1992

Photoinduced hydrogen atom abstraction in natural products synthesis

Li Chen
Iowa State University

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Photoinduced hydrogen atom abstraction in natural products synthesis

Chen, Li, Ph.D.
Iowa State University, 1992
Photoinduced hydrogen atom abstraction in natural products synthesis

by

Li Chen

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa
1992
DEDICATION

To my parents, wife and daughter.
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GENERAL INTRODUCTION

Naturally occurring organic compounds constitute the matter of all life on earth. Their science at the molecular level defines a fundamental language of that life. The chemical synthesis of these naturally occurring compounds and many millions of unnatural organic substances has been one of the major enterprises of science in this century.

Organic synthesis has impacted on our lives and society in an all-pervasive manner. Many of today's medicines are synthetic and many of tomorrow's will be conceived and produced by synthetic chemists. To the field of synthetic chemistry belongs an array of responsibilities which are crucial for the future of mankind, not only with regard to the health, material and economic needs of our society, but also for the attainment of an understanding of matter, chemical change and life at the highest level of which the human mind is capable.

Nature uses an extremely powerful reagent, light, to create the life on earth. Photosynthesis occurs in plants to produce carbohydrates, the basic substances that living organism need for their existence and reproduction. Today, the photochemical reactions have become a powerful tool in the hands of synthetic chemists to prepare the substances that nature does not provide or provides in a limited quantity.

This dissertation is written to achieve an understanding of the basic theory of a photochemical hydrogen atom abstraction reactions and to demonstrate their synthetic potential in the construction of biologically important natural products.
Explanation of the Dissertation Organization

The dissertation is composed of four publishable or published papers. The numbering system adopted for the compounds, schemes and references is independent in each paper.

The first paper of this work includes some fundamental aspects of the photochemical hydrogen atom abstraction reaction. The second paper describes the first stereoselective total synthesis of paulownin, an important component in Chinese traditional medicine, using the type II photocyclization reaction. The remaining two papers demonstrate the synthetic utilization of the photoenolization reaction in the synthesis of aklavinone and pleurotin anticancer antibiotics. There is a general conclusion following the last paper.
PAPER I

PHOTOCHEMICAL HYDROGEN ATOM ABSTRACTION
INTRODUCTION

Hydrogen abstraction is a well known photochemical reaction of the carbonyl group. It can happen both inter- and intramolecularly and can lead either to reduction of the carbonyl function or to the synthesis of new compounds by cyclization or fragmentation. The photophysical basis of hydrogen atom abstraction reactions has been well studied, most notably by Wagner and Scaiano.\textsuperscript{1,2}

The \((\pi,\pi^*)\) excited state of ketones and aldehydes displays its similarity to an alkoxy radical, which can abstract a hydrogen atom. The efficiency of the process depends strongly on the C-H bond strength in the intermolecular reaction, and on the molecular conformation for the intramolecular reaction.\textsuperscript{3} The energy (\textit{i.e.} singlet or triplet) and electronic configuration [\textit{i.e.} \((\pi,\pi^*)\) or \((\pi,\pi^*)\)] of the excited state of the particular carbonyl compound are also important factors which affect the efficiency of hydrogen abstraction.
INTERMOLECULAR HYDROGEN ABSTRACTION

Aliphatic ketones can undergo an *intramolecular* hydrogen abstraction reaction from singlet and triplet excited states. However, the relative reactivity of the singlet excited carbonyl compounds in the *intermolecular* process is not clear. Therefore, only the well-documented triplet state process will be discussed.

It is known that the population of the triplet state of the carbonyl group on direct irradiation is dependent upon the intersystem crossing (ISC) efficiency. For aryl ketones, it is unity, but it is variable for alkyl ketones. For example, acetone $\Phi_{ISC} = 0.9-1.0$; hexan-2-one $\Phi_{ISC} = 0.27$; 5-methylhexan-2-one $\Phi_{ISC} = 0.11$. The substituents on the carbonyl group also have an influence on the position of the $(n,\pi^*)$ absorption maximum in alkyl ketones and aldehydes. Thus, acetone has a maximum at 278.5 nm, 3-methylbutan-2-one a maximum at 284.5 nm, and 2,2,4,4-tetramethylpentan-3-one a maximum at 296.8 nm. With aryl ketones the maximum is pushed toward longer wavelengths. Benzophenone shows the $(n,\pi^*)$ absorption maximum at 348 nm. The intermolecular hydrogen abstraction reaction often generates reduction products of carbonyl compounds.

The photolysis of a carbonyl compound in a solvent can result in abstraction of a hydrogen atom from the solvent. This reaction can occur with a variety of hydrogen donors, such as alkanes, alkenes, alcohols and ethers. The irradiation of acetone in $n$-hexane yields the dimethylhydroxymethyl radical, which in turn gives isopropanol. The addition of a diene (a triplet quenching agent) into this system can quench the formation of the product. This indicates that the reduction arises from the triplet excited state of the acetone carbonyl group. Other alkyl ketones also undergo reduction from the triplet excited state, but the
reactions are less efficient than acetone, because the intersystem crossing
efficiency of other aliphatic ketones is far less than that of acetone. Cyclic
ketones also have a low efficiency of intersystem crossing, and undergo reduction
solely from the triplet excited state.

Aryl ketones undergo photochemical reduction efficiently. Benzophenone is
a good example. It has been studied almost as long as modern photochemistry
has existed. The reduction of benzophenone is highly efficient in a hydrocarbon,
solvent (such as toluene) and affords the pinacol with quantum yield of 0.39. The
solvent often plays a large part in determining the overall efficiency of the photo-
reduction process. In propan-2-ol the quantum yield for the disappearance of
benzophenone has a value of 2. This efficient process is outlined in Scheme 1.

Scheme 1

\[
\begin{align*}
\text{Ph}_2\text{C}=\text{O} &\xrightarrow{hv} \quad ^1(\text{Ph}_2\text{C}=\text{O})^* \\
(\text{Ph}_2\text{C}=\text{O})^* + (\text{CH}_3)_2\text{CHOH} &\longrightarrow \quad \text{Ph}_2\cdot\text{C-OH} + \text{Me}_2\cdot\text{C-OH} \\
\text{Ph}_2\text{C}=\text{O} + \text{Me}_2\cdot\text{C-OH} &\longrightarrow \quad \text{Ph}_2\cdot\text{C-OH} + \text{Me}_2\text{C}=\text{O} \\
2(\text{Ph}_2\cdot\text{C-OH}) &\longrightarrow \quad \text{Ph} \quad \text{Ph} \\
\quad \text{HO} \quad \text{OH} \\
\end{align*}
\]

The (n,\pi^*) triplet state of the carbonyl group abstracts a hydrogen atom
from C-2 of the alcohol to generate two radicals diphenylhydroxymethyl radical (a
partially reduced benzophenone) and dimethylhydroxymethyl radical. The latter
can transfer hydrogen to another molecule of benzophenone to give a molecule of
acetone and another partially reduced benzophenone. The coupling of the two
diphenylhydroxymethyl radicals affords pinacol as the reduction products.
Hydrogen donors in the photochemical reduction of carbonyl compounds also include thiols, sulfides, ethers and amines. An electron transfer process is involved when an amine is used in photoreduction. Because of the intervention of the electron transfer step, the reduction of the ketone cannot be quenched by dienes even though the reaction does go through the triplet state of the carbonyl group. Sulfides and aryl amines behave the same as amines.

Many ketones fail to undergo photoreduction in an alcohol media. The ability of diaryl ketones to abstract hydrogens depends to a large extent on the electron configuration of the excited state of the carbonyl group. The substituents on the molecule can change the nature of the lowest triplet state from \((n,\pi^*)\) to \((\pi,\pi^*)\). In the \((n,\pi^*)\) state the excitation energy is localized on the carbonyl group while in the \((\pi,\pi^*)\) state the excitation is associated with the whole system of the aromatic molecule. The increase of the electron density on oxygen diminishes its electrophilicity. Therefore, compounds which fail to photoreduce are those where the \((\pi,\pi^*)\) triplet state is lower in energy than the \((n,\pi^*)\) state.

It is possible, however, to bring about the photoreduction of ketones with low-lying \((\pi,\pi^*)\) excited states using an electron transfer process. More generally, all types of aryl ketones, whether they have low-lying \((n,\pi^*)\) or \((\pi,\pi^*)\) excited states can be efficiently reduced or give photoadducts in the presence of compounds, such as amines and sulfides, with low oxidation potentials. In particular, the reaction of ketones in the presence of amines have attracted considerable attention in organic synthesis. Evidence shows that these processes are fundamentally different from the direct hydrogen abstractions considered above. First, the rate constants for the quenching of the triplet ketones by amines are very large. For example, benzophenone is quenched
approximately 2000 times faster by triethylamine \((k_q = 2.3 \times 10^9 \text{ dm}^3\text{mol}^{-1}\text{s}^{-1})\) than by propan-2-ol \((k_q = 1.26 \times 10^6 \text{ dm}^3\text{mol}^{-1}\text{s}^{-1})\). Also the triplets of fluorenone and 4-aminobenzophenone, which are unreactive in cyclohexane, are quenched by triethylamine with \(k_q\) values of \(3.2 \times 10^7\) and \(5.4 \times 10^7 \text{ dm}^3\text{mol}^{-1}\text{s}^{-1}\) respectively.

Scheme 2

\[
\text{Et}_3\text{N}^* \rightarrow \text{Et}_2\text{N}^*\text{-CHCH}_3 + \text{pinacol} + \text{hydroxyamine}
\]

It is also evident that the rate-determining step in the quenching process does not involve abstraction of an \(\alpha\)-hydrogen from the amine due to the fact that within the pairs of triethylamine and \(\tau\)-butyldimethylamine, and of \(\tau\)-butylamine and \(s\)-butylamine, the rate constants of the triplet quenching is approximately the same. The second difference is that in the presence of amines, the limiting quantum yields for the consumption of the ketones are considerably lower than those for the process involving propan-2-ol. Thus, the mechanism for photo-reduction of ketones in the presence of amines has to account for the rapid quenching of the excited triplet state of the ketones resulting in both chemical reaction and physical quenching. The characteristics of this process are shown in
Scheme 2, and the reactions generally go through electron transfer and proton transfer steps to produce the radicals which lead to different products, such as fluorenone pinacol and the hydroxyamine.

Intermolecular photochemical reduction of carbonyl compounds through an electron transfer process is of significance in organic synthesis\(^{6,7}\) (Scheme 3).

Scheme 3

\[
\text{Scheme 3}
\]

Mariano's extensive studies on electron transfer photochemistry in general and on \(\alpha\)-silylated amines in particular, include the addition to cyclohexenones to produce
γ-aminoketones. Cossy and Portella reported on photoreductive cyclization of δ,ε-unsaturated ketones in the presence of hexamethylphosphoric triamide (HMPA) or triethylamine in acetonitrile. By this method bicyclic cyclopentanols can be synthesized in high yields.

Another interesting result of the study of the intermolecular hydrogen abstraction reactions involves substituent effects on the tertiary/primary (t/p) selectivity that triplet benzophenone displays towards 2,3-dimethylbutane. The two radicals were trapped by carbon tetrachloride as the alkyl chlorides. The t/p ratio increased by a factor of 8 in going from 4,4'-dimethoxybenzophenone to 4-cyano-benzophenone. Thus, the most electron demanding ketone triplet is most selective towards tertiary C-H bonds.
INTRAMOLECULAR HYDROGEN ABSTRACTION

Ketones and aldehydes, in which the molecular structure allows a close approach between the excited carbonyl group and a hydrogen attached to an sp³ hybridized carbon atom within the same molecule, undergo intramolecular hydrogen abstraction. This hydrogen abstraction process is favored from the γ-carbon atom, since in this 1,5-hydrogen shift the abstraction can occur in a strain-free chair-like transition state. Intramolecular hydrogen atom abstraction also occurs from other positions when there is no hydrogen at the γ position and when the molecular conformation allows the other sites to come close to the excited carbonyl group. The mechanistic studies have suggested that the rate constants for hydrogen abstraction and the behavior of the resulting 1,x-biradicals have revealed the strong influence of conformational effects on such an intramolecular process. However, due to the fact that the main fate of the large 1,x-biradicals (x is greater than 4) is cyclization, these reactions provide new synthetic possibilities for the construction of cyclic compounds. Since the γ-hydrogen abstractions provide much of the early structure-reactivity relationships in triplet state photochemistry, it is important to understand this process.

1. γ-Hydrogen Abstractions

The γ-hydrogen abstraction generates a 1,4-biradical and the products observed from the process can be conveniently rationalized in terms of such a species. Photochemical hydrogen atom abstraction, followed by cyclization and cleavage reactions, is often referred to as the Norrish Type II reaction. The major factors that affect the reaction process and the characteristics of the photochemically excited carbonyl groups have been studied in terms of 1) the
electronic effects on reactivity; 2) the orientation requirements for the γ-hydrogen abstraction; 3) the behavior of 1,4-biradicals, particularly the structural influence on the lifetime of the biradicals and their reactions; and 4) the environmental effects.

It has been well established that the polarization of the carbonyl group in the ground state, which accounts for the facile nucleophilic attack at the carbonyl carbon, is replaced in the excited state by an unpaired electron in both a π* antibonding orbital and in a p-type orbital on oxygen. The net result is that the oxygen, as well as its n orbital, is now electron-deficient while the carbon atom of the carbonyl becomes somewhat electron-rich. Thus, (n, π*) triplet carbonyls have chemical and physical characteristics of a biradical and have similarities to alkoxy radicals with respect to their hydrogen atom abstraction abilities. The strongly electron-deficient nature of (n, π*) triplets has been demonstrated by Wagner. For example, rate constants for triplet state γ-hydrogen abstraction in δ-substituted valerophenones display a Hammett linear free energy relation when plotted against σ1 values, with a ρ value of -1.85. The rate constants of γ-hydrogen abstraction (kH) values for a number of simple δ-, and ring substituted phenyl ketones, indicate that the presence of an electron-withdrawing group at the δ position significantly decreases the rate of γ-hydrogen abstraction, whereas the substituents on the phenyl ring alter the kH values by changing the excitation mode of the carbonyl group.

The efficiency of hydrogen abstraction and the formation of the 1,4-biradical is also largely dependent on the preferred molecular geometry in the ground state. This influence of the conformation on the reaction is illustrated by the photoreaction of 1-methylcyclohexyl phenyl ketone (Scheme 4). The
products from the photolysis are benzaldehyde (from α-cleavage) and 1-methyl-6-phenylbicyclo[3.1.1]heptan-6-ol (from γ-hydrogen abstraction and cyclization).

The results obtained from quenching experiments revealed that both of the products are generated from the $3(n,\pi^*)$ reaction of the carbonyl compound, but from the two different conformers: the axial conformer and the equatorial.
conformer of the phenylcarbonyl group. From the molecular structures, it is
evident that the equatorial isomer is expected to lead to α cleavage, whereas the
axial isomer is ideally oriented to undergo γ-hydrogen abstraction. Furthermore,
from the rate data shown above both processes are appreciably more rapid than
ring inversion does. This indicates that the product composition and the
efficiencies of the processes reflect the population of the ground-state conformers.
It is, therefore, to be expected that imposing structural limitations on rotations of
the bonds between carbonyl and the γ-C-H will reduce the population of
unfavorable conformations. Therefore, the rate constant for γ-hydrogen
abstraction will increase, when the freedom of rotation is decreased. This has
been accomplished by the photolysis of the following three compounds. The $k_H$
values do increase with increasing constraint towards the required abstraction
conformation.\footnote{Turro and Weiss have reported $^3\left(n,\pi^*\right)$ reactions of the 2-n-propyl-4-t-
butylcyclohexanones. Irradiation of cyclohexane solutions of cis- and trans-2-n-
propyl-4-t-butylcyclohexanones results in different photochemistry, both
qualitatively and quantitatively (Scheme 5). The cis isomer gave only 4-t-butyl-
cyclohexanone from an intramolecular hydrogen abstraction/elimination process;
whereas, the trans isomer gave the cis isomer as the major product, presumably
as the result of α cleavage followed by epimerization. The results of quenching

$\begin{align*}
    k_H & \quad 1.2 \times 10^8 \text{s}^{-1} \\
    & \quad 6.0 \times 10^8 \text{s}^{-1} \\
    & \quad 7.0 \times 10^9 \text{s}^{-1}
\end{align*}$
experiments showed that the type II process was not affected by addition of 1,3-pentadiene, which implied either that nearly all of the type II cleavage of the cis isomer occurred in the singlet state or that the type II cleavage occurred in the triplet state with a rate constant greater than $8 \times 10^8 \text{s}^{-1}$. On the other hand, the conversion of the trans to the cis isomer was strongly quenched by 1,3-pentadiene.

They suggested that the striking contrast in the photochemistry of the cis- and the trans isomer results from a stereoelectronic requirement for $\gamma$-hydrogen abstraction and this requirement should also exist in all photochemical hydrogen abstraction reactions by the $n,\pi^*$ states of alkyl ketones.

The lifetimes of the 1,4-biradicals derived from 1,5-hydrogen abstractions in triplet phenyl alkyl ketones are generally of the order of 30-100 ns, whereas those from triplet aliphatic ketones are much longer (c. 10 $\mu$s). These biradicals undergo partitioning between reverse hydrogen transfer to re-form the starting materials and (or) their stereoisomers, combination to yield the cyclobutanols or fragmentation to the alkenes and enols ($\beta$ cleavage) as shown in Scheme 6.
It is difficult to predict how a particular species will partition since the competing processes are independently affected by structural variations. For efficient cleavage, the biradical needs to take up a conformation in which the

![Scheme 6](image)

singly occupied p orbitals overlap significantly with the C$_2$-C$_3$ bond (i.e. the bond to be broken) and hence a parallel arrangement of the orbitals is required. Substituents on C-2 cause marked eclipsing interactions along the C$_1$-C$_2$ bond of the biradical and hence twist the parallel geometry for elimination towards a non-planar conformation from which the cyclization can still occur. There are, however, no significant eclipsing interactions introduced by substitution at C-3 and indeed in such cases the distortion of planarity of the biradical will cause an 1,3-interaction between the substituent at C-3 and either the phenyl or hydroxyl group. These substituent influences on the conformations of the biradical are clearly evidenced in the reactions of butyrophenones as shown in Scheme 7.
Scheme 7

\[
\begin{align*}
\text{cleavage} & \quad \text{cyclization} \\
(\text{ratio of quantum yields}) \\
R' & = H, R'' = Me & 8.6 & 1 \\
R = R' = H, R'' = Me & 2.3 & 1 \\
R = H, R' = R'' = Me & 0.125 & 1 \\
R = Me, R' = R'' = H & 850.0 & 1 \\
\end{align*}
\]

The cleavage reaction has certain utility in organic synthesis. Some examples are shown in Scheme 8. Descotes has shown that the photolysis of a sugar derivative can induce hydrogen abstraction from the anomeric carbon to give a lactone. When the distance between the anomeric carbon and the carbonyl is extended by two methylenes, the type II cleavage produces a vinyl ether.\textsuperscript{18} Generation of a spiro-bicyclic enone from the 2+2 photocycloaddition product illustrates another example of the \( \beta \)-cleavage reaction in organic chemistry.\textsuperscript{19} The most interesting use of \( \beta \)-cleavage was Goodman and Berson’s preparation of \textit{meta}-xylylene.\textsuperscript{20} Another example of the synthetic utilization of the type II cleavage reaction is the photoxidation. This reaction involves a photolysis of pyruvates of an alcohol. After \( \gamma \)-hydrogen abstraction and \( \beta \)-cleavage, the alcohol can be oxidized to the corresponding aldehyde or ketone.\textsuperscript{18}

Cyclization can also become the major process for many compounds having rigid molecular structures. In these molecules, the cleavage product, if produced, would be extremely strained. An example of the control by such structural
Scheme 8

\[
\begin{align*}
\text{OAc} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{n=0} & \quad \text{hv} & \quad \text{OAc} \\
\text{AcO} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{R} & \quad \text{hv} & \quad \text{n=2} & \quad \text{OAc}
\end{align*}
\]
features is the exclusive formation of the cyclobutanol from 1-adamantyl acetophenone.\textsuperscript{21} Several other examples\textsuperscript{22} that produce cyclobutanols are shown in Scheme 9. Since the type II photocyclization is often complicated by the photocleavage and sometimes by the type I photo process, application of type II photocyclization in the total synthesis of natural products is quite rare. One notable exception was demonstrated by Paquette in the synthesis of punctantin.\textsuperscript{23}

Scheme 9
2. δ-Hydrogen Abstraction

δ-Hydrogen abstraction is also fairly common and arises in the situations where γ-hydrogens are not available.\textsuperscript{1,4,22,24} Since the 1,5-biradicals derived from the 1,6-hydrogen abstraction between the excited carbonyl and δ-hydrogens cannot afford fragmentation products, the major behavior of these radicals is cyclization. Therefore, δ-hydrogen abstraction is more easily studied and of greater synthetic interest for compounds which have no γ-hydrogen. These compounds include β-alkoxyketones and aldehydes, as well as the ketones that have a quaternary carbon at the γ-position. Earlier studies dealt mostly with photocyclizations of ortho-substituted aryl ketones as shown in Scheme 10.

Scheme 10

It was believed that excited ketones abstract only γ-hydrogen if both γ- and δ-hydrogen are present; however, Wagner recently showed that δ-methoxy-
valerophenone underwent both γ- and δ-hydrogen abstraction with comparable rate constants.\textsuperscript{25} The δ-methoxy group activates the δ C-H bonds by hyper-conjugation and deactivates the γ C-H bonds by an inductive effect (Scheme 11). Generally, however, the γ/δ selectivity in triplet ketones is 20:1, as it is in alkoxy radicals.\textsuperscript{26} The conformational restraints imposed by cyclic systems are nowhere better illustrated than in Paquette's synthesis of dodecahedrane, which relied on several δ-hydrogen abstractions by cyclopentanone units\textsuperscript{27}. The polycyclic frame holds δ-hydrogens close to, and γ-hydrogens away from, the carbonyl group.

Scheme 11

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{hv}};
\draw[->] (0,0) -- (1.5,0);
\node at (1.5,0) {t-BuOH};
\node at (-1.5,0) {Ph \ wrongdoing - OMe};
\node at (1.5,0) {Ph \ wrongdoing - OMe};
\node at (3,0) {OMe};
\node at (3.5,0) {OMe};
\node at (4,0) {OMe};
\node at (4.5,0) {OMe};
\node at (5,0) {OMe};
\node at (5.5,0) {OMe};
\node at (-3,-1) {Ph \ wrongdoing};
\node at (-3,-2) {HO \ wrongdoing};
\node at (-2.5,-2) {\textcircled{}};
\node at (-1.5,-2) {\textcircled{}};
\node at (0,-2) {\textcircled{}};
\node at (1,-2) {\textcircled{}};
\node at (1.5,-2) {\textcircled{}};
\node at (2,-2) {\textcircled{}};
\node at (3,-2) {\textcircled{}};
\node at (3.5,-2) {\textcircled{}};
\node at (4,-2) {\textcircled{}};
\node at (4.5,-2) {\textcircled{}};
\node at (5,-2) {\textcircled{}};
\node at (5.5,-2) {\textcircled{}};
\node at (-3,-3) {Ph \ wrongdoing - HO \ wrongdoing};
\node at (-3,-4) {\textcircled{}};
\node at (-2.5,-4) {\textcircled{}};
\node at (-1.5,-4) {\textcircled{}};
\node at (0,-4) {\textcircled{}};
\node at (1,-4) {\textcircled{}};
\node at (1.5,-4) {\textcircled{}};
\node at (2,-4) {\textcircled{}};
\node at (2.5,-4) {\textcircled{}};
\node at (3,-4) {\textcircled{}};
\node at (3.5,-4) {\textcircled{}};
\node at (4,-4) {\textcircled{}};
\node at (4.5,-4) {\textcircled{}};
\node at (5,-4) {\textcircled{}};
\node at (5.5,-4) {\textcircled{}};
\node at (-3,-5) {HO \ wrongdoing};
\node at (-3,-6) {\textcircled{}};
\node at (-2.5,-6) {\textcircled{}};
\node at (-1.5,-6) {\textcircled{}};
\node at (0,-6) {\textcircled{}};
\node at (1,-6) {\textcircled{}};
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\node at (4.5,-6) {\textcircled{}};
\node at (5,-6) {\textcircled{}};
\node at (5.5,-6) {\textcircled{}};
\node at (0,-5) {\textbf{.37}};
\node at (1.5,-5) {\textbf{.06}};
\node at (3,-5) {\textbf{.03}};
\node at (4.5,-5) {\textbf{.015}};
\node at (6,-5) {\textbf{.085}};
\end{tikzpicture}
\end{center}

Wagner\textsuperscript{24} also reported that the 1,5-biradicals often do not cyclize very efficiently, as shown in the case of the photocyclization of β-ethoxypropioxiphene. The triplet abstracts a δ-hydrogen relatively slowly ( \( k=2\times10^7 \text{ s}^{-1} \)) and the resulting biradical forms two diastereomeric tetrahydrofuranols. The cis/trans ratio of products depends upon solvent, as expected with hydroxy biradicals. Study of the α-deuterated ketone revealed the migration of deuterium to the δ-carbon. This provides another reaction pathway for the 1,5-biradicals (Scheme 12).
Descotes has applied a δ-hydrogen abstraction reaction to modify the structure of various sugars. When the THP derivative of 4-hydroxy-4-methyl-2-pentanone was irradiated, hydrogen abstraction occurred only from the acetal C-H bond and not from the methyl group. This selectivity is produced by strong deactivation of the methyl C-H bond by the β-oxygen and by the intrinsic reactivity of an acetal C-H bond. Likewise, glycosides made from 4-hydroxy-2-
butanone undergo photocyclization at the anomeric carbon (Scheme 13). The drawback of these processes are the poor stereoselectivity in the formation of cyclization products.

3. Photoenolization

Photoenolization also involves a \( \gamma \)-hydrogen abstraction reaction.\(^4\,12,29\) This reaction occurs when the carbonyl functionality and the site of the \( \gamma \)-hydrogen are separated by an ethene or an aromatic ring unit. In such cases, photocleavage reactions cannot occur, but both of these compounds do produce photoenols with varying efficiency. In the aliphatic series, the lowest triplet state has \( (\pi,\pi^*) \) character and this decays by geometrical isomerization between the cis and trans isomers. The cis isomer does, however, undergo a low-efficiency hydrogen abstraction from the \( (n,\pi^*) \) state and the diene thus formed ketonizes to give the \( \beta,\gamma \)-unsaturated ketone in an overall process of photodeconjugation.

\[
\begin{align*}
\text{R} & \quad \text{R} \quad \text{R} \\
\text{O} & \quad \text{O} \\
& \quad \text{OH} \\
& \quad \text{H} \\
\end{align*}
\]

Intramolecular hydrogen abstraction of \( \alpha \)-alkyl aryl ketones can also generate photoenols from the 1,4-biradicals. The photoenols are generally unstable and are evidenced by flash photolysis studies and trapping processes.\(^30\) Mechanistic studies have demonstrated that the photoenols derived from the 1,4-biradicals have two configurations \( Z \) and \( E \). The \( Z \) isomer, which can undergo a fast \([1,5]\) sigmatropic shift back to the starting ketone, is kinetically unstable and has a shorter lifetime (\( \tau \sim 30 \text{ ns} \)) than the \( E \) photoenol (\( \tau \sim 4 \text{ s} \)) which can be trapped intermolecularly by a Diels-Alder reaction process. The formation of benzocyclo-butene provides further evidence for the presence of photoenols (Scheme 14).
Wagner studied the mechanism for the photocyclization of ortho-alkyl aryl ketones to cyclobutenols.\textsuperscript{31} He found that a variety of acetophenones and benzophenones furnished benzocyclobutenols in high yield upon UV irradiation. In Scheme 14

\[
\begin{align*}
R & \quad \xrightarrow{k=10^7 \text{s}^{-1}} \quad \text{Z} & \lambda_{\text{max}} &= 420\text{nm} \\
& \quad \xrightarrow{t = 30 \text{ ns}} \quad \text{E} & \lambda_{\text{max}} &= 430\text{nm} \\
\text{Z} \quad \xrightarrow{t = 4 \text{ s}} \quad \text{E} & & \text{R} \quad \xrightarrow{t = 4 \text{ s}} \quad \text{E}
\end{align*}
\]

all cases only the trans diastereomer was formed. The reaction was completely quenched by the presence of acid. It was concluded that cyclobutenols were formed in a three step process: 1) triplet $\gamma$-hydrogen abstraction to yield a $1,4$-

\[
\begin{align*}
R & \quad \xrightarrow{\text{hv}} \quad \text{E} & \text{R} \quad \xrightarrow{\text{hv}} \quad \text{E}
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{CH}_3, \text{Ph} \\
\text{R}' = \text{H, OMe, OCH}_2\text{CH}=\text{CH}_2, \text{O(CH}_2)_2\text{CH}=\text{CH}_2
\end{align*}
\]
biradical triplet enol; 2) decay of the twisted triplet enol to the planar ground state; 3) conrotatory electocyclization of the enol to form a cyclobutenol. Acid catalyzed the reversion of the enol to the starting ketone; it did not catalyze the reversion of cyclobutenol to ketone, but did catalyze their trans-cis interconversion. The fact that acid quenches cyclobutenol formation thus demonstrates that cyclobutenols are formed from the enols. This mechanism demands that only one of the two possible enols is formed and lives long enough to rearrange thermally (Scheme 15).

Since the ortho-quinodimethane can undergo a Diels-Alder reaction, the ground state photoenols become a valuable reactive synthetic intermediate. One example of the synthetic utility of photoenols is the photochemical synthesis of estrone demonstrated by Quinkert\textsuperscript{32} (Scheme 16). An aryl ketone, synthesized from a phenyl vinyl ketone and a cyclopentanone derivative, was photolyzed with light of wavelength greater than 340 nm at 95° C in methylcyclohexane (boiling point 100.9° C) to produce two diastereomeric tetracyclic hydroxyketones. The dehydration product was isolated in 65% overall yield.

Oppolzer\textsuperscript{33} reported a photocyclization reaction of a benzaldehyde derivative which underwent a photoenolization/Diels-Alder process to produce a
Scheme 16

MeO

TMS

+ MeO

MeO

MeO

hν

MeO

MeO

MeO

MeO

- H₂O

MeO

MeO

R=H, estrone
diastereomeric mixture of tricyclic compounds in a 3:1 ratio (Scheme 17). The major isomer was formed through a rapid thermal cycloaddition of the E-enol to the neighboring olefinic double bond via the endo transition state; the minor isomer was formed via the exo transition state.

Scheme 17

Transformation of the reactive photoenol into 1,3-dihydrobenzo[c]thiophene 2,2-dioxides offers an alternative way to use the photoenolization reaction in organic synthesis. Durst and coworkers reported that the photolysis of benzaldehyde in the presence of sulphur dioxide can generate 1-hydroxy-1,3-dihydrobenzo[c]thiophene 2,2-dioxide, which can regenerate the E-enol under thermal conditions. Trapping the E-enol with various dienophiles can produce tetrahydronaphthalenes. Such compounds have considerable potential in the synthesis of lignans of the podophilotoxin family (Scheme 18).

As part of our study of the synthetic potential of photochemical hydrogen abstraction reactions, we have explored several synthetic routes to the naturally
occurring compounds with interesting biological activities. In this thesis, we will concentrate on the direct synthesis of paulownin, aklavinone and pleurotin.

Scheme 18

\[
\text{CHO} \xrightarrow{h, \text{SO}_2} \text{CHO} \xrightarrow{110^\circ C} \xrightarrow{\text{ZCH}=\text{CHY}} \xrightarrow{R'XH, H^+} \text{podophyllotoxin}
\]
REFERENCES


PAPER II

STEREOSELECTIVE TOTAL SYNTHESIS
OF PAULOWNIN
INTRODUCTION

Photochemical reactions have been employed for the construction of a wide range of natural products. Smith, Crimmins and Winkler have made effective use of the 2+2 cycloaddition reaction for the synthesis of terpenes and alkaloids. Mariano has studied electron transfer cyclizations of amino ketones, providing novel strategies for the synthesis of fused and spirocyclic compounds. Schultz has generated clever and direct syntheses of cyclopentenones using the photochemical rearrangements of cyclohexadienones. In contrast, the hydrogen atom abstraction-cyclization chemistry, often termed the type II photocyclization, has been almost unused in natural products synthesis. One notable exception is the elegant use of this reaction by Paquette to create the cyclobutane ring in punctatin. Photoenolization, a related reaction, has been used by Oppolzer and others for alkaloid synthesis. The photophysical basis of the type II photocyclization reaction has been well studied, most notably by Wagner and Scaiano. They have demonstrated that an n-π* triplet state is involved in the type II photocyclizations of diaryl and aryl alkyl ketones. They also reported that subtle conformational effects can profoundly influence product distributions. The type II photocyclization reactions of aryl glyoxylates have been rigorously examined by Pappas and by Lappin. Pappas discovered a dramatic solvent effect on the stereochemistry of the cyclization.
Studies of type II photocyclization reactions of dialkyl ketones are less common. The vast majority focus on the formation of cyclobutanols. Indeed, unless the 1,5-hydrogen atom abstraction pathway is blocked, it will be the predominant one. Paquette made good use of 1,6-hydrogen atom abstraction reactions in the latter stages of his classic synthesis of dodecahedrane. A limited study of five-membered ring formation was made by Descotes. His studies, which dealt largely with carbohydrate systems, showed that such cyclizations generally afforded stereoisomeric mixtures of tetrahydrofuranols.

![Reaction Scheme]

Additionally, Carless and coworkers noted the following cyclization.

![Reaction Scheme]

Despite the poor stereoselectivity observed in the acyclic systems described above, we felt that stereoselectivity could be improved if the type II photocyclization was used to append a ring onto a rigid ring system. The furan ring system of the lignans was chosen as a test case. Not only does this ring system pose the challenge of creating four contiguous stereogenic centers, but there are also several members of this lignan family which exhibit biological activity.
Natural lignans with furo[3,4-c]furan structure are fairly well known. They can be classified into three groups: type A, type B and type C, according to their structure.

Fused bis-ethers of type A are found as constituents in various Chinese traditional medicines. Nikaido and coworkers have reported that the lignans isolated from Forsythia fruit (a Chinese medicinal drug used as an anti-inflammatory, diuretic and detoxicant agent) showed inhibitory activity against the cyclic adenosine monophosphate (c-AMP) phosphodiesterase. The most potent compounds among the lignans tested are pinoresinol A1 (IC₅₀: 7.5x10⁻⁵ M) and its congeners: the 1-acetoxy pinoresinol A2 (IC₅₀: 3.2x10⁻⁵ M) and its β-D-glucoside A3 (IC₅₀: 4.4x10⁻⁵ M). The corresponding 1-hydroxy analogues also exhibited c-AMP inhibition activity (IC₅₀ ranging from 21 to 30x10⁻⁵ M). Deyama and coworkers have found that lignans isolated from the bark of Eucommia ulmoides Oliv. (Eucommiaceae), such as (+)-medioresinol di-O-β-glucoside (A4), and the diglucosides of (+)-pinoresinol derivatives (A5-7), showed strong inhibitory activity against c-AMP phosphodiesterase. An extensive study of the comprehensive medicinal utilization of various parts of the whole tree of Paulownia has been reported by a group of Chinese scientists in 1982. Paulownin (1) was isolated along with other lignans, such as sesamin (A8).
Since Sutherland found cyclic adenosine monophosphate (AMP) as a second messenger inside cells, compounds that act to alter cyclic AMP metabolism have been the subject of studies not only from a biochemical point of
view, but also with the aim of the development of new medicinal drugs. Extensive screening tests aiming to find inhibitors of cyclic AMP phosphodiesterase have shown that a variety of synthetic compounds and natural products possess inhibitory effect against this enzyme.\textsuperscript{20} Weinryb and coworkers have reported that a considerable number of therapeutic agents tested show an inhibitory effect against phosphodiesterase.\textsuperscript{21} In addition to well-known phosphodiesterase inhibitors, such as papaverine and theophylline, ethynyl estradiol, testosterone, diazepam, dipyridamol and oxytocin are potent inhibitors of phosphodiesterase. Although such a finding does not necessarily mean that pharmacological activity in vivo is due to the alteration of cyclic AMP metabolism, these observations indicate that phosphodiesterase inhibitors found in the natural products might show a variety of pharmacological activities. Cyclic AMP phosphodiesterase has become a valuable tool for screening to detect biologically active compounds contained in medicinal plants used in traditional medicine, since biological activities of traditional medicinal drugs are sometimes very difficult to detect by in vivo tests due to the mildness of their actions.\textsuperscript{16}

The lactones of type B have been shown to be plant germination inhibitors and some of them were reported to have antitumour activity.\textsuperscript{22} Several bis-lactones of structure C have been isolated from a cultured mushroom, \textit{Inonotus} sp. k-1410, and are reported to show interesting biological activities.\textsuperscript{23}

There is considerable interest in the synthesis of furofuran lignans of types A, B and C. Four basic strategies have been successfully employed to synthesize the furo[3,4-c]furan lignans. One strategy\textsuperscript{24} is exemplified by a creative synthesis by Snieckus and features the reaction of two equivalents of an aldehyde
with a succinamide dianion. The resulting dihydroxydiamide was then cyclized under acidic conditions and converted to a lignan. This process is extremely direct.

However, the production of diastereomeric mixtures and elimination products in the cyclization step are drawbacks.

A stepwise condensation of succinate with different aromatic aldehydes was established by Pelter. Starting from the dimethyl 2-methylthiosuccinate, an LDA-mediated condensation between the more reactive enolate and ArCHO provided, after an acid-catalyzed cyclization, the trisubstituted γ-lactone as a mixture of diastereomers. The enolate derived from the major (cis) isomer was then reacted with another aromatic aldehyde (Ar¹CHO) to give the asymmetric bis-lactone of type C in about 50% yield.

A second strategy was developed by Pelter and coworkers. It involved the dimerization of a substituted cinnamic acid with thallium trifluoroacetate followed by lactone reduction and deoxygenation. This process offered only a 9% yield of the bis-lactone in the coupling step.
The third strategy, the Whiting strategy, featured an intramolecular cyclization of the enol silyl ether of a lactone. The bis-ethers prepared by this process through lactone intermediates were obtained as a mixture of α,β isomers.

Finally, an enantiocontrolled route centered around an intramolecular Diels-Alder reaction has recently been reported by Takano. Starting from diethyl L-tartrate, the precursor for the Diels-Alder reaction was prepared in eight steps in about a 50% overall yield. The hetero Diels-Alder reaction gave only the product with a cis ring junction, which may be attributable to the preferential intervention of the endo transition state. Further transformations completed the enantiocontrolled synthesis of furofuran lignans.
The strategies discussed above have their unique features; however, the type A compounds with oxygen-containing substituents located at C-1 of the furo[3,4-c]furan skeleton could not be easily obtained through these methods.
RESULTS AND DISCUSSION

The significant biological activity of furo[3,4-c]furan lignans and their unique structural features are of interest to us. Development of a direct synthetic route to this class of compounds would benefit the study of their structure-activity relationship and the discovery of chemotherapeutic agents. The compounds that have strong inhibitory activity against cyclic AMP phosphodiesterase generally have aryl groups at C-2 and C-6 and an oxygen-containing substituent at C-1 position. Since transformation of the hydroxyl group into other functionalities has been well developed, paulownin (1) was selected as our target molecule for synthetic studies towards a general approach to the type A bis-ether lignans.

Scheme 1

The retrosynthetic analysis is shown in Scheme 1. It requires the preparation of ketone 2, which in turn would be constructed from piperonal through 3-tetrahydrofuranone 3. We anticipated that the photocyclization of ketone 2 would generate a cis ring fusion and that the diradical intermediate in the
photocyclization reaction would be more stable with the aryl group on the developing exo face.

The ketone 3 was easily synthesized in 49% overall yield from piperonal by reaction with allyl magnesium bromide, followed by osmium tetroxide hydroxylation, acid-mediated triol cyclization and PCC oxidation (Scheme 2).

Scheme 2

Originally, we envisioned that 2 would be prepared by the reaction of enol silyl ether 4 with the appropriate chloromethyl alkyl ether. We reasoned that the predominant kinetic enolate produced by the reaction of 3 with lithiumdiisopropyl amide (LDA) would be derived from deprotonation of the methylene not adjacent to the oxygen of the tetrahydrofuran ring. The reaction of 4 and chloromethyl benzyl ether did not produce ketone 2 (Ar = Ph) despite several variations in Lewis acid and temperature. Fortunately, the enolate prepared from 3 and LDA reacted with gaseous formaldehyde to afford hydroxyketone 5 (Ar = 3,4-methylenedioxyphenyl)
in 50% yield. The 10.2 Hz coupling constant for the benzylic methine proton indicated that the aryl and hydroxymethyl groups were trans. Ketone 2 was then produced in 42% yield using the trichloroimidate methodology developed by Wessel.

The type II photocyclization of 2 was conducted in a quartz tube at ambient temperature using a medium pressure Hanovia lamp. The reaction was complete on a millimole scale in less than an hour. In practice, the reaction was run to approximately 90% completion and the product separated from 2 by silica gel chromatography. Our racemic bicyclic alcohol 1 was identical to natural palownin by proton NMR and $^{13}$C NMR spectroscopy. Significantly, 1 was the only product, as evidenced by TLC and liquid chromatographic analysis of the solution directly after photolysis.
Using this synthetic route, compound 6 of type A can also be synthesized. Starting from benzaldehyde, 4-hydroxymethyl-5-phenyl-tetrahydrofuran-3-one (7) was prepared in a 27% overall yield. This hydroxyketone was then treated with \( p \)-methoxybenzyl trichloroimidate to provide a benzyl ether 8 in 65% yield. Photolysis of the benzyl ether 8 gave the compound 6 in 72% yield.

The synthetic utility of the type II photocyclization reaction has been demonstrated by a stereoselective total synthesis of racemic paulownin. The synthesis proceeds in only seven steps from piperonal. The high stereoselectivity observed when the type II photocyclization is conducted on a cyclic compound should make this reaction quite attractive to synthetic organic chemists. This synthesis also provides a convergent method for the construction of bis-ether lignans of type A.
EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all the reaction were conducted under an argon atmosphere. All organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported relative to tetramethylsilane as an internal standard. Coupling constants were reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sb = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of CDCl₃ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400).

(1,3-Benzodioxol-5-yl)-3-buten-1-ol

To a solution of piperonal (4.50g, 30 mmol) in 60 mL of THF at 0°C was added allyl magnesium bromide (1M, 31 mL, 31 mmol). The solution was allowed to warm slowly to ambient temperature over 2 h. The solution was poured into
water and extracted twice with methylene chloride. The combined organic layers were dried and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with 5:1 H:EA to afford 5.13g (89.1% yield) of alcohol. The alcohol was a clear liquid. NMR(CDCl3) δ (ppm) 2.01 (d, J=2.7 Hz, 1H), 2.47 (t, J=6.9 Hz, 2H), 4.65 (dt, J=2.7, 6.9 Hz, 1H), 5.10-5.20 (m, 2H), 5.79 (ddt, J=6.9, 9.6, 17.4 Hz, 1H), 5.95 (s, 2H), 6.75-6.87 (m, 3H). IR (film) 3390, 3065, 2890, 1635, 1605, 1500, 1485, 1440, 1240, 1035, 925, 810 cm⁻¹. TLC(5:1 H:EA) Rf = 0.36.

(1,3-Benzodioxol-5-yl)-tetrahydrofuran-3-one (3)

To a solution of 1-(1,3-benzodioxol-5-yl)-3-buten-1-ol (2.67g, 13.9 mmol) in 70 mL of 8:1 acetone:water was added N-methylmorpholine-N-oxide (1.95g, 16.7 mmol) followed by osmium tetroxide (3.5 mL of t-BuOH solution, 0.69 mmol). The solution was stirred for 23 h at ambient temperature. The reaction was quenched by 2.20 g of sodium thiosulfate and 2.20 g of Florisil. The suspension was stirred for 30 min and filtered through silica gel using ethyl acetate. The organic layer was dried and concentrated in vacuo to provide 2.8g of a sticky liquid which was taken on to the next step.

To a solution of the triol (2.8g) in 250 mL of chloroform was added p-toluenesulfonic acid (0.500g). The solution was stirred at 50°C for 12 h. The solvent was removed in vacuo to yield a light yellow oil.

To a suspension of PCC (4.38g, 20 mmol) and Florisil (4.5g) in 40 mL of anhydrous methylene chloride at -10°C was added the alcohol (12.7 mmol). The suspension was allowed to slowly warm to ambient temperature over 20 h. The suspension was filtered through silica gel with 2:1 H:EA. The filtrate was
concentrated to afford a residue. This residue was purified by flash chromatography on silica gel with 9:1 H:EA to afford 1.68g (57% yield) of ketone 3. This compound was a white solid with m.p. 70-71°C. NMR (CDCl₃)  δ (ppm) 2.50 (dd, J=9.6, 18 Hz, 1H), 2.81 (dd, J=6.0, 18 Hz, 1H), 3.98 (d, J=17.1 Hz, 1H), 4.22 (d, J=17.1 Hz, 1H), 5.19 (s, 2H), 6.79-6.90 (m, 3H). IR (CH₂Cl₂) 1755, 1500, 1440, 1250, 1050, 1035, 940, 810, 735 cm⁻¹. MS: m/z 89, 135, 147, 148, 163, 176, 206. HRMS: calcd for C₁₁H₁₀O₄: 206.0579, found 206.0577. TLC (3:1 H:EA) Rf = 0.46.

(1,3-Benzodioxol-5-yl)-4-hydroxymethyl-tetrahydrofuran-3-one (5)

To a solution of lithium diisopropylamide (prepared from 2.1 mmol of diisopropylamine and 2.0 mmol of n-butyl lithium) in 4 mL of THF at -78°C was added ketone 3 (0.412g, 2.0 mmol) in 1 mL of THF. The solution was stirred at -78°C for 30 min and gaseous formaldehyde (prepared by heating 20 mmol of paraformaldehyde at 150°C with a nitrogen stream) was introduced into the solution. The reaction was quenched with acetic acid (0.25g, 4.1 mmol). Methylene chloride and water were added. The organic layer was washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel with 2:1 H:EA to provide 0.090g (50%) of hydroxy ketone 5. NMR (CDCl₃)  δ (ppm) 2.02 (bt, J=3 Hz, 1H), 2.44-2.53 (m, 1H), 3.68-3.77 (m, 2H); 3.97 (d, J=17 Hz, 1H), 4.36 (d, J=17 Hz, 1H), 5.02 (d, J=10.2 Hz, 1H), 5.98 (s, 2H), 6.79-6.96 (m, 3H). IR (CHCl₃): 3460, 2878, 1750, 1485, 1440, 1245, 1035, 905, 730 cm⁻¹. TLC (2:1 H:EA) Rf = 0.22.
5-(1,3-Benzodioxol-5-yl)-4-(1,3-benzodioxol-5-ylmethoxymethyl)tetrahydrofuran-3-one (2)

To a solution of hydroxyketone 3 (0.130 g, 0.55 mmol) and 1,3-benzodioxol-5-ylmethyl trichloroacetimidate (0.356 g, 1.20 mmol) in 5 mL of methylene chloride at ambient temperature was added a crystal of camphorsulphonic acid. The solution was stirred for 44 h. The solution was diluted with brine and was extracted twice with ether. The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel with 10:1 H:EA to provide 0.015 g (42% yield) of 2. Ketone 2 was a viscous oil. NMR (CDCl3) δ (ppm) 2.41-2.43 (m, 1H), 3.50 (dd, J=3.3, 9.6 Hz, 1H), 3.83 (dd, J=3.3, 9.6 Hz, 1H), 3.97 (d, J=17.1 Hz, 1H), 4.31 (d, J=17.1 Hz, 1H), 4.32 (d, J=11.7 Hz, 1H), 4.43 (d, J=11.7 Hz, 1H), 5.11 (d, J=9.9 Hz, 1H), 5.95 (s, 2H), 5.96 (s, 2H), 6.70-6.86 (m, 6H). IR (CHCl3): 2880, 1754, 1485, 1440, 1245, 1035, 905, 725 cm⁻¹. MS: m/z 77, 135, 149, 205, 218, 235, 260, 370. HRMS calcd for C20H18O7: 370.1053, found 370.1049. TLC(3:1 H:EA) Rf = 0.35.

Paulownin (1)

A solution of 2 (0.030 g, 0.081 mmol) in 20 mL of benzene was degassed with argon. The solution was irradiated with a medium pressure Hanovia lamp for 1 h. The solution was concentrated. The residue was purified by chromatography on silica gel with 5:1 H:EA to afford 0.0165 g (68% based on recovered 2) of 1. Alcohol 1 was a white solid with m.p. 82-85°C. Both the proton NMR and the 13C NMR were identical to those reported in the literature31. NMR(CDCl3) δ (ppm) 1.62 (s, 1H), 3.04-3.06 (m, 1H), 3.83 (dd, J=6.3, 9 Hz, 1H), 3.91 (d, J=9.3 Hz, 1H), 4.04 (d, J=9.3 Hz, 1H), 4.51 (dd, J=8.1, 9 Hz, 1H), 4.82 (s, 1H), 4.84 (d, J=5.1 Hz, 1H), 5.96
(s, 2H), 5.98 (s, 2H), 6.78-6.94 (m, 6H). CMR (CDCl₃): 60.40, 71.63, 74.76, 85.77, 87.47, 91.65, 101.10, 101.23, 106.87, 107.37, 108.19, 108.57, 119.77, 120.07, 129.21, 134.56, 147.24, 147.98. IR (CHCl₃): 3430, 1490, 1435, 1245, 900, 730 cm⁻¹. MS: m/z 69, 77, 93, 103, 135, 149, 163, 205, 220, 235, 370. HRMS calcd for C₂₀H₁₈O₇: 370.1053, found 370.1052.

**Compound 6**

Compound 6 was prepared through the same procedures as in the synthesis of paulownin. This compound has the following properties: NMR (CDCl₃) δ (ppm) 7.36 (m, 7H), 6.94 (d, J = 5.7 Hz, 2H), 4.95 (d, J = 5.1 Hz, 1H), 4.88 (s, 1H), 4.55 (t, J = 9 Hz, 2H), 4.08 (d, J = 9.3 Hz, 1H), 3.93 (d, J = (9.3 Hz, 1H), 3.90 (dd, J₁ = 6.0 Hz, J₂ = 9.0 Hz, 1H), 3.82 (s, 3H), 3.12 (m, 1H). IR (CDCl₃) 3370, 3060, 2960, 1610, 1510, 1250, 1060 cm⁻¹. MS: m/e 312.1, 226.1, 137.1, 117.0, 77. HRMS: m/e for C₁₉H₂₀O₄ calcd. 312.13616, measured 312.13571. TLC (EA:H = 5:1) Rf = 0.27.
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PAPER III

A DIRECT SYNTHESIS OF AKLAVINONE
Anthracyclinones are the aglycones of anthracycline antibiotics. The basic structure of the anthracyclinones has been elucidated by intensive investigations on the colored metabolites of \textit{Streptomyces purpurascens} by Brockmann and his group.\cite{1,2} The variety of structures encountered can be neatly shown in the examples of a biogenetic scheme. The work of Ollis on the biosynthesis of \(\varepsilon\)-pyrromycinone (3) has shown that polyketides, such as 1, which consist of nine acetate units and one propionate unit, can be considered as precursors of anthracyclinones which are produced by \textit{Streptomyces} species.\cite{3} Later works,\cite{4} including the labeling of precursors with \(^{13}\text{C}\), have presented further details of the biosynthesis pathway from aklavinone (2) to daunomycinone\cite{4d} (4) as shown in the following scheme.

A particular interesting fact is the incorporation of the tricyclic aklanoic acid 5 into \(\varepsilon\)-rhodomycinone 6 by certain mutants of \textit{Streptomyces}.\cite{4b} Although
this finding may not necessarily correspond to the usual biosynthetic pathway, a synthetic design going through this tricyclic intermediate to aklavinone could be devised.

The following numbering system is used for the nomenclature of the anthracycline compounds in this thesis.

Since their discovery, anthracycline antibiotics have become of great importance. Daunorubicin (7) (formerly daunomycin) and especially adriamycin (8) (the hydrochloride is marketed as doxorubicin), which are often referred to as the "first generation" anthracycline antitumor agents, are valuable drugs for the treatment of a range of human cancers, such as leukemias. These successes have stimulated enormous research activity aimed at the discovery of new chemo-therapeutic agents devoid of side effects. Some ninety anthracyclines have been studied to determine structure-activity relationships. The structure-activity relationships of daunomycin and adriamycin type anthracyclines have been studied intensively and summarized by Arcamone. These results led to
the discovery of the "second generation" anthracyclines that have as a common structural feature an 11-deoxy B-ring, thus differing in that respect from the first generation. Among the new agents, 11-deoxydaunomycin (10), 11-deoxyadriamycin (11) and 11-deoxycarminomycin (12) were discovered by the Arcamone group at Farmitalia.6a Aclacinomycin A (13) was isolated and purified by Umezawa in 1974 from a culture of *Streptomyce galilaeus*.6b Basic studies of aclacinomycin A have revealed the following characteristics of this agent compared with daunomycin and adriamycin:

1) aclacinomycin A may be classified among the drugs of the anthracycline group, such as daunomycin and adriamycin; 2) the LD$_{50}$ of aclacinomycin in mice, rats and hamsters by any route of administration are 2-3 times as high as those of daunomycin and adriamycin; 3) Both acute and subacute cardiotoxicity of aclacinomycin measured in terms of ECG (Electro-CardioGraphic) patterns proved far less than that of adriamycin, being only about 1/15 that of the later.6c
Reports of good antitumor properties and reduced cardiotoxicities, as well as the nonmutagenicity and good clinical activity exhibited by aclacinomycin A, attracted the scrutiny of synthetic chemists. Their interest was further stimulated by the report from the Japanese groups that extremely efficient bioconversion of aklavinone and its congeners to intact aclacinomycins could be achieved by mutant strains of *Streptomyces galilaeus*. This opened up the possibility that new synthetic aglycones closely resembling aklavinone could be transformed in practical yields to novel, non-natural aclacinomycin antitumor agents.

During the past two decades, a colossal effort has gone into anthracyclinone synthesis and more than forty total synthesis have been reported. The first total synthesis of racemic daunomycinone (4) was achieved by Wong in 1973, and the first "practical" synthesis of 4 was carried out using a Diels-Alder sequence by Kende in 1976. The required aminosugar L-daunosamine, the
glycone part of daunomycin (4), had been synthesized \(^1^1\) and efficient procedures to couple this sugar to the aglycone had been developed in several laboratories.\(^1^2\) With the improved synthesis by Kelly which gave the aglycone daunomycinone (4) in a 36% yield over 10 steps from naphthazarin,\(^1^3\) and striking improvements in the chiral synthesis of L-daunosamine by the Roche group,\(^1^4\) the total synthesis of "first generation" anthracycline antibiotics was essentially a chapter in organic synthesis by 1984.\(^1^5\)

Kelly's synthesis\(^1^3\) features a regioselective Diels-Alder strategy which allowed him to prepare the tetracyclic intermediate 15 in three steps from 14. After deprotection, addition of ethynyl magnesium bromide and oxidation,

\[
\text{compound 15 was converted into 16, from which daunomycinone (4) was prepared in a 36% overall yield from commercially available naphthazarin. The sequence from 14 to 16 was best effected without purification, and afforded 16 in 89% overall yield. This study provided not only a practical synthesis of daunomycinone}
\]
(4), but also the details of the regioselectivity of the Diels-Alder reaction of naphthoquinone derivatives.

In 1981 Kende and coworkers reported a synthesis of 11-deoxydaunomycinone (11). The synthesis is highly convergent. It involved an AB + D ring construction strategy. The key step in Kende's approach was the condensation of the ortho-lithiated benamide 17 and the aromatic aldehyde 18. The lactone 19 was then transformed in several steps into the tetracyclic intermediate 20 which was converted into 11 in 13 percent overall yield over 17 steps. The number of operations devoted to functional group manipulation is a disadvantage of the route.

Confalone and Pizzolato reported a synthesis of aklavinone (2) via a different type of AB + D ring strategy. Aromatic ester 21 underwent an ortho-specific Fries rearrangement to produce the keto acid 22. Friedel-Crafts cyclization yielded the anthraquinone 23 in 57% yield. The approach, however, failed to introduce the functionality in ring A effectively. A rather lengthy
sequence of steps afforded aklavinone (2) from 23. Although the synthesis is regioselective, the final target was formed in extremely poor overall yield.

Hauser and coworkers reported in 1984 a synthesis of anthracyclinone also based on the AB + D strategy. The AB ring system 24 was prepared from a
cyclohexenone in 33% overall yield through a four-step process. Condensation of 24 with a phthalide sulfone 25, a useful intermediate in the synthesis of polycyclic aromatic compounds,\(^1\) provided the tetracyclic ketone 26, which underwent oxidation to afford the anthraquinone 27. An additional seven steps led to the total synthesis of 2.

Another type of strategy involved an aldol condensation protocol developed by Kishi and Krohn. In Kishi's synthesis,\(^2\) a bromojuglone derivative 28 was reacted with a vinylfuran 29 to produce the benzofuran 30 after elimination of hydrogen bromide and air oxidation. The benzofuran was then cleaved by ozonolysis and the resulting anthraquinone aldehyde was condensed with 1-trimethylsilyl-2-butanone under titanium tetrachloride catalysis to afford the aldol product 31. This was cyclized to afford aklavinone by treatment with potassium carbonate.

![Chemical Structures](image)

This synthetic route is very direct; however, the starting materials are not readily available. Krohn\(^3\) used the same strategy for the construction of the A
ring. The anthraquinone 32, which was prepared by a Diels-Alder reaction and aromatization, was converted into 33 through a Marschalk reaction and additional transformations. The obvious drawback of his synthesis is this lengthy sequence of side chain construction and the very poor yield in making compound 33. Cyclization of 33 using Triton-B/pyridine provided a 7-deoxyaklavinone (34) which had been transformed into aklavinone (2) in two steps by Kende.\textsuperscript{22}

\textbf{32} \quad \textbf{33}

Some other interesting strategies for the construction of these compounds have also been devised. They are collated in a timely review by Krohn.\textsuperscript{2}
RESULTS AND DISCUSSION

The 11-deoxyanthracyclines are of significant medicinal interest, because these compounds exhibit dramatically lower cardiac toxicities than their 11-hydroxy counterparts. Some anthracycline antibiotics such as aclacinomycin A, have become clinically useful anticancer drugs. Our synthesis of aklavinone (2) features a photoenolization reaction, followed by a regioselective Diels-Alder reaction and a selective Pd(0)-mediated decarboalkoxylation/aromatization. However, it does rely on the Kishi-Krohn protocol for the construction of the labile hydroxy ester subunit in the A ring.

A key intermediate in our synthesis is bicyclic ketone 35. It will be prepared from aldehyde 36 using a photoenolization reaction.

Our initial objective was to study a photoenolization/Diels-Alder sequence in the preparation of an α-tetralone, such as 35. Irradiation of a benzene solution of 36 and diallyl glutaconate (37) at ambient temperature using a medium pressure Hanovia lamp with a nonex glass filter led to a mixture of hydroxy diesters 38 in 60-70% yield regioselectively. This mixture could be converted into the keto diester 35 in 62% yield using CrO3-pyr. Other oxidation conditions (Jones
oxidation, PCC) were less efficient. The reaction of 35 with Triton B and ethyl vinyl ketone (EVK) in ethanol produced a diketo diester 39 (R = allyl) in 64% yield.

\[
\begin{array}{c}
\text{OMe} \\
\text{CH}_3 \\
\text{OMe} \\
\text{CHO} \\
\end{array} + \begin{array}{c}
\text{CO}_2\text{R} \\
\text{CO}_2\text{R} \\
\end{array} \xrightarrow{\text{hv}} \begin{array}{c}
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OH} \\
\end{array}
\]

A number of conditions were considered for the decarboalkoxylation of 39. In a parallel sequence using dimethyl glutarate, it was found that decarboxymethoxylation was always accompanied by undesired intramolecular condensations. Fortunately, Tsuji and coworkers have demonstrated that certain allyl ketoesters afford enones when treated with catalytic quantities of palladium(0) reagents. Extension of this reaction to our system provided naphthol 40 (R = allyl) in 45% yield from 39. The selectivity of this reaction is interesting, in that the more hindered ester reacts, while the less hindered one is not affected. We postulate that the proximate ketone groups act as ligands for the palladium(0) reagent and direct it to the more hindered ester.

\[
\begin{array}{c}
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{O} \\
\text{C} \\
\text{B} \\
\end{array} \quad \begin{array}{c}
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{O} \\
\text{C} \\
\text{B} \\
\end{array} \quad \begin{array}{c}
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{CO}_2\text{R} \\
\text{OMe} \\
\text{OH} \\
\text{C} \\
\text{B} \\
\text{CO}_2\text{Et} \\
\end{array}
\]
However, we found later that transformation of compound 40 into the corresponding naphthoquinone 41, which is required for the construction of the D ring, often presented problems. Fortunately, oxidative demethylation of 39a using the method of Rapoport\textsuperscript{30} afforded the unstable quinone 42 which could not be purified by silica gel chromatography. Compound 42 was the only organic product of the oxidation and could be used in subsequent Diels-Alder reactions without purification.

![Chemical structures](image)

The monoallyl ester 39a was formed in the Michael addition of 35 (R = allyl) with ethyl vinyl ketone (EVK) and Triton-B in methanol. The selective transesterification of the less hindered ester was not planned; however, it was very welcome since it simplified the subsequent palladium chemistry and the methyl ester was a subunit in the structure of aklavinone (2).

With compound 42 in hand, our next objective was to construct the D ring through a Diels-Alder method using 42 as a dienophile. The diene we used in the cycloaddition reaction was 1-trimethylsilyloxy-1,3-butadiene (43). The cycloaddition products (mixture of diastereomers) were subjected to the palladium mediated decarboxylation-aromatization to produce compound 44, which has been transformed into 4-deoxyaklavinone by Krohn. Compound 44 was identical by 300 MHz \textsuperscript{1}H NMR and IR to Krohn's intermediate.\textsuperscript{21}
It is well established that acyl quinones, such as acetylbenzoquinone, react with dienes at the double bond bearing the acyl group. The Diels-Alder reactions of quinones such as 42 which contain a acyl group as part of a ring have not been studied. We speculated that a Diels-Alder reaction might occur at the unsubstituted double bond. The regiochemistry of such an addition was also an open question. Interestingly, the cycloaddition of 42 with 1-trimethylsilyloxy-1,3-butadiene (43) afforded two products (probably exo/endo isomers) which were converted into diketodiester 45 after Jones oxidation. As we had mentioned before, the mixture of adducts could also be treated with palladium acetate in hot acetonitrile to produce hydroxyanthraquinone 44 in a one pot reaction.

Palladium-mediated aromatization of 45 produced anthraquinone 46 in an 87% yield. This anthraquinone was not identical to Maruyama's intermediate 47 as evidenced by 300 MHz $^1$H NMR. However, anthraquinone 46 had the same molecular weight as 47 and the $^1$H NMR of 46 did exhibit two sharp resonances at δ 12.65 and δ 13.11 which are indicative of an intramolecularly hydrogen-bonded hydroxyquinone unit.

In view of the classic studies by Boeckmann and coworkers, it was expected that a 5-hydroxy-1,4-naphthoquinone unit would react with diene 43 to generate the desired regiochemistry. In order to synthesize the requisite
dienophile, quinone 42 was treated with palladium acetate and 1,2-bis(diphenylphosphino)ethane (dppe), followed by DDQ oxidation to produce naphthoquinone.
41 \( (R = \text{Me}) \). The DDQ step was necessary in order to convert the ketohydroquinone byproduct 48 into 41. In practice, the DDQ oxidation step could be conducted on the unpurified product from the palladium reaction without any decrease in the overall yield.

Using this methodology, naphthoquinone 41 could be prepared from 39a in 42% overall yield. The reaction of 41 with diene 43, followed by Jones oxidation of the Diels-Alder adduct afforded anthraquinone 47 in 83% yield. The 300 MHz \(^1\)H NMR spectrum of 47 correlated exactly with the spectral data published by Maruyama\(^{27}\).

Cyclization of 47 using Krohn's Triton B/pyridine conditions returned starting material\(^{29}\). The reason for the recovery of 47 using Krohn's conditions is unclear. It may be significant that Krohn has developed more than one recipe for cyclization and that conditions for conducting this reaction are very specific. In contrast, the reaction of anthraquinone 47 with Triton B and pyridine in methanol, conditions also developed by Krohn\(^{21}\), afforded 7-deoxyaklavinone 34a along with the cis isomer 34b in 76% yield as a 2:1 ratio of trans:cis isomers. The melting point of 34a was 217-219°C, which compares very favorably with that reported by Kende (220-222°C).\(^{22}\) The \(^1\)H NMR spectrum of 34a was identical to that reported by Krohn.\(^{21}\) The melting point of isomer 34b was 205-208 °C.
The use of quinone 42 as an intermediate for anthraquinones bearing either the 1,5- or 1,8-dihydroxyanthraquinone substitution pattern increases the utility of our photoenolization/Diels-Alder methodology. The synthesis of 7-deoxy- aklavinone in seven steps from 35 demonstrates the efficiency of our approach. Since 34a has been converted into 2 by several researchers, the synthesis of 34a constitutes a formal total synthesis of 2.
Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all the reactions were conducted under an argon atmosphere. All organic extracts were dried over anhydrous sodium sulphate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported relative to tetramethylsilane as an internal standard. Coupling constants are reported in Hz. Abreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of CDCl₃ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400).

**General procedure for photoenolization/Diels-Alder**

The benzaldehyde 36 (1.44 g, 8.0 mmol) and diester 37 (3.36 g, 16 mmol) was dissolved in 35 ml of dry benzene. After the solution was degassed with argon (20 min), it was photolyzed by a medium pressure Hanovia lamp with a nonex
glass filter for 48 hr. The solvent was then evaporated, the residue was purified to give 2.31 g of 38 as a mixture of diastereomers in 74% yield. This mixture can be separated to give 38a and 38b by silica gel chromatography (EA:H = 1:3).

38a: H NMR (CDCl₃) δ (ppm) 6.73 (d, J = 9.0 Hz, 1 H), 6.69 (d, J = 9.0 Hz, 1 H), 5.95 (m, 2 H), 5.30 (m, 5 H), 4.69 (dt, J₁ = 5.7 Hz, J₂ = 1.5 Hz, 2 H), 4.60 (dt, J₁ = 5.7 Hz, J₂ = 1.2 Hz, 2 H), 3.86 (s, 3 H), 3.76 (s, 4 H), 3.15 (dd, J₁ = 17.7 Hz, J₂ = 5.1 Hz, 1 H), 2.75 (m, 3 H), 2.55 (dd, J₁ = 8.8 Hz, J₂ = 15.3 Hz, 1 H), 2.28 (dd, J₁ = 11.1 Hz, J₂ = 17.7 Hz, 1 H); IR (neat) 3525, 1735, 1649 cm⁻¹; MS: m/z 390 (M⁺) 272; HRMS: m/z for C₂₁H₂₆O₇ calcd. 390.16785, measured 390.16777; TLC (3:1 = H:EA) Rₙ = 0.2.

38b: H NMR (CDCl₃) δ (ppm) 6.70 (d, J = 5.4 Hz, 1 H), 5.93 (m, 2 H), 5.23 (m, 5 H), 4.84 (d, J = 5.4 Hz, 2 H), 4.60 (d, J = 5.7 Hz, 2 H), 4.18 (d, J = 1.2, 1 H), 3.84 (s, 3 H), 3.76 (s, 1 H), 3.05 (dd, J₁ = 16.8 Hz, J₂ = 3.3 Hz, 1 H), 2.71 (dd, J₁ = 10.2 Hz, J₂ = 9.3 Hz, 1 H), 2.45 (m, 4 H); IR (neat) 3541, 1730, 1649 cm⁻¹; MS: m/z 390 (M⁺), 272, 257, 232; HRMS: m/z for C₂₁H₂₆O₇ calcd. 390.16785, measured 390.16777; TLC (3:1 = H:EA) Rₙ = 0.3.

5-8-Dimethoxy-1,2,3,4-tetrahydro-4-oxo-3-(3-oxopentyl)-3-(2-oxa-1-oxo-4-pentenyl)-2-naphthaleneacetic acid, methyl ester (39a)

To a solution of 38 (740 mg, 1.90 mmol) in 40 mL of acetone at 0°C was added Jones reagent (1.0 mL). The reaction was stirred at 0°C for 15 min and at 25°C for 30 min. The excess Jones reagent was quenched with isopropanol. The acetone was diluted with brine and extracted with ethyl acetate. The organic layer was dried and concentrated in vacuo. To the crude residue (35, R = allyl) was added 60 mL of MeOH and the solution was cooled to 0°C. To this solution was
added ethyl vinyl ketone (2.0 mL) and 200 mL of Triton B. The solution was stirred at 25°C for 12 h. The solvent was removed in vacuo. The residue was purified by sg chromatography using 3:1 H:EA to afford 446 mg (50% yield) of 39a.

35 (R = allyl): 1H NMR (CDCl3) δ (ppm) 13.03 (0.5 H, s), 6.96 (m, 1 H), 6.82 (m, 1 H), 5.93 (m, 2 H), 5.28 (m, 4 H), 4.64 (m, 4 H), 3.87 + 3.85 (s, 3 H), 3.81 + 3.78 (s, 3 H), 3.39 (m, 1 H), 3.24 (m, 1 H), 2.57 (m, 2 H), 2.26 (m, 1 H), 2.95 (m, 1 H); IR (neat) 3454, 1738, 1688 cm⁻¹; TLC (3:2 = H:EtOH) Rf = 0.25.

39a: 1H NMR (CDCl3) δ (ppm) 6.95 (d, J = 9.0 Hz, 1 H), 6.79 (d, J = 9.0 Hz, 1 H), 5.71 (m, 1 H), 5.11 (m, 2 H), 4.49 (m, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.18 (dd, J₁ = 16.5 Hz, J₂ = 13.5 Hz, 1 H), 2.78 (dd, J₁ = 16.5 Hz, J₂ = 13.8 Hz, 1 H), 2.55 (m, 6 H), 2.41 (q, J = 7.5 Hz, 2 H), 2.08 (m, 1 H), 1.02 (t, 7.5 Hz); IR (neat) 1738, 1683 cm⁻¹; HRMS: m/z for C24H30O₈ calcd. 446.19366, measured 446.19366; CMR (CDCl3) δ (ppm) 210.42, 193.59, 172.50, 170.66, 153.91, 149.82, 132.01, 131.22, 122.69, 118.49, 115.35, 110.29, 65.61, 60.34, 56.38, 55.91, 51.87, 37.05, 35.92, 35.66, 26.83, 25.88; TLC (1:1 = H:EA) Rf = 0.5.

8,9,10-Trihydroxy-4-oxo-1,2,3,4-tetrahydro-3-(3-oxopentyl)-3-(2-oxa-1-oxo-4-pentenyl)anthracene-2-acetic acid, methyl ester (45)

To a suspension of 39a (100 mg, 0.22 mmol) and AgO (200 mg, 1.61 mmol) in 8 mL of THF at 25°C was added 300 μL of 6N HNO₃. After 15 min, the suspension was diluted with 10 mL of 4:1 CHCl₃:H₂O. The organic layer was dried and concentrated. The unstable quinone was dissolved in 6 mL of CH₂Cl₂ and the solution was cooled to -15°C. To this solution was added 1-trimethylsilyloxy-1,3-butadiene (0.5 mL). The solution was stirred at -15°C for 1 h and was allowed to warm to 25°C over 5 h. The mixture was treated with an excess of Jones reagent
in 1 mL of acetone at 0°C for 15 min. Isopropanol was added to destroy any excess Jones reagent. The crude product was purified by sg chromatography using 2:1 H:EA to afford 45.

45: $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 13.30 (s, 1 H), 8.51 (s, 1 H), 8.43 (s, 1 H), 7.85 (d, $J = 7.8$ Hz, 1 H), 7.21 (t, $J = 7.8$ Hz, 1 H), 6.88 (d, $J = 7.8$ Hz, 1 H), 5.79 (m, 1 H), 5.17 (m, 2 H), 4.56 (m, 2 H), 3.75 (s, 3 H), 3.30 (m, 1 H), 2.55 (m, 9 H), 2.30 (m, 1 H), 1.07 (t, $J = 7.5$ Hz, 3 H); IR (CH$_2$Cl$_2$) 3600, 3460, 1735, 1715, 1670 cm$^{-1}$; MS: m/z CI MS: (M$^+$ + 1) 485; TLC (2:1 = H:EA) $R_f = 0.36$.

4,8-Dihydroxy-9,10-dioxo-3-(3-oxopentyl)-2-anthracene acetic acid, methyl ester (46).

A solution of 45 (11 mg, 0.023 mmol), palladium acetate (3 mg) and 6 mg of dppe in 3 mL of acetonitrile was heated at reflux for 40 min. The solvent was removed in vacuo and the residue purified by sg chromatography using 4:1 H:EA to afford 7.3 mg (81% yield) of 46.

46: $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 13.11 (s, 1 H), 12.65 (s, 1 H), 7.83 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.2$ Hz, 1 H), 7.70 (s, 1 H), 7.67 (dd, $J_1 = 7.5$ Hz, $J_2 = 7.8$ Hz, 1 H), 7.31 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.2$ Hz, 1 H), 3.92 (s, 2 H), 3.72 (s, 3 H), 3.03 (t, $J = 7.5$ Hz, 2 H), 2.80 (t, $J = 7.5$ Hz, 2 H), 2.44 (q, $J = 7.5$ Hz, 2 H), 1.06 (t, $J = 7.5$ Hz, 3 H); IR (CH$_2$Cl$_2$) 3050, 1735, 1715, 1630 cm$^{-1}$; MS: m/z CI MS (NH$_3$) 397; HRMS: m/z for C$_{22}$H$_{20}$O$_7$ calcd. 396.12090, measured 396.12111; TLC (4:1 = H:EA) $R_f = 0.38$; mp 170-172°C.
4-Hydroxy-5,8-dihydro-5,8-dioxo-3-(3-oxopentyl)-naphthalene acetic acid, methyl ester (41).

To a suspension of ester 39a (100 mg, 0.22 mmol) and AgO (200 mg, 1.61 mmol) in 10 mL of THF was added 300 µL of 6N HNO₃. After 15 min, the reaction was quenched by the addition of 4:1 CHCl₃:H₂O. The aqueous layer was extracted with CHCl₃. The combined organic layers were dried and concentrated in vacuo. The residue was used directly in the next step.

A solution of Pd(OAc)₂ (17 mg, 0.075 mmol) and 30 mg of dppe in 10 mL of CH₃CN was heated at reflux under argon for 2 min. The solution was cooled and the crude quinone was added. The solution was heated at reflux for 50 min, cooled to 25°C, diluted with CH₂Cl₂ and filtered through Florisil. The solvent was removed in vacuo. To the residue was added 10 mL of toluene and DDQ (50 mg, 0.22 mmol). The solution was heated at 110°C for 5 h. Purification by sg chromatography afforded 30.5 mg (42% yield) of 41.

41: ¹H NMR (CDCl₃) δ (ppm) 12.36 (s, 1 H), 7.48 (s, 1 H), 6.92 (s, 2 H), 3.88 (s, 2 H), 3.71 (s, 2 H), 2.99 (t, J = 7.5 Hz, 2 H), 2.77 (t, J = 7.5 Hz, 2 H), 2.43 (q, J = 7.2 Hz, 2 H), 1.05 (t, J = 7.2 Hz, 3 H); IR (CH₂Cl₂) 3025, 1738, 1715, 1670, cm⁻¹; MS: m/z 330 (M⁺) 274.1; HRMS: m/z for C₁₈H₁₈O₆ calcd. 330.11034, measured 330.10999; TLC (3:1 = H:EA) Rf = 0.375.

4,5-Dihydroxy-9,10-dioxo-3-(3-oxopentyl)-anthracene-2-acetic acid, methyl ester (47).

To a solution of 41 (12 mg, 0.036 mmol) in 1.5 mL of CH₂Cl₂ at -30°C was added 1-trimethylsilyloxy-1,3-butadiene (0.5 mL). The solution was stirred at -30°C for 20 h and at 25°C for 9 h. The solvent was removed in vacuo. To a
solution of the unpurified product in 5 mL of acetone was added Jones reagent (0.3 mL). The excess Jones reagent was destroyed with isopropanol. The product was purified by sg chromatography using 5:1 H:EA to afford 12.1 mg (83% yield) of 47. Compound 47 was a yellow solid with m.p. 178-179°C. In addition, 1.3 mg (9% yield) of 46 was produced.

47: 1H NMR (CDCl₃) δ (ppm) 12.53 (s, 1 H), 12.07 (s, 1 H), 7.83 (dd, J₁ = 1.2 Hz, J₂ = 7.8 Hz, 1 H), 7.70 (s, 1 H), 7.69 (t, J = 7.8 Hz, 1 H), 7.30 (dd, J₁ = 1.2 Hz, J₂ = 7.8 Hz, 1 H), 3.92 (s, 2 H), 3.72 (s, 3 H), 3.03 (t, J = 7.5 Hz, 2 H), 2.80 (t, J = 7.5 Hz, 2 H), 2.44 (q, J = 7.2 Hz, 2 H), 1.07 (t, J = 7.2 Hz, 3 H); IR (CH₂Cl₂) 3050, 1740, 1715, 1670 cm⁻¹; MS: m/z 396.1 (M⁺) 340, 307, 279, 265; HRMS: m/z for C₂₂H₂₀O₇ calcd. 396.1290, measured 396.12054; TLC (3:1 = H:EA) Rf = 0.458, mp 178-179°C.

7-Deoxyaklavinone (34a).

To a solution of 47 (10 mg, 0.025 mmol) in 6 mL of MeOH at -15°C was added 1 mL of pyridine followed by 300 mL of Triton B. After 3 h at -15°C, the reaction was allowed to warm slowly to 8°C. The solution was poured into cold 2N HCl and the aqueous layer was extracted twice with CH₂Cl₂. The organic layer was washed with brine, dried and concentrated. The residue was purified by sg chromatography using 6:1 H:EA to afford 5.0 mg (50% yield) of 34a and 2.6 mg (26% yield) of 34b.

34a: 1H NMR (CDCl₃) δ (ppm) 12.50 (s, 1 H), 12.10 (s, 1 H), 7.82 (dd, J₁ = 7.5 Hz, J₂ = 1.2 Hz, 1 H), 7.67 (dd, J₁ = 8.1 Hz, J₂ = 7.5 Hz, 1 H), 7.66 (s, 1 H), 7.29 (dd, J₁ = 8.1 Hz, J₂ = 1.2 Hz, 1 H), 3.94 (s, 1 H), 3.73 (s, 3 H), 3.07 (ddd, J₁ = 19.2 Hz, J₂ = 6.9 Hz, J₃ = 2.1 Hz, 1 H), 2.85 (ddd, J₁ = 19.2 Hz, J₂ = 10.5 Hz, J₃ =
6.9 Hz, 1 H), 2.31 (ddd, \( J_1 = 14.1 \) Hz, \( J_2 = 10.5 \) Hz, \( J_3 = 6.9 \) Hz, 1 H), 1.94 (ddt, \( J_1 = 14.1 \) Hz, \( J_2 = 6.9 \) Hz, \( J_3 = 2.1 \) Hz, 1 H), 1.72 (dq, \( J_1 = 14.7 \) Hz, \( J_2 = 7.2 \) Hz, 1 H), 1.60 (dq, \( J_1 = 14.7 \) Hz, \( J_2 = 7.2 \) Hz, 1 H), 1.08 (t, \( J = 7.5 \) Hz, 3 H); IR (CH\textsubscript{2}Cl\textsubscript{2}) 3590, 3055, 2928, 2855, 1734, 1622, 1471, 1419, 1384, 1289, 1249, 1160, 909 cm\(^{-1}\); MS: m/z 396 (M\(^+\)), 378, 340, 319, 307, 279; HRMS: m/z for C\textsubscript{22}H\textsubscript{20}O\textsubscript{7} calcd. 396.12090, measured 396.12099; TLC (2:1 = H:EA) \( R_f = 0.58 \), mp 217-219°C.
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PAPER IV

A DIRECT SYNTHETIC APPROACH TO PLEUROTIN
Pleurotin (1a) is a fungal metabolite. It has a complex polycyclic structure in which a sesquiterpenoid system is fused to a quinone ring. Pleurotin was first isolated from *Pleurotis grieseus* in 1947 and then from *Hohenbuehelia geogennius*. Two related fungal metabolites are dihydropleurotin acid (1b) and pleurogrisein (1c). Pleurotin exhibits significant activity against Erlich ascites carcinoma, L-1210 lymphoid leukemia and mammary tumors. Recently, Hart and coworkers reported a clever synthesis of 1 which featured a highly stereoselective radical cyclization.

In Hart's work, he constructed pleurotin by using a radical cyclization of A to the tricyclic ester B (Scheme 1). The double bond in B could then be utilized to attach the quinone unit. The eight membered ring ether was constructed by mixed
acetal formation. This acetal unit also served as an electrophile in the boron trifluoride-mediated intramolecular alkylation of the dimethoxybenzene ring to give the pentacyclic ether C. Compound C was then converted to the dihydroleurotin acid (1b) through introduction of a cyano group at C-14. Biomimetic conversion of 1b to pleurotin was accomplished by manganese dioxide in dichloro-methane. Thus, pleurotin was synthesized in 26 steps from benzoic acid in 0.3% overall yield.

Scheme 1

It has been suggested that quinone compounds, such as nanaomycin D (E), exhibit their antibiotic activity through a bioreductive alkylation pathway (Scheme 2). In fact, the concept of bioactivation as a mechanism of drug action is very attractive to medicinal and synthetic organic chemists. In the bioreductive
alkylation model, the common feature of the bioactive compounds is the quinone methide and its analog, such as compound F. Therefore, leaving groups at the benzylic positions play a key role in the bioreductive alkylation (Scheme 2).

Since pleurotin has significant antibiotic and antitumor activity, its mode of action could fit into this bioreductive alkylation pathway. Therefore, it is advantageous to develop a strategy that will allow us both to achieve a total synthesis of this molecule and to study structure-activity relationships along the synthetic process.
RESULTS AND DISCUSSION

As part of our examination of the synthetic potential of hydrogen atom abstraction reactions, we have initiated a route to 1a which features a tandem photoenolization/Diels-Alder reaction sequence.

The "bioreductive alkylation" sequence proposed by Moore involves a reactive quinone methide intermediate and has been invoked to rationalize the biological activity of pyranonaphthoquinone antibiotics, such as nanaomycin C. Although the primary reason for selecting our synthetic pathway was to extend the scope of the photoenolization reaction, we also wanted to determine whether the "bioreductive alkylation" pathway might be operative in pleurotin. Since the intermediates early in our synthetic sequence possess the two leaving groups at

\[ \text{Scheme 3} \]

1a \[ \rightarrow \] 2 \[ \rightarrow \] 3

\[ \text{4} \quad \text{a: } X = Y = H \]
\[ \text{b: } X, Y = \text{CH}_2\text{CH} = \text{CH} \]
the benzylic position and the masked benzoquinone unit, the mode of action question could readily be evaluated by oxidation of the aromatic ring in some of our early intermediates to release the quinone unit and by biological testing.

The retrosynthetic analysis is shown in Scheme 3. The presence of the methoxyl groups in aldehyde 4 served both to mask the very sensitive quinone unit and to stabilize the hydroxyquinone methide intermediate produced by the photoenolization reaction. Kitaura and Matsuura have demonstrated that stabilization of an intermediate such as 3 by hydrogen bonding dramatically shifts the partition between conrotatory cyclization and trapping with dienophiles in favor of the latter reaction.6

In order to test the feasibility of the key step in our route, compounds 4a and 4b were synthesized as described below. The reaction of alcohol 5 with n-BuLi, followed by DMF and aqueous hydrolysis, afforded hemiacetal 6.7

![Chemical Reaction](image)

The attempted acylation of 6 with NaH and 3-butenoyl chloride in THF or THF/HMPA to generate the benzaldehyde 4a (X = Y = H) resulted in recovered starting material. This problem was circumvented by treatment of hemiacetal 6 with 1,2-ethanedithiol and a catalytic amount of boron trifluoride etherate to produce thioketal alcohol 7 which was readily acylated with 3-butenolic acid and DCC/DMAP.
Regeneration of the aldehyde using Mel in aqueous acetonitrile at room temperature produced aldehyde 4a in modest yield (50%). However, when 4a was prepared on a gram scale, PhI(OCOCF$_3$)$_2$ was used for deprotection of the aldehyde to improve the yield (80%).
Irradiation of 4a in benzene in an argon atmosphere with a Rayonet reactor equipped with a black-light lamp (λ = 360 nm) afforded the lactones 9a and 9b accompanied with benzocyclobutenol 10 in 1:1:1.2 ratio in a 70-80% combined yield. Benzocyclobutenol 10 could be converted into 9a in 95% yield by heating in benzene at 130°C for 38 h. The structures of 9a and 9b were supported by $^1$H
NMR resonances at 5.58 (J = 5 Hz) and at 5.57 (J = 4.6 Hz) which are strongly indicative of the cis fused gamma lactones.9

Since the lactone 9a can be produced by both photoenolization/Diels-Alder of 4a and electrocyclic reaction/Diels-Alder of 10, the hydroxyl group in lactone 9a should be syn to the \( \gamma \)-lactone unit. The correlation of the stereochemistry of 9a and 9b was carried out by oxidation of these compounds separately with Jones reagent. Both 9a and 9b produced ketolactone 11 in above 90% yield. This result indicates that the stereochemistry of 9a and 9b is different only at the benzylic carbon bearing the hydroxyl group.

It is known that when the ortho-alkyl benzaldehyde is irradiated by UV light, it will produce the 1,4-biradical which can afford ground state enols10. The
enols can exist in both E and Z configurations. Wagner\textsuperscript{11} has demonstrated that the E-enol can generate benzocyclobutenol through a conrotatory electrocyclization process. Based on the results that we obtained, the mechanistic aspects of the reaction can be depicted as following (Scheme 4):  
1). The 1,4-biradical generated from irradiation of 4a gave both the E and Z-enols.  
2). The E and Z-enols produced the hydroxylactones 9a and 9b respectively through the intramolecular Diels-Alder reaction \textit{via} an \textit{endo} transition state, since
any products formed *via* an *exo* transition state would possess the trans $\gamma$-lactone unit.

3). The benzocyclobutenol 10 can generate the E-enol upon thermolysis. The E-enol in turn afforded intramolecular/Diels-Alder product 9a *via* the *endo* transition state. 12

In order to study the scope of photoenolization/Diels-Alder sequence, aldehyde 4b was synthesized by coupling the alcohol 7 with dihydrobenzoic acid followed by deprotection of the thioacetal as in the synthesis of 4a. Aldehyde 4b was converted into 12 in 50% yield by irradiation followed by thermolysis at 165°C for 40 hours. A 1:1 mixture of 12 and benzocyclobutenol 13 was produced in the irradiation step. Compound 13 is not stable in air and was partially converted into the benzoic acid derivative 14 upon silica gel separation. In practice, it was most expedient to take the unpurified product from the irradiation step and subject this material directly to the thermolysis step. The structure of 12 was supported by spectroscopic data, especially by the COSY and NOESY 2D-NMR experiments. A strong NOE effect was observed between the methine protons on each adjacent tertiary carbons formed in the photoenolization/Diels-Alder reaction. This result demonstrated that these protons were cis to each other.
Compound 12 was generated by a photoenolization reaction, followed by a Diels-Alder reaction which proceeded via an endo transition state. This result correlates well with those obtained in the photolysis of 4a. We attribute the endo selectivity to the lack of significant nonbonded interactions and the lower strain energy in the endo transition state. Similar results were observed by Oppolzer in his synthetic studies of intramolecular cycloaddition of ortho-quinodimethanes.
generated from 15. Thermolysis of compound 15 at 180°C produced the
tetracyclic adduct 16 in 66% yield with stereochemical control over as many as
four adjacent stereogenic centers.

Compound 12 contains four out of six rings and three of the correct
stereogenic centers of pleurotin. Importantly, lactone 12 also contains the
benzylic lactone and benzylic alcohol moieties, as well as a protected quinone.
Oxidation of 12 with silver(II) oxide and nitric acid in THF\textsuperscript{13} afforded the desired
benzoquinone 17 in 80% yield. This material gave a satisfactory proton NMR
spectrum and was used for biological testing without further purification.

\[
\begin{array}{c}
\text{OMe} \quad \text{OH} \\
\text{MeO} \quad \text{H}
\end{array}
\quad \text{AgO, HNO}_3 \quad \text{THF} 
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\]

The biological testing of compound 17 was carried out at the National
Cancer Institute. The preliminary results indicated that this compound has
comparable reactivity with pleurotin against SR leukemia (log\textsubscript{10} GI50 = -5.33)
and most colon cancers (log\textsubscript{10} GI50 ranging from -4.65 to -4.77). The mean value
of log\textsubscript{10} GI50 of pleurotin is about -5.51 against leukemia cell lines and -5.17
against colon cancer cell lines. This finding provides a new lead for the discovery of
new therapeutic anticancer agents with simpler chemical structures.

The success in the photoenolization/Diels-Alder reaction provided valuable
intermediates, such as products 9 and 12, for the construction of pleurotin (1).
The strategy initially was based on the utility of the tetracyclic compound 12. However, the transformation of 12 to 18 could not be performed without aromatization of the central ring.

Trost has recently established a [3 + 2] cycloaddition process by using a trimethylenemethane (TMM) palladium complex. This reaction was very attractive to us since it could produce the tetracyclic compound 19 as an advanced intermediate in pleurotin synthesis. To test the feasibility of this reaction, we synthesized the α,β-unsaturated ketone 20 as precursor. Compound 20 was prepared from the keto lactone 11 by Gras' method. The selectivity of the α-methylenation of the ketone in the presence of the lactone was attributed to the more acidic protons alpha to the ketone. Although 20 was prepared in only 50% yield, there was enough material for us to test the Trost process. Treatment
of 20 with the TMM palladium complex in boiling toluene indeed provided
cycloaddition product 19 in 36% yield. The low overall yield of this process was due
to the low stability of compound 20, which convinced us to abandon this approach.

We have proposed that an intermediate such as 21 would be desirable for
the construction of the pleurotin ring system, if the transformation of 11 to 21

could be accomplished. It is known that the anion derived from a β-ketoester
reacts with a cyclopropanephosphonium salt 23\textsuperscript{16}, through a tandem alkylation
-Wittig reaction to produce a cyclopentenyl ester, a subunit in compound 21.
Therefore, we started a model study beginning with 5-methoxy-1-tetralone (24), to test this alkylation-cyclization strategy. Condensation of 24 with ethyl formate under basic conditions produced the hydroxymethylene ketone 25 in 90% yield. Treatment of the sodium enolate of 25 with 23 in HMPA produced the tricyclic ketoester 26 in 50% yield.

The success in the model study provided a pathway for completing the total synthesis of pleurotin from 21 which could be synthesized from our photoenolization/Diels-Alder products 9. The approach based on an alkylation-cyclization strategy is currently being studied in this laboratory.
Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Dichloromethane was distilled from calcium hydride. Unless otherwise noted, all reactions were conducted under an argon atmosphere. All organic extracts were dried over anhydrous sodium sulfate. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 1320 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported relative to tetramethylsilane as an internal standard. Coupling constants were reported in Hz. Abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sb = broad singlet, m = multiplet, ABq = AB quartet. Carbon-13 NMR spectra were determined on a Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of CDCl$_3$ (77.07 ppm). High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Low resolution mass spectra were obtained from a Finnegan 4023 mass spectrometer. Flash chromatography was performed on silica gel Kieselgel 60 (mesh 230-400).

1,3-Dihydro-1-hydroxy-4,7-dimethoxyisobenzofuran (6)

To the solution of 29.4 g (175 mmol) of 2,5-dimethoxybenzyl alcohol (5) in 600 ml of dry THF was added 140 ml of n-BuLi (2.5 M) at -15 °C under argon. The resulting solution was refluxed for 6 hr and then cooled to 0 °C with ice-water bath.
Fifteen ml of N,N-dimethylformamide was then introduced into the solution and the mixture was stirred further for 12 hr. After the reaction was quenched with 200 ml of saturated NH₄Cl solution and 50 ml of 1N HCl. The solution was allowed to stand overnight. The white precipitate was collected and the aqueous layer was then extracted with ethyl acetate (200 ml three times). The combined organic layer was washed with brine and dried with MgSO₄. The solvent was then concentrated to about 30 ml and the white solid was collected by filtration to yield 22.7 g (66%) of 6 after re crystallization for ether. ¹H NMR (CDCl₃) δ (ppm) 6.78 (d, J = 7.4 Hz, 1 H), 6.74 (d, J = 7.4 Hz, 1 H), 6.58 (dd, J₁ = 7.2 Hz, J₂ = 2.1 Hz, 1 H), 5.30 (dd, J₁ = 13.2 Hz, J₂ = 2.1 Hz, 1 H), 5.00 (d, J = 13.2 Hz, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.07 (d, J = 7.2 Hz, 1 H); IR (CH₂Cl₂) 3560, 2940, 1500, 1300, 1020 cm⁻¹; MS: m/e 196.1, 178.1, 163.0, 77.0; HRMS: m/e for C₁₀H₁₂O₄ calcd. 196.07356, measured 196.07402; TLC (1:1 = H:EA) Rᵢ = 0.33; m.p. = 156-7 °C.

2-(2-Hydroxymethyl-3,6-dimethoxyphenyl)-1,3-dithiolane (7)

The hemiacetal 6 (8.9 g, 45 mmol) and 1,2-ethanedithiol (5.5 ml, 60 ml) was mixed in 150 ml of CH₂Cl₂. BF₃·Et₂O (0.5 ml, 4 mmol) was then added to the solution at 0 °C. The resulting mixture was stirred for 12 hr at room temperature. To the above mixture, 10 ml of 2 M NaOH solution was added and the mixture was stirred for another 2 hr. Then the mixture was diluted with 200 ml of CH₂Cl₂ and washed with 50 ml of 2 N HCl and brine (50 ml x 2), and dried with MgSO₄. Silica gel column purification gave 11.21 g (41.2 mmol) of 7 as a white solid in 91% yield. CMR (CDCl₃) δ (ppm) 153.05, 151.63, 131.14, 124.36, 111.42, 111.08, 56.50, 55.90, 55.26, 46.23, 40.11; TLC (2:1 = H:EA) Rᵢ = 0.26.
2-[2-(2-Oxa-3-oxo-5-hexenyl)-3,6-dimethylphenyl]-1,3-dithiolane (8)

The thioacetal alcohol 7 (5.44 g, 20 mmol), vinylacetic acid (1.892 g, 22 mmol) and DMAP (0.24 g, 2 mmol) were dissolved in 200 ml of dry CH$_2$Cl$_2$. The solution was then cooled to 0 °C with ice bath and DCC (4.5 g, 22 mmol) was added to the solution with 20 ml of CH$_2$Cl$_2$. The solution was warmed to RT and stirred for 5 hr. After filtration, the filtrate was concentrated and the residue was purified to give 4.80 g of the desired product 8 (78% yield) and 500 mg of thioketal alcohol 7. Compound 8 has the following properties: NMR (CDCl$_3$) $\delta$ (ppm) 6.89 (d, $J = 9.0$ Hz, 1 H), 6.84 (d, $J = 9.0$ Hz, 1 H), 6.37 (s, 1 H), 5.97 (m, 1 H), 5.51 (s, 2 H), 5.16 (m, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 3.56 (m, 2 H), 3.35 (m, 2 H), 3.13 (dt, $J_1 = 6.9$ Hz, $J_2 = 1.2$ Hz, 2 H); IR (CDCl$_3$) 3080, 2940, 2840, 1720, 1640, 1590, 1250 cm$^{-1}$; CMR (CDCl$_3$) $\delta$ (ppm) 171.38, 153.30, 152.11, 130.44, 127.00, 124.95, 118.02, 113.15, 111.63, 57.85, 56.65, 56.20, 46.68, 40.37, 39.09, 25.78; TLC (3:1 = H:EA) $R_f$ = 0.40.

2,5-Dimethoxy-6-(2-oxa-3-oxo-5-hexenyl)-benzaldehyde (4a)

The thioacetal ester (6.8 g, 20 mmol) was dissolved in 200 ml of acetonitrile-H$_2$O (4:1) and to the solution 12 ml of methyl iodide was added. The mixture was then stirred at room temperature for 28 hr and the solvent was then evaporated. The residue was purified by silica gel chromatography (3:1 = H:EA) to give 3.57 g of white solid in 67% yield. $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 10.56 (s, 1 H), 7.13 (d, $J = 9.0$ Hz, 1 H), 7.05 (d, $J = 9.0$ Hz, 1 H), 5.91 (m, 1 H), 5.47 (s, 2 H), 5.15 (m, 2 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.08 (d, $J = 6.0$ Hz, 2 H); IR (CH$_2$Cl$_2$) 3010, 2940, 2840, 1730, 1690, 1480, 1080 cm$^{-1}$; MS: m/e 195.1, 178.1, 163.0, 121.1, 91.1; HRMS: m/e for C$_{14}$H$_{16}$O$_5$ calcd. 264.09977, measured 264.09999; CMR (CDCl$_3$)
General Procedure for the Photoenolization Reaction

A benzene solution (1800 ml) of the aldehyde (2.5 g, 9.47 mmol) was degassed with argon for 30 min and was then photolyzed with a Rayonet reactor equipped with black-light lamps (λ = 360 nm) for 4 hr with stirring. Evaporation of benzene gave the residue which was purified by chromatography (3:1 = H:EA and then 2:1 = EA:H). The three products, benzocyclobutenol 10, syn-hydroxylactone 9a and anti-hydroxylactone 9b were isolated in 0.87 g, 0.62 g and 0.68 g, respectively in an 86% combined yield. Compound 3a,4,5,9b-tetrahydro-5-hydroxy-6,9-dimethyl-(3α,5β,9βα)-naphtho[1,2-b]furan-2(3H)-one (9a) has the following properties: $^1$H NMR (CDCl$_3$) δ (ppm) 6.91 (d, J = 9.0 Hz, 1 H), 6.81 (d, J = 9.0 Hz, 1 H), 5.73 (d, J = 5.4 Hz, 1 H), 5.03 (dd, J$_1$ = 5.4 Hz, J$_2$ = 9.3 Hz, 1 H), 4.33 (sb, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 2.91 (dd, J$_1$ = 17.1 Hz, J$_2$ = 7.5 Hz, 1 H), 2.72 (m, 1 H), 2.57 (dd, J$_1$ = 17.1 Hz, J$_2$ = 1.8 Hz, 1 H), 2.12 (dt, J$_1$ = 13.2 Hz, J$_2$ = 5.4 Hz, 1 H), 1.80 (ddd, J$_1$ = 13.2 Hz, J$_2$ = 11.7 Hz, J$_3$ = 9.3 Hz, 1 H); IR (CDCl$_3$) 3530, 2940, 1772, 1480, 1260 cm$^{-1}$; MS: m/e 264.1, 231.1, 187.1, 165.1, 115.1, 77.0, 91.1; HRMS: m/e for C$_{14}$H$_{16}$O$_5$ calcd. 264.09977, measured 264.09955; CMR (CDCl$_3$) δ (ppm) 176.22, 152.90, 150.91, 129.65, 120.39, 111.85, 109.91, 73.78, 64.58, 55.88, 55.72, 36.66, 31.70, 31.41; TLC (2:1 = EA:H) R$_f$ = 0.40.

Compound 3a,4,5,9b-tetrahydro-5-hydroxy-6,9-dimethyl-(3α,5α,9βα)-naphtho[1,2-b]furan-2(3H)-one (9b) has the following properties: $^1$H NMR (CDCl$_3$) δ (ppm) 6.92 (d, J = 9.0 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 5.57 (d, J = 4.5 Hz, 1 H), 5.19 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 2.95 (m, 3 H), 2.08 (m, 1 H),
1.68 (m, 1 H), 2.34 (s, 1 H); IR (CDCl₃) 3600, 2940, 2840, 1770, 1260 cm⁻¹; MS: m/e 264.1, 246.1, 231.1, 205.1, 187.1; HRMS: m/e for C₁₄H₁₆O₅ calcd. 264.09977, measured 264.09990; TLC (2:1 = EA:H) Rf = 0.36.

Benzaldehyde 4b (90 mg) was photolyzed under the same conditions as 4a. The reaction mixture was then heated to 165°C for 40 hr. After removal of the solvent, the residue was purified by silica gel chromatography (EA:H = 6:4) to give a 50% yield of compound 12 (45 mg). Compound 2a,5,5a,6,10b,10c-hexahydro-6-hydroxy-7,10-dimethoxy-(2aa,5aa,6p,10ba,10ca)-2H-anthra[9,1-bc]furan-2-one (12) shows the following properties: NMR (CDCl₃) δ (ppm) 6.88 (s, 2 H), 6.29 (d, J = 8.4 Hz, 1 H), 6.07 (m, 2 H), 5.26 (sb, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.43 (m, 1 H), 3.18 (ddt, J₁ = 10.8 Hz, J₂ = J₃ = 8.4 Hz, 1 H), 2.52 (m, 1 H), 2.35 (dd, J₁ = 18.6 Hz, J₂ = 4.5 Hz, 1 H), 1.95 (sb, J = 8.1 Hz, 1 H), 1.77 (s, 1 H); IR (CDCl₃) 3600, 2960, 2840, 1762, 1260 cm⁻¹; MS: m/e 302.1, 284.1, 209.1, 188.1, 165.1; HRMS: m/e for C₁₇H₁₈O₅ calcd. 302.11542, measured 302.11610; TLC (2:1 = EA:H) Rf = 0.33.

Thermal Conversion of 8-Hydroxy-2,5-dimethylbicyclo[4.2.0]octa-1,3,5-trien-7-yl Butenoate (10) into 9a

A 0.05 M solution of benzocyclobutenol 10 in toluene was heated at 200 °C for 48 hr. After removal of the solvent, the yellow solid was recrystallized from CHCl₃-hexane to give 9a as white needles in 85-90% yield. Compound 10 has the following properties: ¹H NMR (CDCl₃) δ (ppm) 6.81 (m, 2 H), 5.95 (m, 1 H), 5.536 (s, 1 H), 5.24 (m, 1 H), 5.19 (m, 1 H), 5.08 (d, J = 3.9 Hz, 1 H), 3.92 (s, 3 H), 3.84 (s, 3 H), 3.20 (d, J = 6.9 Hz, 2 H), 3.13 (d, J = 3.9 Hz, 1 H); IR (CH₂Cl₂) 3570, 3010, 2940, 1730, 1500, 1160, 1040 cm⁻¹; MS: m/e 264.1, 195.1, 180.0, 163.0, 151.0;
Oxidation of Compound 9 to 3a,4,5,9b-Tetrahydro-5-oxo-6,9-dimethoxy-(3α, 9β)-naphtho[1,2-b]furan-2(3H)-one (11)

To an acetone solution of 9a (or 9b) (1.1 g, 4.2 mmol) was added five equivalents of Jones reagent (2.7 M) at 0 °C. The mixture was stirred at 0 °C for 30 min and then quenched with isopropanol. The mixture was then diluted with ethyl acetate and washed with brine. After evaporation of the solvent, the residue was purified by silica gel chromatography (EA:H = 2:1) to give 4.0 g of compound 11. NMR (CDCl₃) δ (ppm) 7.14 (d, J = 9.3 Hz, 1 H), 7.05 (d, J = 9.3 Hz, 1 H), 5.78 (d, J = 5.4 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 1 H), 3.18 (m, 1 H), 2.94 (dd, J₁ = 17.2 Hz, J₂ = 7.2 Hz, 1 H), 2.66 (m, 2 H), 2.43 (dd, J₁ = 7.4 Hz, J₂ = 2.1 Hz, 1 H); IR (CH₂Cl₂) 3010, 2940, 1780, 1692, 1480, 1420, 1260, 1200, 900, 810 cm⁻¹; MS: m/e 262.1, 203.1, 194.1, 179.1; HRMS: m/e for C₁₄H₁₄O₅ calcd. 262.08412, measured 262.08469; TLC (1.5:1 = EA:H) Rₐ = 0.33; m.p. 148-151 °C.

(2-Formyl-3,6-dimethoxyphenyl)methyl 2,5-cyclohexadiene-1-carboxylate (4b).

The thioacetal alcohol 7 (544 mg, 2 mmol), dihydrobenzoic acid (248 mg, 2 mmol) and DMAP (25 mg) were dissolved in 8 ml of dry methylene chloride. The solution was then cooled to 0 °C with ice bath and the DCC (453.2 mg, 2.2 mmol) was added to the solution with 3 ml of methylene chloride. The solution was warmed up to room temperature and stirred for 5 hr. After filtration, the filtrate was concentrated and the residue was purified to give 470 mg of the thioacetal
ester. $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 6.89 (d, $J = 9.0$ Hz, 1 H), 6.84 (d, $J = 9.0$ Hz, 1 H), 6.37 (s, 1 H), 5.85 (d, $J = 1.8$ Hz, 4 H), 5.51 (s, 2 H), 3.83 (s, 3 H), 3.79 (m, 1 H), 3.77 (s, 3 H), 3.56 (m, 2 H), 3.34 (m, 2 H), 2.68 (m, 2 H); IR (CH$_2$Cl$_2$) 3040, 2930, 2860, 1710, 1478, 1260, 1075 cm$^{-1}$; TLC (3:1 = H:EA) $R_f$ = 0.37.

The thioacetal ester (200 mg) obtained above was dissolved in 15 ml of acetonitrile-H$_2$O (4:1) mixture and to this solution 5 ml of methyl iodide was added. The mixture was then stirred at room temperature for 28 hr and the solvent was evaporated. The residue was purified by silica gel chromatography (EA:H = 3:1) to give 90 mg of 4b in 55% yield. 4b: $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 10.56 (s, 1 H), 7.11 (d, $J = 9.0$ Hz, 1 H), 6.99 (d, $J = 9.0$ Hz, 1 H), 5.83 (m, 4 H), 5.49 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.70 (m, 1 H), 2.67 (m, 2 H); IR (CDCl$_3$) 3040, 2960, 2840, 1735, 1690, 1265 cm$^{-1}$; MS: m/e 302.1, 195.1, 179.1, 79.1; HRMS: m/e for C$_{17}$H$_{18}$O$_5$ calcd. 302.11542, measured 302.11476; TLC (3:1 = H:EA) $R_f$ = 0.37.

1,2,3,4a,5,9a-Hexahydro-1-oxa-2,5-dioxo-6,9-dimethoxy-4'-methylene-(4aa, 9ba)-spiro[4H-benz[e]indene-4,1'-cyclopentane] (19)

To the solution of 11 (180 mg, 0.68 mmol) in 10 ml of THF, was added N-methylanilinium trifluoroacetate (240 mg, 1.09 mmol) and paraformaldehyde (60 mg, 2.0 mmol). The reaction mixture was refluxed for 12 hr under argon. Then another 1 equivalent of the ammonium salt was added and the refluxing was continued for 12 hr. The mixture was then diluted with ether (200 ml) and washed with brine. After the solvent had been evaporated, the residue was purified by silica gel chromatography (EA:H = 3:2) to give 80 mg of 20 in 43% yield. The ketone 11 was recovered in 37 mg. 20: $^1$H NMR (CDCl$_3$) $\delta$ (ppm) 7.18 (d, $J = 9.3$ Hz, 1 H), 7.08 (d, $J = 9.3$ Hz, 1 H), 6.42 (d, $J = 2.1$ Hz, 1H), 5.56 (d, $J = 2.1$ Hz, 1H),
5.54 (d, J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.74 (m, 1H), 3.02 (dd, J1 = 17.1 Hz, J2 = 7.5 Hz, 1H), 2.82 (dd, J1 = 17.1 Hz, J2 = 3.3 Hz, 1H). IR (CH2Cl2) 3010, 2941, 2840, 1785, 1679, 1283, 1184 cm⁻¹; MS: m/e 274.1, 257.1, 232.1, 215.1; HRMS: m/e for C15H14O5 calcd. 274.08412, measured 274.08360. TLC (EA:H = 2:1) Rf = 0.55.

To the solution of 20 (55 mg, 0.2 mmol) and (2-trimethylsilyl)methyl-2-propen-1-yl acetate (42.5 μl, 0.2 mmol) in 1 ml of degassed toluene, was added palladium acetate (5 mg, 0.02 mmol) and triisopropylphosphite (25 μl, 0.10 mmol). The mixture was refluxed for 18 hr under nitrogen. Silica gel separation provided 25 mg of 19 in 36% yield. 19: ¹H NMR (CDCl₃) δ (ppm) 7.12 (d, J = 9 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 5.97 (d, J = 8.1 Hz, 1H), 4.96 (sb, 1H), 4.89 (sb, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.26 (m, 1H), 3.14 (d, J = 16.5 Hz, 1H), 2.65 (dd, J1 = 18.0 Hz, J2 = 9.0 Hz, 1H), 2.33 (dd, J1 = 18.0 Hz, J2 = 11.4 Hz, 1H), 2.35 (m, 2H), 2.10 (dd, J1 = 16.5 Hz, J2 = 1.2 Hz, 1H), 1.91 (m, 1H), 1.70 (dt, J1 = 12.9 Hz, J2 = 11.4 Hz, 1H); IR (CH2Cl2) 3010, 2960, 1775, 1690, 1585, 1480, 1170 cm⁻¹; MS: m/e 328.1, 310.1, 269.1, 193.0; HRMS: m/e for C19H20O5, calcd. 328.13107, measured 328.13060; TLC (EA:H = 6:4) Rf = 0.25.

2-Formyl-5-methoxy-1-tetralone (25)

This compound was prepared according to Corey’s procedure¹⁷. 5-Methoxy-1-tetralone (24) (5.0 g, 28.3 mmol) was treated with NaH in a mixture of ethyl formate and 1,2-dimethoxyethane (1:1). A 0.5 ml of ethanol was added to initiate the reaction. After silica gel separation, 4.41 grams of compound 25 were obtained as a light yellow solid. ¹H NMR (CDCl₃) δ (ppm) 14.56 (d, J = 5.7 Hz, 1H), 8.19 (d, J = 5.7 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 7.01
(d, J = 8.1 Hz, 1H), 3.86 (s, 3H), 2.87 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H).

IR (CH$_2$Cl$_2$) 2960, 1640, 1580, 1450, 1210 cm$^{-1}$. MS: m/e 204.2, 175.2, 160.2,
115.1, 91.1, 77.1. HRMS: m/e for C$_{12}$H$_{12}$O$_3$ calcd. 204.07864, measured
204.07887. TLC (EA:H) Rf = 0.54.

3',4'-Dihydro-1'-oxo-5'-methoxy-3-(1'-oxo-2-oxa-butyl)-spiro[ cyclopent-2-
en-1,2'(1'H)-naphthalene] (26)

To the suspension of 60% of NaH (1.24 g, 31 mmol) in 60 ml of HMPA, was
added 25 (6.18 g, 30 mmol) in four portions under argon at 0$^\circ$C. After a clear
solution was obtained, the phosphonium salt was added and the reaction was
allowed to stir at 30$^\circ$ C for 48 hr. The reaction mixture was then extracted with
hexane (3 X 200 ml). The combined hexane layer was washed with brine. The
solvent was then evaporated and the residue was purified by silica gel chroma-
tography (EA:H = 6:1). Compound 26 (2.20 g) was obtained as colorless oil.

Compound 25 was recovered in 2.53 g. 26: 1H NMR (CDCl$_3$) $\delta$ (ppm) 7.83 (dd, $J_1$
= 7.8 Hz, $J_2$ = 0.4 Hz, 1H), 7.30 (t, $J$ = 7.8 Hz, 1H), 7.03 (d, $J$ = 7.8 Hz, 1H), 6.67 (t,
$J$ = 1.8 Hz, 1H), 4.18 (q, $J$ = 7.2 Hz, 2H), 3.88 (s, 3H), 2.97 (t, $J$ = 6.3 Hz, 2H), 2.73
(m, 2H), 2.59 (m, 1H), 2.18 (m, 2H), 1.91 (m, 1H). IR (neat) 3070, 2940, 1680,
1580, 1260, 1060 cm$^{-1}$. MS: m/e 300.2, 254.2, 226.2, 148.2, 120.1, 90.1, 77.1.
HRMS: m/e for C$_{18}$H$_{20}$O$_4$ calcd. 300.13616, measured 300.13621. TLC (EA:H =
6:1) Rf = 0.33.
REFERENCES


GENERAL CONCLUSIONS

Photochemical hydrogen atom abstraction reactions have been used in the construction of bioactive natural products. The convergent total synthesis of paulownin, an important component in Chinese traditional medicine, features a highly stereoselective type II photocyclization reaction. The synthesis proceeds in only seven steps from an aryl aldehyde. The high stereoselectivity observed when the type II photocyclization is conducted on the tetrahydrofuranone system should make this reaction quite attractive to synthetic organic chemists.

A direct formal synthesis of an anthracycline antibiotic aklavinone has been accomplished by utilizing a photoenolization/Diels-Alder reaction and a palladium-catalyzed aromatization. A valuable tetralone intermediate can be prepared through the photoenolization and intermolecular Diels-Alder sequence. From this compound, aklavinone can be synthesized in only seven steps. Our synthesis provides a highly efficient method for the construction of anthracycline antitumor antibiotics.

Finally, the synthetic utility of our tandem photoenolization/Diels-Alder methodology has been applied in a direct synthetic approach to pleurotin, an anticancer agent. A five-step synthetic sequence provides stereoselectively a tetracyclic intermediate, which contains four out of the six rings and three crucial stereogenic centers of pleurotin. Our strategy also provides a new lead for the discovery of new therapeutic anticancer agents with simpler chemical structures.
ACKNOWLEDGMENTS

I would like to thank my major professor George A. Kraus for his teaching me how to treat science with great respect, discipline, and persistence. His invaluable guidance, support, and encouragement made my stay at Iowa State a highly productive and extremely pleasant one.

I offer my thanks to the Kraus group members for their friendship, particularly Jianmin Shi for his advice and help during the early part of my tenure at this university. I would like to express my appreciation to the Department of Chemistry and the Iowa State University Graduate College for offering me a Gilman fellowship and graduate research awards.

I would like to thank my parents, Xiang Chen and Xiurong Li, who have made me the person I am today. Their support and encouragement made me succeed in my career development.

I must express my special gratitude to my wife Xingfang Hong and daughter Xiao Chen for their love, for supporting my commitment to science, and for helping me with many aspects of my life.