllithium (0.110 moles) was added followed by stirring for 30 min. Lactol 175 (36.137 mmoles) in 50 ml THF was added. The reaction mixture was allowed to warm to room temperature, then heated to reflux. When the reaction was complete by TLC (approx. 1 hr), the mixture was allowed to cool. To workup, the solution was first diluted with hexane and then quenched with saturated aqueous NH₄Cl solution. In order to remove Ph₃P=O and any other solid contaminants, the mixture was vacuum filtered using a hexane wash. The filtrate was washed with saturated aqueous NaCl solution and the organic extracts were then dried over NaSO₄. Evaporated to give the crude product. The product was purified by column chromatography using 40% EtOAc/hexane. Received 3.00 g (31% pure); Rf (40% EtOAc/hexanes) 0.36.

**¹H NMR**

5.54 (c. m, 1H), 5.00 (c. m, 2H), 3.97 (app. q, 2H, J = 4.8 Hz), 3.63 (c. m, 3H), 3.46 (m, 4H), 2.31 (m, J = 6.4 Hz) and 2.20 (m) 3H total, 1.68 (c. m, 3H), 1.50 (c. m, 2H), 0.97 (s, 3H), 0.89 (s, 3H).

**¹³C NMR**

some resonances overlap, others are unique; 141.8, 131.9, 128.5, 128.3, 115.6, 115.0, 108.2, 108.1, 76.6, 74.7, 74.5, 72.7, 60.7, 60.5, 41.3, 40.6, 40.3, 38.1, 38.0, 37.9, 37.5, 29.9, 22.2, 22.1.
Alcohol 176

IR  3442, 2964, 2924, 2864, 1470, 1397, 1364, 1184, 1078, 1045, 1005.

MS  270 (M+), 161, 155 (100%), 144,141,128,69.

HRMS  expected 270.1831; observed 270.1842
Alcohol 176

Subtraction Result 07 Dec 04 17:45:40

Wavenumber (cm\(^{-1}\))

941224  NVD 1485
AMP: 000559928

Frequency (Hz)

100

270
Synthesis of mesylate 177

A dry, 250 ml round bottom flask was charged with alcohol 176 (11.11 mmoles) and triethylamine (33.06 mmoles) in 60 ml CH₂Cl₂. The mixture was cooled to 0°C. Methanesulfonyl chloride (16.80 mmoles) was then added and the solution was allowed to warm to room temperature. Upon completion (followed by TLC), the reaction was worked up by washing with saturated aqueous solutions of NaHCO₃ and NaCl. The CH₂Cl₂ extracts were dried over Na₂SO₄ and evaporated down to give the crude product. 3.8237 g (99%); Rf (20% EtOAc/hexanes) 0.21.

**¹H NMR**

5.51 (m, 1H), 5.09 (m, 2H), 4.21 (c. m, 2H), 3.98 (m, 2H, J = 9.3 Hz), 3.69 (dd, 1H, J₁ = 9.5 Hz, J₂ = 3.1 Hz), 3.47 (m, 4H), 2.99 (s) and 2.98 (s) 3H total, 2.35 (m, 1H), 2.32 (m, 1H, J = 6.2), 1.92 (m, 1H), 1.83-1.43 (c. m, 4H), 1.00 (s, 3H), 0.92 (s, 3H).

**¹³C NMR**

some resonances overlap; others are unique; 140.2, 140.1, 117.1, 116.5, 108.2, 108.1, 76.4, 74.6, 74.5, 72.8, 68.1, 41.4, 40.7, 40.2, 37.8, 37.5, 37.3, 37.2, 34.2, 33.7, 30.0, 22.3, 22.3, 22.1, 21.6.

**IR**

2951, 2864, 1477, 1357, 1178, 1131, 1085, 959, 919.

**MS**

318 [(M⁺ + 1) - CH=CH₂], 270 [(M⁺ + 1) - Ms], 269 (M⁺ - Ms), 240, 171, 155, 79, 69 (100%).

**HRMS**

expected 269.1752 (M⁺ - Ms); observed 269.1745
Mesylate 177
Synthesis of iodide 178

A dry, 250 ml round bottom flask was charged with mesylate 177 (10.99 mmole) and sodium iodide (60.26 mmole) in 100 ml acetone. The flask was fitted with a reflux condenser and the mixture was then heated to reflux for approx. 4 hrs (followed by TLC). To workup, the reaction mixture was first washed with a saturated aqueous NaS2O3 solution, to remove any excess iodide, followed by washes with DI H2O and aqueous saturated NaCl solution. The CH2Cl2 extracts were then dried over NaSO4 and evaporated down to give the crude product as a colorless gel. Received 3.6425 g (87%); Rf (20% EtOAc/hexanes) 0.63.

1H NMR 5.45 (m, 1H), 5.09 (c. m, 2H), 3.97 (c. m, 1H; dd, 1H, B part of AB, J1 = 9.5 Hz, J2 = 3.6 Hz), 3.69 (dd, 1H, A part of AB, J1 = 9.5 Hz, J2 = 1.5 Hz), 3.49 (several s, 4H), 3.22 (c. m, 1H), 3.04 (m, 1H), 2.34 and 2.20 (m, 2H), 1.94 (m, 1H), 1.71 (c. m, 3H), 1.50 (c. m, 1H), 0.99 (two s, 3H), 0.92 (two s, 3H).

13C NMR some resonances overlap, other are unique: 140.0, 116.9, 116.3, 108.2, 76.8, 74.7, 74.56, 72.7, 42.2, 41.9, 41.5, 40.8, 40.4, 39.8, 38.8, 38.2, 30.0, 22.3, 22.1, 4.7, 4.4.

IR 2951, 2931, 2864, 1470, 1397, 1184, 1131, 1085, 1045, 998, 919.

MS 381 (M+ + 1), 380 (M+), 352, 253, 224, 155 (100%), 69.

HRMS expected 253.1803 (M+ - 1); observed 253.1809
Iodide 178

[Graph of Iodide 178]

[Graph of Iodide 178]

[Graph of Iodide 178]
Synthesis of furanone 179

A 100 ml round bottom flask was charged with ketal 178 (6.905 mmoles) in 35 ml aqueous 80% AcOH. The mixture was heated to reflux for 4 hours (followed by TLC). To workup, the solution was first neutralized using saturated aqueous NaHCO₃ solution. The crude product was then extracted several times with Et₂O. The Et₂O extracts were further washed with saturated aqueous solutions of NaHCO₃ and NaCl. The combined organic layers were then dried over NaSO₄ and evaporated down to give the crude furanone as a colorless oil. The compound was quickly purified by chromatography using 25% EtOAc/hexanes. The compound obtained after purification by column was still contaminated with the diacetate of neopentyl glycol. 2.2890 g (100%).

**¹H NMR**

5.47 (m, 1H), 5.13 (c. m, 2H), 4.24 (c. m, 1H), 4.04 (br. dd, 1H, B part of AB, J₁ = 17.1 Hz, J₂ = 2.3 Hz), 3.81 (d, 1H, A part of AB, J = 17.0 Hz), 3.24 (m, 1H), 3.06 (c. m, 1H), 2.60-2.15 (complex AB system and c. m, 3H), 1.94 (c. m, 1H), 1.80 (c. m, 2H), 1.63 (c. m, 1H).

**¹³C NMR**

some resonances overlap, others are unique; 214.9, 214.7, 139.7, 117.4, 116.7, 76.3, 75.9, 71.3, 71.1, 43.4, 42.7, 41.7, 40.5, 39.9, 38.7, 38.1, 4.3, 4.1.

**IR**

3077, 2924, 1762, 1423, 1171, 1065, 925.

**MS**

196, 167 (M⁺ - I), 155, 98, 85, 67, 57 (100%).

**HRMS**

expected 294.0117; observed 294.0131
Furanone 179
Furanone 179

[Graph of infrared spectrum with wavenumber (cm⁻¹) on the x-axis and transmission (%) on the y-axis]

[Graph showing data labeled SSO25 23, NVO 1843, AMP >100 X 4]
Synthesis of bicyclic 180

A 250 ml flame-dried round bottom flask was charged with potassium tert-butoxide (19.404 mmoles) in 50 ml distilled THF. The flask was cooled to 0° C. Iodide 179 (7.786 mmoles) was then added in solution with 20 ml THF. The mixture was stirred for approximately 15 minutes and the reaction was found to be complete (followed by TLC). For workup, the reaction mixture was washed two times with saturated aqueous NaHCO₃ solution, which also quenched any excess KOtBu present. Et₂O extracts were then washed one time with saturated aqueous NaCl solution and dried over Na₂SO₄. The extracts were evaporated down to give the bicyclic compound 180 as a light yellow oil (2.0566 g). The crude product was immediately chromatographed using 10% EtOAc/hexanes as the elutant. Received 0.7018 g (54% pure); Rf (20% EtOAc/hexanes) 0.51.

\(^1\text{H NMR}\)
5.75 (m, 1H), 4.97 (c. m, 2H), 4.61 (m) and 4.29 (br. q, 1H), 4.21 (d, B part of AB, J = 17.2 Hz) and 4.07 (dd, B part of AB, J₁ = 17.5 Hz, J₂ = 1.1 Hz; 1H), 3.90 (d, A part of AB, J = 17.3 Hz) and 3.85 (d, A part of AB, J = 16.2 Hz; 1H), 2.65 (br. t, 1H, J = 7.0 Hz), 2.38-0.8 (several c. m, 7H).

\(^1\text{C NMR}\)
some resonances overlap, others are unique; 215.6, 142.6, 142.1, 113.2, 112.9, 71.0, 68.0, 46.8, 45.7, 27.9, 65.0, 34.0, 33.1, 29.4, 28.2, 22.4, 21.1.

IR
3077, 2931, 2864, 1756, 1722, 1178, 1052, 919.
Bicyclic 180

MS 166 (M+), 135, 89.

HRMS expected 166.0994; observed 166.0993.
Bicyclic 180

Subtraction Result 23 May 85 16:09:48

940991  MVD 1416 BICYCLIC
= 25
100 >35 X 5

20 50 100 150
Synthesis of $\beta$-diketone 215

A 200 ml flame-dried flask was charged with potassium tert-butoxide (0.119 moles) in 80 ml of THF. The flask was then cooled to 0° C. A mixture of acetophenone (43.78 mmoles) and ethyl diethoxyacetate (44.72 mmoles) in 20 ml THF was added and the reaction solution was allowed to warm to room temperature. After 1.5 hrs (followed by TLC), the reaction was quenched to pH = 5 using an aqueous 4N HCl solution. The product was extracted with Et$_2$O. The Et$_2$O extracts were further washed with saturated aqueous NaCl solution. The organic extracts were then dried over NaSO$_4$ and evaporated down to give a yellow oil. Received 10.6301 g (97%); R$_f$ (20% EtOAc/hexanes) 0.67.

$^1$H NMR  7.90 (c. m, 2H), 7.45 (c. m, 3H), 6.59 (s, 1H), 4.90 (s, 1H), 3.66 (c. m, 4H), 1.27 (t, 6H).

$^{13}$C NMR  190.3, 184.4, 134.2, 132.6, 128.5 (X 2), 127.1 (X 2), 99.8, 93.6, 62.4 (X 2), 15.0 (X 2).

IR  2977, 2931, 2884, 1609, 1576, 1457, 1330, 1264, 1178, 1111, 1058, 779, 700.

MS  205 (M+ - OEt), 103 (100%), 75, 69, 47.

HRMS  expected 205.0865 (M+ - OEt); observed 205.0879
β-diketone 215
β-diketone 215

CONFORMATION 11 May 95 15:22:00

950529  MVD CONDENSATION

n 28
Synthesis of isoxazolinol 216

A 250 ml round bottom flask was charged with diketone 215 (42.52 mmole) and solid NaHCO₃ in 80 ml MeOH. (The NaHCO₃ is present simply to maintain a neutral pH to prevent loss of the acetal.) Hydroxylamine hydrochloride (65.46 mmole) is then added and more NaHCO₃ is added, as needed, to maintain pH = 7 throughout reaction. The mixture was stirred at room temperature for 30 min. followed by gentle heating for 1 hour (followed by TLC). Upon completion, the reaction mixture was cooled and washed several times with DI H₂O. The CH₂Cl₂ extracts were dried over NaSO₄ and evaporated down to give a white crystalline solid (m. p. = 78 - 80° C). 11.1980 g (100%); Rf (20% EtOAc/hexanes) 0.32.

\[1H\text{ NMR} \qquad \begin{align*} & 7.56 \text{ (c. m, 2H)}, \qquad 7.37 \text{ (c. m, 3H)}, \qquad 5.21 \text{ (s, 1H)}, \qquad 3.64 \text{ (c. m, 4H)}, \qquad 3.37 \text{ (d, 1H, B part of AB, } J = 18.2 \text{ Hz)}, \qquad 3.17 \text{ (d, 1H, A part of AB, } J = 18.2 \text{ Hz)}, \qquad 1.21 \text{ (several t, 6H)}. \end{align*} \]

\[13C\text{ NMR} \qquad \begin{align*} & 158.1, \quad 140.6, \quad 128.8, \quad 128.4 \text{ (X 2)}, \quad 125.5 \text{ (X 2)}, \quad 107.3, \quad 97.3, \quad 63.0, \quad 46.8 \text{ (X 2)}, \quad 15.0 \text{ (X 2)}. \end{align*} \]

\[\text{IR} \qquad \begin{align*} & 3362, \quad 2977, \quad 2931, \quad 2884, \quad 1696, \quad 1629, \quad 1450, \quad 1330, \quad 1211, \quad 1171, \quad 1058, \quad 773, \quad 700. \end{align*} \]

\[\text{MS} \qquad \begin{align*} & 220 \text{ (M+ - OEt)}, \quad 105 \text{ (100%)}, \quad 77, \quad 47. \end{align*} \]

\[\text{HRMS} \qquad \begin{align*} & \text{expected 220.0973 (M+ - OEt); observed 220.0964}. \end{align*} \]
Isoxazolinol 216
Isoxazolinol 216

[Graph of infra-red spectrum]

[Graph of another compound spectrum]

950536
MVD ISOXAZOLINOL

= 48
Synthesis of isoxazole acetal 218

A dry round bottom flask was charged with isoxazolinol 216 (42.237 mmoles) in 90 ml CH$_2$Cl$_2$. A catalytic amount of trifluoroacetic acid was added and the mixture was stirred at room temperature for approx. 1 hr (followed by TLC). The reaction was then worked up by washing with saturated aqueous solutions of NaHCO$_3$ and NaCl. The CH$_2$Cl$_2$ extracts were dried over NaSO$_4$ and evaporated down to give the crude product as a colorless gel. The crude compound was purified by column chromatography using 5% EtOAc/hexanes. 4.9738 g (48% pure); R$_f$ (20% EtOAc/hexanes) 0.61.

$^1$H NMR 7.77 (c. m, 2H), 7.44 (c. m, 3H), 6.63 (s, 1H), 5.62 (s, 1H), 3.69 (c. m, 4H), 1.27 (t, 6H).

$^{13}$C NMR 170.0, 163.2, 130.2, 128.9, 127.1, 125.7, 97.5, 96.2, 62.3, 15.0.

IR 2997, 2930, 2884, 1576, 1470, 1443, 1330, 1111, 1065, 766, 693.

MS 247 (M$^+$), 246 (M$^+$ - 1), 202 (M$^+$ - OEt), 174, 159, 105, 77, 75, 47 (100%).

HRMS expected 247.1208; observed 247.1195
Isoxazole acetal 218
Synthesis of isoxazole carboxaldehyde 219

A 50 ml round bottom flask was charged with isoxazole acetal 218 (20.137 mmols) and 20 ml of 80% AcOH. The mixture was heated to a gentle reflux. Upon completion (indicated by TLC), the solution was neutralized with saturated aqueous NaHCO₃ solution. The formed aldehyde was then extracted using CH₂Cl₂. The organic extracts were dried over NaSO₄ and evaporated down to give the desired aldehyde as white crystalline solid (m. p. 53-55°C). Received 3.0123 g (86%); Rf (20% EtOAc/hexanes) 0.41.

¹H NMR 10.17 (s, 1H), 7.79 (m, 2H), 7.48 (t, 3H), 6.88 (s, 1H).

¹³C NMR 184.7, 171.9, 162.5, 130.9, 129.1, 126.3, 125.9, 96.2.

IR 3137, 3064, 2844, 1716, 1570, 1457, 945, 806, 766, 686.

MS 174 (M⁺ + 1), 173 (M⁺), 105 (100%), 77.

HRMS expected 173.0477; observed 173.0475
Isoxazole carboxaldehyde 219
Isoxazole carboxaldehyde 219
Synthesis of acid 229

A 5 ml round bottom flask was charged with bicyclic 180 (0.266 mmoles) and KIO₄ (1.079 mmoles) in a mixture of CH₃CN (0.6 ml) and DI H₂O (0.9 ml). A catalytic amount of RuCl₃(H₂O)ₖ (~2 mg) was added causing the solution to turn black, then green. The reaction was followed by TLC and worked up when complete (~6 hours). To workup, the reaction mixture was diluted with CH₂Cl₂ and DI H₂O, then extracted two times with CH₂Cl₂. The organic extracts were dried over NaSO₄ and evaporated down to give the crude acid as a yellow crystalline material. 0.0275 g (56%); Rₕ (10% MeOH/CHCl₃) 0.20.

1H NMR  4.60 (c.m, 1H, minor diastereomer), 4.38 (q, 1H, major diastereomer, J = 3.8), 4.20 (d, 1H, B part of AB, major diastereomer, J = 17.3 Hz), 4.08 (d, 1H, B part of AB, minor diastereomer, J = 17.6 Hz), 3.95 (d, 1H, A part of AB, minor diastereomer, J = 17.6 Hz), 3.88 (d, 1H, major diastereomer, J = 17.3 Hz), 2.67 (c.m, 1H), 2.31 (c.m, 3H), 2.09-1.75 (c.m, 2H), 1.75-1.20 (c.m, 3H)

13C NMR  Major diastereomer:  214.9, 180.8, 75.6, 70.8, 45.3, 39.0, 29.3, 25.9, 21.6.  Minor diastereomer:  216.0, 179.8, 76.3, 68.4, 46.4, 37.0, 30.0, 24.8, 20.6

IR  3502, 2938, 2864, 2725, 1756, 1722, 1450, 1178, 1058, 932, 806.

MS  184 (M+), 168, 137, 114, 112, 109, 81 (100%), 80, 79 (100%), 70, 67, 55, 51.

HRMS  expected 184.0736; observed 184.0732
Acid 229

RUC3 OXIDATION IS May 00 00:54:55

Navenumber (cm⁻¹)

950534  NVJ OXIDATION

n 35

50 100 150
Synthesis of furanone 230

A 10 ml round bottom flask was charged with bicyclic acid 229 (0.664 mmoles) and isoxazole aldehyde 219 (0.673 mmoles) in 2.5 ml EtOH. 1.5 ml aqueous 20% LiOH solution was then added causing the solution to become yellow and cloudy. The mixture was stirred for approx. 45 min (followed by TLC). The rearrangement was then induced by the addition of aqueous 4N HCl until the solution tested acidic by pH paper. The acidic mixture was heated gently for 1.5 hours (followed by TLC). The crude product was extracted using CH$_2$Cl$_2$. The organic extracts were dried over NaSO$_4$ and evaporated down to give a yellow gel. 0.2140 g (90%); R$_f$ (100% EtOAc) 0.54.

$^1$H NMR 7.74 (c. m, 2H), 7.43 (c. m, 3H), 6.45 (s, 1H), 4.78 (m, 1H), 3.41 (dt, 1H, B part of AB, $J_1 = 15.3$ Hz, $J_2 = 3.2$ Hz), 3.00 (ddd, 1H, A part of AB, $J_1 = 15.5$ Hz, $J_2 = 8.8$ Hz, $J_3 = 3.6$ Hz), 2.73 (c. m, 2H), 2.42-2.00 (c. m, 3H), 1.95-1.55 (c. m, 2H).

MS 339 (M$^+$), 294 (M$^+$ - COOH), 172, 105 (100%), 77.

HRMS expected 339.1089; observed 339.1109.
Furanone 230
Synthesis of ester 231

A 25 ml Erlenmeyer flask was charged with carboxylic acid 230 (0.598 mmole) in 3.0 ml Et₂O. The flask was cooled to 0° C in an ice water bath. Previously prepared diazomethane (CH₂N₂) was then added slowly until reaction was shown to be complete by TLC. The mixture was warmed to room temperature with stirring. The Et₂O solution was dried over NaSO₄ and evaporated down to give the crude product as a yellow oil. 0.1818 g (82%).

¹H NMR  
7.73 (c. m, 2H), 7.41 (c. m, 3H), 6.44 (two s, 1H), 4.74 (c. m, 1H), 3.66 (two s, 3H), 3.38 (ddd, 1H, B part of AB, J₁ = 15.5 Hz, J₂ = 3.5 Hz, J₃ = 0.9 Hz), 2.97 (ddd, 1H, A part of AB, J₁ = 15.6 Hz, J₂ = 8.6 Hz, J₃ = 1.3 Hz), 2.85-2.55 (c. m, 2H), 2.35-1.90 (c. m, 3H), 1.85-1.65 (c. m, 2H).

¹³C NMR  
200.6, 186.9, 173.8, 170.0, 159.6, 130.1, 128.9 (X2), 127.2, 125.7 (X2), 112.4, 99.5, 83.1, 52.0, 38.6, 28.1, 27.7, 24.7, 16.8.

IR  
2951, 2858, 1736, 1702, 1629, 1437, 1164, 766, 693.

MS  
354 (M+ + 1), 353 (M+), 294 (M+ - COOMe), 248, 198, 172, 105 (100%), 77, 55.

HRMS  
expected 353.1263; observed 353.1265.
Synthesis of silyloxy furan 232

A 10 ml round bottom flask was charged with methyl ester 231 (0.255 mmoles), 2.0 ml triethylamine and 1.0 ml distilled CH₂Cl₂. tert-Butyl dimethylsilyl triflate was then added dropwise, in a titration mode, until the reaction showed completion by TLC. To workup, the mixture was washed twice with a saturated aqueous NaHCO₃ solution. The CH₂Cl₂ extracts were then dried over NaSO₄ and evaporated down to give the crude product as a colorless oil. The crude compound was quickly chromatographed using 5% EtOAc/hexanes to give the pure silyloxy furan 232. Received 0.0640g (54% pure).

$^1$H NMR

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.75 (c. m, 2H)</td>
<td>7.42 (c. m, 1H)</td>
</tr>
</tbody>
</table>

$^{13}$C NMR

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>175.0</td>
<td>169.7</td>
</tr>
</tbody>
</table>

IR

<table>
<thead>
<tr>
<th>ν (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2951</td>
</tr>
</tbody>
</table>

MS

<table>
<thead>
<tr>
<th>m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>468 (M+ + 1)</td>
</tr>
</tbody>
</table>

HRMS

expected 353.1263 (M+ - t-Butyl(Me)₂Si); observed 353.1261
Silyloxy furan 232
Silyloxy furan 232

Subtraction Result 18 May 88 00:48:22

980544  NVO SILYL
= 59

>210 X 3

AMP.: 0008464

>450 X 100

280 300 350 400 450
Synthesis of α-hydroxy furan 233

A 10 ml round bottom flask was charged with silyloxy furan 232 (0.113 mmole) in a mixture of 0.8 ml hexane and 0.3 ml CHCl₃. The mixture was cooled to 0 °C. mCPBA (0.120 mmole) was added as a solid to the cold solution. The reaction was stirred for 1 hour but TLC shows it to be incomplete. More mCPBA was added until complete. The reaction mixture was allowed to warm to room temperature. 0.5 ml aqueous 1N HCl was added and the mixture was stirred for 30 minutes. To workup, the solution was extracted two times with CH₂Cl₂. The extracts were washed one time with saturated aqueous NaHCO₃ and then dried over Na₂SO₄. The Na₂SO₄ was filtered off and the filtrate was evaporated down to give the crude product as a colorless oil. The crude compound was quickly chromatographed using 20% EtOAc/hexanes to give the pure hydroxy furan 233. Received 0.0160g (38% pure).

**¹H NMR**
7.75 (c.m, 2H), 7.42 (c.m, 3H), 6.54 (s, 1H, single diastereomer), 6.52 (s, 1H, single diastereomer), 3.69 (s, 3H, single diastereomer), 3.66 (s, 3H, single diastereomer), 3.35 (dd, 1H, B part of AB, J₁ = 14.8 Hz, J₂ = 1.5 Hz), 3.11 (d, 1H, A part of AB, J = 14.8 Hz), 2.85-2.50 (c.m, 2H), 2.40-1.90 (c.m, 3H), 1.90-1.50 (c.m, 1H), 1.40-0.75 (c.m, 1H).

**IR**
3376, 2957, 2930, 2858, 1729, 1616, 1450, 1171, 766, 693.

**MS**
369 (M⁺), 352 (M⁺ - OH), 294, 246, 198, 186, 183, 159 (100%), 123, 105, 77, 55.
α-hydroxy furan 233
α-hydroxy furan 233