NEW ALTERNATIVES TO OXIDATIVE PHENOLIC COUPLING IN NATURAL PRODUCTS TOTAL SYNTHESIS

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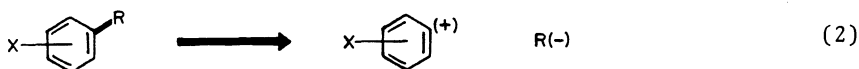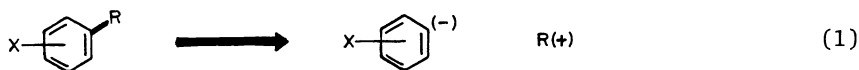
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Abstract - New concepts will be presented which employ quinones in the synthesis of alkaloids and antibiotics. In many instances carbon-carbon bonds, which are constructed biogenetically via oxidative phenolic coupling, can be synthesized from quinoid precursors. The application of these concepts to the total synthesis of colchicine will be presented.
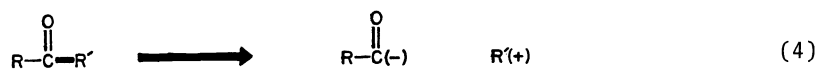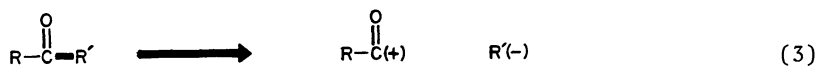
INTRODUCTION

Aromatic rings are ubiquitous structural subunits of numerous naturally occurring organic compounds. Consequently, new approaches to the construction of aryl-carbon bonds remain as relevant objectives in chemical synthesis. Assuming that the synthetic objective is the union of a specific aromatic synthon to an aliphatic moiety, there are two "polar" disconnections that are possible (eq. 1, 2). Commonly, electrophilic aromatic substitution (eq. 1), wherein the aromatic ring is the nucleophilic partner in the polar coupling process, provides the most expedient solution. Nonetheless, the alternate mode of disconnection (eq. 2) where the aromatic synthon is defined as the electrophile and the appendage, R, the nucleophile, remains as an important option to be developed. For example, consider the problems associated with the synthesis of phenylacetone. Over the last few years the creation of a manifold of carbonyl anion equivalents (c.f. eq. 4) has occupied the attention of numerous investigators (1). In spite of the recognized synthetic utility of "reversed polarity" equivalents such as carbonyl anions, comparatively little effort has been invested in the definition of operationally effective aryl cation equivalents.

Synthon: Benzene Ring

$$X - C_6H_4 - R \longrightarrow X - C_6H_4^{(-)} \qquad R(+) \qquad (1)$$

$$X - C_6H_4 - R \longrightarrow X - C_6H_4^{(+)} \qquad R(-) \qquad (2)$$

Synthon: $RC(=O)-$

$$R - \overset{O}{\underset{\parallel}{C}} - R' \longrightarrow R - \overset{O}{\underset{\parallel}{C}}(+) \qquad R'(-) \qquad (3)$$

$$R - \overset{O}{\underset{\parallel}{C}} - R' \longrightarrow R - \overset{O}{\underset{\parallel}{C}}(-) \qquad R'(+) \qquad (4)$$

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The purpose of this discussion will be to demonstrate how quinone substrates, in concert with specified carbon-carbon bond-forming reactions (bond constructions) and refunctionalization processes, can be viewed as useful aryl cation equivalents. As an example, consider the bond construction resulting from the 1,2-addition of an organometallic reagent to p-benzoquinone (Scheme I). The illustrated refunctionalization reactions that could be applied to the resultant p-quinol define the family of aryl cation equivalents shown in Scheme I
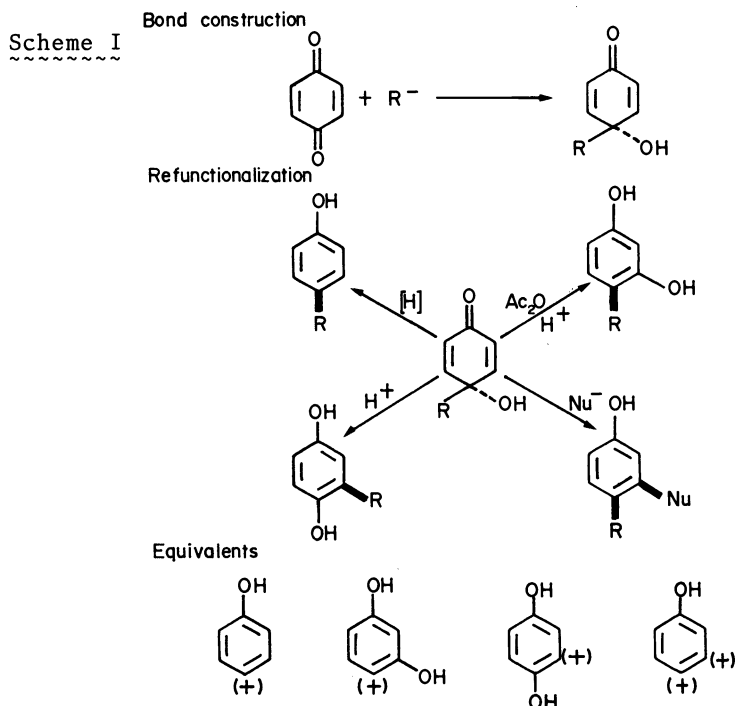
Scheme I

One projected application of quinoid substrates is shown in Scheme II. In the oxidative coupling of diphenolic substrates, both dienones and biaryls are formed. In principle, one might expect similar products to arise from related p-quinol substrates upon acid catalysis. Consequently, many natural
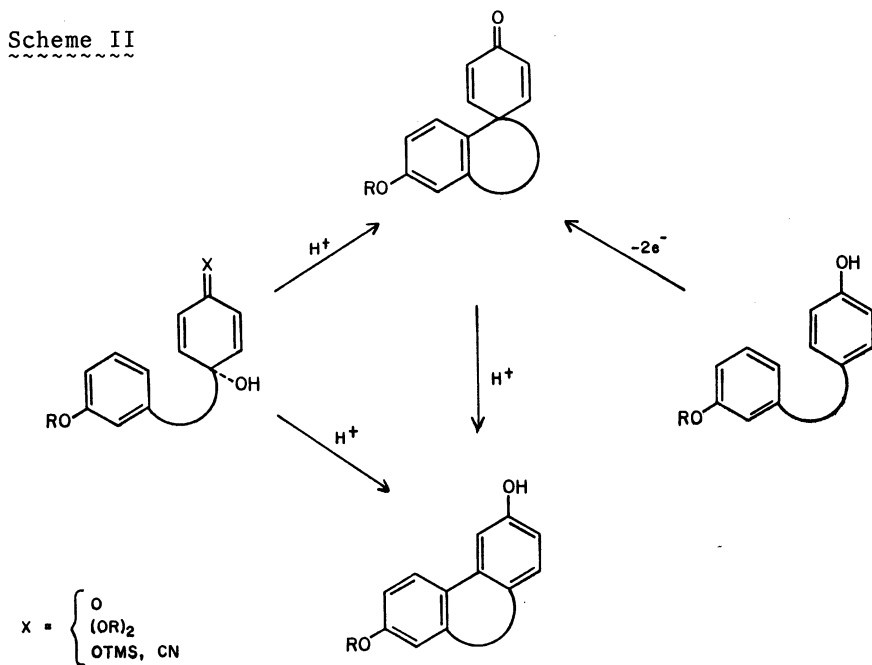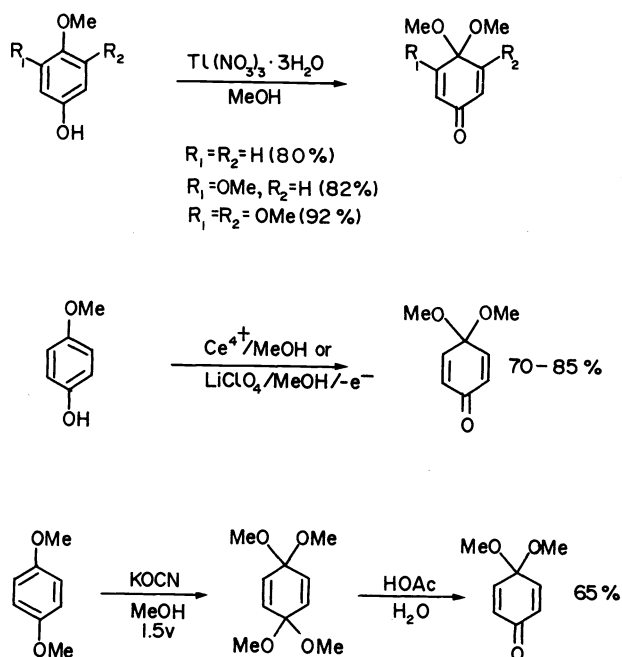

Scheme II

products derived from phenol oxidation might be constructed from quinone precursors.
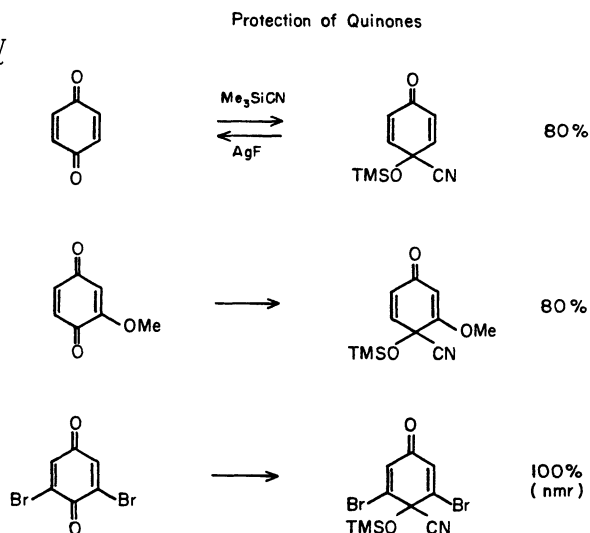
THE SYNTHESIS OF PARA-QUINOLS

The major problem associated with p-quinol synthesis (c.f. Scheme I) via the addition of nucleophiles to quinones is associated with the intervention of unwanted quinone redox chemistry. Fortunately, such problems can be effectively circumvented via the use of quinone mono-ketals and mono-cyano-hydrin derivatives.

Scheme III summarizes some of the procedures which have been found to be reliable for the synthesis of quinone ketals while Scheme IV provides a brief survey of the utility of trimethylsilyl cyanide in quinone protection (2).

Scheme III
~~~~~~~~~~

Tℓ(NO$_3$)$_3$·3H$_2$O / MeOH

R_1=R_2=H (80%)
R_1=OMe, R_2=H (82%)
R_1=R_2=OMe (92%)

Ce^{4+}/MeOH or LiClO$_4$/MeOH/-e$^-$ 70-85%

KOCN / MeOH / 1.5v   HOAc / H$_2$O   65%

Protection of Quinones

Scheme IV
~~~~~~~~~~

Me$_3$SiCN / AgF   80%

80%

100% (nmr)

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The utility of these masked quinones in the construction of richly function-
alized p-quinols (3) is summarized with the representative trans-
formations illustrated in Scheme V. Application of this methodology to
the expedient syntheses of the dibromo-p-quinol acetate 1 (4), isolated from
marine sources and Jaccarone (2, X = H) are illustrated below (Scheme VI).

Scheme V

95%

80-90%

81%

75%

Scheme VI

77%

1

Jacaranone: X = H 54%
   X = OMe 58%

2
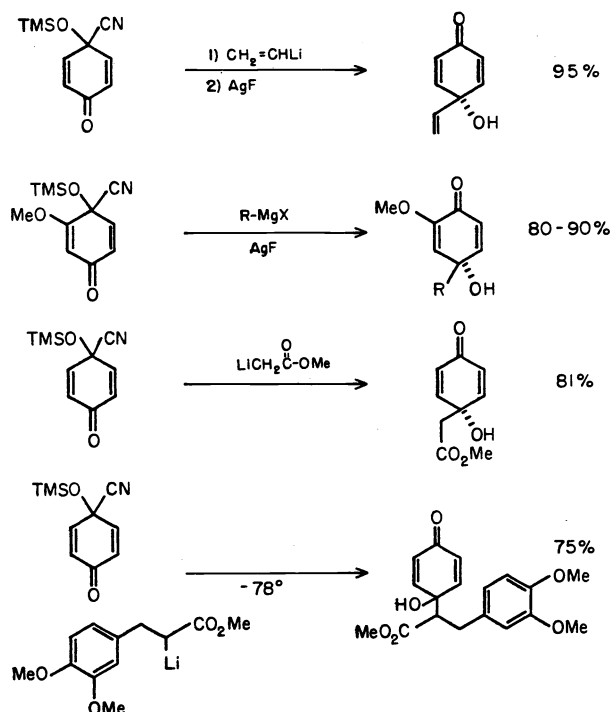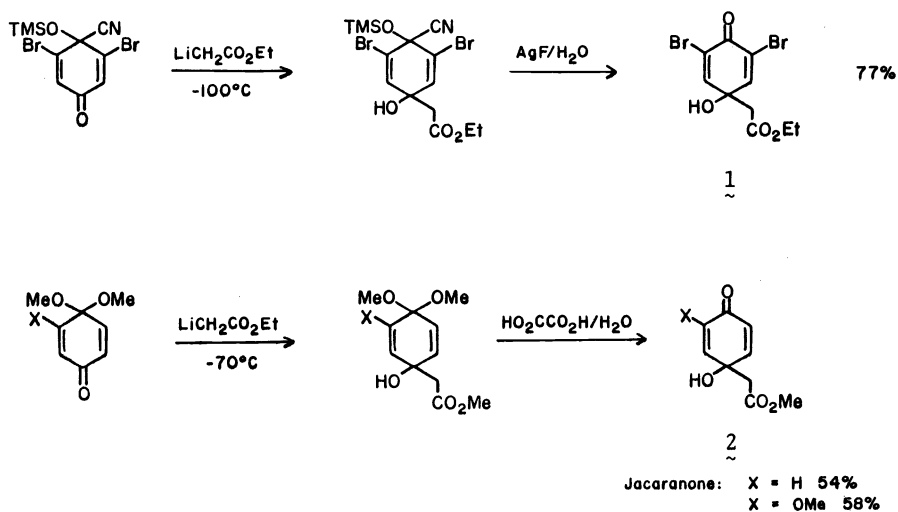
A new annelation concept which employs quinone substrates is shown below
(Scheme VII) (5). Representative examples illustrate the facile, convergent
construction of 9,10-dihydrophenanthrene as well as fluorene derivatives
(Scheme VIII). These acid-catalyzed cyclizations appear to be limited to the
formation of five and six-membered central rings.
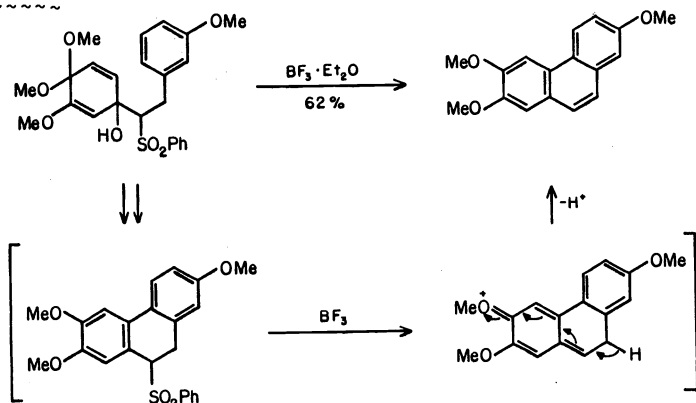
Scheme VII
~~~~~~~~~

A

B

R = H
R = OMe

Scheme VIII
~~~~~~~~~~~

SnCl₄
61%

P₂O₅/MeSO₃H
78%

SnCl₄
78%

X = H, OMe

BF₃·Et₂O
61%
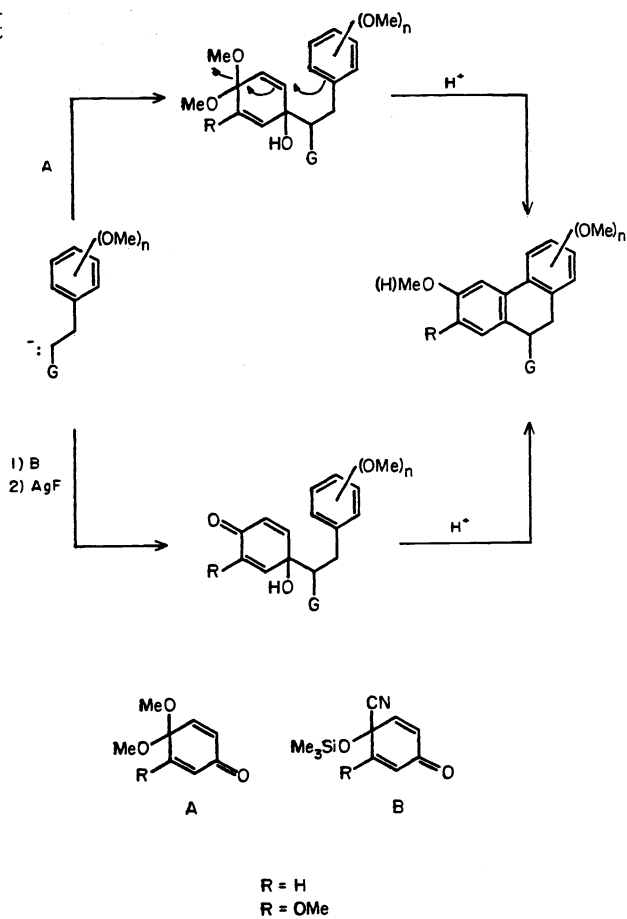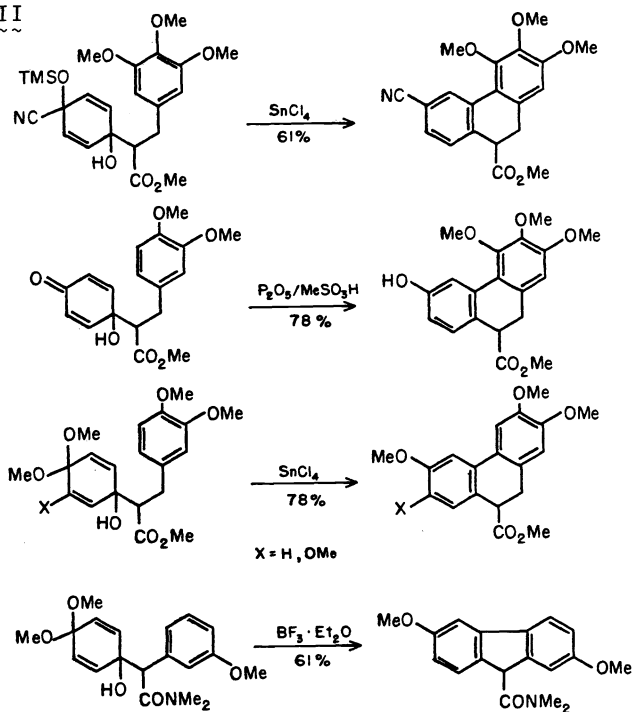
It has been found that the general annelation concept illustrated in Scheme VII can be modified to afford phenanthrenes directly (Scheme IX).

Scheme IX

The mechanistic intricacies of these acid-catalyzed cyclizations are yet to be revealed. Among the several cyclization modes illustrated in Scheme X, Path I has been shown not to be tenable. No deuterium loss was noted in cyclizations of the illustrated methyl ester incorporating a deuterium α to the carbomethoxy group. At the present time no information is available which would support the intervention of spiran intermediates (Path II), and all products can be adequately rationalized as being derived from cyclizations initiated by ketal ionization (Path III).

Scheme X
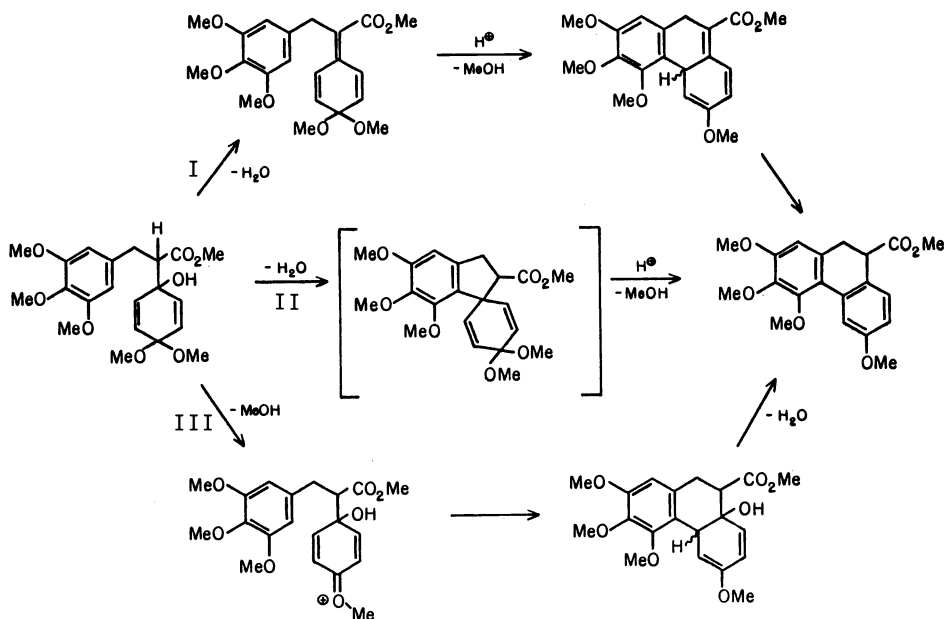
Numerous applications of the aforegoing annelation process may be readily perceived. For example, a general approach to the total synthesis of the class of phenanthroindolizidine alkaloids is illustrated in Scheme XI.
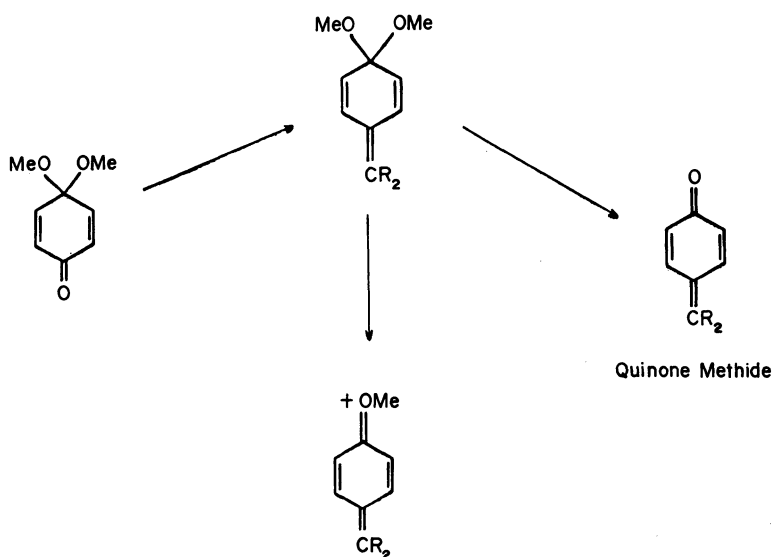
Scheme XI

X = H, OMe
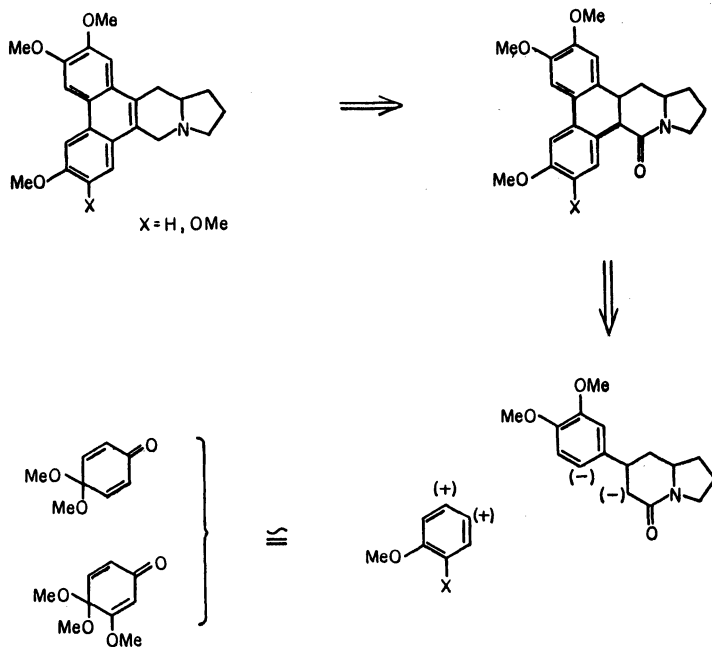
SYNTHESIS AND REACTIONS OF p-QUINONE METHIDE KETALS

Quinone methides constitute a class of highly electrophilic molecules that are frequently encountered in natural products chemistry. We speculated that olefination reactions, when applied to quinone monoketals could provide access to quinone methide derivatives which could be exploited in various ways in natural products synthesis (Scheme XII).
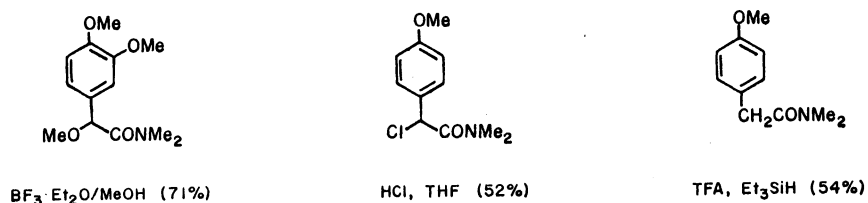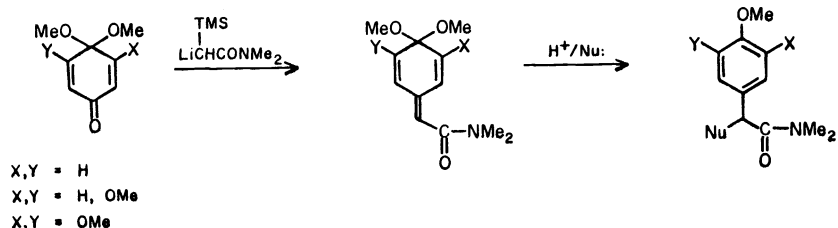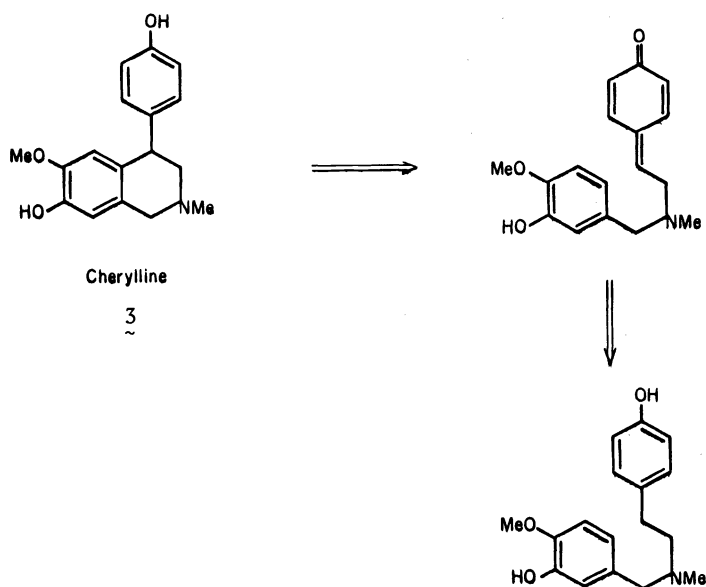
Scheme XII

Quinone Methides via Quinone Ketals

Quinone Methide

We have found that alkylidene phosphoranes as well as silyl-substituted
carbanions react smoothly with p-quinone monoketals to give p-quinone
methide ketals in good yield (Scheme XIII).

Scheme XIII

X,Y = H
X,Y = H, OMe
X,Y = OMe

BF₃·Et₂O/MeOH (71%)   HCl, THF (52%)   TFA, Et₃SiH (54%)

The success of these transformations served to establish reliable precedent
for a total synthesis of the isoquinoline alkaloid cherylline (3) whose
biosynthesis has been proposed to proceed *via* the illustrated p-quinone
methide (Scheme XIV).

Scheme XIV

Cherylline

3

The successful application of quinone monoketals within the context of this
target molecule is illustrated in Scheme XV (6). The desired Wittig
reaction proceeded without incident to give the acid labile ketal 4 which
was subjected to acid-catalyzed cyclization without purification. The
phenolic amine 5, obtained in 47% yield (two steps), was demethylated with
sodium ethylthiolate to cherylline (3) in 53% yield.

Scheme XV
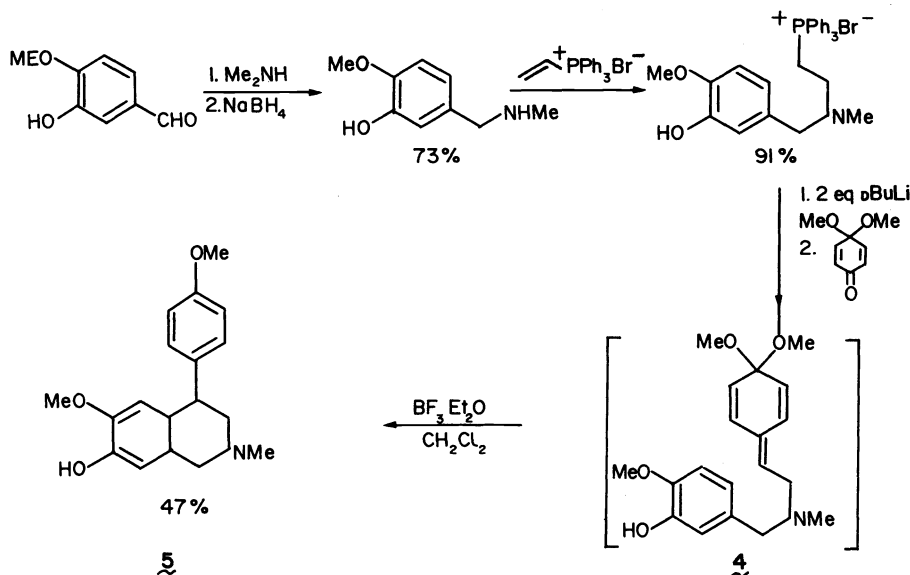
The total synthesis of (±)-colchicine

THE TOTAL SYNTHESIS OF (±)-COLCHICINE

Colchicine (6), one of the major alkaloid constituents of the autumn crocus (Colchicum autumnale L.), has been the target of numerous synthetic studies. Without exception, this molecule has proven to be a far more formidable challenge than its relatively simple structure suggests. Although at least nine total syntheses of colchicine have been reported (7), several problems associated with the construction of this alkaloid have been largely ignored. All but two of the published colchicine syntheses proceed through desacetamidoisocolchicine (7). Since the conversion of 7 is inefficient, projected
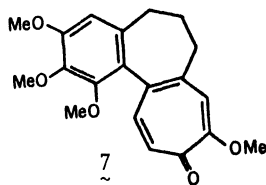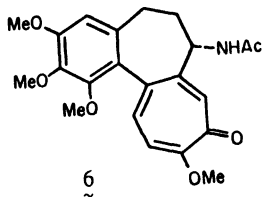
syntheses of colchicine should be capable of incorporating the acetamido function in an alternate manner. In addition, all but one of the syntheses of 6 proceed via the free tropolone, colchiceine. Since the tropolone methylation step proceeds with no regioselectivity free tropolone intermediates should be avoided during all stages of the synthesis.

The current approach to the synthesis of colchicine is outlined below (7). The basic strategy has been: (1) To start from the premise of convergency; (2) to recognize a readily available binucleophilic aromatic subunit which could be employed in an annelation reaction with a substrate which would serve as an equivalent synthon to the hypothetical tropolone dication 8 (Scheme XVI).
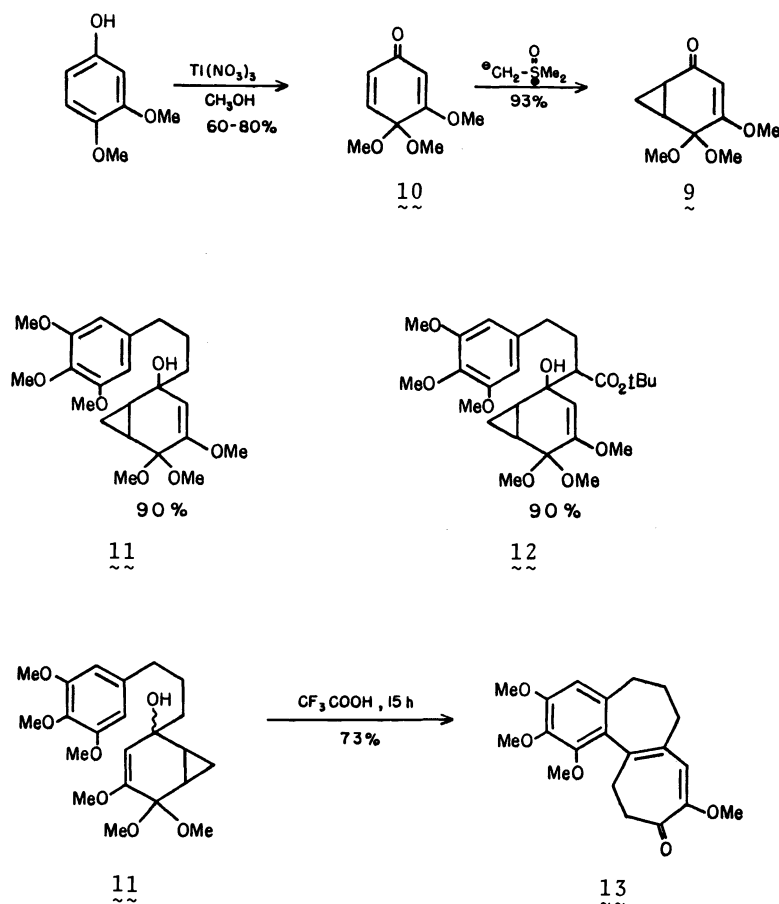
Scheme XVI

G = -CO₂R
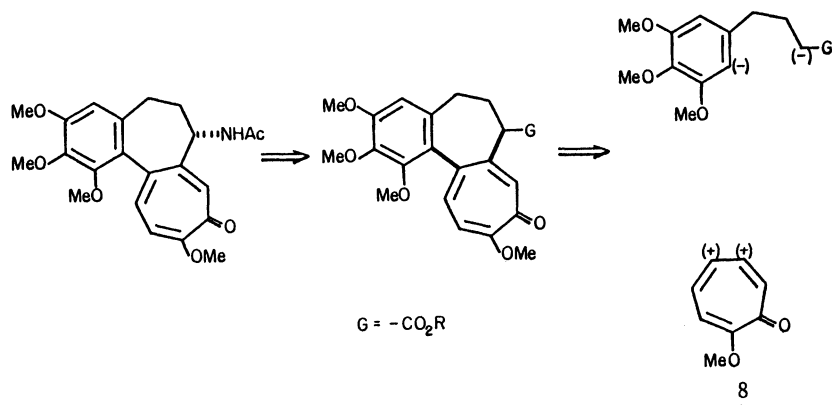
As stated, the projected success of this plan hinges upon the creation of
an equivalent synthon to 8. One possible equivalency for 8 is illustrated
in Scheme XVII.   The synthesis of the required cyclopropyl ketone 9 was
readily accomplished in excellent yield from the quinone monoketal 10.
It was further discovered that the addition of Grignard reagents or ester
enolates to 9 proceeded in accordance with expectation (Scheme XVIII).

Scheme XVII
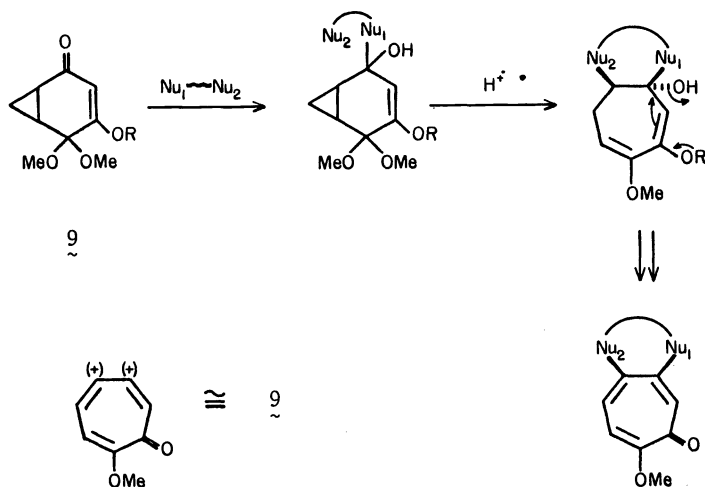
It was gratifying to observe that alcohol 11, upon treatment with trifluoro-
acetic acid (25°C, 15 h), afforded a good yield of the dihydrotropolone
methyl ether 13. The structure of 13 was confirmed via oxidation (DDQ, 72%
to desacetamidoisocolchicine (7) thus completing a formal synthesis of

Scheme XVIII

10

9


90 %

11

90 %

12

CF₃COOH , 15 h

73%

11

13

colchicine (6). Careful examination of the crucial cyclization reaction as a function of time revealed the identifiable intermediates shown in Scheme XIX. After short reaction times alcohol 11 afforded a mixture of dienone 14 and diastereoisomeric spirans 15 and 16 (15:16 = 3). The minor spiran 16 was found to be identical in all respects to an intermediate prepared by Tobinaga and co-workers (8). Further examination of the effects of the acid catalyst on both 15 and 16 revealed that 15 rearranged at comparable rates to both dihydrotropolone 13 and spiran 15. On the other hand, spiran 15 only rearranged to the desired dihydrotropolone 13 via equilibration through the diastereoisomeric spiran 16! Available evidence suggests that a protic acid is essential for the interconversion of 15 and 16 and hence the success of the overall cyclization process. This conclusion is based upon the observation that the major spiran 15 can be recovered unchanged after treatment with boron trifluoride etherate (1 h, 25°C) while the spiran 16 undergoes exclusive rearrangement to 13 during the same time period.

Scheme XIX
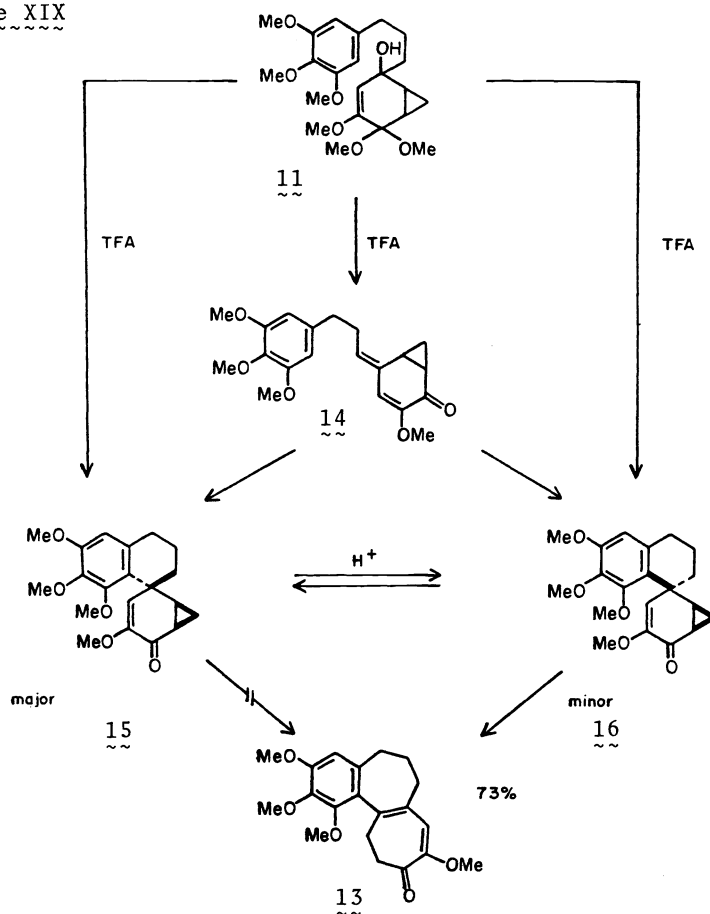
A priori, two isomeric dihydrotropolone methyl ethers could have been obtained from the diastereoisomeric spirans 15 and 16 (Scheme XX). The fact that

Scheme XX
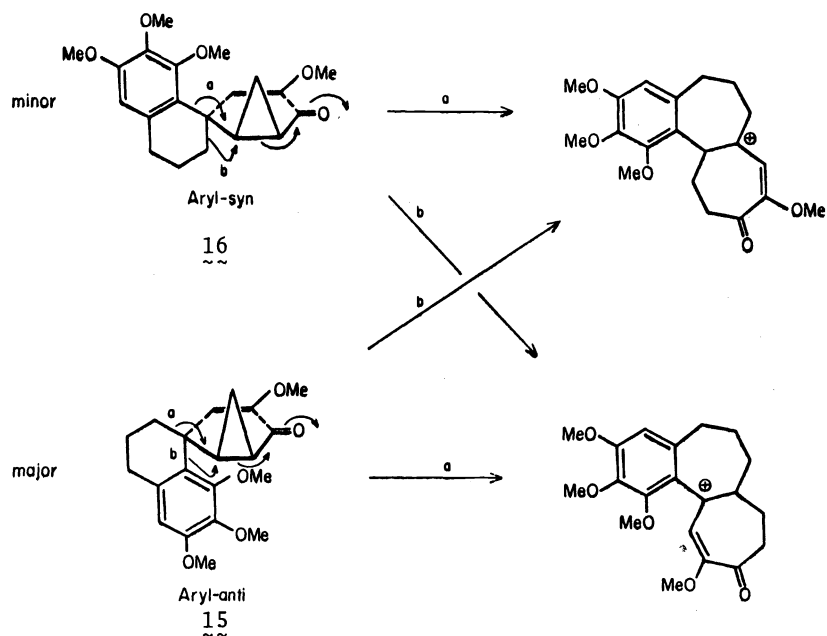
this was not the case suggests that: (1) Aryl migration is preferred over alkyl migration in the cyclopropane ring cleavage step; (2) there is a syn stereochemical requirement between the cyclopropane and migrating group during the ring expansion (Scheme XX, Path a). Similar stereochemical requirements have been noted in related ring expansions (9).

Attention was then directed towards executing a synthesis of colchicine which incorporated requisite functionality for the inclusion of the C-7 acetamido function. Commensurate with this objective, the diastereoisomeric hydroxy esters 12 (c.f. Scheme XVIII) were subjected to a variety acid catalysts. In the presence of boron trifluoride etherate spiran 19 and lactone 18 were isolated in 23% and 56% yields respectively (Scheme XXI). At the present time available evidence suggests that the observed product ratio in this cyclization was derived from the two diastereoisomeric esters 12. Based upon our earlier studies it is assumed that spiran 17 is the progenitor of lactone 18. Given this fact, the ester function is ideally disposed to participate in acid-catalyzed cyclopropane cleavage.
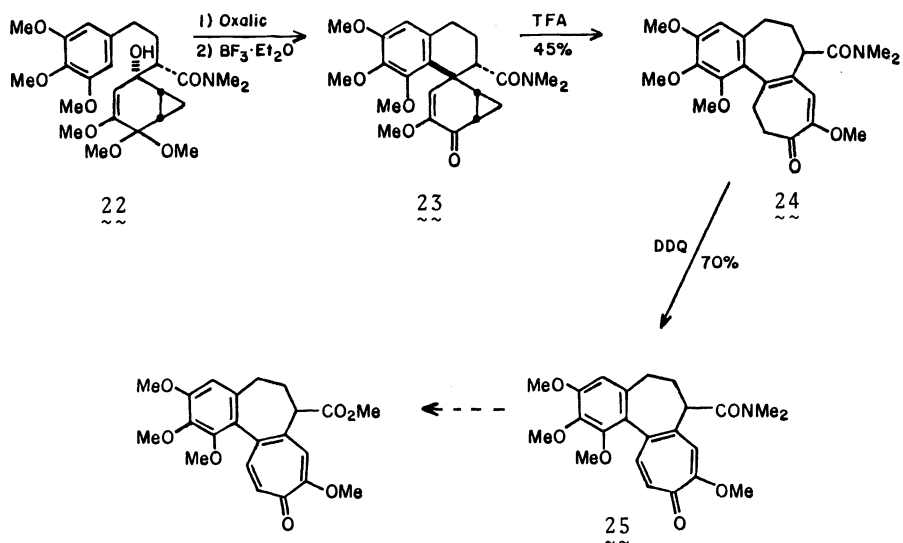
Scheme XXI
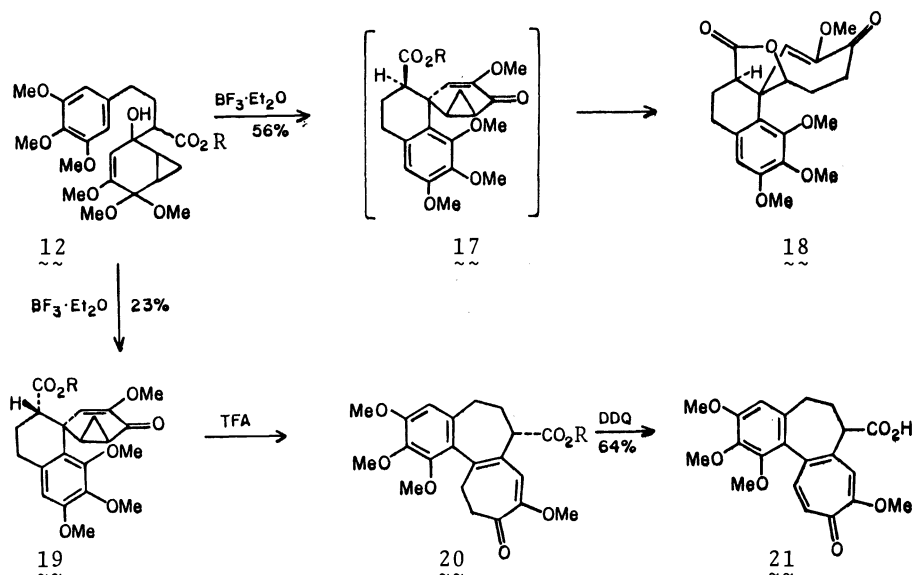
Although spiran ester 19 (R = Me) could be induced to rearrange to 20 and then subsequently oxidized (DDQ) to 21 in an overall yield of 64%, the unfortunate fact remains that lactone 18 has not demonstrated an inclination to undergo rearrangement to dihydrotropolone 20. In an effort to alter the diastereoisomer ratio in the aldol condensation step leading to 13 and related derivatives it was found that a single diastereoisomerically pure hydroxy amide 22 was obtained from the requisite amide enolate condensation. Subsequent acid-catalyzed cyclization afforded the dihydrotropolone amide 24 in 45% yield (Scheme XXII). At the present time, although amide 25 has proven to be quite sensitive to the conditions necessary to effect hydrolysis, a protocol has been established for the efficient synthesis of C-7 functionalized isocolchicine derivatives.

As a consequence of the successful completion of the final stages of the total synthesis (Scheme XXIII), the viability of utilizing C-7 carboxylate functionality as the progenitor of the requisite acetamide group has been verified. To date, the synthesis plan provides access to a host of iso-colchicine derivatives. The next goal of these studies will be to devise an appropriate tropolone dication equivalent which will directly establish the desired tropolone methyl ether in the colchicine series.
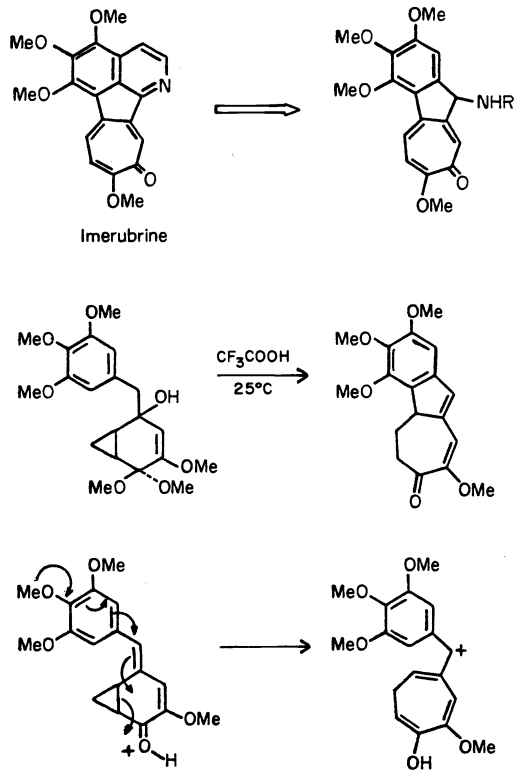
Scheme XXII

Scheme XXIII
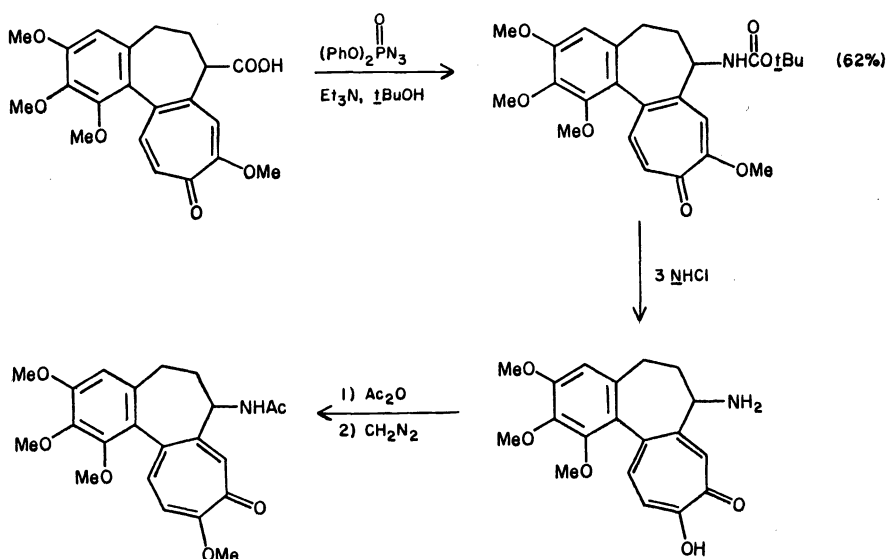
Commensurate with the development of a versatile tropolone synthon, we have optimistically incorporated the methodology gained in this area to the total synthesis of other tropolonoid natural products. Recent efforts from this laboratory have focused on an approach to the total synthesis of imerubrine (Scheme XXIV). The illustrated acid catalyzed cyclization has been found to proceed in good yield to the tricyclic dienone which is suitably function-alized for further elaboration to the target molecule via the bis-nor colchicine derivative shown. The general utility of cyclopropyl ketone 9 is not limited to the cases discussed above. One may rely upon the nor-caradiene-cycloheptatriene elecyrocyclic reaction to reveal the tropolone ring under basic conditions. This process is illustrated within the context of the synthesis of β-dolabrin (Scheme XXV).

Scheme XXIV

Imerubrine

Scheme XXV

β - Dolabrin
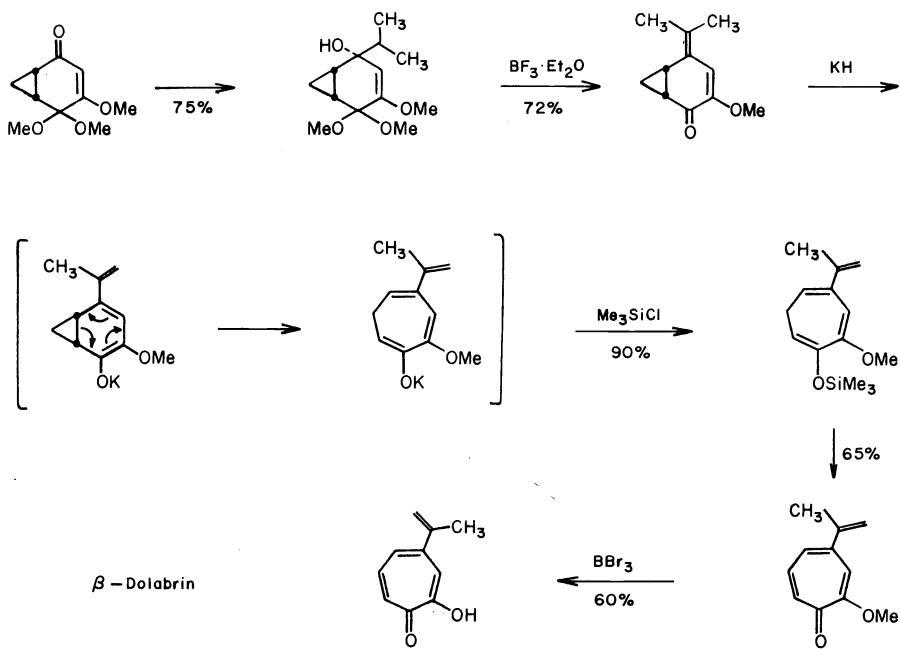
In all of the syntheses described in the aforegoing discussion, quinone-
derived substrates have been employed as progenitors for either benzenoid or
tropolonoid rings. At the initiation of this research program we held con-
siderable optimism in the untapped capabilities of the quinone nucleus as a
source of an "electrophilic" benzenoid synthon. It has been gratifying to
establish some of these objectives.

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