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Total synthesis of angularly fused natural products

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Total synthesis of angularly fused natural products

By

Guohua Zhao

A Dissertation Submitted to the
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DOCTOR OF PHILOSOPHY

Department: Chemistry
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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

1996

DEDICATION

To my parents, wife and son

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GENERAL INTRODUCTION

Organic synthesis remains one of the most challenging fields of chemistry. The key aspect of organic synthesis is finding the most efficient synthetic route. Using good strategy in organic synthesis can greatly improve the synthetic efficiency. This dissertation will illustrate advantages of using new strategies to synthesize angularly fused natural products G-2N and Colchicine.

Dissertation Organization

This dissertation contains three chapters. Chapter II will be submitted as a journal article. The schemes, structures, and references for each chapter are therefore numbered independently. The first chapter includes some fundamental aspects of photoenolization and photoisomerization. The second chapter covers the synthesis of angularly fused quinone natural product G-2N using a photoenolization reaction and a Diels-Alder reaction in the key carbon-carbon bond forming steps. The third chapter demonstrates direct synthesis of colchicine by different approaches. A general summary of this dissertation follows the third chapter.

CHAPTER I
PHOTOENOLIZATION AND PHOTOISOMERIZATION

Introduction

In much of synthetic chemistry, chemical reactions are initiated by the application of thermal energy to the reaction. We understand this in terms of the need to overcome some energy barrier to the formation of products. In order to increase the efficiency of the reaction, we can supply thermal energy by raising the temperature and thereby increasing the average internal (transitional, rotational and vibrational) energy of the molecules. Collisions between molecules with internal energies in excess of the barrier succeed in forming the reaction products. Obviously, the thermal route is the one most adopted in synthetic organic chemistry, but there are many instances where this route is unsatisfactory.

Photochemistry, however, offers the possibilities of initiating chemical processes that appear to have no analog in thermal chemistry. The introduction of electromagnetic radiation into the scheme effectively "changes the rules" and opens up a whole new set of possibilities. It offers a chance to access reactions that cannot be approached by thermal conditions.

In this extremely broad field, the photochemical reactions of the double bond (C=O and C=C) are the most interesting and well-studied reactions due to their photochemical reactivity. For carbonyl compounds, the excitation of a nonbonding (n) electron on oxygen into an antibonding π^* orbital of the carbonyl group results in a considerable change in the electron distribution

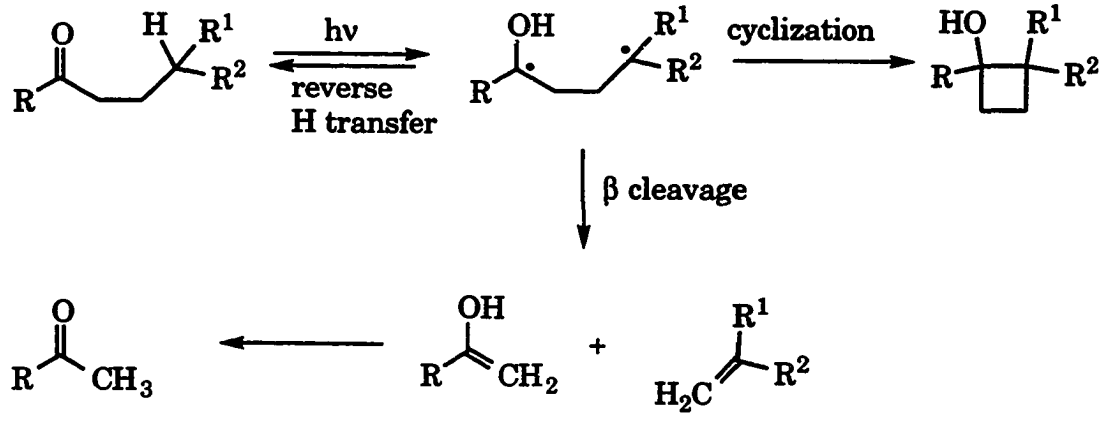
around the carbonyl group. The polarization of the C=O group in the ground state, which accounts for the facile nucleophilic attack at carbonyl carbon, is replaced in the excited state by an unpaired electron in both a π^* antibonding orbital and in a p-type orbital on oxygen. The net result is that the oxygen, as well as its n orbital, is now electron-deficient, while the carbon atom becomes somewhat electron-rich and hence can exhibit marked nucleophilic behavior. In the n, π^* triplet state, any zwitterionic nature of the carbonyl group is destabilized since the electrons, having parallel spins, are as far removed from one another as possible. Thus, (n, π^*) triplet carbonyl chromophores have chemical and physical characteristics of a diradical and in particular have appreciable similarities to alkoxy radical (RO·) with respect to α-cleavage reactions, their hydrogen abstraction abilities, and reaction with carbon-carbon multiple bonds.

The energy difference between the singlet and triplet (n, π^*) state of aliphatic ketones is smaller than that of ethenes, but intersystem crossing (I. S. C.) in some cases is still sufficiently slow to allow a chemical reaction of the (n, π^*) singlet to occur. However, since the energy and electron distribution in the two states are similar, the same type of process, although probably occurring at different rates, are to be expected and reaction may occur from the singlet or triplet states or from a mixture of the two. In conjugated systems, such as aryl ketones and enones, the (n, π^*) and (π, π^*) excited singlet states are lower in energy and hence the associated absorptions are at longer wavelengths compared to those in the isolated chromophores. Furthermore, the rate coefficients for intersystem crossing are increased appreciably by conjugation and the quantum yield of this process for aryl aldehydes and

ketones and for enones is unity or very close to unity. In practice we are, therefore, only concerned with the triplet (n, π^*) and (π, π^*) states of such carbonyl compounds. Which of the two is the lower energy state depends on the nature and position of the substituents on the aryl group or ethene of the conjugated carbonyl compound and on solvent characteristics. In the π-π^* transition, the electron density at the carbonyl group is increased. Thus, electron donor substituents which are in conjugation with the carbonyl group reinforce this effect, stabilizing this triplet and destabilizing the (n, π^*) triplet state. Conversely, since there is a movement of electron density away from the oxygen in a n-π^* transition, this state becomes stabilized relative to the (π, π^*) triplet by the presence of substituents which are inductively electron accepting.

As noted above, an photoexcited carbonyl group displays its essentially radical character, and in particular its similarity to alkoxy radicals, by a number of competitive reactions. Hydrogen atom abstraction is the most important pathway among these reactions. The intramolecular hydrogen abstraction is a well-documented reaction.[1] This process favors γ-hydrogen

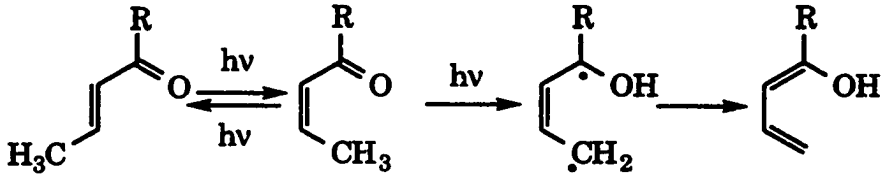
Scheme 1



abstraction to form a 1,4-diradical by a 1,5-hydrogen shift. Together, the cyclization and cleavage reactions are referred to as the Norrish Type II process (Scheme 1).

Compounds in which the carbonyl functionality and the γ-hydrogen are separated by a ethene or a benzene unit (as in α,β-unsaturated carbonyl compounds and 2-alkyl aryl ketones) still undergo photoinduced intramolecular hydrogen abstraction. In such cases, cleavage reactions cannot occur, but both classes of compound undergo **photoenolization**[2,3] to yield photoenols with varying efficiency (Scheme 2).

Scheme 2



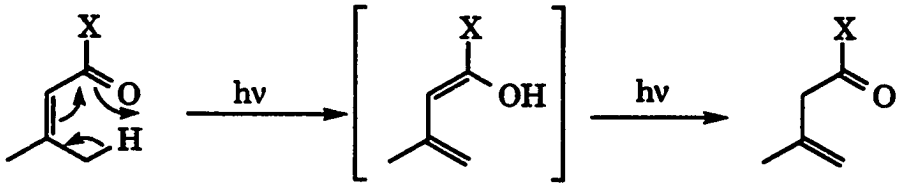
The electronic structure of simple ethenes can be readily described in terms of σ* and π bonding and σ* and π* antibonding orbitals. The lowest energy electronic transition of simple ethenes involves excitation of an electron from the highest occupied π orbital to the lowest unoccupied π* orbital. Compared with the others, this transition is the most intense. The resulting (π, π*) state leads to cis-trans (Z-E) interconversion (geometrical **photoisomerization**) of 1,2-disubstituted ethenes. The photoinduced isomerization of 1,2-disubstituted ethenes is an extremely general and well-studied process which has synthetic uses and is of importance in some biological systems.[4]

Photoenolization

Photoenolization of α,β-unsaturated carbonyl compounds

The photochemical deconjugation of α,β-unsaturated carbonyl compounds to their β, γ-unsaturated carbonyl isomers is a reaction which has been known for many years and which has more recently been shown to proceed via a dienol intermediate as illustrated in Scheme 3. As the scheme implies, dienol formation is stereoselective with the enol hydroxyl and vinyl substituent oriented *cis* to each other across the enol double bond. The stereoselectivities arises because the dienol is produced by transfer of hydrogens to the carbonyl oxygen from the γ-position oriented cis with respect to the carbonyl group. Consequently, photochemical enol formation does not occur in carbonyl compounds such as 3-methylcyclohexenone in which the γ-hydrogens are inaccessible to the carbonyl. The photochemical deconjugation reaction has been observed for unsaturated ketones, esters, acids, aldehydes, lactones, and may also occur for amides.[4]

Scheme 3



X = H, alkyl, OH, OR, NH_2

The singlet excited state formed by absorption of light by acyclic α,β-unsaturated carbonyl compounds decays to the ground state rapidly by E/Z isomerization.[5,6] Intersystem crossing is competitive with decay of the singlet excited state, and the resulting triplet excited state also decays to the ground

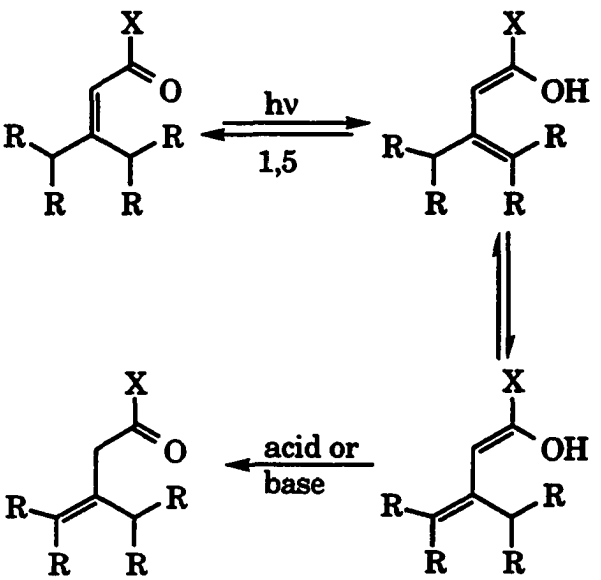
state rapidly by E/Z isomerization. Photoisomerization is slower than E/Z isomerization and only accounts for up to 10% excited state decay.[7,8] The photoenolization occurs from the singlet state only and appears to be a concerted process, since a single geometrical isomer of the enol is formed,[9,10] It can be viewed as a photochemical 1,5-sigmatropic hydrogen shift reaction to the single dienol as shown in Scheme 3.

The dienols formed by photoenolization of α,β-unsaturated ketones have been estimated to have life times in organic solvents on the order of 1 second at room temperature.[11,12] The photochemical prepared dienol reketonizes by acid[13] or base[7,8,14,21,23,25] catalysis, or by a unimolecular route which is thought to involve a thermal 1,5-sigmatropic hydrogen shift. Attempts to trap the photochemically produced dienols by Diels-Alder reaction with dienophiles have failed,[15] presumably due to the relatively short lifetime of the dienol; however, the dienols have been trapped as their silyl ethers.[10,16]

The photochemical deconjugation reaction has long been proposed as synthetic procedure for the conversion of α,β-unsaturated isomers into their thermodynamically less stable β,γ-unsaturated isomers.[17,18] However, the synthetic utility was apparently limited by the inertness of some system. For example, α,β-unsaturated ketones without γ-substituents tend not to undergo the photochemical deconjugation reaction.[19,20] It is now clear that this is because the dienol intermediate produced from the γ-unsaturated system can decay to the starting material by the 1,5-shift mechanism efficiently, whereas if γ-substituents are present these hinder the adoption of the conformation necessary for reketonization via a 1,5-hydrogen shift.[7,14] For latter systems the dienol must decay by catalysis which leads to the deconjugated isomer.[21] This

is illustrated in Scheme 4; if R = H then there is no steric inhibition of the thermal reversion to the starting material, but if R = alkyl it will force the occupation of other conformations which must reketonize by a catalytic mechanism to give the deconjugated isomer. It has been shown that the catalyst can be the solvent or solvent impurities and that the deconjugation

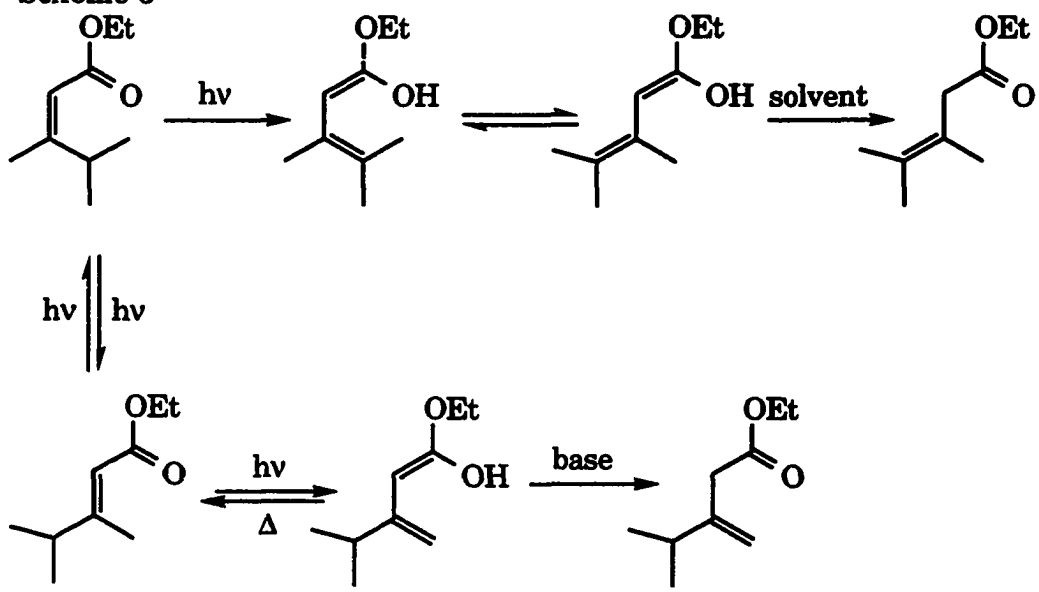
Scheme 4



reaction can be made quite general, even for γ-unsaturated carbonyls, by addition of either acid or base to the reaction mixture. The addition of base intercepts the dienol and equilibrates it with the dienolate which is preferentially protonated at the α-position[22] to give the deconjugated carbonyl compound at a rate faster than the 1,5-hydrogen shift of the dienol back to the conjugated precursor. This works very well for esters, and these can be converted to their deconjugated isomers in essentially quantitative yield if a simple organic base is present.[23] However, for ketones the utility of the photochemical deconjugation reaction is limited by the high efficiency of secondary photochemistry of the deconjugated ketone.[7,24]

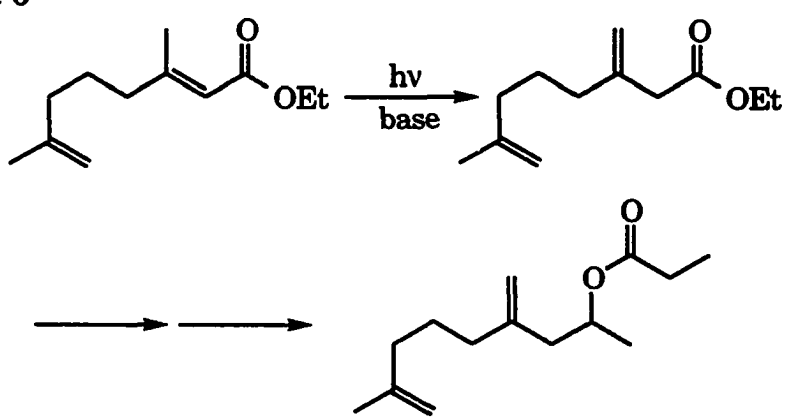
For unsymmetric substituted esters the photochemical deconjugation can be achieved with some degree of regioselectivity by making use of base catalysis. In presence or absence of base, the same starting material can give different results with one of the two deconjugated esters as the major product. An example is shown in Scheme 5.

Scheme 5



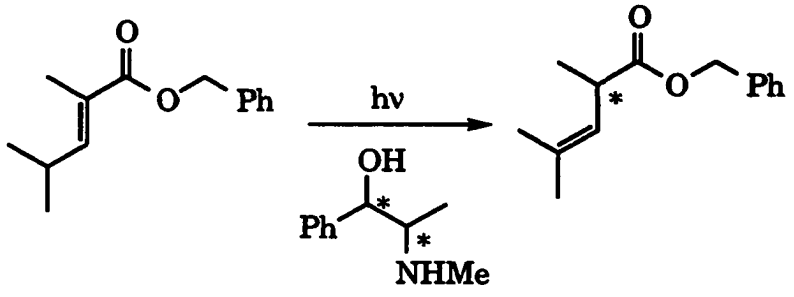
The base mediated partial control of regiochemistry has been applied to the synthesis of the insect pheromone[14] which is shown in Scheme 6.

Scheme 6



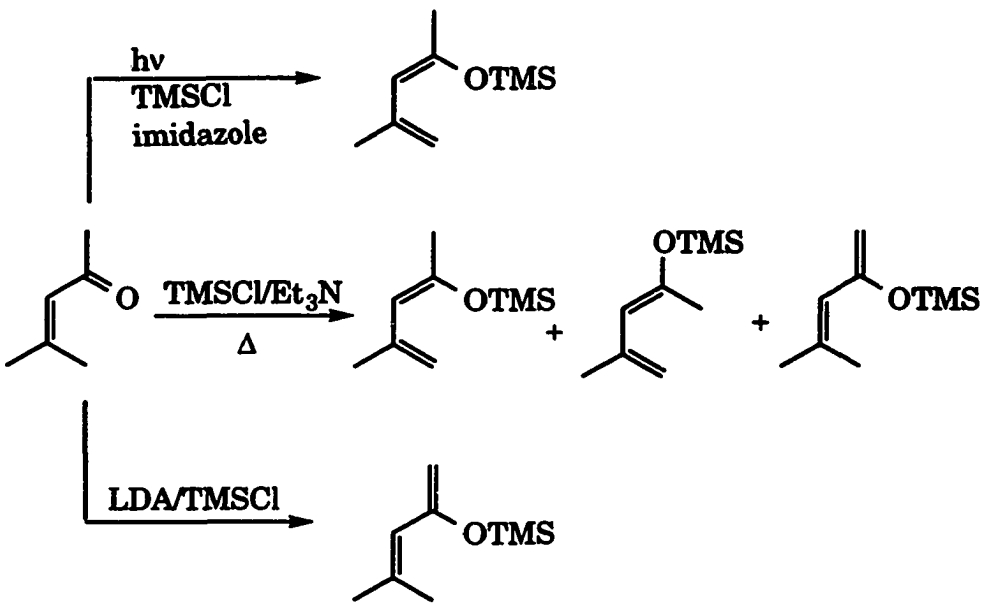
The photochemical deconjugation of α,β–unsaturated esters, which possess a substituent in the α-position, results in the production of a new chiral center in the products. Under normal circumstances, the products are obtained as a racemic mixture, since they are formed by protonation of an achiral dienolate intermediate. It has been demonstrated, however, if a suitable chiral base is used to catalyze the photochemical deconjugation, then the reactions become enantioselective.[26-28] An example[27] is shown in Scheme 7.

Scheme 7



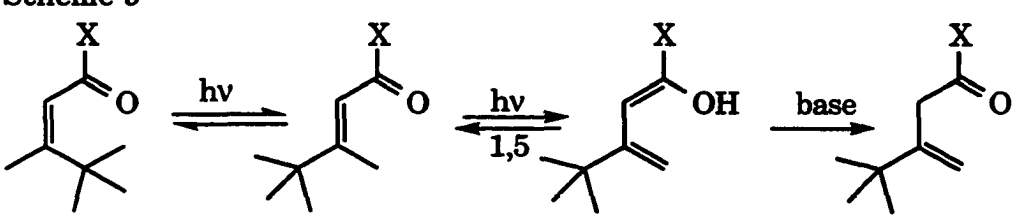
The dienols produced by photoenolization of ketones can be trapped as their silyl ethers.[9,10,16,29] As shown in Scheme 8, the silyl dienol ether is not only formed stereoselectively (only the Z enol is formed), but also regioselectively; the alternative thermal modes of preparation of the silyl dienol ethers from the ketone give either mixtures of isomers or the product of removal of the kinetically more acidic proton. In principle, these photochemically prepared dienol ethers should be useful as Diels-Alder dienes or as precursors to otherwise inaccessible metal dienolates by trans-metallation.

Scheme 8



For the photoenolization reaction to occur, it is necessary for a γ-hydrogen to be both available and *syn* oriented with respect to the carbonyl. In some systems, the latter requirement is not met and yet photoenolization still occurs.[30-32] For example, in esters and ketones of the type shown in Scheme 9 only the E-geometrical isomer can photoenolize.

Scheme 9

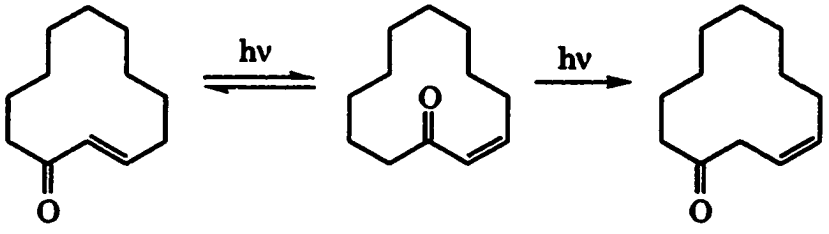


X=R, OR

In cyclic systems such as E-cyclododecenone[33] and cyclodecenone[34] the *syn* requirement of the γ-hydrogen and the carbonyl is also not met, but if the

ring is large enough photoenolization can occur following initial E/Z isomerization as shown for cyclododecenone in Scheme 10.

Scheme 10

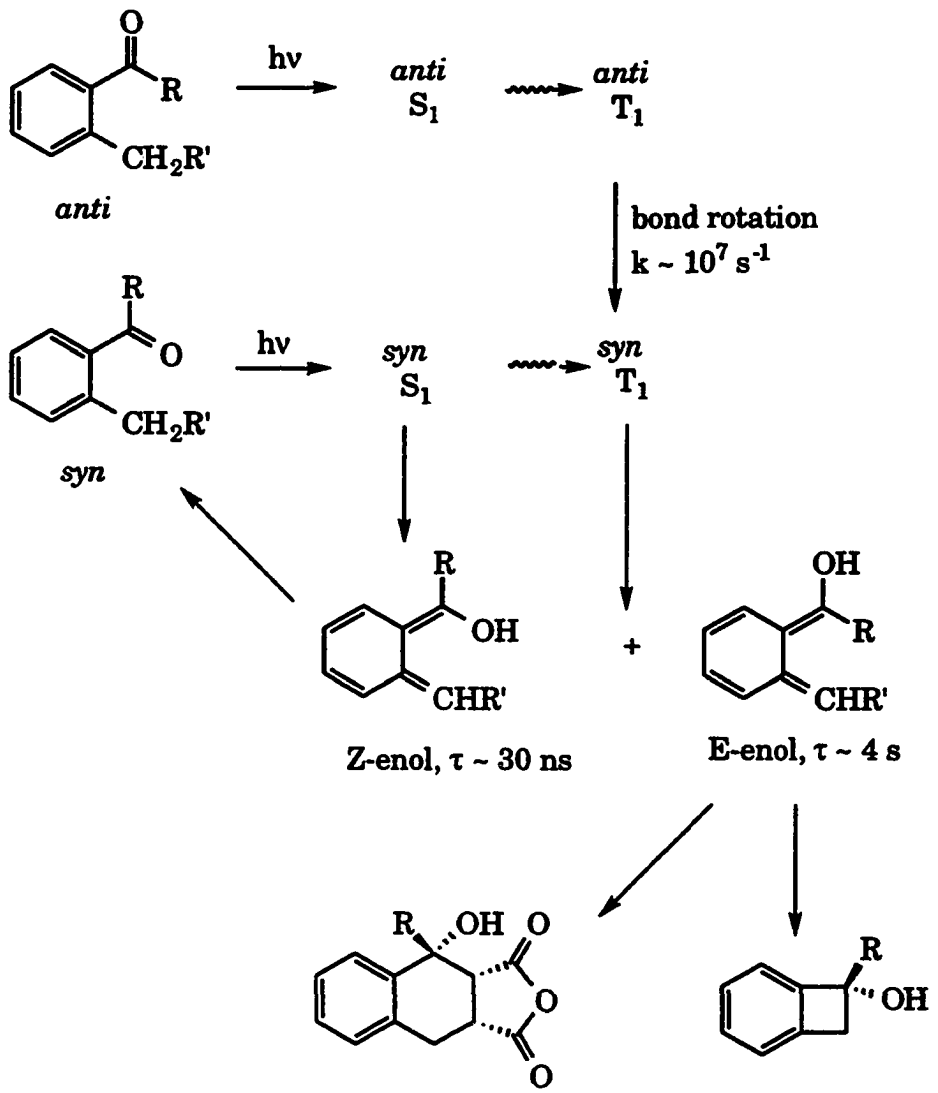


Photoenolization of *ortho*-alkyl substituted aryl carbonyl compounds

The photoenol produced from *ortho*-alkyl substituted aryl carbonyl compounds is also unstable and readily reverts to the starting material. The mechanism of the process is not, however, simple and sensitization and quenching studies (energy transfer) have played a crucial role in unraveling the complexity of the photoenolization of *ortho*-alkyl aryl carbonyl compounds.[35] We have seen earlier that molecular conformations can have a marked effect on efficiencies of γ-hydrogen abstraction. Similar concepts operate for the *ortho*-alkyl aryl carbonyl compounds and, since in the excited state there is no free rotation about the carbonyl phenyl bond, the populations of the *syn* and *anti* conformers in the ground state can have an important influence on the overall reactivity and product formation. The mechanism is shown in Scheme 11. The photoenol derived from *ortho*-alkyl aryl ketones have Z and E isomers. The Z isomer, which is kinetically unstable and has a shorter lifetime (τ ~ 30 ns) can undergo a fast 1,5-hydrogen shift back to starting ketone. However, the E isomer which has a longer lifetime (τ ~ 4 s) can be trapped by a dienophile. Although the Z and E photoenols are detected

from the excited-state pathway in approximately equal amounts, the singlet-state pathway yields essentially the Z-photoenol. The formation of benzocyclobutenols provides further evidence for the presence of photoenols.

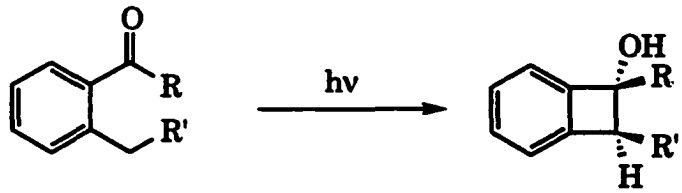
Scheme 11



A variety of acetophenones and benzophenones give benzocyclobutenols in high yield upon UV irradiation.[36] In all cases only the *trans* diastereomer is formed (Scheme 12). The reactions can be quenched completely in the

presence of acid. The mechanism for the photocyclization of *ortho*-alkyl aryl ketones to cyclobutenols has been studied. It is concluded that benzocyclobutenols are formed in a three-step-process: 1) triplet γ-hydrogen abstraction to yield a 1,4-diradical triplet enol; 2) decay of the twisted triplet enol to the planar ground state; 3) conrotatory electrocyclization of the enol to form cyclobutenol. Acid catalyzes the reversion of the enol to the starting

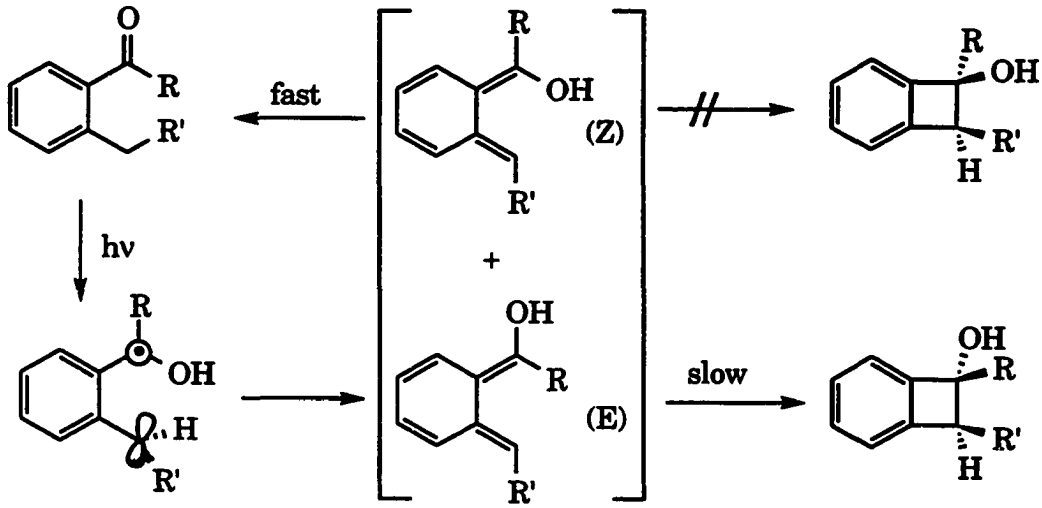
Scheme 12



R = CH_3, Ph
R' = H, OMe, $OCH_2CH{=}CH_2$, $O(CH_2)_2CH{=}CH_2$

material ketone; it does not catalyze the reversion of the cyclobutenol to the ketone, but does catalyze their trans-cis interconversion. The fact that acid quenches cyclobutenol formation thus demonstrates that cyclobutenols are

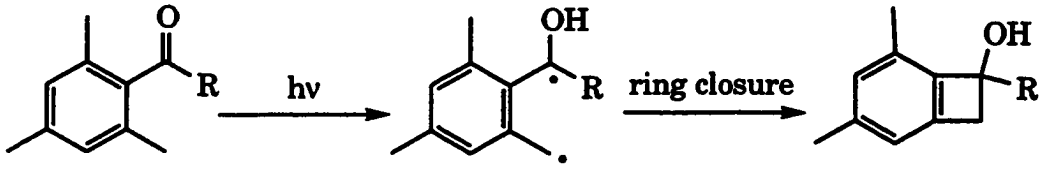
Scheme 13



formed from the enols. The mechanism demands that only one of the two possible enols is formed and lives long enough to rearrange thermally (Scheme 13).

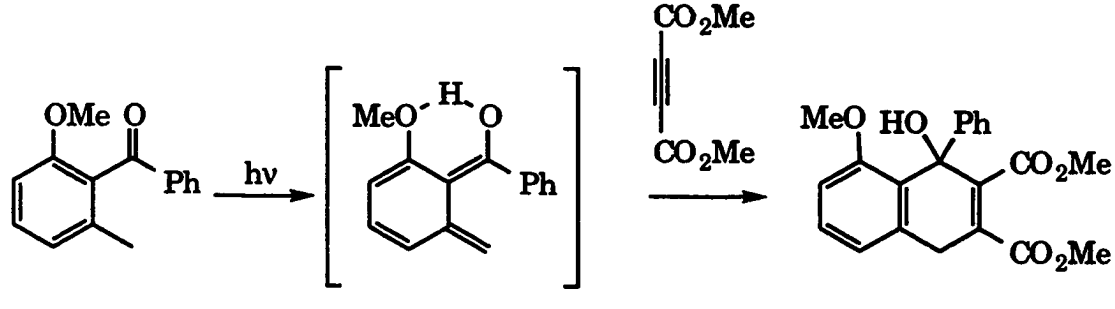
The formation of the benzocyclobutenols during the photolysis of aryl ketones has other precedents, particularly for hindered ketones. In an extensive study of 2,4,6-tri- or 2,6-dialkylphenylketones, cyclobutenol formation is often the preferred course of the reaction.[37] In no case can ground state dienols be trapped by dienophiles. Interestingly, on heating these benzocyclobutenols the starting ketones are formed, but again a diradical process seems to be involved since no trapping of any intermediate dienols by dienophiles is observed. Therefore, photoenolization with 2,4,6-tri or 2,6-disubstituted aryl ketones does not appear to occur (Scheme 14).

Scheme 14



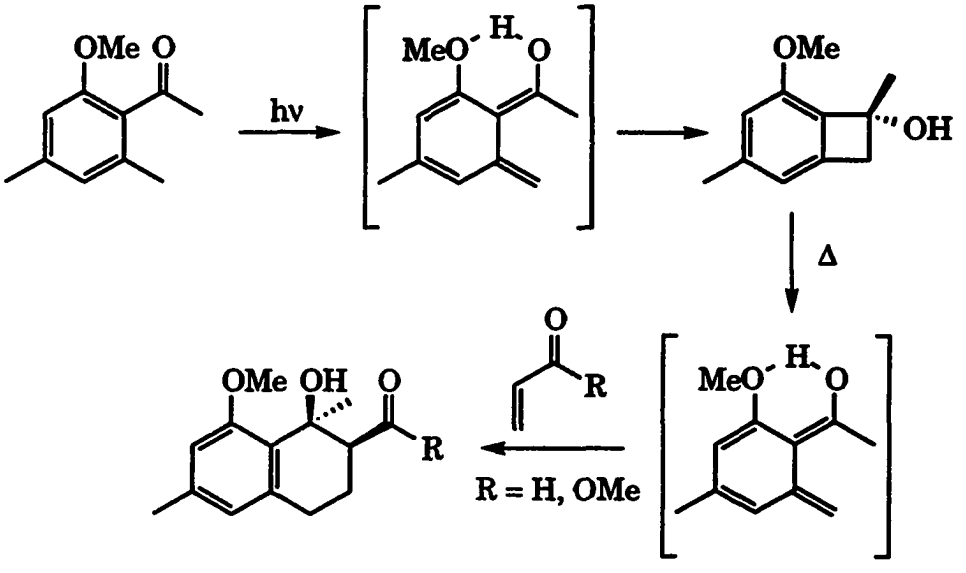
However, the saturation is changed when some influence to stabilize the resulting ground state is present, as in photoenolization of 2-methoxy-6-methylbenzophenone where H-bonding appears to be important to stabilize the

Scheme 15



dienol. Comparable with 2,6-dimethylbenzophenone in steric size, 2-methoxy-6-methylbenzophenone forms a trappable dienol to produce the Dies-Alder adduct in high yield with dimethyl butynedioate (Scheme 15).[38] Our research is also consistent with the above discovery. Photolysis of 2-methoxy-4,6-acetophenone forms a benzocyclobutenol via a dienol. Heating the benzocyclobutenol in the presence of acrolein or methyl acrylate gives Diels-Alder adducts in good yield (Scheme 16).[39]

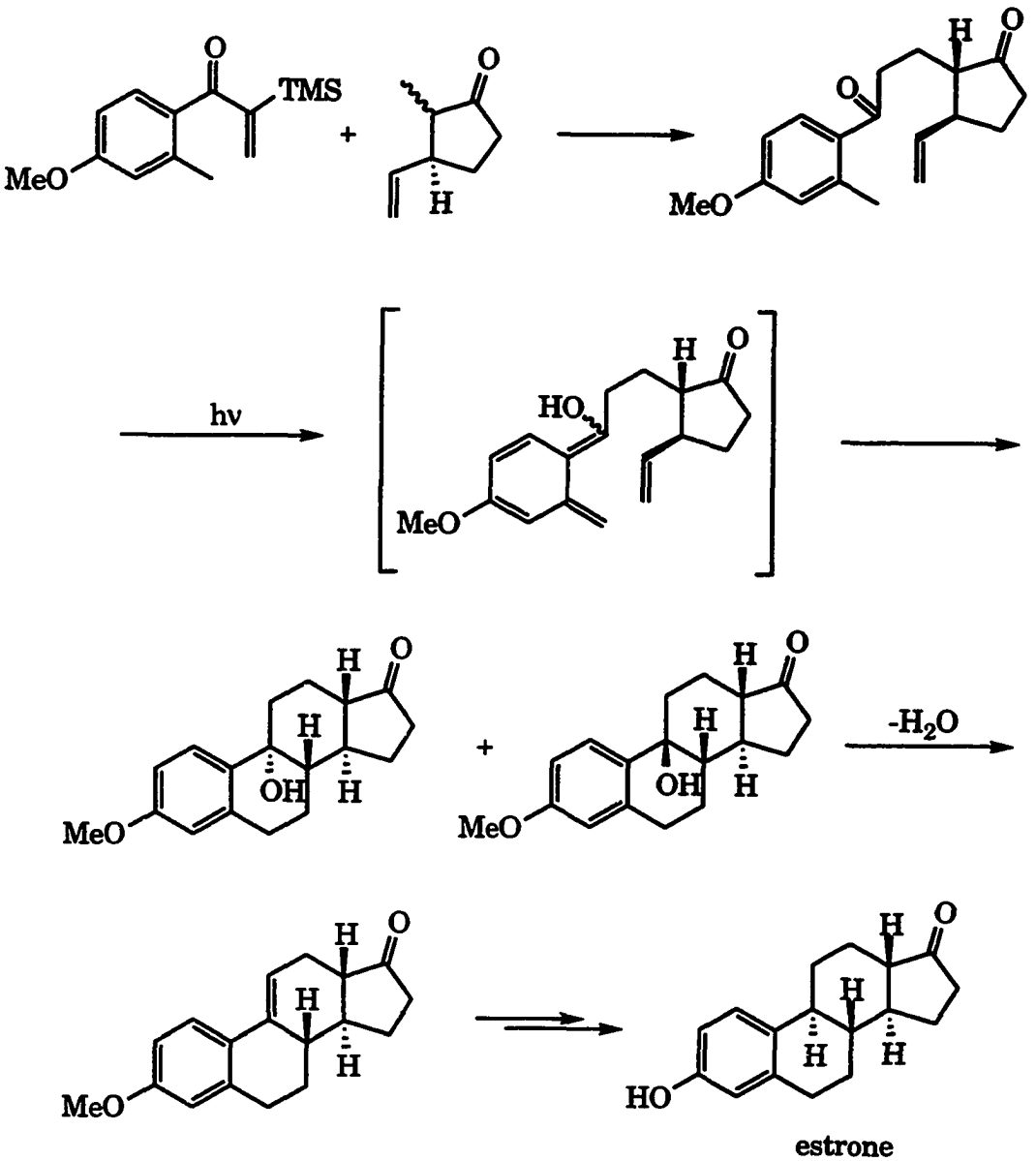
Scheme 16



Since the *ortho*-quinodimethane can undergo inter- or intramolecular Diels-Alder reaction, the ground state photoenols become a valuable reactive intermediate in organic synthesis. An example of the synthetic utility of photoenols is the photochemical synthesis of estrone which is shown in Scheme 17.[40] An *ortho*-methyl aryl ketone, synthesized from a phenyl vinyl ketone and a cyclopentanone derivative, is photolyzed to produce two diastereomeric tetracyclic hydroxyketones with light of wavelength greater than 340 nm at 95°C in methylcyclohexane (boiling point 100.9°C). The

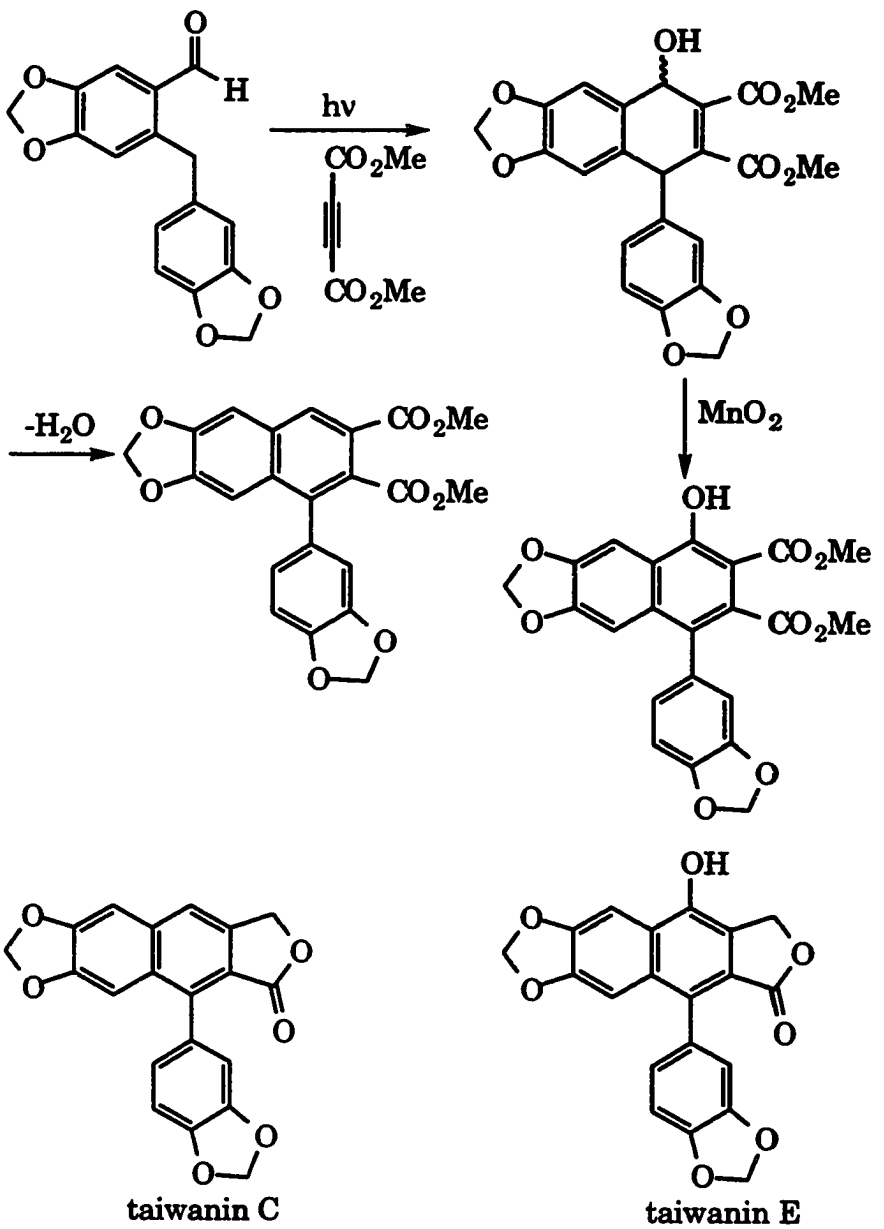
dehydration product is isolated in 65% overall yield from the photolysis precursor.

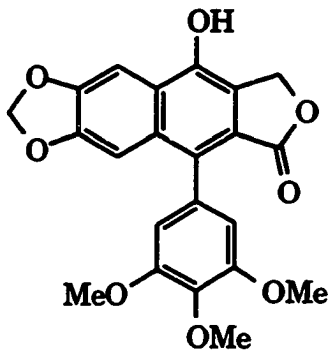
Scheme 17



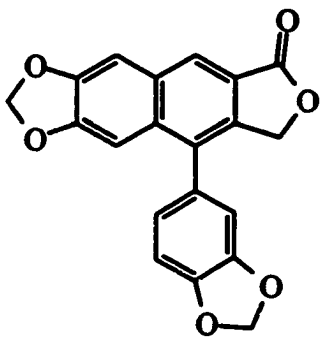
Traping the E-enol with various dienophiles can produce tetrahydronaphthalenes. Such compounds have considerable potential in the synthesis of lignans of the podophilotoxin family (Scheme 18).[41] Photolysis of benzaldehyde derivatives in the presence of dimethyl butynedioate give an

Scheme 18





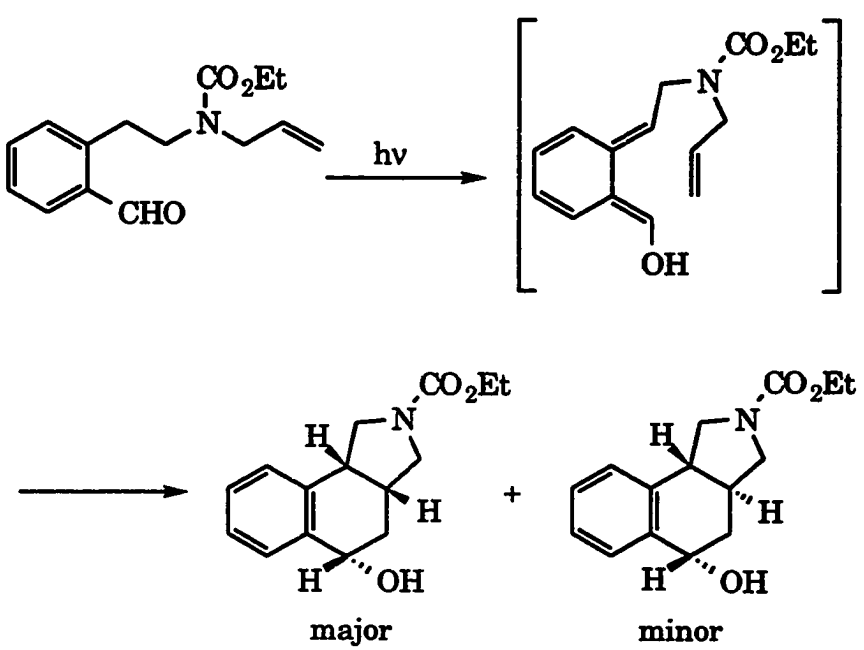
tetrahydropodophyllotoxin



justicidin E

adduct which can be either dehydrated, to obtain the naphthalene derivative or oxidized, with manganese dioxide, to obtain the naphthol derivative. Subsequent chemical manipulations afford the corresponding lactones. In this manner, tetradehydropodophllotoxin, taiwanins E and C, and justicidin E have been prepared.

Scheme 19



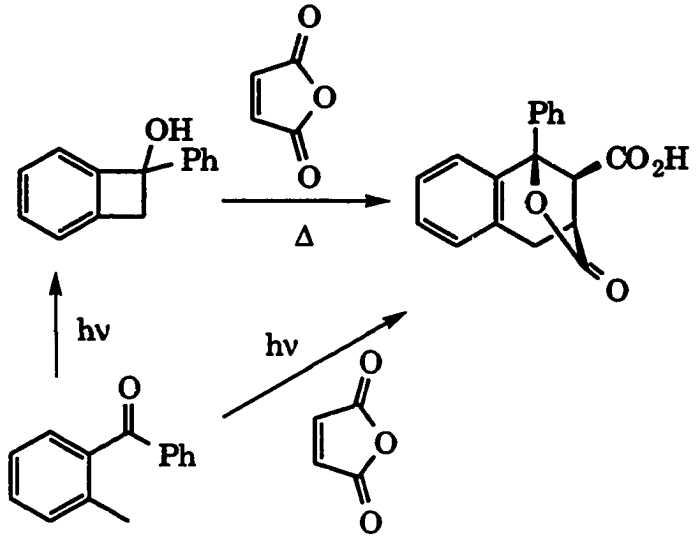
major

minor

The photoenolization/Diels-Alder process has been utilized in the synthesis of heterocyclic compounds. An example is shown in Scheme 19.[42] A benzaldehyde derivative undergoes a photocyclization reaction to produce a diastereomeric mixture of tricyclic compounds in a 3:1 ratio. The major isomer is formed through a rapid thermal cycloaddition of the E-enol to the neighboring olefinic double bond *via* the *endo* transition state; the minor isomer is formed *via* the *exo* transition state. Because of the intramolecular nature of the reaction ring constraints impose a restriction on the mode of cycloaddition allowing competion between the *endo*- and *exo*-addition process.

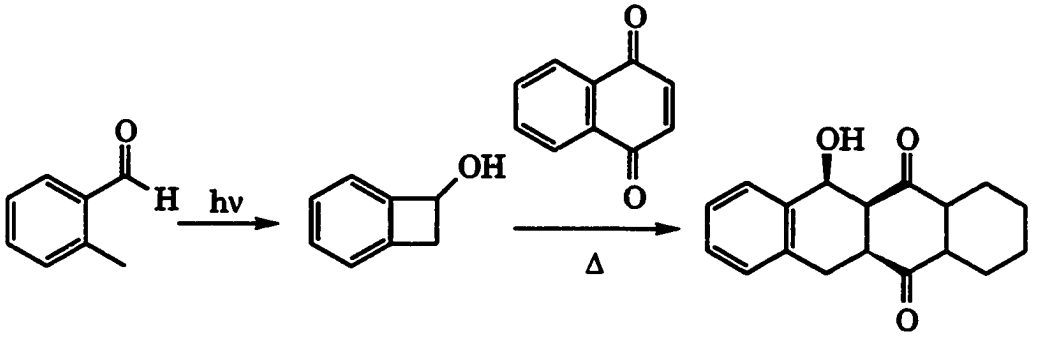
Under thermal conditions, the photobenzocyclobutenols can form dienols which can further undergo Diels-Alder reactions. The immediate consequence is the extension of synthetic potential of photoenolization. An example is shown in Scheme 20. Photolysis of 2-methylbenzophenone gives the benzocyclobutenol which can be thermolyzed to form the dienol. In the

Scheme 20



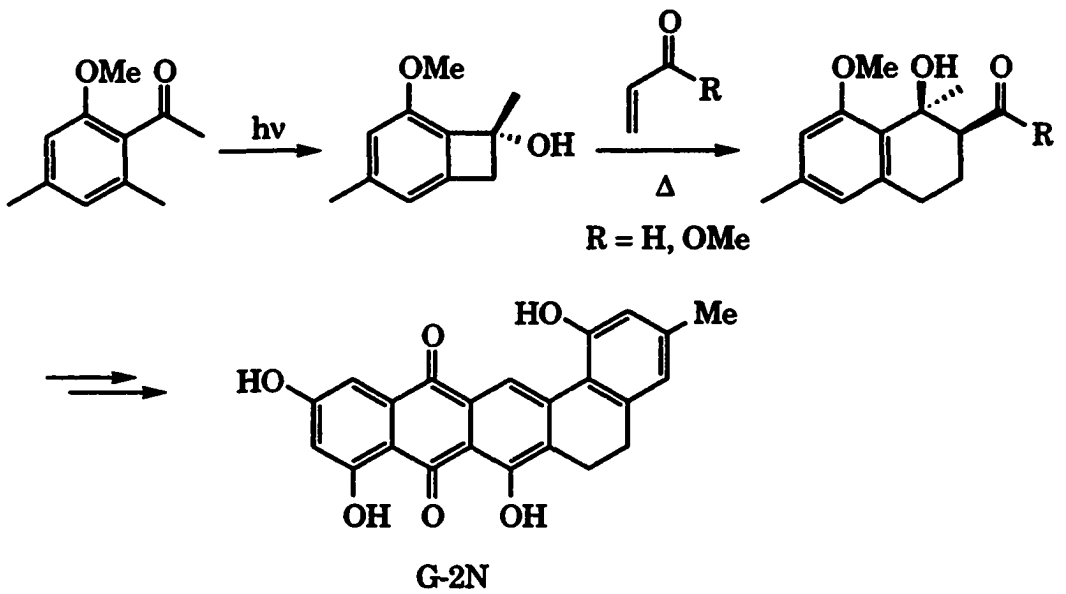
presence of maleic anhydride, the dienol produces the acid lactone.[43] The result of the two-step process is the same as that of the one-step process for the photolysis of 2-methylbenzophenone in the presence of maleic anhydride.[44] However, sometimes the two-step process is superior to the one-step process for some reason. One example is shown in Scheme 21. The benzocyclobutenol prepared from the photolysis of 2-methylbenzaldehyde reacts with 1,4-naphthoqunine in refluxing benzene, to produce good yields of the tetracyclic naphthoacene derivative directly and stereoselectively. The photochemical equivalent of this reaction is not possible, because of the numerous alternative photochemical fates of the quinone.[45]

Scheme 21



Our key step in the synthesis of natural product G-2N also demonstrates the success of the two-step process (Scheme 22). Photolysis of 1-(2-methoxy-4,6 dimethylphenyl)-ethanone in the presence of acrolein or methyl acrylate gives benzocyclobutenol because the dienophiles are not reactive enough to trap the photodienol. Thermolysis of the benzocyclobutenol in the presence of dienophiles gives the desired products which lead to a total synthesis of G-2N.[3]

Scheme 22



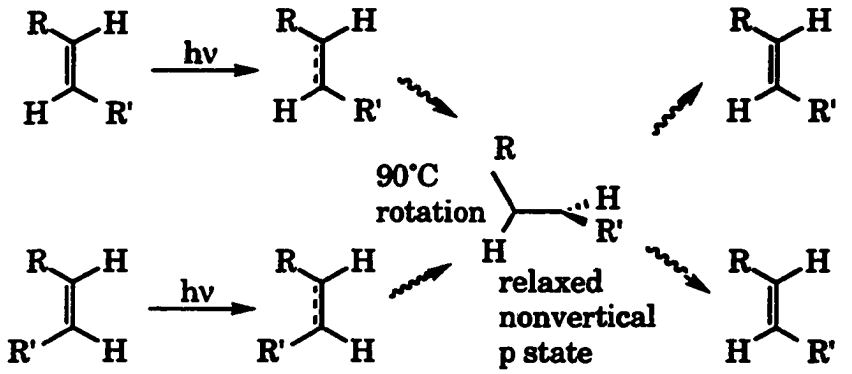
G-2N

Photoisomerization

The photochemical introduced *cis- trans* (Z-E) isomerization of ethene occurs from both the singlet and triplet excited states of the ethene and in appropriate cases can be initiated by electron transfer sensitizers.[46,47] On excitation of *cis* and *trans* ethenes the geometries of the initially formed (π, π^*) excited singlet state molecules are the same as those of the corresponding ground states and are termed the vertical excited states (Franck-Condon principle). In these states there is effectively no π bond and so the central bond may rotate to give the lowest energy conformation: this staggered conformation where there is a 90° angle relaxed nonvertical state is termed the "p state" and, from this, rapid radiationless decay can lead to either geometric

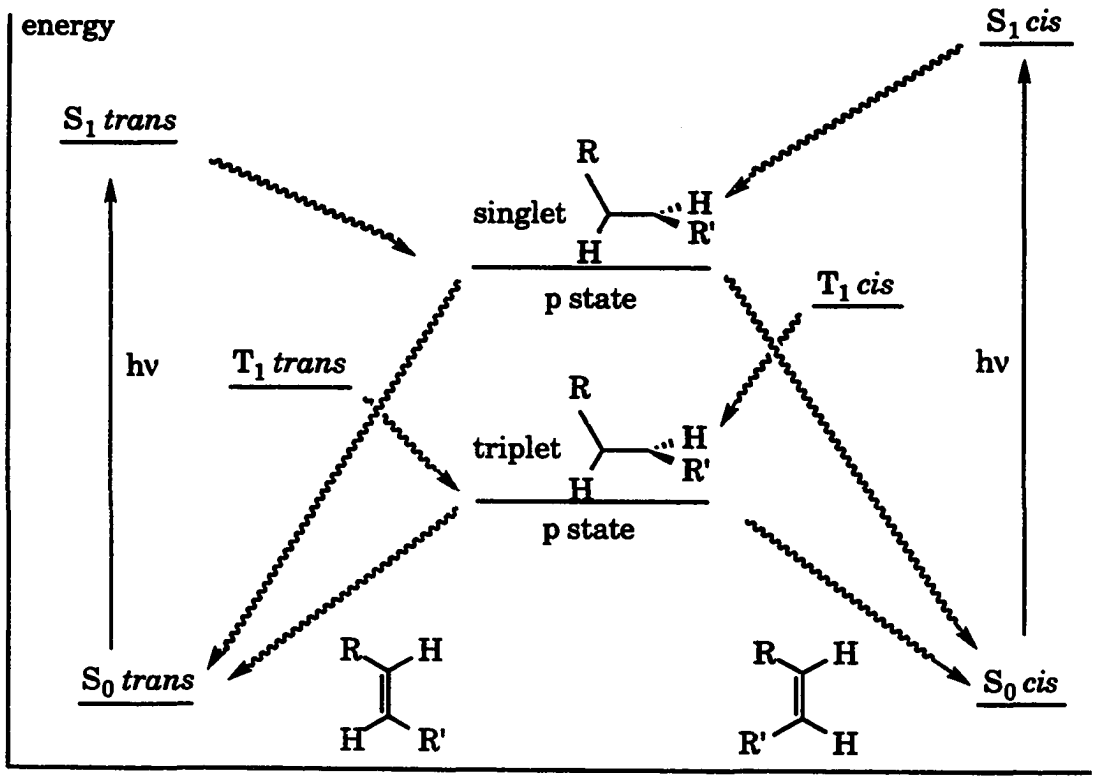
isomer (Scheme 23). This is diagrammatically represented in Scheme 24 for both singlet and triplet excited states of 1,2-disubstituted ethenes.

Scheme 23



Decay from the relaxed nonvertical states to the *cis* and *trans* ground-state ethenes occurs with approximately equal probability and, assuming that

Scheme 24

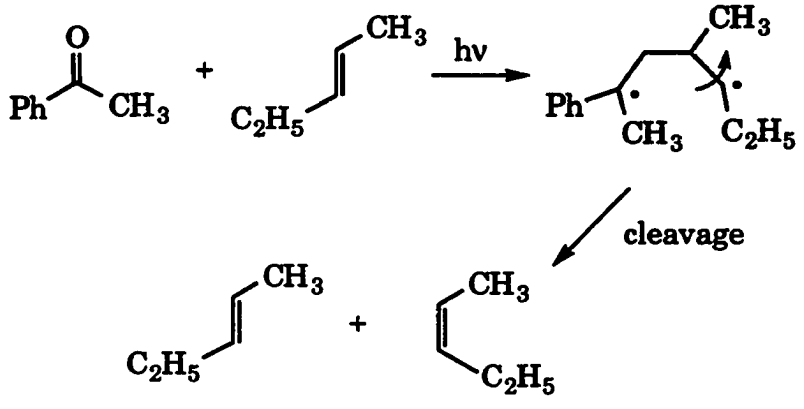


neither isomer undergoes any secondary processes, the concentrations of each of the *cis* and *trans* isomers will reach a steady-state value called the photostationary state: this means that, at this particular ratio of isomers, the rate of formation of each from the relaxed nonvertical state is equal to the of its photoconversion. For the singlet-state reaction, the relative concentration of the isomers in the photostationary state is dependent on their extinction coefficients and the quantum yields of the forward and back reactions at the particular wavelength used in the experiments.

The *cis-trans* interconversion of 1,2-disubstituted ethenes also occurs from the triplet state. The excited *cis* and *trans* isomers (like the singlet excited species) undergo facile relaxation to a common twisted state, followed by rapid radiationless transitions. Formation of the ethene triplet states by intersystem crossing is very inefficient, but their population can readily be achieved by energy transfer from triplet excited molecules. For the sensitized *cis-trans* interconversion of ethenes, the absorbances of the *cis* and *trans* isomers, unlike the singlet-state reactions, do not control their concentrations in the photostationary state and the principal factor which markedly affects this ratio is the triplet energy of the sensitizer in relation to that of the acceptor. For energy transfer to occur, the sensitizer triplet energy must be greater than that of the ethene. However, the *cis* and *trans* isomers of 1,2-disubstituted ethenes have different triplet energies and some sensitizers can be found with energies between these two values so that one isomer becomes preferentially sensitized and a photostationary state rich in the isomer of the higher triplet energy is formed. Aromatic compounds, such as benzene and stilbene, are often used as sensitizers for photoisomerization of ethenes. Sensitized *cis*

-trans interconversion of ethenes can also be initiated in some cases by ketones, which have triplet energies below those of both ethene isomers. For example, the benzene-sensitized *cis:trans* ratio of pent-2-ene at the photostationary state is 1.0, whereas the acetophenone-sensitized reaction produces a ratio of 0.19, which is near to the thermodynamic equilibrium value. These observations are explained by straightforward energy transfer from the benzene triplet state to the ethene, but for the ketone a mechanism involving the formation of a diradical resulting from the ketone-ethene addition reaction and the preferential cleavage of the diradical to yield the trans isomer is suggested. This mechanism is frequently referred to as the Schenck diradical mechanism (Scheme 25).

Scheme 25



The *cis-trans* isomerization of ethenes and related compounds can also be initiated by photosensitized electron transfer.[48] The reaction commonly involves electron transfer from the ethene to the excited sensitizer to give the ethene radical cation, but examples of electron donation to the ethene to give its radical anion are known. Interestingly, studies on the mechanism of electron-transfer-sensitized *cis-trans* isomerization of ethenes have shown that electron-donor ethenes (forming ethene radical cations) and electron-acceptor

ethenes (forming ethene radical anions) undergo the geometrical isomerization by quite different pathways. In the former class of ethene, electron transfer to the triplet excited state of the sensitizer occurs to give the radical ion pair. The separated ethene radical cation may then interconvert giving the two isomerization intermediates, *cis* D and *trans* D radical cations. These *cis* and *trans* ethene radical cations either undergo back electron transfer from the sensitizer radical anion or accept an electron from the reactant and thereby propagate a chain process for the isomerization as shown in Scheme 26. An example of this type is the *cis-trans* of 1-phenylpropene sensitized by chloranil.[48]

Scheme 26

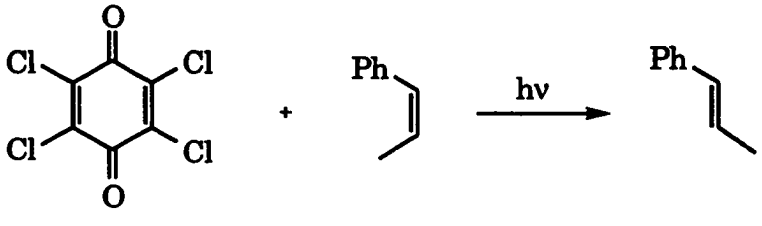
$$A \xrightarrow{h\nu} A^{1*} \xrightarrow[\text{transfer}]{e^-} A^{3*} + cis\ D \longrightarrow {}^3(A\ cis\ D^{+\bullet})$$

$${}^3(A\ cis\ D^{+\bullet}) \longrightarrow A^{-\bullet} + (\text{separated})\ cis\ D^{+\bullet} \rightleftharpoons trans\ D^{+\bullet}$$

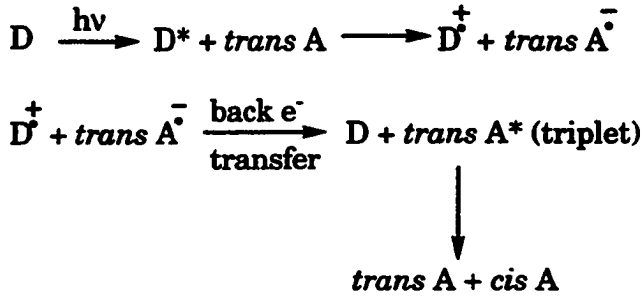
$$cis \text{ or } trans\ D^{+\bullet} + A^{-\bullet} \xrightarrow[\text{transfer}]{\text{back } e^-} A + cis \text{ or } trans\ D$$

$$cis \text{ or } trans\ D^{+\bullet} + cis\ D \xrightarrow[\text{transfer}]{e^-} cis \text{ or } trans\ D + cis\ D^{+\bullet} \rightleftharpoons trans\ D^{+\bullet}$$

A = e^- acceptor sensitizer (chloranil)
D = e^- donor ethene (1-phenylpropene)



Scheme 27

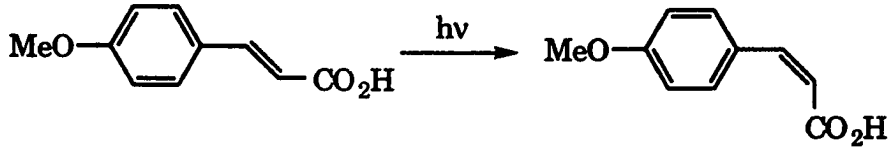


D = e⁻ donor sensitizer (triphenylene)
A = e⁻ acceptor ethene (cinnamonitrile)

For electron-donor ethenes, the energy of the radical ion pair lies below the triplet energy of the ethene, so this excited-state species is not involved in the isomerization process. On the other hand, for electron-acceptor ethenes such as cinnamonitrile, the free energy of the ion pair is higher than the ethene triplet energy, so that back transfer generates the triplet ethene and ground-state sensitizer. Thus, geometrical interconversions of electron-acceptor ethenes have their triplet state as a reaction intermediate (Scheme 27).[48]

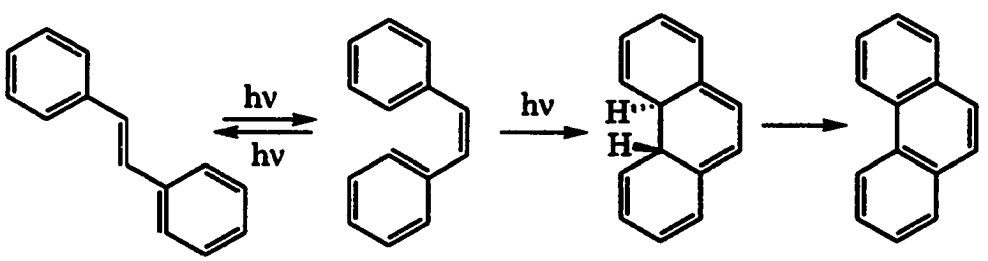
Thus, photo *cis-trans* interconversion of ethenes is a common process and is of importance in organic synthesis. Its synthetic potential lies in the possibility of transforming the more stable geometrical isomer into the less stable isomer. For example, irradiation of the *trans* cinnamic acid derivative produces the cis isomer in 74% yield (Scheme 28).[49]

Scheme 28



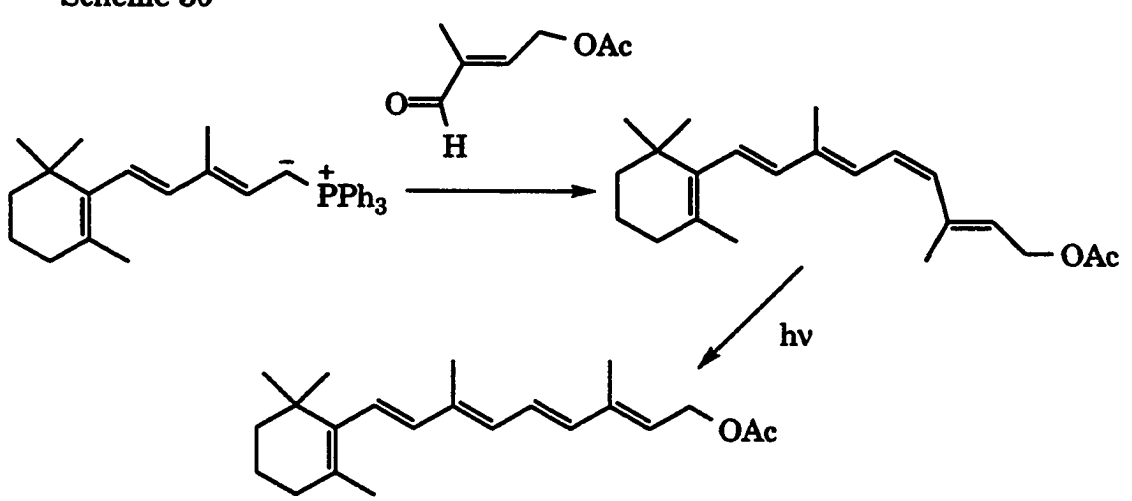
This type of isomerization in diene and polyene systems has been extensively used, particularly where the *cis* isomer is required for subsequent cyclolization. The most widely studied examples of this process involve the formation Of polynuclear aromatic compounds from trans 1,2-disubstituted ethenes. The overall process is illustrated in Scheme 29 by the formation of phenanthrene from *trans* stilbene. A second photoreaction is involved in which the cis isomer cyclises to a readily oxidisable dihydro intermediate.

Scheme 29



Photoinduced geometrical isomerization has been used generally for the preparation of particular geometrical isomers or to enrich mixtures in one isomer and is employed commercially for the formation of the all trans form of

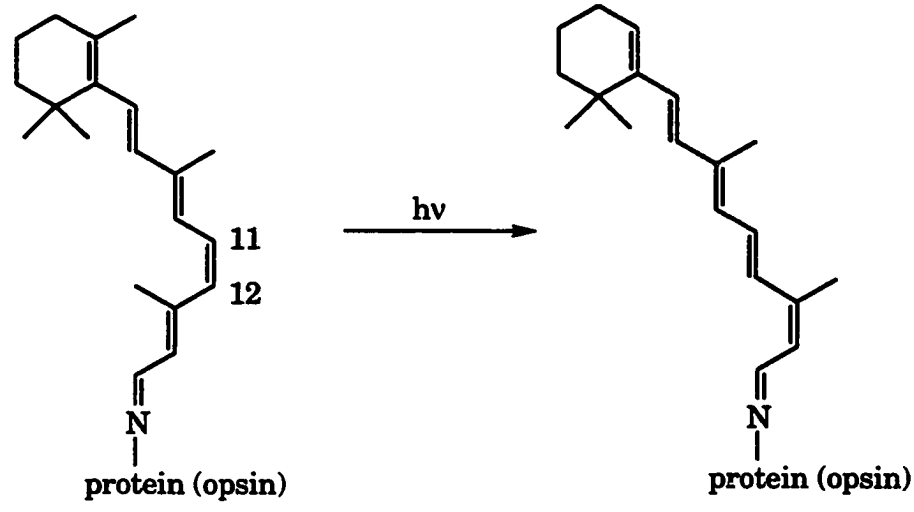
Scheme 30



Vitamin A from the synthetic mixture of cis and trans isomers (Scheme 30): the *trans* isomer is required for nutritional purposes and is used in the pharmaceutical industry.

Photochemistry has considerable importance in biological systems and *cis-trans* isomerization plays a key role in the mechanism of vision and in the treatment of neonatal jaundice. The primary act in the mechanism of vision involves the photoisomerization of the 11-*cis* double bond of the retinal chromophore in rhodopsin to give all *trans* metarhodopsin (Scheme 31).[50]

Scheme 31

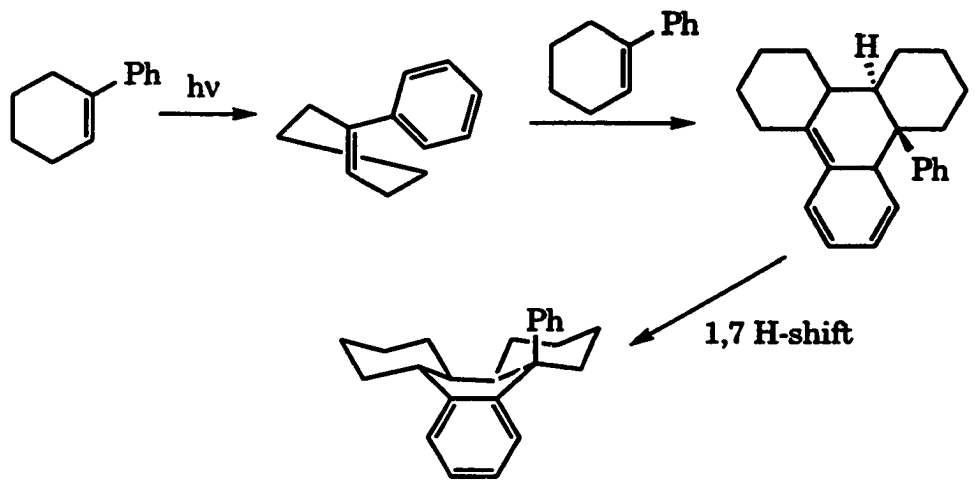


rhodopsin metarhodopsin

Besides photo *cis-trans* isomerization of acyclic ethenes, that of cyclic ethenes has drawn much attention. Cyclic ethenes usually exist in the cis geometry, but conversion to the trans isomer can be photosensitized by aromatic hydrocarbons provided that the ring is sufficiently large to accommodate the trans ethene unit.[46] In practice, this means that ring compounds with eight or more carbon atoms readily form the isolable *trans* isomer. For the analogous C7 and C6 ring compounds, the transient *trans*

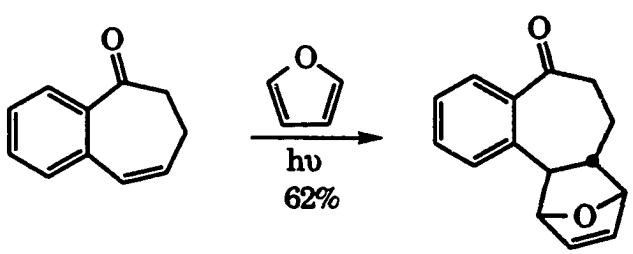
isomers can be trapped chemically, especially by dienophiles undergoing a Diels-Alder reaction. Irradiation of 1-phenylcyclohexene gives a Diels-Alder adduct of a highly strained *trans* isomer and the styrene moiety of the *cis* isomer (Scheme 32).[46]

Scheme 32



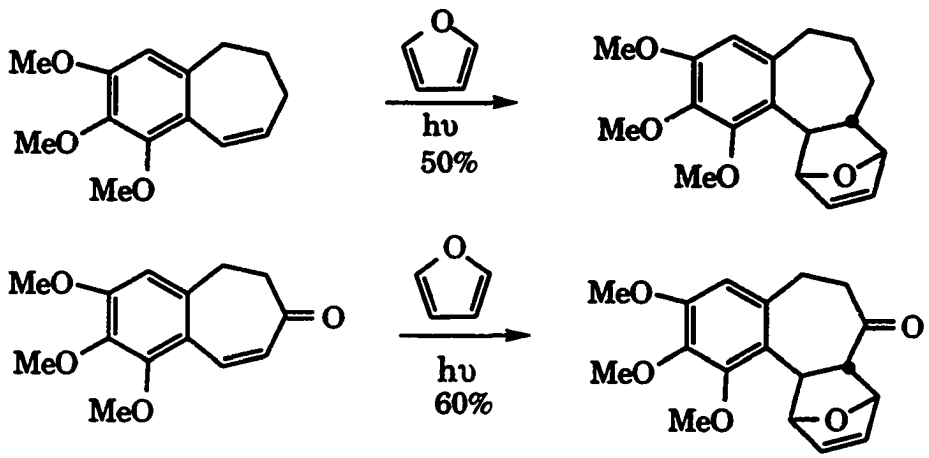
Benzocycloheptadienone can also undergo photoinduced *cis-trans* isomerization. The resulting trans isomer can be trapped by furan in good yield(Scheme 33).[51]

Scheme 33



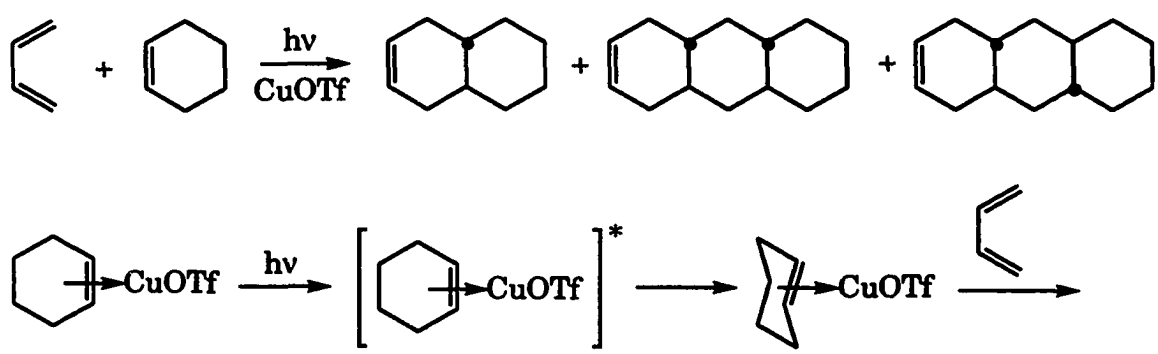
In our synthetic approach towards colchicine, irradiation of benzocycloheptene and benzocycloheptadienone derivatives in the presence of furan produces trans fused Diels -Alder adducts (Scheme 34) (see Part III).

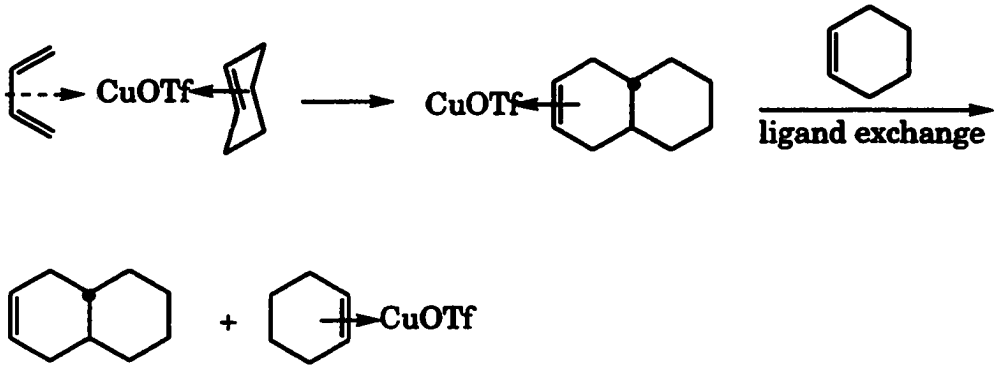
Scheme 34



Some reagents, such as copper(I) triflate can catalyze the transformation of cis cyclic ethenes to the *trans* isomer which consequently undergo Diels-Alder reaction. Irradiation of cyclohexene and 1,3-butadiene in the presence of catalytic amounts of copper(I) triflate produces polycyclic products. A mechanistic study has shown that cyclohexene copper(I) triflate complex isomerizes to its *trans* isomer, which is more stable. The *trans* complex coordinates with 1,3-butadiene, consequently giving cycloaddition product (Scheme 35).[52]

Scheme 35





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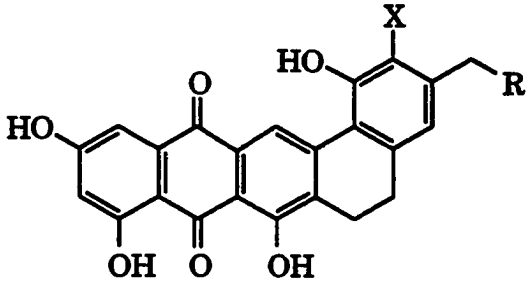
CHAPTER II
A DIRECT SYNTHESIS OF G-2N

A paper to be submitted to the Journal of Oganic Chemistry

Gorege A. Kraus and Guohua Zhao

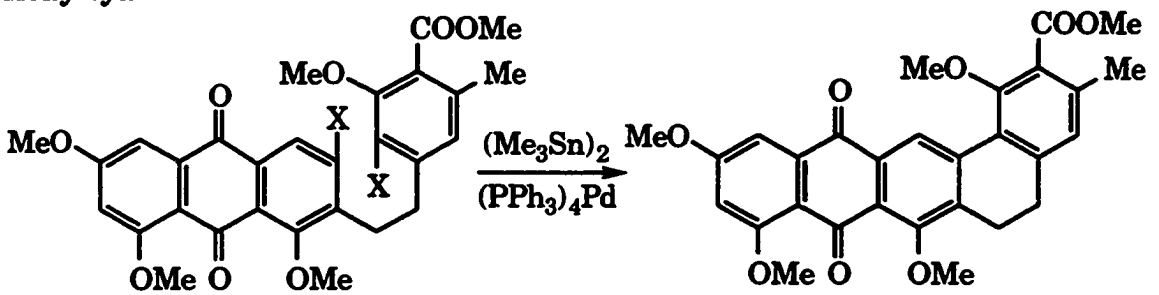
Introduction

Linearly fused anthraquinone natural products, such as aclacinomycin and daunomycin, have been the subject of extensive synthetic and toxicological studies for over two decades.[1,2] Recent reports of the isolation of biologically active quinones that are angularly fused have provided the impetus for the creation of synthetic routes for angularly fused quinones. Some members of this quinone family exhibit phosphodiesterase inhibitory activity, significant antiretroviral activity or inhibitory activity against funguses.[3] The structures of three members of this class, G-2N (**1**) and G-2A (**2**) isolated from the genus *Frankia*[4] and KS-619-1 (**3**) isolated from *Streptomyces californicus*,[5] are shown below.



1: X = H, R = H
2: X = CO_2H, R = H
3: X = CO_2H, R = $COCH_3$

A synthesis of G-2N and G-2A has been achieved by Kelly using an innovative palladium-mediated intramolecular coupling of a bis-triflate 4.[6] We report herein a direct synthetic route to angularly fused anthraquinones exemplified by the preparation of G-2N which is strategically distinct from the Kelly synthesis.

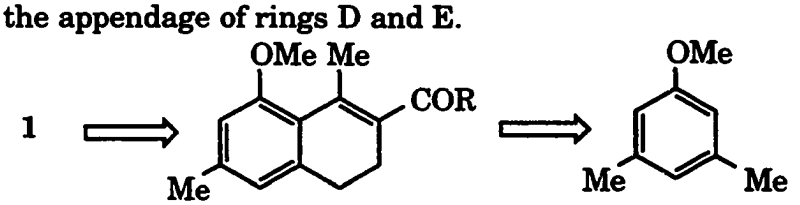


4: X = OTf

⟹ 1 and 2

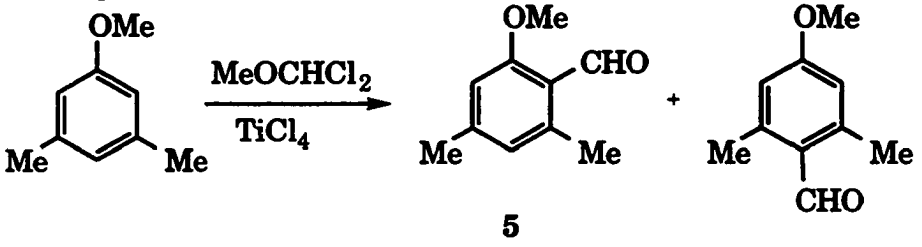
Results and Discussion

We envisioned the A ring of 1 coming from commercially available 3,5-dimethoxyphenol. The acylation of 3,5-dimethylanisole followed by an intermolecular photoenolization reaction would generate an AB ring system suitable for the appendage of rings D and E.



8: R = H
13: R = OMe

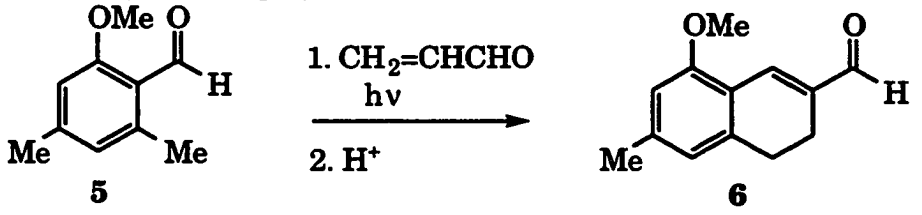
The first compound that we studied was aldehyde **5**.[7] It could be synthesized by a Vilsmeier formylation reaction using DMF and phosphorus oxychloride; however, the isomer wherein the aldehyde was introduced para to the methoxyl group was co-produced in almost equal amounts. Fortunately, a variant of the Vilsmeier, which employed dichloromethyl methyl ether and titanium tetrachloride, proceded in 99% yield and generated a 9:1 ratio of **5** to the undesired para isomer.[8]



5

9 : 1

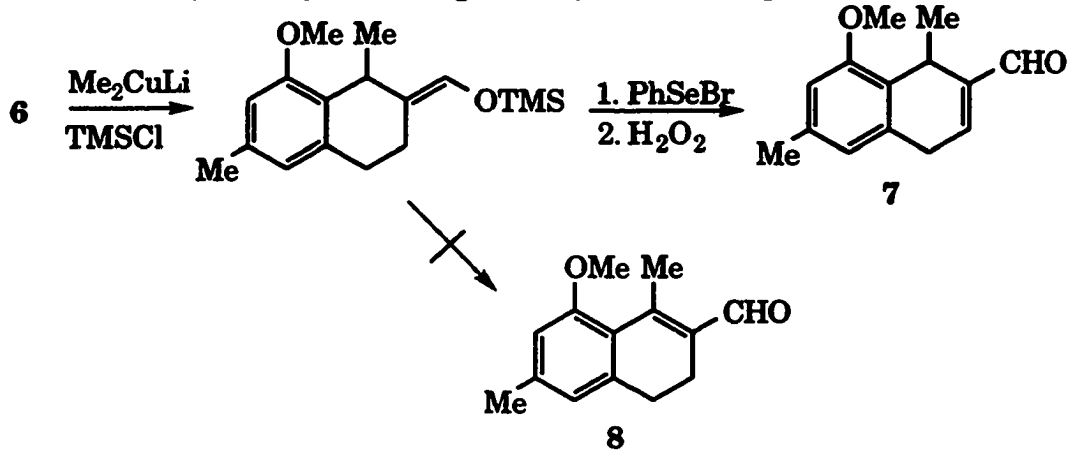
The photoenolization reaction of **5** with acrolein produced the expected hydroxy aldehyde which could be readily dehydrated to the unsaturated aldehyde **6** in 85% overall yield.[9] The photoenolization reaction was slow, affording an 86% conversion over the course of three days. Efforts to increase the rate led to significant polymerization of the acrolein.



5 **6**

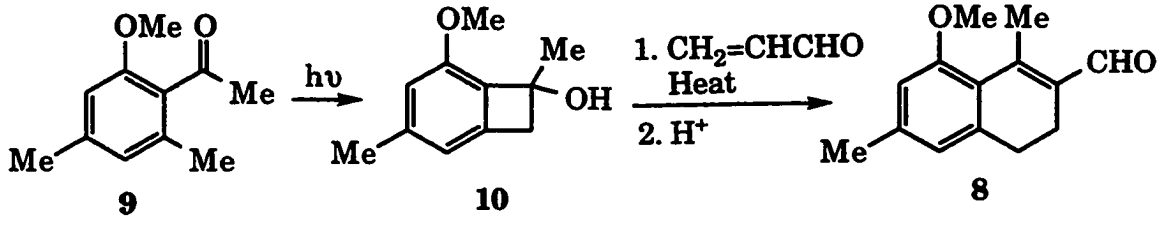
The next task was the transformation of **6** into aldehyde **8**. The addition of a cuprate reagent, followed by trapping with trimethylchlorosilane, afforded an enol silyl ether which could not be oxidized to **8**. The addition of phenylselenenyl chloride and subsequent oxidation produced the isomeric aldehyde **7** in 61% yield. The failure of the enol silyl ether to afford **8** might be

attributed to $A^{1,3}$ strain, which forces the methyl group to adopt an axial conformation, thereby rendering the allylic methine proton less accessible.



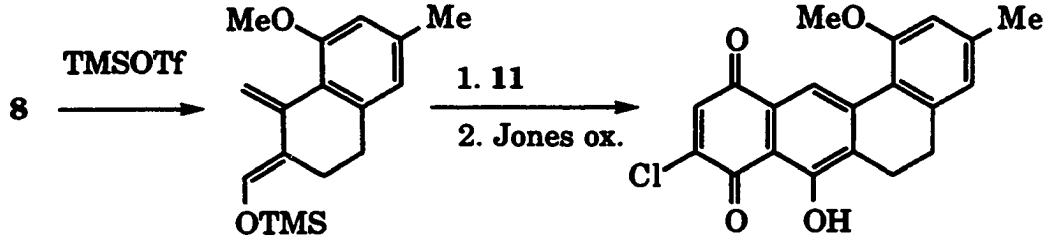
Treatment with palladium acetate in acetonitrile generated the corresponding naphthalene carboxaldehyde, a product of overoxidation.

Aldehyde **8** could be obtained from ketone **9**.[10] In this case the photoenolization reaction of **9** with acrolein afforded the cyclobutenol **10** in 90% yield. However, the cyclobutenol could be induced to react with acrolein at 200 °C over twenty hours. PTSA-mediated dehydration of the resulting hydroxy ketone provided aldehyde **8** in 80% yield over three steps.



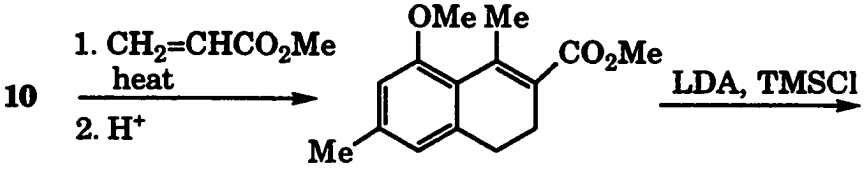
Attempted deprotonation of aldehyde **8** with lithium diisopropylamide (LDA), followed by trapping of the enolate with trimethylchlorosilane, did not afford the desired enol silyl ether. However, aldehyde **8** did give the desired enol silyl ether when treated with trimethylsilyl triflate in the presence of diisopropylethylamine in methylene chloride at 0 °C. Reaction of the enol silyl

ether with 2,6-dichlorobenzoquinone (**11**)[11] produced an unstable adduct which was not purified, but was treated directly with Jones reagent. The resulting product, quinone **12**, was produced in only 6% yield.

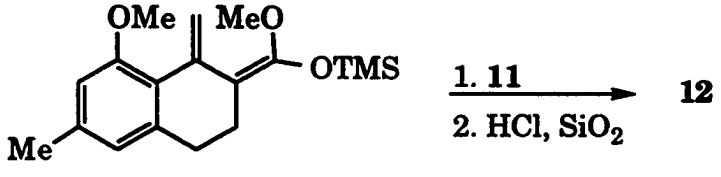


12

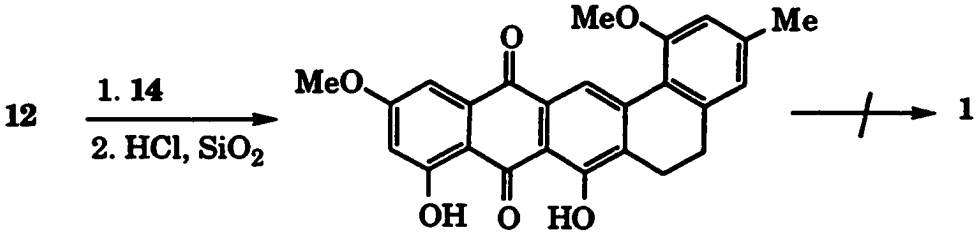
Since the lability of the Diels-Alder adduct appeared to be responsible for the poor yield, we elected to prepare the ester **13**. This compound could be generated from cyclobutenol **10** by thermolysis with methyl acrylate, followed by PTSA-mediated dehydration. Ester **13** could readily be deprotonated using lithium diisopropylamide in THF at -78 °C. Trapping of the enolate with trimethylchlorosilane produced the desired enol silyl ether which was combined with quinone **11** and was allowed to slowly warm from -78 °C to ambient temperature. The resulting Diels-Alder adduct was treated with silica gel and aqueous HCl to afford quinone **12** in 95% yield from **13**.



13

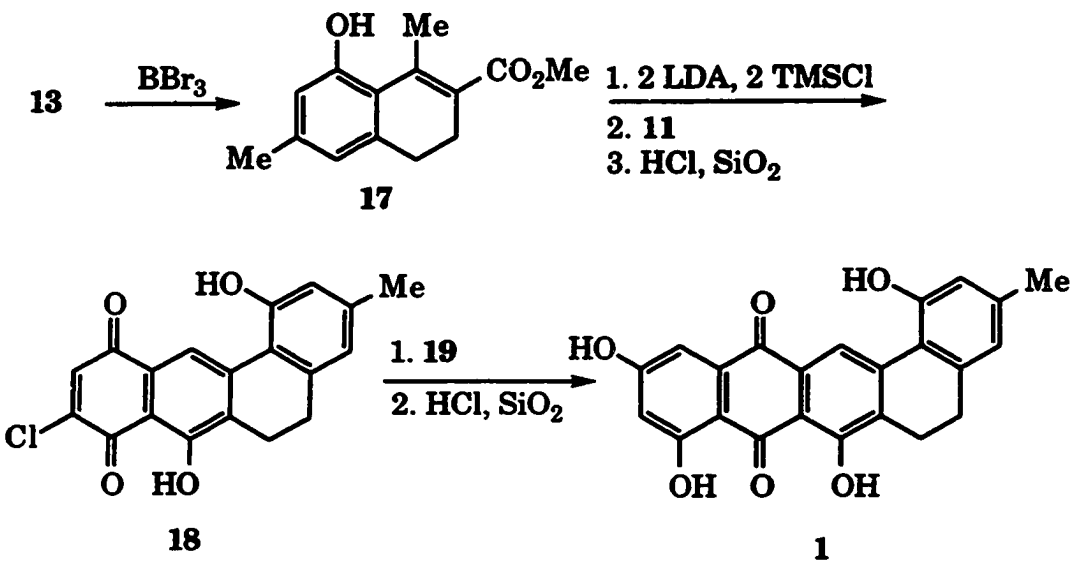


The synthesis of anthraquinone **15**, the bis-methyl ether of **1**, was achieved by reacting quinone **12** with 1,3-dimethoxy-1-trimethylsilyloxy-1,3-butadiene (**14**) in THF at -30 °C. After treating the unpurified adduct with silica gel and 6N HCl, a 95% yield of **15** was obtained. Demethylation of **15** was attempted using a variety of reagents (BBr_3; BCl_3; $AlCl_3$, Me_2S; TMSI; pyr-HCl).[12] Unfortunately, these reagents either produced a mono-demethylated product or returned starting material.



15

In view of the problems encountered in the demethylation step, we studied deprotection at earlier stages of the synthesis. We found that ester **13** could be demethylated using BBr_3 at -78 °C in 95% yield. The reaction of phenol ester **17** with two equivalents of LDA and two equivalents of TMSCl afforded a diene which was converted into naphthoquinone **18** by reaction with 2,6-dichlorobenzoquinone (**11**) followed by aromatization using silica gel and 6N HCl. Compound **18** reacted with 1-methoxy-1,3-bistrimethylsilyloxy-1,3-butadiene (**19**)[13] to produce **1** in 83% yield. Our spectra of **1** were identical to data reported by Kelly.



Conclusion

The synthesis of G-2N from 3,5-dimethylanisole will make available quantities of this natural product for extensive biological testing. We intend to extend this successful synthetic route to the preparation of more functionalized quinones such as G-2A and KS-619-1.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methylene chloride was distilled from calcium hydride. Apparatus for experiments requiring anhydrous conditions wre flame-dried under a steam of argon or dried in 150

°C oven oven for 12 h and cooled under a steam of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Merck TLC plates (silica gel 60) with a thickness of 0.25 mm. The sovent system was suitable mixtures of hexane (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sgc represents silica gel chromatography. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using Nicolet magnetic Corporation NT-300 spectrometer and all chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR were obtained using Nicolet magnetic Corporation NT-300 spectrometer and all chemical shifts are reported in δ relative to $CDCl_3$ (77.0 ppm). High resolution mass spectra were collected on a Kratos model MS-50 spectrometer. Low resolution mass spectra were collected on a Finnegan 4023 mass spectrometer. Melting poits were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of all title compounds was determined to >95% by 300 MHz proton NMR and/or elemental analysis.

2-Methoxy-4,6-dimethylbenzaldehyde (5). To a solution of 3-5-dimethylanisole (8.00 g, 58.8 mmol) in 120 mL of dry CH_2Cl_2 was added titanium tetrachloride (12.9 mL, 117 mmol) at 0 °C. Dichloromethyl methyl ether (7.40 mL, 82.3 mmol) was added at -78 °C and stirring was continued for 30 min. The resulting solution was warmed to 0 °C over 1 h, stirred for additional 15 min at 0 °C, poured into a mixture of 5 mL of conc HCl and 10 g of crushed ice and

shaken vigorously in a separatory funnel until the layers were clear. The organic phase was then separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by sgc (H:EA=50:1), to give 8.60 g (89% yield) of **5** and 0.96 g (10% yield) of 4-methoxy-2,6-dimethylbenzaldehyde.

3,4-Dihydro-8-methoxy-6-methyl-2-naphthalene carboxaldehyde (6). To a solution of aldehyde **3** (4.00 g, 24.4 mmol) in 120 mL of dry benzene was added acrolein (2.74 g, 48.8 mmol). The resulting solution was degassed with argon at 5 °C for 20 min. It was irradiated in a Rayonet reactor (with a 3500 Å light source) for 3 days. PTSA (388 mg, 2.04 mmol) was added to the above solution. The solution was stirred for 48 h at rt, worked up with saturated sodium bicarbonate solution and extracted with ether. The ether layer was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. After sgc (10:1=H:EA), 4.18 g (85% yield) of **6** was obtained as a white solid (mp 96 °C). NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.51 (t, J = 7.8 Hz, 2H), 2.78 (t, J = 7.8 Hz, 2H), 3.87 (s, 3H), 6.58 (s, 1H), 6.63 (s, 1H), 7.69 (s, 1H), 9.63 (s, 1H); IR ($CDCl_3$) cm^{-1}: 2942, 2815, 1662, 1614, 1567, 1376, 1201, 1091, 909; MS: m/e 100, 115, 128, 143, 159, 174, 181, 202; HRMS: m/e for $C_{13}H_{14}O_2$ calcd. 202.0988, measured 202.0988; CMR ($CDCl_3$) δ 18.7, 21.9, 27.2, 55.3, 109.5, 118.5, 121.0, 136.8, 139.4, 140.5, 142.4, 150.5, 192.6.

3,4-Dihydro-8-methoxy-1,6-dimethyl-2-naphthalenecarboxaldehyde (8). To a solution of benzocyclobutanol **10** (2.00 g, 11.2 mmol) in benzene in a sealable tube was added acrolein (3.14 g, 56.1 mmol). The resulting solution was degassed with argon for 15 min at 0 °C and heated to 200 °C for 20 h. PTSA (213 mg, 1.12 mmol) was added to the solution. The mixture was stirred for 48 h at

rt, worked up with saturated sodium bicarbonate solution, and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by sgc (H:E=30:1) to afford 2.16 g (89% yield) of **8** as a white solid (mp 74-75 °C).

NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.34-2.37 (m, 2H), 2.52-2.57 (m, 2H), 2.60 (t, J = 1.3 Hz, 3H), 3.83 (s, 3H), 6.63 (s, 2H), 10.31 (s, 1H); IR ($CDCl_3$) cm^{-1} 2939, 1650, 1593, 1195, 1111, 1031, 834; MS: m/e 43, 63, 77, 91, 115, 128, 172, 187, 201, 216; HRMS: m/e for $C_{14}H_{16}O_2$ calcd. 216.1150, measured 216.1153; CMR ($CDCl_3$) δ 16.4, 19.6, 21.4, 28.9, 55.1, 110.9, 120.9, 122.3, 134.2, 141.0, 141.5, 150.4, 157.9, 190.1.

6-Methoxy-1,4-dimethylbenzocyclobutenol (10). A solution of **9** (3.00 g, 16.8 mmol) in 150 mL of acetone was degassed with argon for 20 min and irradiated in a Hanovia apparatus (450 Watt medium pressure lamp in quartz immersion vessel) for 5 days. The solvent was removed in vacuo. The residue was purified by sgc (H:EA=5:1), giving 2.70 g (90% yield) of **10** and 0.29 g of **9**. The product **10** was a white solid (mp 79 °C).

NMR ($CDCl_3$) δ 1.69 (s, 3H), 2.29 (s, 3H), 2.64 (s, 1H), 3.24 (d, J = 14.1 Hz, 1H), 3.10 (d, J = 14.1 Hz, 1H), 3.88 (s, 3H), 6.49 (s, 1H), 6.56 (s, 1H); IR ($CDCl_3$) cm^{-1} 3593, 3412, 2973, 1607, 1576, 1226, 908, 835; MS: m/e 43, 51, 65, 77, 91, 105, 120, 148, 163, 178; IRMS: m/e for $C_{11}H_{14}O_2$ calcd. 178.0994, measured 178.0995; CMR ($CDCl_3$) δ 20.8, 26.0, 27.7, 47.3, 55.7, 114.9, 117.7, 131.3, 140.8, 142.5, 153.2; TLC (H:EA=5:1) Rf = 0.4.

Methyl 3,4-dihydro-8-methoxy-1,6-dimethyl-2-naphthalene carboxylate (13). To a solution of the benzocyclobutenol **10** (1.00 g, 5.61 mmol) in 20 mL of benzene in a sealable tube was added methyl acrylate (3.86 g, 44.9 mmol). The resulting solution was degassed with argon for 15 min at 0 °C and heated to 200 °C for 20

h. PTSA (107 mg, 0.561 mmol) was added to the above solution. The mixture was stirred for 48 h at rt, worked up with saturated sodium bicarbonate solution and extracted with ether. The ether layer was washed with brine, dried and concentrated in vacuo. The residue was purified by sgc (H:EA=50:1) to give 1.19 g (86% yield) of **13** as a colorless oil.

NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.40-2.45 (m, 2H), 2.47 (br. s, 3H), 2.57-2.62 (m, 2H), 3.79 (s, 3H), 3.87 (s, 3H), 6.63 (s, 2H); IR ($CDCl_3$) cm^{-1} 2946, 1707, 1609, 1352, 1278; MS: m/e 51, 70, 91, 115, 128, 156, 172, 187, 199, 215, 231, 246; HRMS: m/e for $C_{15}H_{18}O_3$ calcd. 246.1256, measured 246.1255; CMR ($CDCl_3$) δ 20.3, 21.5, 24.5, 29.6, 51.3, 55.3, 111.1, 120.5, 123.3, 126.3, 139.4, 140.5, 143.5, 157.4, 169.2.

9-Chloro-5,6-dihydro-7-hydroxy-1-methoxy-3-methyl benz[a]anthracene-8,11-dione (12)

From **8**: To a solution of aldehyde **8** (240 mg, 1.11 mmol) and triethylamine (2.49 mL, 17.8 mmol) in 20 mL of THF was added trimethylsilyl triflate (1.72 mL, 8.88 mmol) dropwise at -78 °C. After 5 min, the mixture was put in an ice bath then and allowed to warm to rt over 3 h. The THF was replaced with 50 mL of pentane and the mixture was flushed through a short Celite pad. The pentane solution was concentrated in vacuo to afford a yellowish unstable oil. The oil was dissolved in 6 mL of THF and was added to a solution of 2,6-dichlorobenzoquinone (216 mg, 1.22 mmol) in 6 mL of THF at rt. The resulting solution was boiled for 10 h. The THF was replaced with acetone (12 mL). Jones reagent (0.82 mL, 2.2 mmol) was added to the acetone solution at 0 °C. After 30 min, the mixture was diluted with water and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$ and concentrated in

vacuo. The residue was purified by sgc (H:E=30:1) to give 24 mg of **12** (6% yield) as a dark red solid (mp ~230 °C with decomposition).

From **13**: To a solution of LDA (0.15 mmol) in 1 mL of THF (prepared from diisopropylamine (0.021 mL, 0.15 mmol) and butyllithium (0.06 mL, 0.15 mmol)) was added a solution of ester **13** (38 mg, 0.15 mmol) in 1 mL of THF at -78 °C. The resulting solution was stirred for 40 min. TMSCl (0.024 mL, 0.18 mmol) was added to the solution. After 30 min, the solution was slowly warmed to rt (1.5 h). The THF was replaced with pentane. The resulting suspension was quickly flushed through a short Celite pad. The solution was concentrated in vacuo. A labile yellowish oil was obtained. The oil was dissolved in 1 mL of THF and was added to a solution of 2,6-dichloroquinone (28 mg, 0.15 mmol) in 1 mL of THF at -78 °C. The resulting solution was slowly warmed to rt and stirred overnight. Several drops of 6N HCl were added to the solution, followed by the addition of 1 g of silica gel. The THF was removed in vacuo and the residue was allowed to stand overnight. The residue was then washed with ether. The ether solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by sgc (H:EA=30:1) to afford 52 mg (95% yield) of **12** as a red solid (mp ~230 °C with decomposition). NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.74-2.78 (m, 2H), 2.89-2.92 (m, 2H), 3.94 (s, 3H), 6.74 (s, 2H), 7.17 (s, 1H), 8.61 (s, 1H), 12.13 (s, 1H); IR ($CDCl_3$) cm^{-1} 3415, 1654, 1626, 1596, 1280, 1033; MS: m/e 45, 77, 101, 145, 170, 189, 219, 251, 275, 339, 354; HRMS: m/e for $C_{20}H_{15}O_4Cl$ calcd. 354.0659, measured 354.0657; CMR ($CDCl_3$) δ 20.7, 21.8, 28.8, 55.7, 109.1, 111.1, 111.9, 120.9, 121.5, 128.9, 133.4, 136.8, 141.0, 141.4, 142.2, 145.8, 157.9, 159.1, 182.3, 182.5; TLC (H:E=30:1) Rf = 0.11.

Dimethyl ether of G-2N (15) To a solution of **12** (50 mg, 0.14 mmol) in 1 mL of THF was added a solution of 1,3-dimethoxy-1-trimethylsilyloxybutadiene (**14**) (57 mg, 0.28 mmol) in 1 mL of THF at -30 °C. The resulting solution was slowly warmed to rt and stirred overnight. Several drops of 6N HCl were added to the above solution followed by the addition of 1.0 g of silica gel. The THF was removed and the residue was allowed to stand overnight. The solid was washed with ether, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by sgc (H:E=20:1) to give 53 mg (91% yield) of **15** as an orange solid (mp > 300 °C).

NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.75-2.80 (m, 2H), 2.90-2.95 (m, 2H), 3.94 (s, 3H), 3.96 (s, 3H), 6.69 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 7.40 (d, J = 2.3 Hz, 1H), 8.79 (s, 1H), 12.43 (s, 1H), 12.56 (s, 1H); IR (KBr) cm^{-1} 3358, 1629, 1596, 1333, 1266, 1156, 1037; MS: m/e 45, 91, 158, 208, 232, 285, 332, 416; HRMS: m/e for $C_{25}H_{20}O_6$ calcd. 416.1260, measured 416.1260; CMR ($CDCl_3$) δ 20.7, 21.7, 28.8, 55.6, 56.0, 106.5, 107.9, 110.6, 111.0, 113.2, 119.1, 120.9, 121.4, 130.5, 133.5, 135.7, 140.8, 141.0, 141.4, 157.8, 159.0, 165.1, 166.4, 182.3, 190.7; TLC (H:EA=5:1) Rf = 0.32. Anal. Calcd. for $C_{25}H_{20}O_6$: C 72.11, H 4.84. Found: C 72.36, H 4.47.

Methyl 3,4-dihydro-8-hydroxy-1,6-dimethyl-2-naphthalene carboxylate (17). To a solution of ester **13** (0.100 g, 0.41 mmol) in 4 mL of dry CH_2Cl_2 was added BBr_3 (0.16 mL, 1.64 mmol) at -78 °C dropwise. The mixture was stirred for 0.5 h at -78 °C, warmed up to -20 °C slowly and stirred for 1 h. The mixture was warmed to 0 °C, stirred for 2 h, and quenched with Et_2O followed by the addition of saturated $NaHCO_3$ solution. The resulting solution was stirred for 2 h and then extracted with ether. The ether layer was dried and concentrated

in vacuo. The residue was purified by sgc (H:EA=10:1) to give 90 mg (95% yield) of **17** as white solid (mp 156-157 °C).

NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.41-2.46 (m, 2H), 2.54 (t, J = 1.5 Hz, 3H), 2.58-2.63 (m, 2H), 3.79 (s, 3H), 4.98 (s, 1H), 6.46 (s, 1H), 6.60 (s, 1H); IR ($CDCl_3$) cm^{-1} 3379, 2982, 1693, 1615, 1205, 1166, 1086, 903, 758; MS: m/e 51, 77, 103, 115, 128, 145, 158, 173, 185, 201, 217, 232; HRMS: m/e for $C_{14}H_{16}O_3$ calcd. 232.1099, measured 232.1103; CMR ($CDCl_3$) δ 20.0, 21.0, 24.6, 29.5, 51.5, 116.1, 120.8, 121.4, 126.6, 139.7, 140.8, 142.7, 153.5, 169.3; TLC (H:E=10:1), Rf = 0.17.

9-Chloro-5,6-dihydro-1,7-dihydroxy-3-methyl benz[a]anthracene-8,11-dione (18)

To a solution of LDA (0.80 mmole) in 2 mL of THF (prepared from diisopropyl amine (0.11 mL, 0.84 mmol) and butyllithium (0.32 mL, 0.80 mmol)) was added a solution of ester **17** (90 mg, 0.39 mmol) in 2 mL of THF at -78 °C. The resulting solution was stirred for 40 min. TMSCl (0.10 mL, 0.79 mmol) was added to the solution. After 30 min, the solution was slowly warmed to rt over 1.5 h. The THF was replaced with pentane. The resulting suspension was quickly flushed through a short Celite pad. The solution was concentrated. The ketene acetal was obtained as a yellowish unstable oil. The oil was dissolved in 2 mL of THF and was added to a solution of 2,6-dichlorobenzoquinone (124 mg, 0.70 mmol) in 2 mL of THF at -78 °C. The resulting solution was slowly warmed to rt and stirred overnight. Several drops of 6N HCl were added into the solution followed by the addition of 2 g of silica gel. The THF was removed in vacuo and the residue was allowed to stand overnight. The residue was then washed with ether. The ether solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by

sgc (H:E=5:1), giving 115 mg (93% yield) of **18** as red dark solid (mp ~240 °C with decomposition).

NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.75-2.79 (m, 2H), 2.90-2.95 (m, 2H), 3.75 (s, 1H), 6.58 (s, 1H), 6.72 (s, 1H), 7.18 (s, 1H), 8.65 (s, 1H), 12.13 (s, 1H); IR (KBr) cm^{-1} 3424, 2917, 1657, 1628, 1256, 952; MS: m/e 49, 88, 138, 152, 189, 219, 259, 277, 322, 340; HRMS: m/e for $C_{19}H_{13}O_4Cl$ calcd. 340.0502, measured 340.0505; CMR ($CDCl_3$) δ 20.4, 20.9, 28.0, 111.8, 115.8, 116.4, 119.4, 120.1, 128.9, 131.5, 136.6, 140.2, 140.5, 141.7, 144.7, 155.9, 157.5, 181.8, 182.3; TLC (H: EA = 5:1) Rf = 0.15. Anal. Calcd.for $C_{19}H_{13}O_4Cl$: C 66.97, H 3.84. Found: C 66.83, H 3.83.

G-2N (1) To a solution of the chloroquinone **18** (20 mg, 0.059 mmol) in THF (0.5 mL) was added a solution of 1,3-dimethoxy(trimethylsilyloxy)butadiene (30 mg, 0.12 mmol) in 0.5 mL of THF at -30 °C. The resulting solution was slowly warmed to rt and stirred overnight. Several drops of 6N HCl were added to the solution followed by the addition of 1.0 g of silica gel. The THF was removed. The residue was allowed to stand overnight and then washed with ether. The ether solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by sgc (H:E=5:1) to give 19 mg (yield 83%) of G-2N as a dark red solid (mp > 300 °C).

UV (EtOH) 266 nm, 310 nm, 470 nm; NMR (DMSO-d_6) δ 2.24 (s, 3H), 2.69-2.72 (m, 2H), 2.78-2.81 (m, 2H), 6.60 (d, J = 2.4 Hz, 1H), 6.62 (s, 1H), 6.70 (s, 1H), 7.15 (d, J = 2.4 Hz, 1H), 8.81 (s, 1H), 10.17 (s, 1H), 12.15 (s, 1H), 12.53 (s, 1H); IR (KBr) cm^{-1} 3389, 2948, 1616, 1594, 1311, 1263, 1168, 1026, 840; MS: m/e 70, 84, 165, 205, 251, 306, 370, 388; HRMS: m/e for $C_{23}H_{16}O_6$ calcd. 388.0947, measured 388.0958; CMR (DMSO-d_6) δ 20.9, 25.1, 28.1, 107.8, 108.8, 109.2, 112.7, 115.2,

116.5, 119.8, 120.1, 130.2, 132.0, 135.5, 140.2, 140.3, 141.2, 155.9, 158.0, 164.4, 165.6, 181.6, 189.6; TLC (H:E=5:1) Rf = 0.15.

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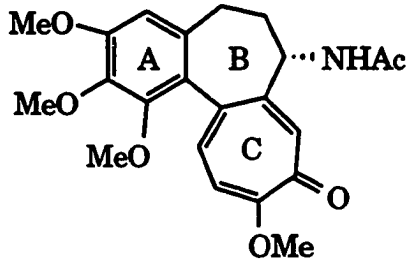
CHAPTER III
SYNTHETIC STUDIES ON COLCHICINE

Introduction

Colchicine is one of the major alkaloid constituents of the autumn crocus, *Colchicum automnale L.* The name *Colchicum* is derived from an area near the Black Sea (Colchis). *Cochicum* species are common in most of Europe and the Middle East. Colchicine has the interesting property of arresting cell division during mitosis.[1] Although colchicine has been used in the treatment and diagnosis of gout for a thousand years, the high toxicity of this alkaloid has precluded its use in cancer chemotherapy. The pharmacology of cochicine is still under investigation. More than 100 years of structural studies proved structure (1) to be the correct representation for colchicine from x-ray analysis, total synthesis, and interpretation of a large amount of degradative data.[2]



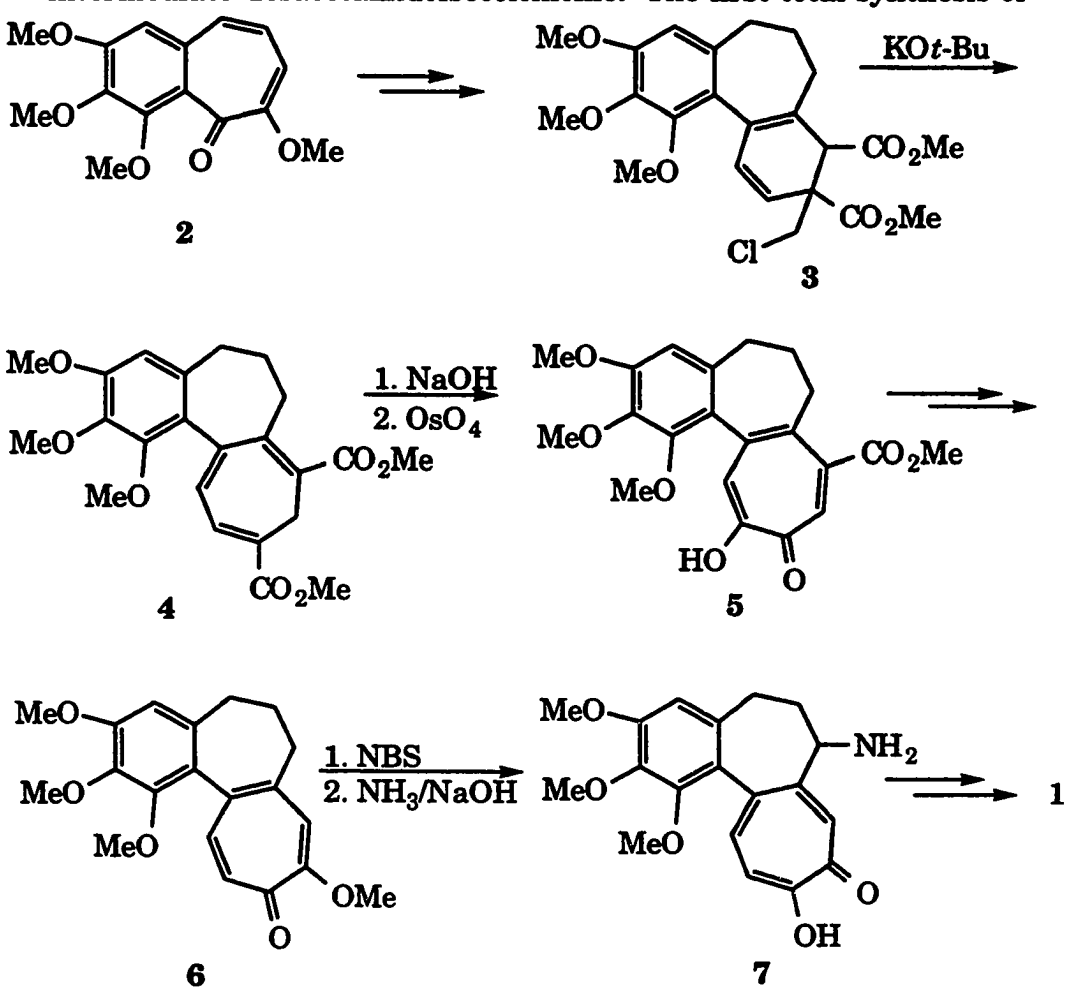
1

Despite the interest in biological activity study of colchicine, most investigations are limited to those employing colchicine, or derivatives readily prepared from naturally occurring colchicine, because of the difficulty encountered in the total synthesis of structurally related

tropolones. Therefore, the synthesis of colchicine has been an attractive project in organic synthesis. The history of synthetic approaches to colchicine spans more than 30 years. To date, eleven total syntheses of colchicine have been reported and many synthetic approaches to colchicine have been attempted.

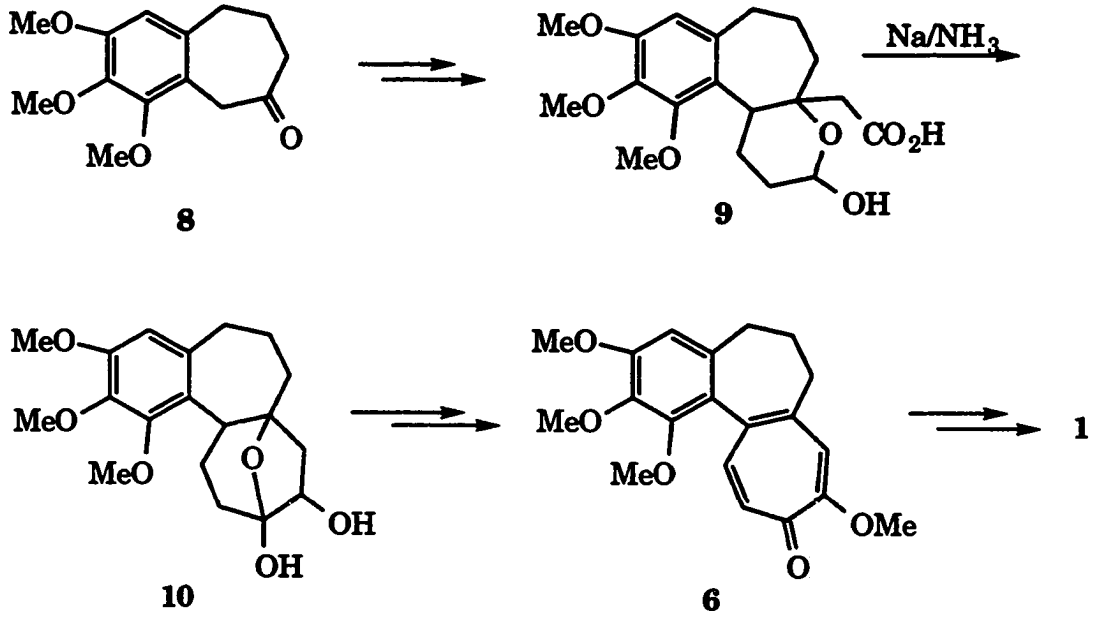
Synthesis of colchicine via desacetamidoisocolchicine

There are nine total syntheses of colchicine via a common intermediate desacetamidoisocolchicine. The first total synthesis of



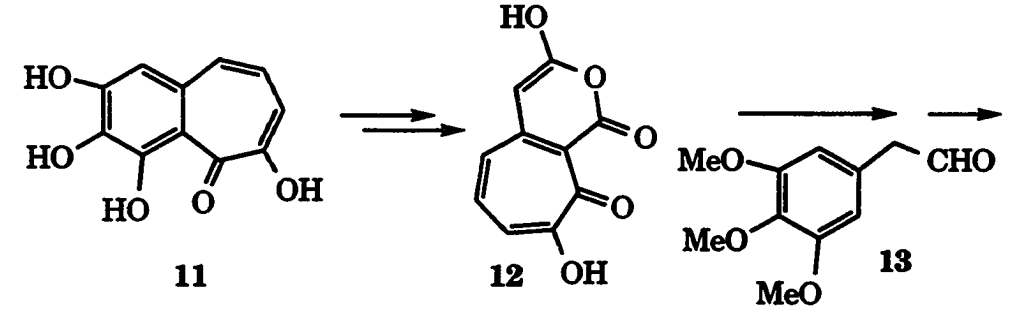
colchicine was devised by Eschenmoser in 1961.[3] His synthesis began with the well known compound purpurogallin trimethylether (**2**), which already has the carbon skeleton of the A and B rings. He used intramolecular enolate alkylation to build the C ring. The crucial steps were the conversion of **3** to **4** by dihydroxylation and oxygen transformation using tropolone chemistry. The amido group was generated by allylic bromination and reaction with ammonia. The resulting intermediate was converted to colchicine.

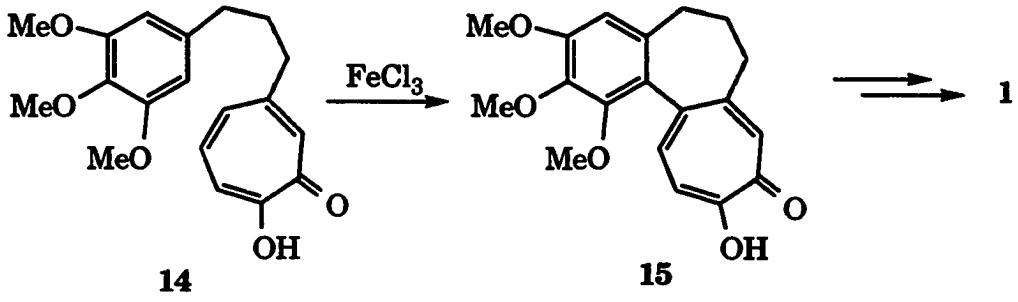
The second synthesis, by van Tamelen,[4] was carried out at the same time as Eschenmoser's and followed a similar general plan. It also began with purpurogallin, which was converted to the benzosuberone (**8**). The key step is conversion of **9** to **10** by an intramolecular acyloin consendation.



After several operations, intermediate **10** was transformed to desacetamidoisocolchicine **6** which can be converted to colchicine using Eschenmoser's method.

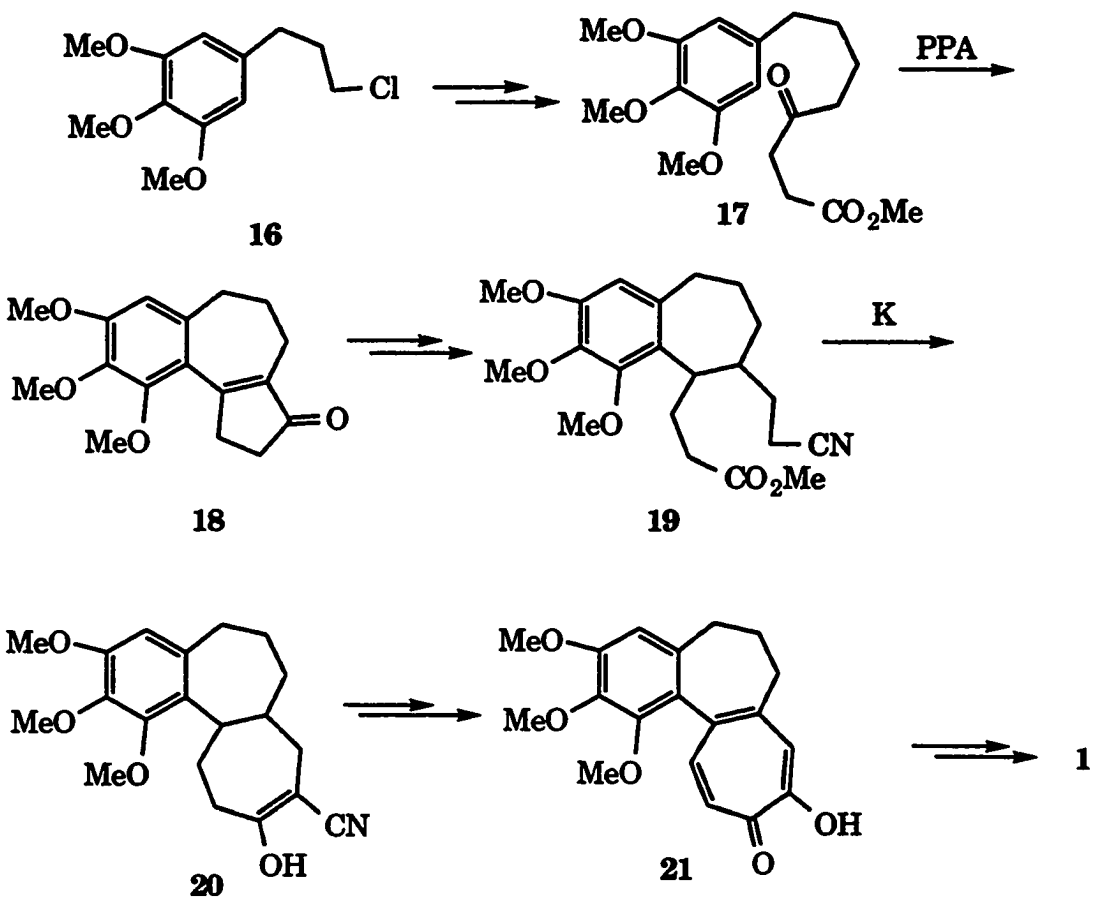
The third synthesis, by Scott,[5] also began with purpurogallin (**11**), and also took advantage of the conversion of deacetamidoisocochicine to colchicine, which had been established in the earlier syntheses. But there the resemblance ends, because Scott used the tropolone ring of purpurogallin to provide ring C. The key step involves oxidative coupling of ring A and ring C in intermediate **14**.



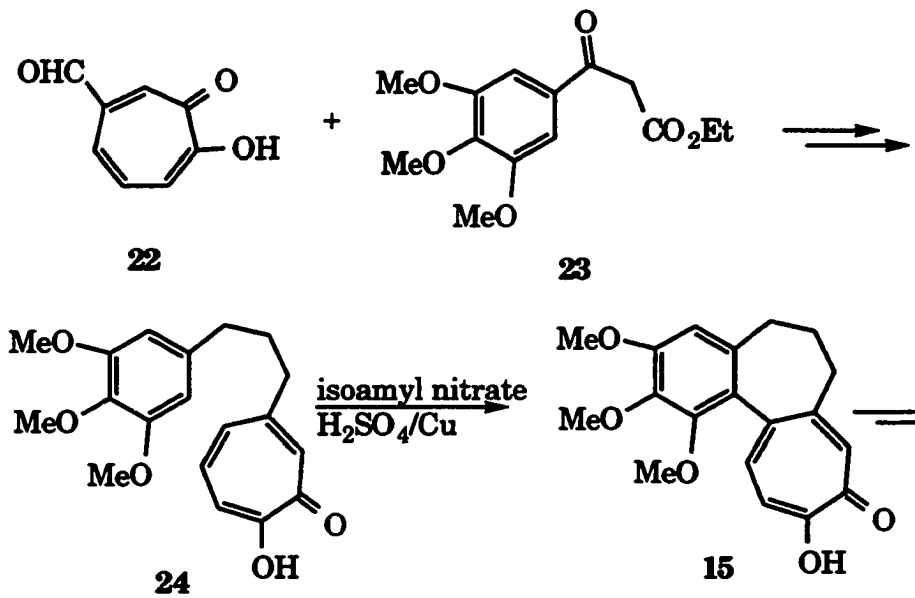


The fourth synthesis, by Martel,[6] started from 1-chloro-3-(3',4',5'-trimethoxyphenyl)propane (**16**), which already has the A ring. The B ring was constructed by using an acid-catalyzed cyclization reaction of **17**. The key step, C ring formation involved a Dieckmann-type cyclization in **19** to give the skeleton of colchicine **20**, which was transformed to

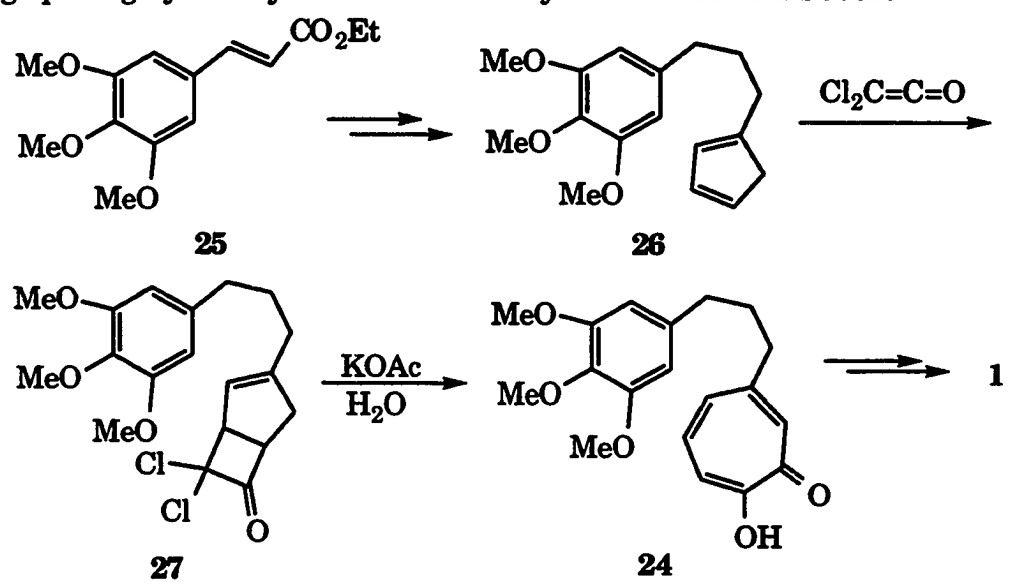
desacetamidocolchicine **21**. Compound **21** can be converted to colchicine by the known method via desacetamidocolchicine **6**.



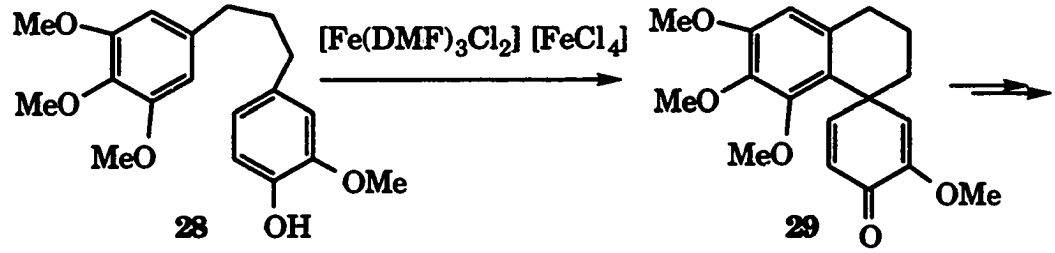
In 1968, Matsui[7] reported another formal synthesis of colchicine via desacetamidocolchicine (**15**), which began with 4-formyl-tropolone (**22**) and 3,4,5-trimethoxybenzoylacetate (**23**). The key step involves a Pschorr reaction of amino tropolone **24** to give desacetamidocolchicine (**15**) which can be converted to colchicine by means of Eschenmoser's method.



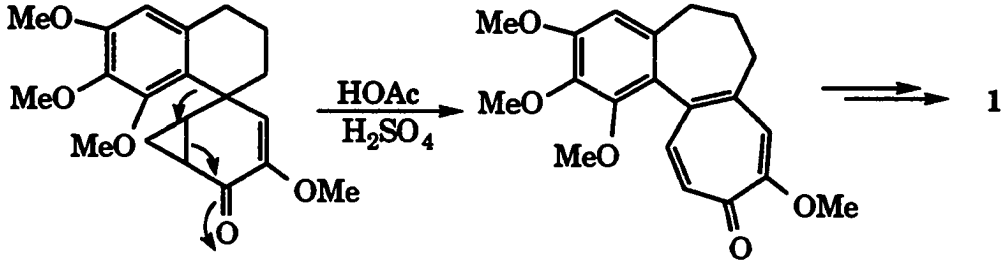
In 1974, Kato[8] developed a direct route to make Matsui's key intermediate **24**. His synthesis started from methyl *trans*-3,4,5-trimethoxycinnamate (**25**). The crucial step is the cycloaddition of dichloroketene ketal to cyclopentadiene ring of compound **27** followed by ring opening by solvolysis to **24** in better yield than Matsui's route.



In the same year as Kato modified Matsui's synthesis, Tobinaga[9] used two spiro-connected six-numbered rings to build up the A and B rings. The known compound **28** was chosen as the starting material. After an intramolecular oxidative coupling, followed by cyclopropanation, the intermediate spirodienone **30** was obtained, which underwent acid catalyzed rearrangement and dehydrogenation to give **6**. This consists of a formal total synthesis of colchicine together with the transformation established by Eschenmoser.

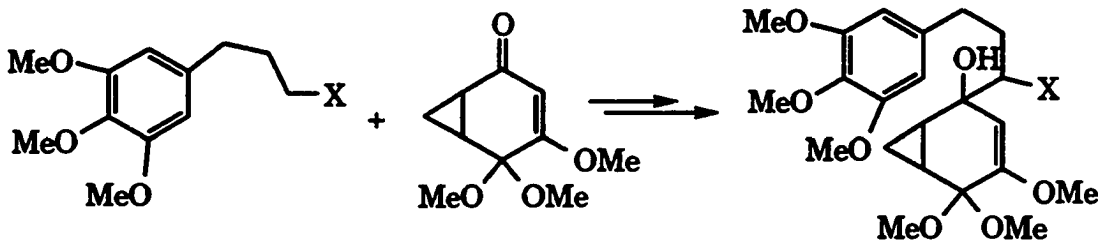


28 29



30 6

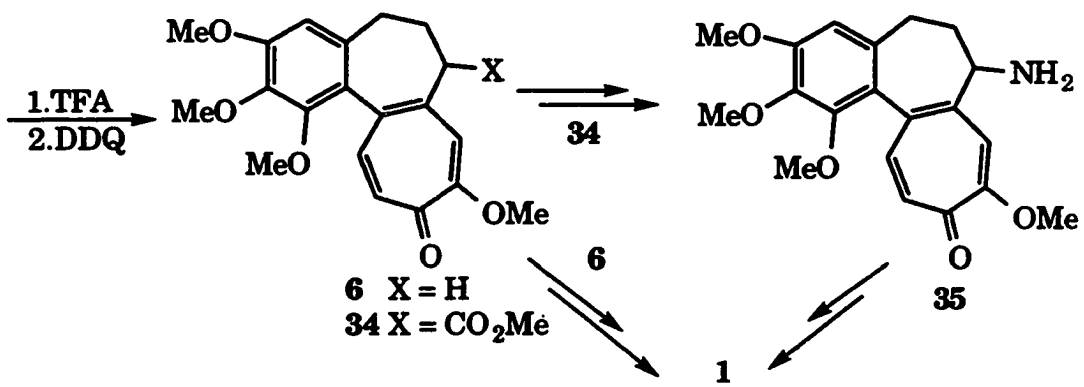
In 1981, Evans[10] achieved a total synthesis of desacetamidoisocolchicine (**6**) and colchicine (**1**). Key features of his synthetic sequence are the facile incorporation of a tropolone dication equivalent via **32** and introduction of the 7-acetamido group using a Curtius rearrangement. The B ring and the C ring are formed by an acid catalyzed electrophilic addition to the A ring, followed by rearrangement.



31a X = Br
31b X = CO_2Me

32

33a X = Br
33b X = CO_2Me

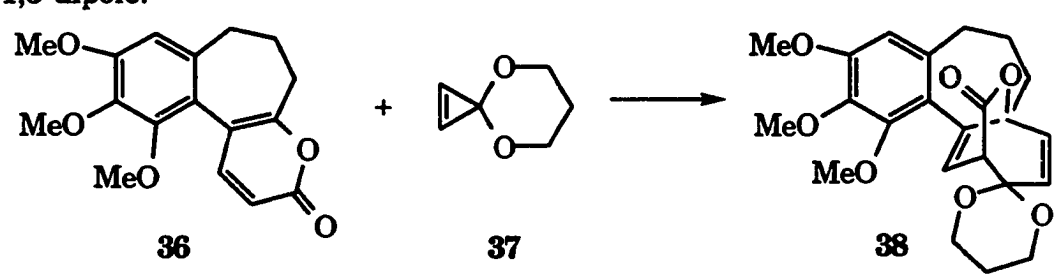


6 X = H
34 X = CO_2Me

35

1

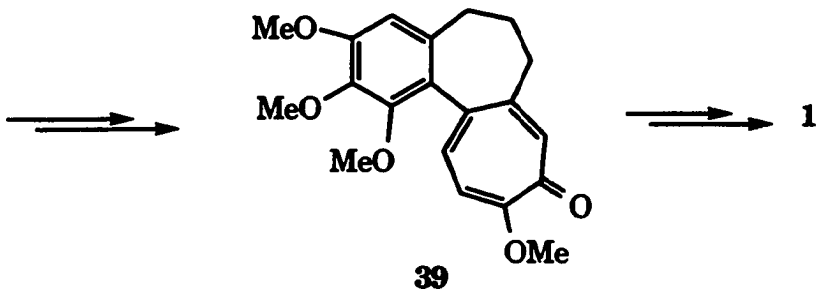
Recently Boger[11] has detailed an alternative preparation of desacetamidocolchicine, constituting a formal synthesis of colchicine. This synthesis is based on the thermal [3+4] cycloaddition of Eschenmoser's pyrone (**36**) with cyclopropenone 1,3-propanediyl ketal **37** in a process proceeding by way of the reversible, thermal generation of a three-carbon 1,3-dipole.



36

37

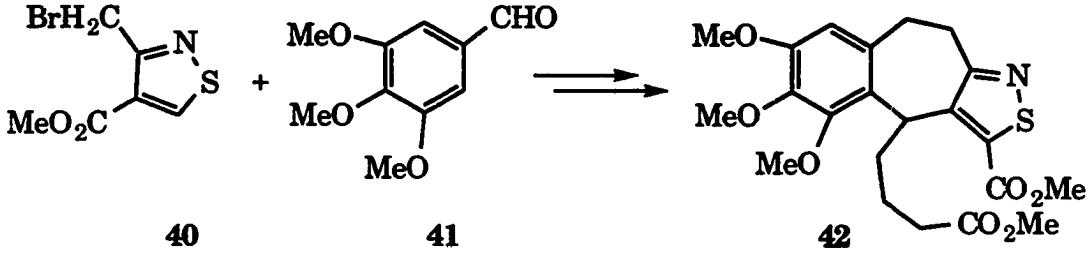
38



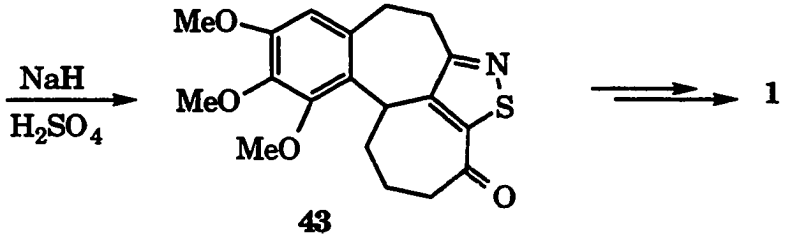
39

Other syntheses of colchicine

There are two routes to synthesize colchicine not via desacetamidocolchicine. The first one is described by Woodward,[12] and is entirely different from the above syntheses. Another feature is that it does not rely on the bromination-ammonolysis reaction to insert the nitrogen atom. Instead the nitrogen atom is present from the start in the form of an isothiazole ring. Rings A, B, and C are constructed in turn with the most noteworthy steps being the facile cyclization of **41** to **42** and the novel construction of the tropolone involving structure **43**.

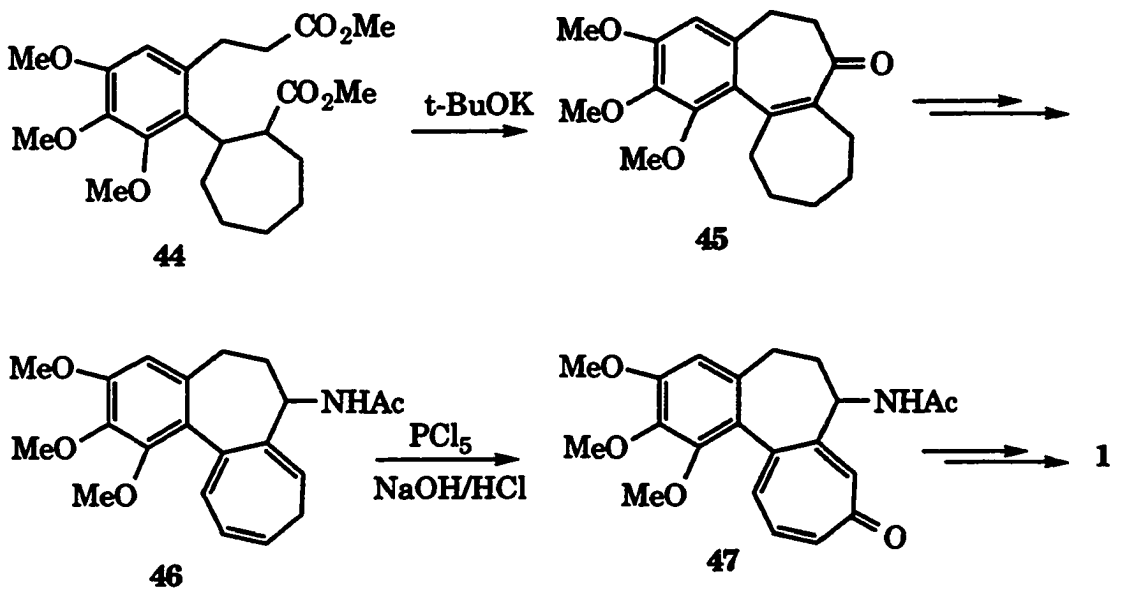


40 41 42



43

The second one is done by Nakamura.[13] A known compound which already has rings A and C was used as the starting material, which underwent claisen reaction to ring B. The elaboration of the tropolone ring system lead to a total synthesis of colchicine. The interesting step is the oxidation of ring C to tropone **47**.



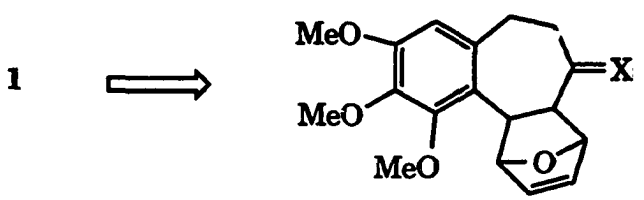
In view of the previous work, a synthesis of colchicine has several substantial synthetic problems. Noteworthy among these difficulties is the lack of general methodology for construction of the tropolone nucleus. Although eleven total synthesis of colchicine have been reported to date, several problems associated with the synthesis of this alkaloid have been largely ignored. All of the syntheses are not efficient. All of but three of the reported syntheses proceed through desacetamidoisocolchicine (**6**). Since the conversion of **6** via allylic bromination (12% yield) to colchicine is inefficient, projected syntheses of colchicine would provide for the

introduction of C7-acetamido group in an alternate manner. In addition, all but one of the syntheses of **6** proceed through desacetamidocolchiceine (**15**) and all of the reported syntheses of colchicine involve the intermediacy of the free tropolone colchiceine (**7**). This creates several regiochemical problems, since the methylation of these tautomers gives nearly equal amount of ethers. Therefore, an efficient route towards the total synthesis of colchicine is still needed.

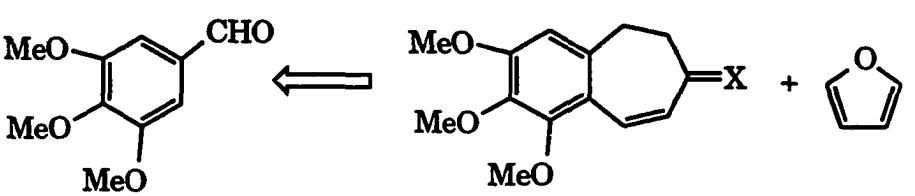
Results and Discussion

First approach: photochemical Diels-Alder reaction as the key step

In view of the previous works, initial construction of the A, B rings would provide an efficient entry to the total synthesis of colchicine. We



48: X=H_2
49: X=O

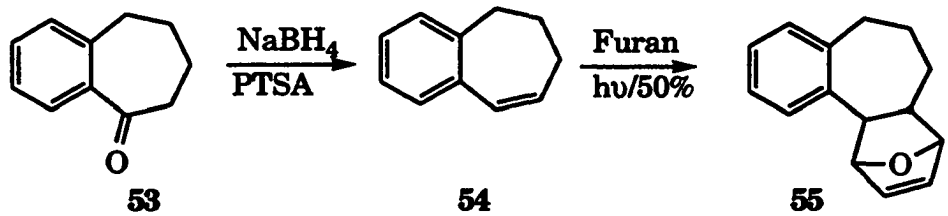


52

50: X=H_2
51: X=O

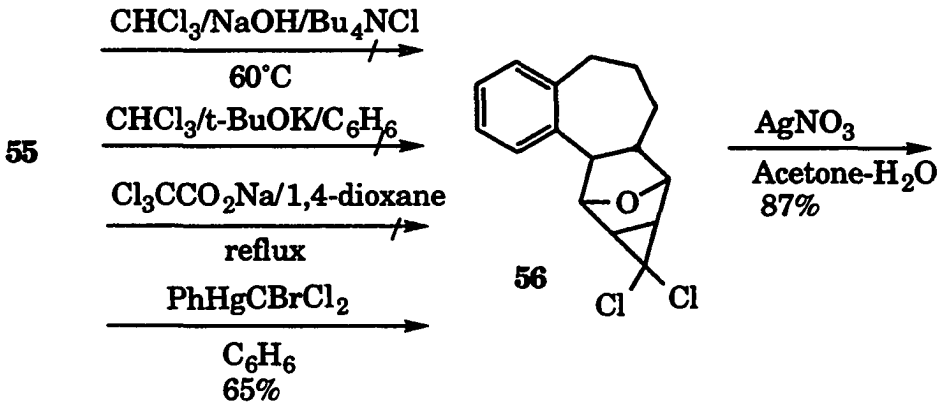
used a photochemical Diels-Alder reaction as a key step, followed by dichlorocarbene addition and cyclopropane ring opening to build the C ring. The retrosynthetic analysis is shown above.

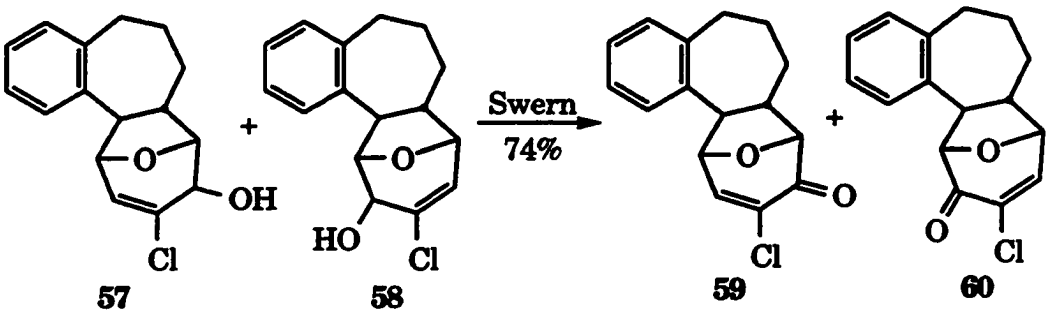
To test this idea, we carried out a model study starting from benzoheptadiene (**54**), prepared from benzosubrone (**53**) by reduction with sodium borohydride, followed by dehydration with PTSA (*para*-toluene sulfonic acid) in 94% overall yield. Irradiation of compound **54** in furan using a Hanovia lamp gave Diels-Alder adduct **55** in 50% yield.



53 **54** **55**

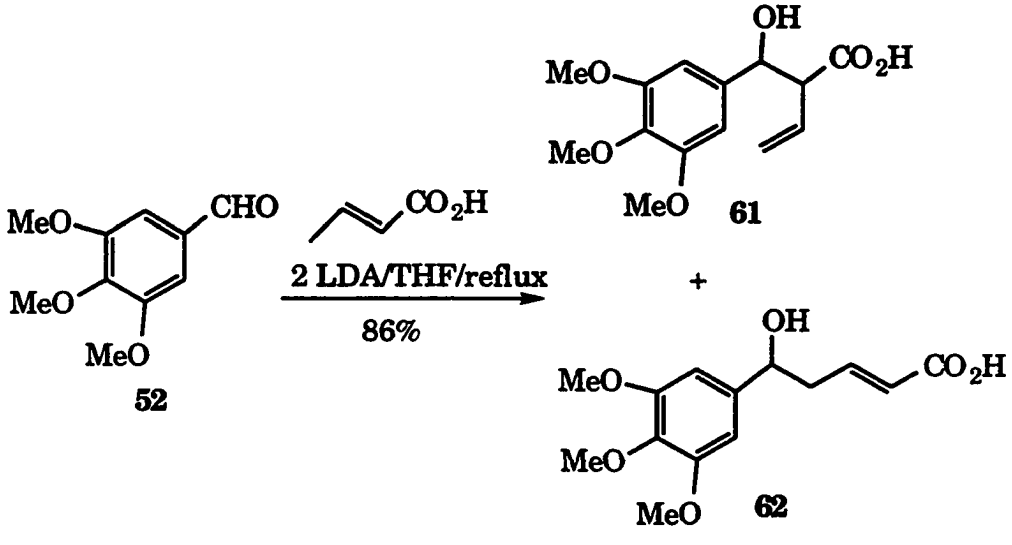
With compound **55** in hand, we tried to do cyclopropanation with dichlorocarbene. Under several conditions, only Seyferth's reagent ($PhHgCBrCl_2$) afforded the desired product **56** in 65% yield. Compound **56** was treated with silver nitrate in a 1:1 mixture of acetone and water to give two isomers **57** and **58**, which were not separable. The mixture of **57** and **58** underwent Swern oxidation to give a mixture of ketones **59** and **60**.





57 58 59 60

After the successful model study, we addressed the real system. The first task was synthesis of benzocycloheptadiene **65** from 3,4,5-trimethoxybenzaldehyde (**52**). Compound **52** reacted with the dianion prepared from crotonic acid and two equivalents of LDA (lithium diisopropylamide) in THF at reflux, giving a 1:1 mixture of α-substituted acid **61** and γ-substituted acid **62** in 86% yield, which was difficult to separate.

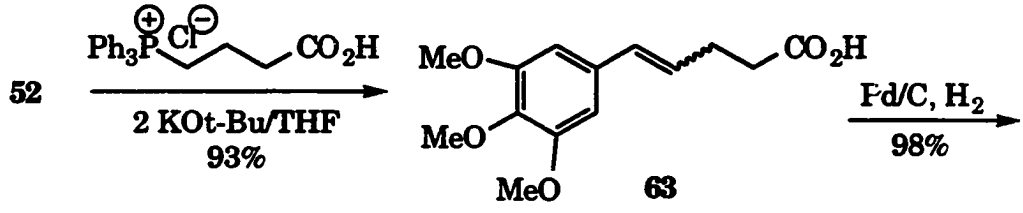


52

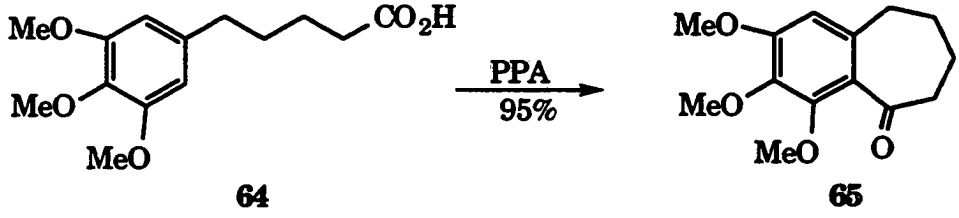
1 : 1

A Wittig reaction might perform better than an aldol condensation. The phosphonium salt, prepared from 4-chlorobutyric acid and triphenylphosphine according to Smith's procedure,[14] reacted with 3,4,5-

trimethoxybenzaldehyde by treatment with potassium t-butoxide in THF to provide acid **63** (E:Z = 10:1) in 93% yield. Acid **63** then underwent hydrogenation in EtOH catalyzed by palladium on carbon to afford acid **64** in 98% yield. Ketone **65** was obtained using intramolecular cyclization in PPA (polyphosphoric acid) at 80°C.

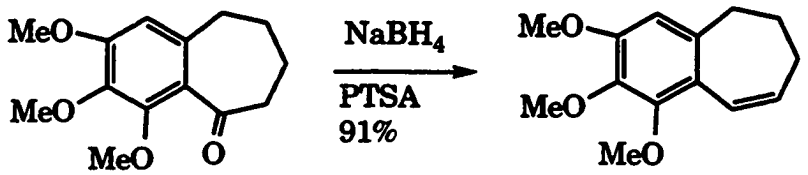


E : Z = 10 : 1

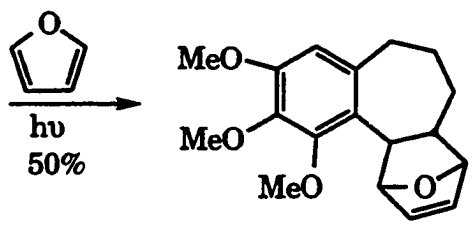


With ketone **65** in hand, which already contains the A and B rings, our next attempt was construction of the C ring using methodology developed previously. First of all, ketone **65** was reduced with sodium borohydride followed by dehydration with PTSA to give benzocycloheptadiene **67** in 91% overall yield. Then **69** was irradiated in furan using a Hanovia to afford Diels-Alder product **68** in 50% yield. The following transformation was cyclopropanation of compound **68** with dichlorocarbene. Unfortunately, treatment of compound **68** with Seyferth's reagent lead to decomposition of starting material. Probably, the benzene ring bearing the three methoxy groups is so electron-rich that dichlorocarbene adds to the benzene ring

instead of the double bond. Cyclopropanation under other conditions ($CHCl_3$/KOH, CH_2Cl_2/LiTMP) resulted in recovery of the starting material.

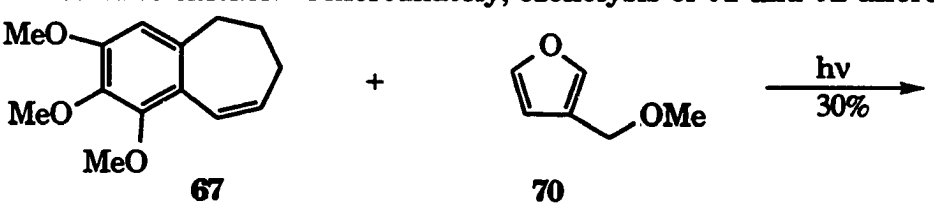


66 67

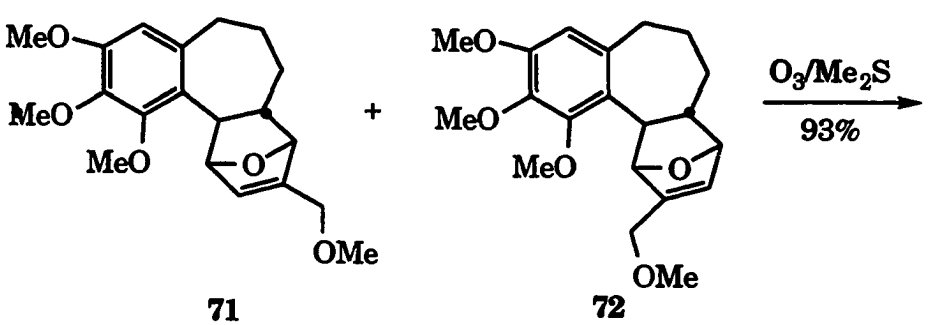


68

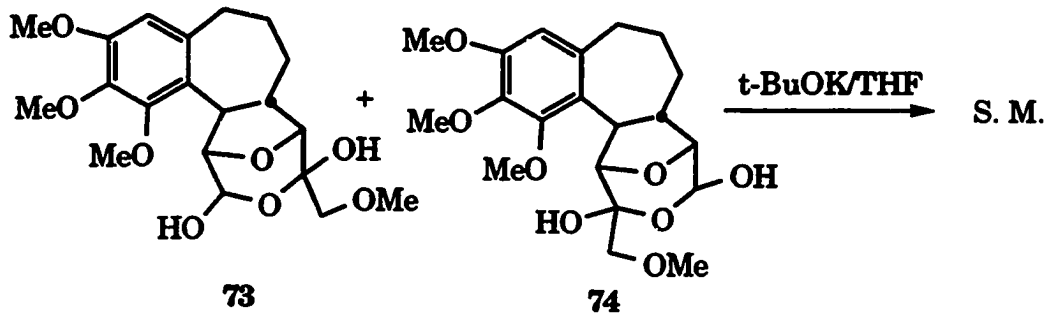
Another idea involved reaction of 3-(methoxymethyl)furan with compound **67** under photochemical conditions to obtain Diels-Alder products **71** and **72**, followed by ozonization and aldol condensation to give the skeleton of colchicine. Unfortunately, ozonolysis of **71** and **72** afforded a



67 70



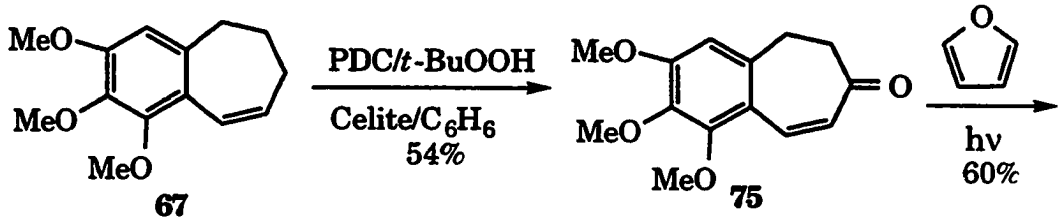
71 72



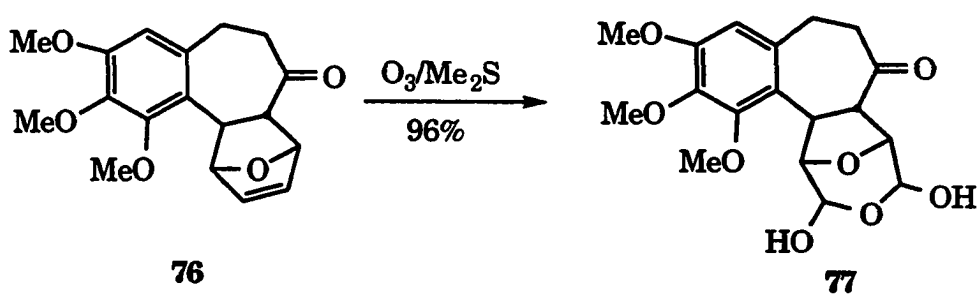
73 74

mixture of dihemiketal in 93% yield. This mixture was then treated with t-BuOK, but only starting material was recovered.

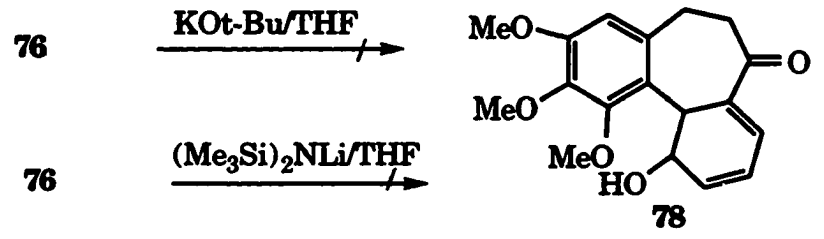
Because the photochemical reaction proceeded in low yield, we attempted to increase the yield using benzocycloheptadienone **75**, instead of benzocycloheptadiene **69**. Enone **76** was generated from **67** by treatment with PDC (pyridinium dichromate) and *tert*-butylhydroperoxide in presence of Celite. Then enone **75** was irradiated in furan with Hanovia lamp to furnish the Diels-Alder product **76** in 60% yield, which was better than the corresponding alkene **67**. Ozonolysis of compound **76** provided dihemiacetal



67 75



76 77

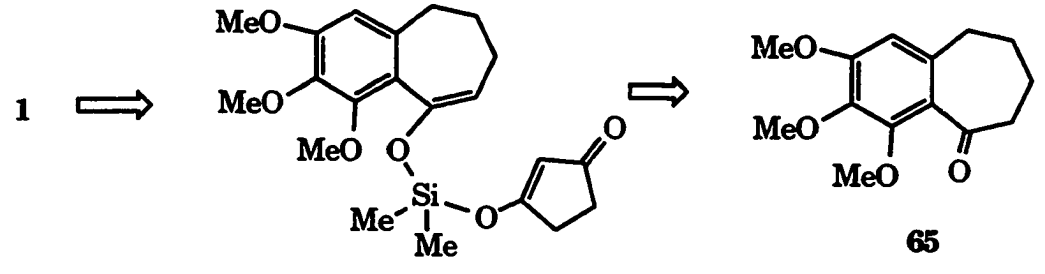


78

77. Both attempts to open the oxygenring under basic conditions (*t*-BuOK/THF and $(Me_3Si)_2NLi$/THF) failed.

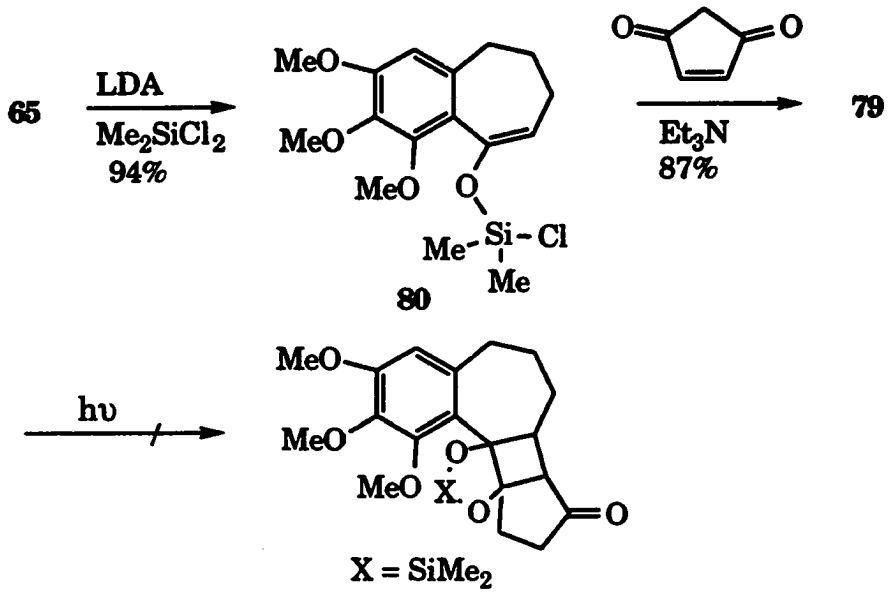
Second approach: (2+2) photochemical addition as the key step

The second approach to synthesize cochicine involved a (2+2) photochemical reaction as key step. The basic idea was that the skeleton of **1** could be achieved by an intermediate **79**, using a readily removed silyl ether tether from ketone **65**.

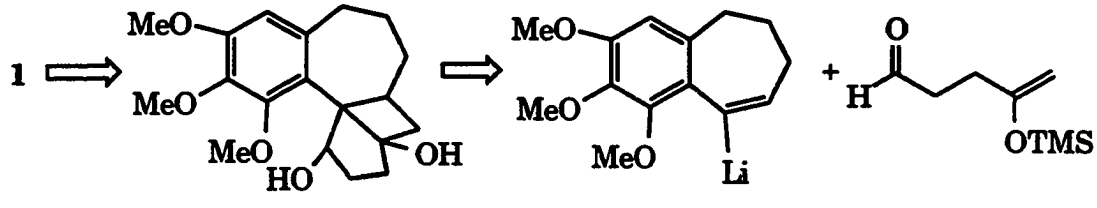


79 65

To test this idea, we treated ketone **65** with LDA in THF at -78°C followed by quench with dimethyl dichlorosilane to give crude enol silyl ether **80** in 94% yield. Without further purification crude **80** reacted with 1,3-pentadienone in the presence of triethylamine to generate tether compound **79** in 87% yield. Unfortunately, irradiation of compound **79** lead to decomposition of the starting material.

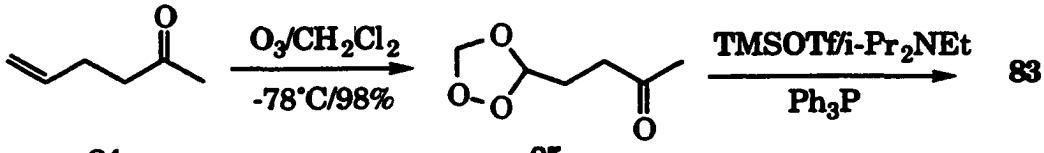


Another idea we tried involved a key intermediate **80** which could be achieved by an intramolecular (2+2) photochemical reaction from the corresponding diene prepared from anion **82** and aldehyde **83**.



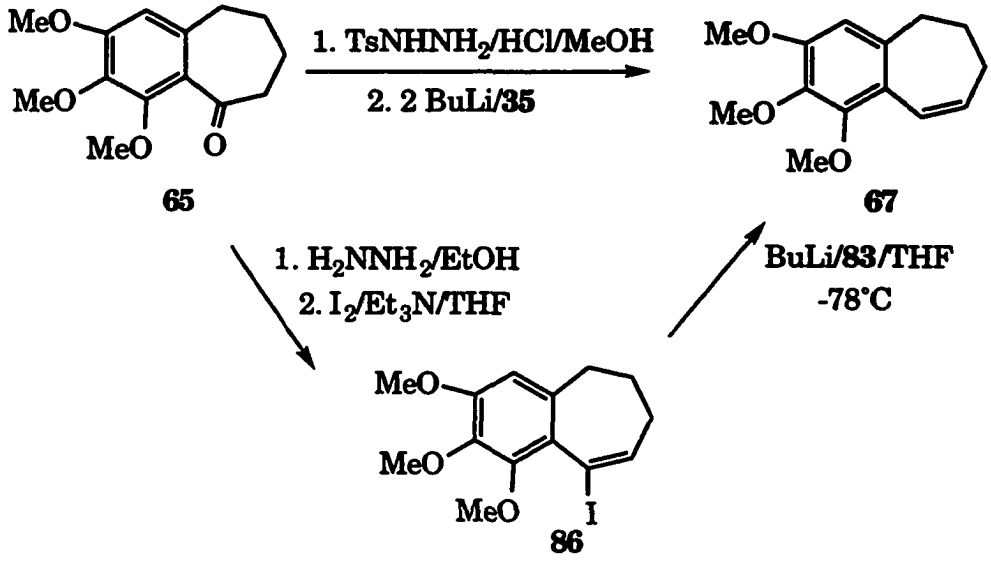
The first task was synthesis of aldehyde **83**. Obviously this compound cannot be made using a normal enol silation method which would give ketone enol silyl ether, because the aldehyde is more reactive than the ketone. To solve this problem, we used the ozonide as a protecting group. The synthesis started from 5-hexen-2-none (**84**). Ozonolysis of **84** in methylene chloride at -78°C afforded ozonide **85** in 98%. Ozonide **85** was

then treated with TMSOTf in the presence of diisopropylethylamine, followed by reduction with triphenyl phosphine to get compound **83**.



84 **85**

The next task was preparation of the intermediate for the photochemical reaction by treatment of compound **83** with anion **82**. Our first attempt was a Shapiro reaction. Unfortunately, this reaction only gave alkene **67**, probably because of steric effects, which can be proved by the following result. Ketone **65** was converted to iodide **86** using Barton's procedure.[15] Treatment of iodide **86** with *n*-butyl lithium, followed by quenching with compound **83** also afforded alkene **67**.

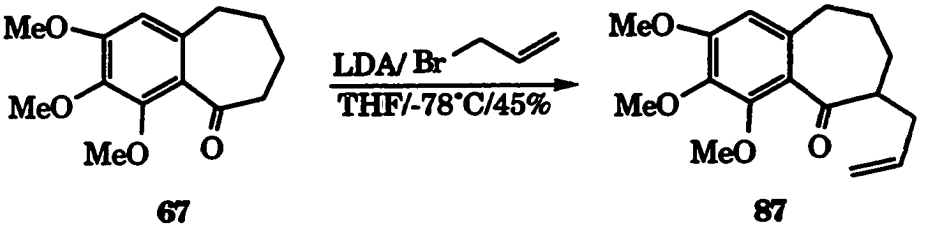


65 **67** **86**

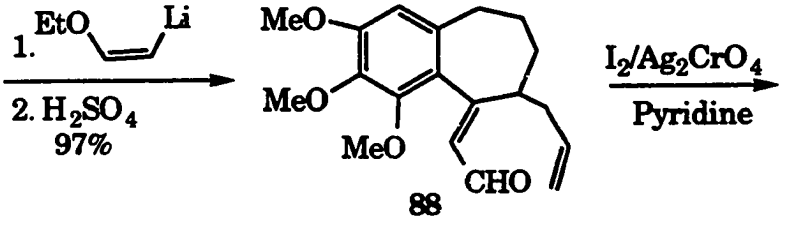
Third approach: acid base catalyzed cyclization as the key step

Another approach toward colchicine involved the base catalyzed cyclization of ketoaldehyde **89**, which first underwent nucleophilic

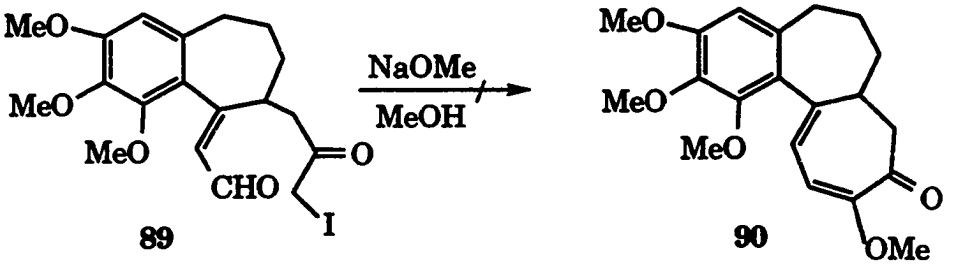
substitution with methoxide. To try this idea, we synthesized allyl ketone **87** by treatment of ketone **66** with LDA in THF at -78°C followed by quenching



67 **87**



88

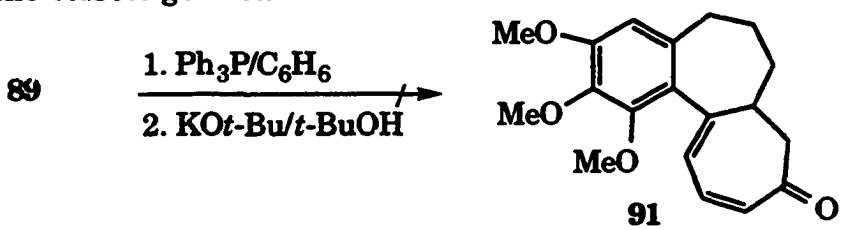


89 **90**

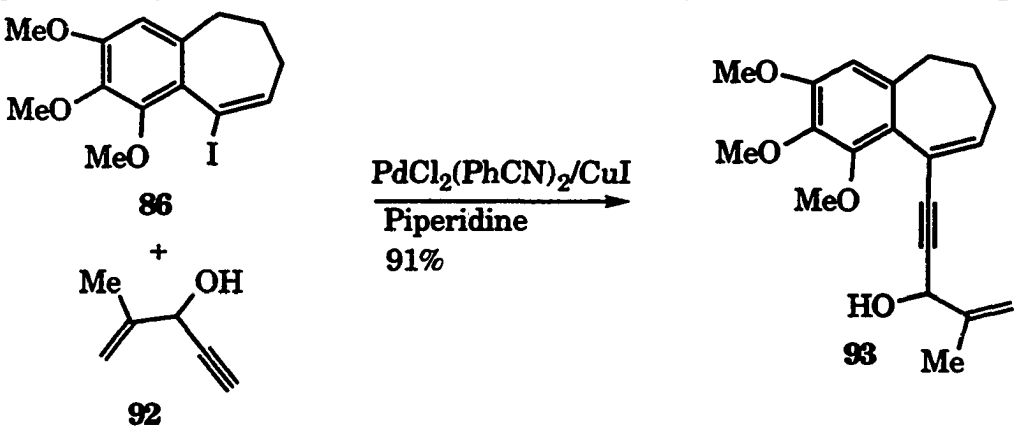
with allyl bromide. Compound **87** then underwent nucleophilic addition with 2-ethoxy vinyl lithium prepared from 2-bromovinyl ethyl ether and hydrolyzed with sulfuric acid in THF to furnish aldehyde **88** in 97% yield. Compound **88** was converted to iodoketone aldehyde **89** by oxidation with iodine and silver chromate in the presence of pyridine. Treatment of crude product **89** with sodium methoxide did not provide the desired product.

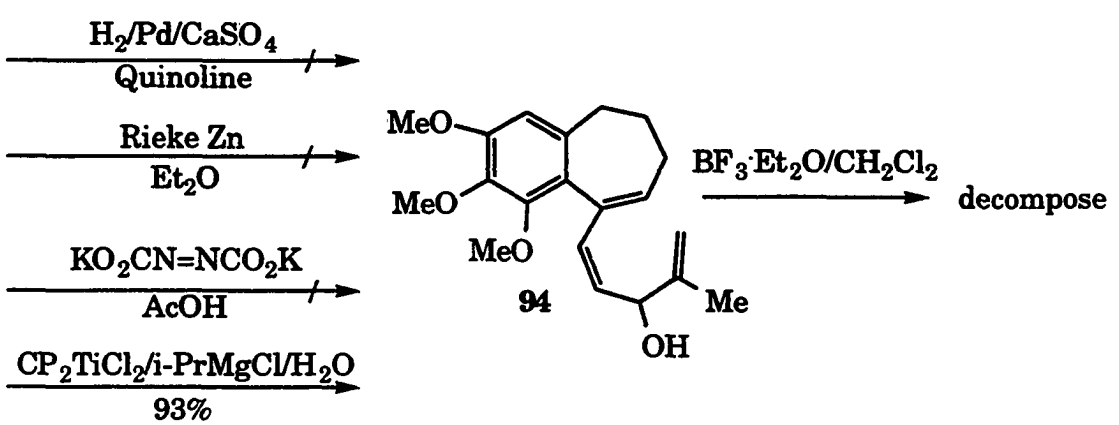
Compound **89** reacted with triphenylphosphine forming the corresponding salt. However, this salt did not undergo the following Wittig reaction. From the above results, we can infer that the iodoketone aldehyde

89 was probably sluggish to cyclize due to the aldehyde being unable to achieve the correct geometrical conformation.



As an alternative way to furnish the C ring of colchicine, we attempted the acid catalyzed cyclization of alcohol **93**. Alcohol **92**, prepared from methylacrolein and ethyl magnesium bromide, was coupled with the previously prepared iodide **86** in a reaction catalyzed by $PdCl_2(PhCN)_2$ and

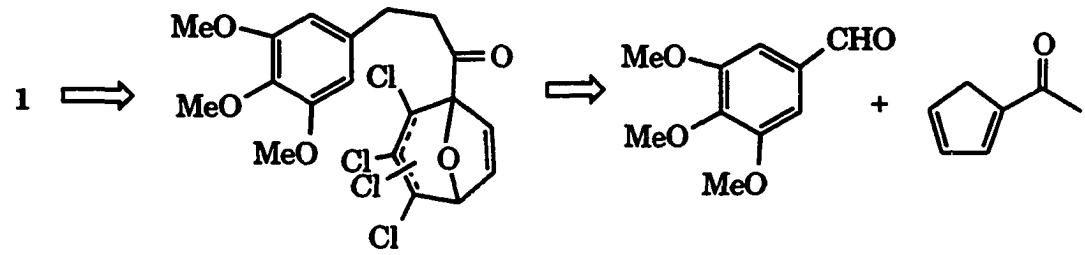




CuI to give coupling product **93** in 91% yield. Reduction of **93** using Lindlar hydrogenation, Rieke zinc, and diazoimide only lead to the recovery of starting material. However, isopropylmagnesium chloride in the presence of a catalytic amount of titanocene dichloride worked very well to give alcohol **94** in 93% yield. Unfortunately, cyclization of **94** catalyzed by trifluroboron etherate did not work, giving a mixture.

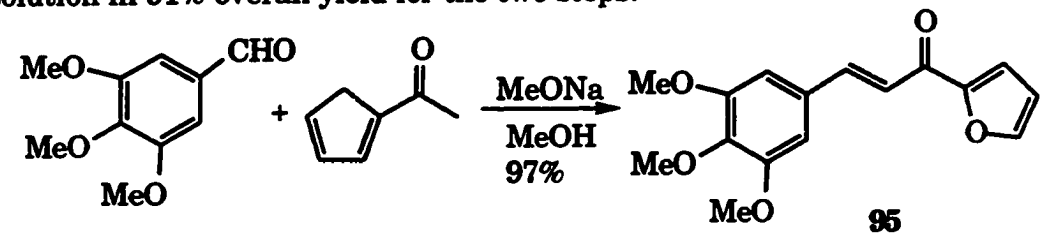
Forth approach: electrophilic addition to A ring as the key step

In view of the above approaches, it seems difficult to build up the C ring from starting materials which already have the A and B rings present. At this point, we changed our idea and tried to start from the material which has the A ring, then construct the C ring, and finally the B ring. We disconnected the juncture of the A and C rings in our retrosynthetic analysis as follow.

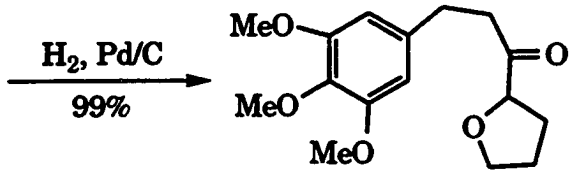


This approach started from an aldol condensation of commercially available 3,4,5-trimethoxybenzaldehyde and 2-acetylfuran catalyzed by sodium methoxide in methanol to furnish enone **95** in 97% yield. Hydrogenation of enone **95** in the presence of palladium on carbon gave ketone **96** in which both the double bond and the furan ring were reduced. However, reduction of enone **95** with triethylsilane catalyzed by tristriphenylphosphinerhodium chloride provided enol silyl ether **97**. This

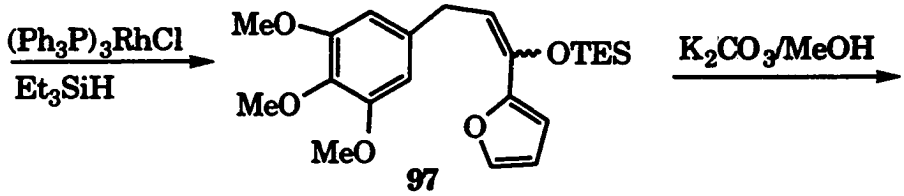
was followed by hydrolysis with potassium carbonate in aqueous methanol solution in 91% overall yield for the two steps.



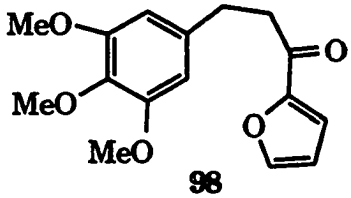
95



96



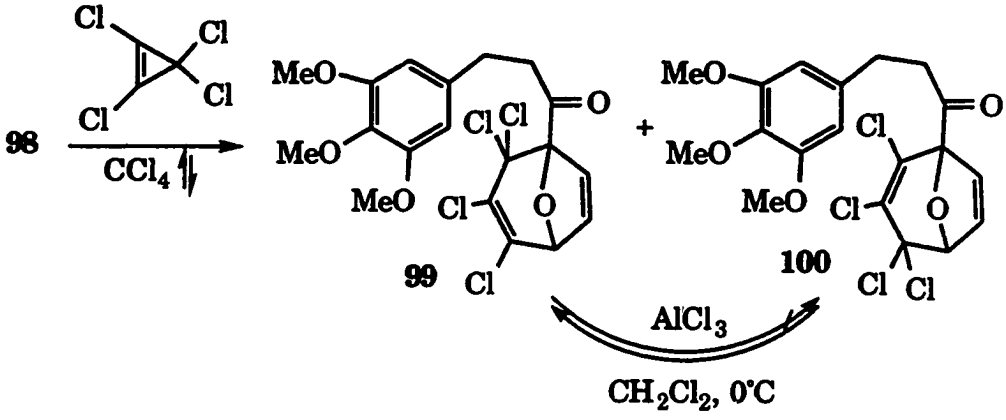
97



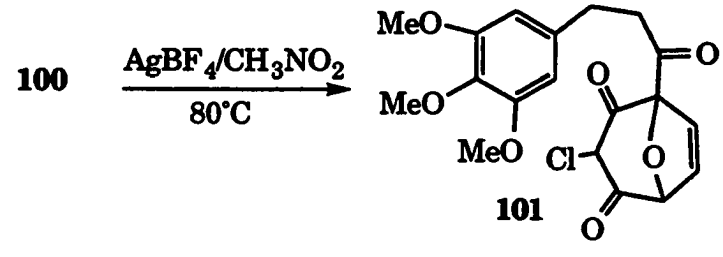
98

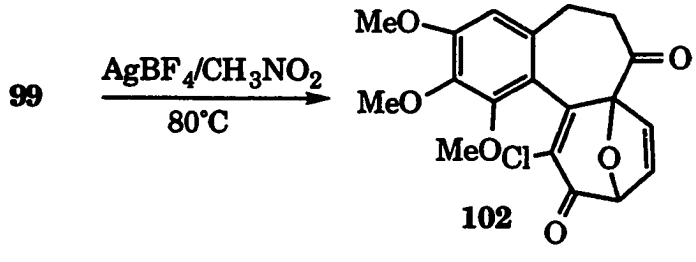
With ketone **98** in hand, we tested the Diels-Alder reaction of ketone **98** and tetrachlorocyclopropene.[16] The mixture of these two compounds was heated in carbon tetrachloride to afford a mixture of **99** and **100** (**99** : **100** = 1.5 : 1) in 41% yield for three days. Treatment of compound **99** with aluminum chloride at 0°C for 2 h lead to recovery of starting material. Under the same conditions, compound **100** gave compound **99** quantitatively. This result demonstrates that the allylic cations generated from **99** and **100** do not relocate very well or are not the same. The inertness of compounds **99** and **100** to Lewis acid are probably due to cordination of the Lewis acid with the

electron-rich A ring, which inhibits electrophilic addition of the cation. The explanation and structure of **99** and **100** can be proven by the following experiments.



Treatment of **100** with silver tetrafluoroborate in nitromethane at 80°C quantitatively afforded trione **101**. However, under the same conditions, **99** provided desired product **102** in 98% yield which has the skeleton of colchicine. The further conversion to colchicine from **102** is still under investigation.





Conclusion

The skeleton of colchicine has been achieved using a Diels-Alder reaction, followed by electrophilic addition to the A ring as the key steps. Our synthetic approach is direct, with further transformation to colchicine still under investigation.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Benzene was distilled from lithium aluminum hydride. Methanol was distilled from calcium hydride. Carbon tetrachloride was distilled from phosphorus oxide. Nitromethane was dried with 4A molecular sieves. Apparatus for experiments requiring anhydrous conditions were flame-dried under a steam of argon or dried in 150 °C oven for 12 h and cooled under a steam of argon or in a desiccator. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using Merck TLC plates (silica gel 60) with a thickness of 0.25 mm. The solvent system was suitable mixtures of hexane (H) and ethyl acetate (EA) unless otherwise noted. The abbreviation sgc represents silica gel chromatotography. Infrared spectra were obtained on a Bio-Rad FTS-7 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (400 MHz) were obtained using

Bruker Instruments Corporation DX-400 spectrometer and all chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), and m (multiplet); a br prefix indicates a broadened pattern. Carbon-13 NMR were obtained using a Bruker Instruments Corporation DX-400 spectrometer and all chemical shifts are reported in δ relative to $CDCl_3$ (77.0 ppm). High resolution mass spectra were collected on a Kratos model MS-50 spectrometer. Low resolution mass spectra were collected on a Finnegan 4023 mass spectrometer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. The purity of all title compounds was determined to >95% by 400 MHz proton NMR and/or elemental analysis.

***trans*-1-Furyl-3-(3',4',5'-trimethoxyphenyl)-2-propen-1-one (95).** To a solution of 3,4,5-trimethoxybenzaldehyde (10.0 g, 51 mmol) and 2-acetyl furan(5.6 g, 51 mmol) in 25 ml of methanol was added sodium (152 mg, 6.6 mmol) in portions. The resulting mixture was stirred for 2 h. Then a crystalline precipitate was collected, washed with methanol and water, and dried in vacuo to give 14.2 g (yield 97%) of product as a yellow solid. NMR (CDCl3) δ 3.88 (s, 3H), 3.90 (s, 6H), 6.58 (m, 1H), 6.85 (s, 2H), 7.32 (d, J = 15.7 Hz, 1H), 7.32 (m, 1H), 7.64 (m, 1H), 7.78 (d, J = 15.7 Hz, 1H); IR ($CDCl_3$) cm^{-1} 2978, 2916, 1653, 1601, 1558, 1504, 1465, 1287, 1127, 739; HRMS: for $C_{16}H_{16}O_5$ calcd. 288.0998, measured 288.0997; CMR ($CDCl_3$) δ 56.2, 56.3, 61.0, 105.8, 112.6, 117.5, 120.4, 130.2, 130.3, 140.5, 144.2, 146.5 153.5, 153.7, 153.8, 177.9.

1-Furyl-3-(3',4',5'-trimethoxyphenyl)-2-propan-1-one (98). To a suspension of enone **95** (10.0 g, 34.7 mmol) in triethylsilane (16.1 g, 69.4 mmol) was added tris(triphenylphosphine) rhodium (I) chloride (160 mg, 0.17 mmol) . The mixture was stirred for 24 h. Then the resulting clear solution was diluted with pentane, filtered and concentrated to the crude enol silyl ether as a yellow oil. The crude product dissolved in 50 ml of methanol was treated with 10 ml of 10% K_2CO_3 aqueous solution. The resulting mixture was stirred for 2 h, worked up with water, extracted with ether, dried over $MgSO_4$, and concentrated. The residue was separated by sgc (H : EA = 5 : 1) to give 10.0 g of ketone **98** (91% overall yield) as white solid.

NMR ($CDCl_3$) δ 2.99 (t, J = 7.6 Hz, 2H), 3.15 (t, J = 7.6 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 6H), 6.46 (s, 2H), 6.53-6.54 (m, 1H), 7.18 (dd, J_1 = 0.5 Hz, J_2 = 3.5 Hz), 7.56 (d, $J3$ = 0.7 Hz); IR (CDCl3) cm^{-1} 2999, 2939, 1674, 1589, 1558, 1507, 1464, 1421, 1238, 1127, 1005, 770; HRMS: for $C_{16}H_{18}O_5$ calcd. 290.1154, measured 290.1159; CMR ($CDCl_3$) δ 30.1, 39.9, 55.7, 60.5, 105.0, 112.0, 116.8, 116.7, 136.5, 146.1, 152.9, 188.1.

Ketone 99 and 100. A solution of ketone **98** and tetrachlorocyclopropene in 5 ml of dry CCl_4 was refluxed for 3 days. Then the resulting dark brown solution was concentrated, purified by sgc (H : EA = 4 : 1) to 108 mg of **99** and 72 mg of **100** (41% total yield) as yellow oils. The ratio of **99** to **100** was 1.5 to 1.

99: NMR ($CDCl_3$) δ 2.86-2.92 (m, 2H), 2.96-3.20 (m, 2H), 3.80 (s, 3H), 3.82 (s, 6H), 5.05 (d, J_1 = 1.9 Hz, 1H), 6.40 (s, 2H), 6.40 (d, J_2 = 5.6 Hz, 1H), 6.87 (dd, J_1 = 1.8 Hz, J_2 = 5.6 Hz, 1H); IR ($CDCl_3$) cm^{-1} 2939, 1728, 1591, 1508, 1458, 1238, 1128, 737; MS: m/e 77, 137, 181, 267, 317, 369, 468; HRMS: for $C_{19}H_{18}Cl_4O_5$

calcd. 467.9879, measured 467.9861; CMR ($CDCl_3$) δ 29.2, 41.1, 56.1, 60.9, 82.7, 83.0, 97.1, 105.4, 128.4, 130.8, 136.0, 139.2, 153.2, 202.2.

100: NMR ($CDCl_3$) δ 2.84-2.92 (m, 3H), 3.06-3.15 (m, 1H), 3.80 (s, 3H), 3.84 (s, 6H), 5.49 (d, J_1 = 2.1 Hz, 1H), 6.41 (s, 2H), 6.42 (dd, J_1 = 2.1 Hz, J_2 = 5.8 Hz, 1H), 7.04 (d, J_2 = 5.8 Hz, 1H); IR ($CDCl_3$) cm^{-1} 2939, 1732, 1591, 1580, 1500, 1458, 1238, 1128, 1008, 733; MS: m/e 77, 137, 181, 23, 317, 369, 433, 468; HRMS: for $C_{19}H_{18}Cl_4O_5$ calcd. 467.9879, measured 467.9860;CMR ($CDCl_3$) δ 29.1, 40.4, 56.1, 60.9, 82.4, 90.4, 93.4, 105.4, 129.3, 129.4, 135.1, 136.2, 136.5, 139.5, 153.2, 200.4.

Interconversion 100 to 99. To a solution of **100** (10 mg, 0.021 mmol) in 1 ml of methylene chloride was added aluminum trichloride (5.6 mg, 0.042 mmol) at 0 °C. The resulting solution was stirred for 2 h, then poured into a mixture of ice and two drops of con. HCl acid, extracted with ether, dried over $MgSO_4$, and concentrated. The residue was purified by sgc to afford **99** in quantitative yield.

Dione 102. To a solution of **99** (30 mg, 0.064 mmol) in 6 ml of nitromethane was added $AgBF_4$ (25 mg, 0.23 mmol). The resulting mixture was stirred for 2 h at 80 °C, then cooled to rt, worked up with water, extracted with ether, dried over $MgSO_4$, and concentrated. The residue was purified by sgc (H : EA = 5 : 1) to provide 24.0 mg of **102** (98% yield) as a white solid. NMR ($CDCl_3$) δ 2.66-2.78 (m, 2H), 3.21-3.28 (m, 1H), 3.32-3.41 (m, 1H), 3.82 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 5.29 (d, J_1 = 2.2 Hz, 1H), 6.58 (s, 1H), 6.59 (dd, J_1 = 2.2 Hz, J_2 = 5.8 Hz, 1H), 7.10 (d, J_2 = 5.8 Hz, 1H); IR ($CDCl_3$) cm^{-1} 2969, 2939, 1721, 1709, 1597, 1486, 1462, 1347, 1324, 1202, 1095; MS: m/e 63, 99, 139, 181, 227, 254, 273, 297, 317, 341, 376; HRMS: m/e for $C_{19}H_{17}O_6Cl$ calcd.

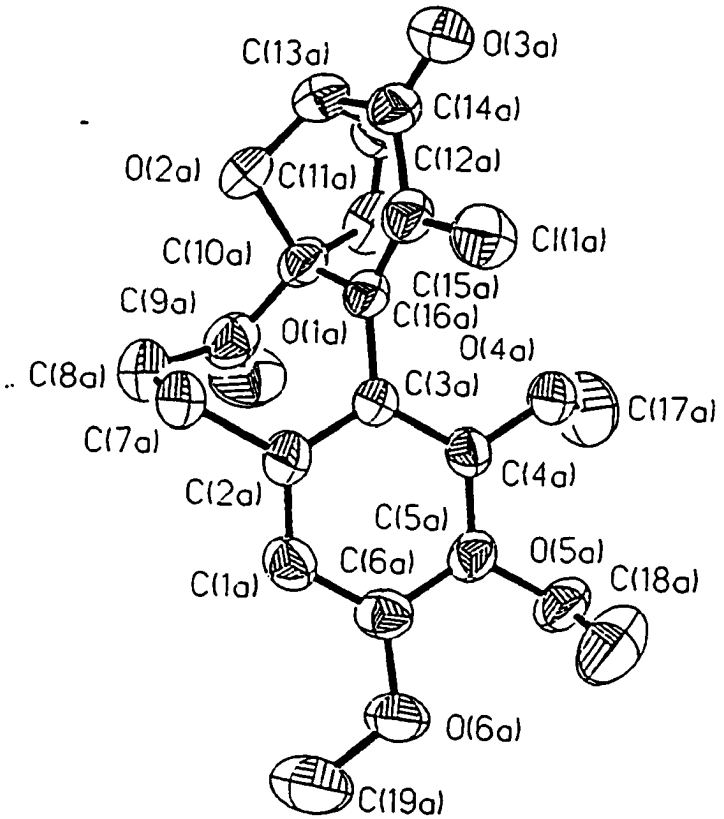
376.0714, measured 376.0722; CMR (CDCl3) δ 29.0, 41.5, 56.1, 61.0, 61.4, 88.6, 94.3, 107.4, 117.7, 123.6, 129.5, 133.8, 140.0, 140.6, 150.7, 153.8, 155.4, 186.0, 201.5.

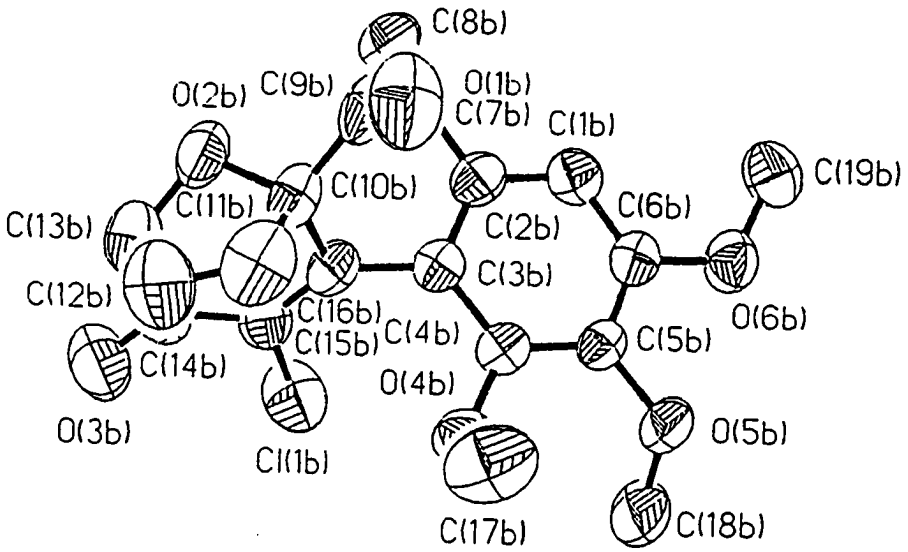
Single-crystal X-ray structures of dione 102

(1) crystal data

Empirical Formula	$C_{19}H_{17}Cl\,O_6$
Color, Habit	Yellowish, Rectangular plate
Crystal Size (mm)	0.5 x 0.25 x 0.05
Crystal System	Monoclinic
Space Group	$P2_1/c$
Unit Cell Dimensions	a = 22.141(4) Å
	b = 9.150(2) Å
	c = 19.601(4) Å
	α = 90 °
	β = 115.61(3) °
	γ = 90 °
Volume	3580.8(13) $Å^3$
Z	8
Formula Weight	376.78
Density(calc.)	1.398 Mg/m^3
Absorption Coefficient	2.186 mm^{-1}
F(000)	1568

(2) Crystal structures of dione 102





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GENERAL SUMMARY

The synthesis of angularly fused quinone natural products has been achieved using a photoenolization reaction and a Diels-Alder reaction in the key carbon-carbon bond forming steps. The skeleton of colchicine has been achieved using a Diels-Alder reaction, followed by electrophilic addition to A ring, as key steps. Our synthetic approach is direct. Further transformation to colchicine is under investigation.

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