USE OF MASKED QUINONES IN ORGANIC SYNTHESIS: EFFORTS DIRECTED TOWARDS THE SYNTHESIS OF TROPOLONOID NATURAL PRODUCTS

Thesis by
Peter Martin Koelsch

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To My Parents

ACKNOWLEDGEMENTS

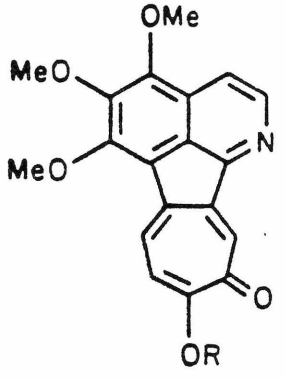
I would like to thank my advisor, Dave Evans, for his guidance throughout the performance of the work described within. His remarkable enthusiasm for and understanding of Chemistry combine to provide a stimulating atmosphere for research and intellectual development.

Several collaborators in the area of quinone chemistry are also thanked: they include Paul Cain, Dave Hart, and Steve Tanis. In particular, the contributions made by Dr. Hart to my laboratory skills and chemical knowledge during my initial year at Caltech are greatly appreciated. I would also like to thank the other members of the Evans group throughout the past four years for providing a stimulating and enjoyable learning environment, as well as for their friendship.

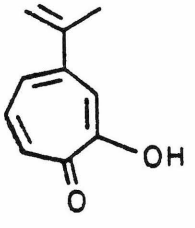
Finally, a special thanks is extended to Dot Lloyd for her excellent work in typing this lengthy manuscript.

ABSTRACT

The application of quinone-derived substrates as building blocks for the synthesis of tropolonoid natural products is described. A preparation of the terpene β-dolabrin involving electrocyclic ring-opening of a bicyclo[4.1.0]heptenone enolate is outlined. A number of approaches to the recently characterized alkaloid imerubrine involving a highly efficient annelation procedure to form the benzazulenoid carbocyclic skeleton are also discussed.



R=H, Grandirubrine
R=Me, Imerubrine



ß-Dolabrin

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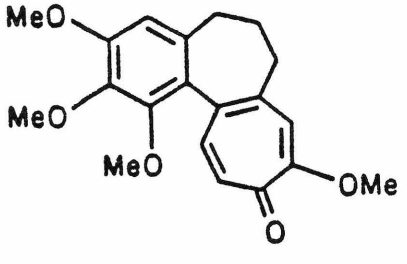
Introduction

In the past several years, the use of mono-protected quinones and their derivatives has found considerable application in natural product total synthesis.[1] Recent work in our laboratories utilizing such substrates has culminated in convergent syntheses of desacetamidoisocolchicine (1)[2] and colchicine (2).[3] Although ten previous syntheses of 2 had been reported,[4] very little general methodology has been developed for the construction of the tropolone nucleus. Our successful p-quinone monoketal-based synthesis of this molecule provided a potentially general solution to this problem, and we were eager to test its usefulness in the synthesis of other tropolonoid natural products.



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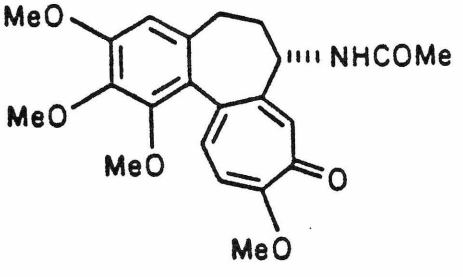

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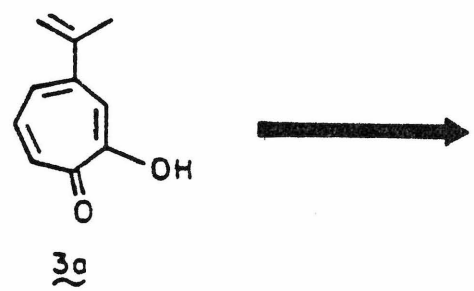
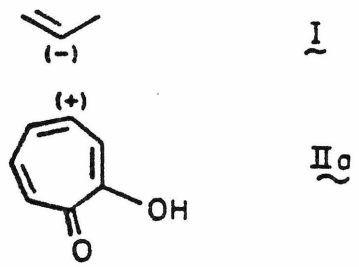
Two compounds were chosen as targets for this endeavor: the terpene β-dolabrin (3a)[5] and the alkaloid imerubrine (4a).[6] Conceptually, the general bond formation strategies for the syntheses of these molecules would appear to be the same as for the colchicine synthesis. Hypothetical cationic tropolone equivalent II, combined with the respective nucleophilic synthons I and III, was projected to allow for rapid construction of β-dolabrin and imerubrine. As in the colchicine work, cyclopropanated quinone monoketal 5 was employed as the tropolone cation equivalent.

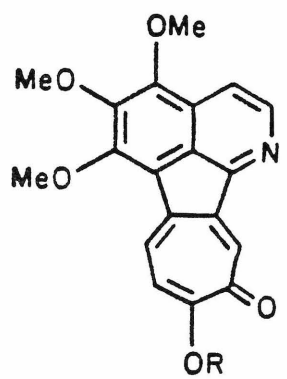


3a

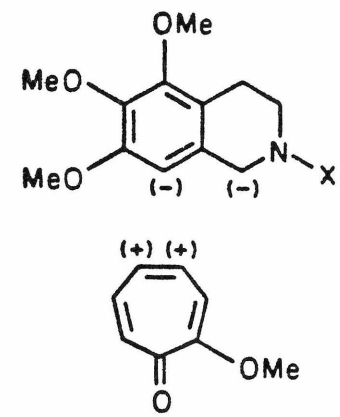


I

IIa

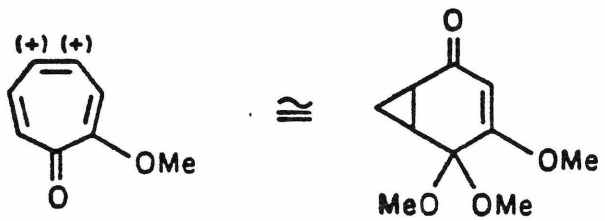


4a R=H, Grandirubrine
b R=Me, Imerubrine



III

IIb



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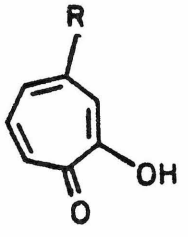
Despite the similarity of the basic format of the two projected syntheses with that of colchicine, it was apparent that the methodology used in the actual formation of the tropolone moiety would be different in each of the three cases. Thus, synthesis of 3a and 4 would greatly amplify the genrality and utility of 5 as a tropolone synthon. In this report we will outline the successful preparation of β-dolabrin (3a) , as well as substantial progress towards the synthesis of imerubrine (4a). In addition, the results of related studies which should provide further insight into these means of tropolone synthesis will be presented.

Results and Discussion

Synthesis of Monocyclic Tropolones: Preparation of β-Dolabrin. The tropolonoid monoterpenes β-dolabrin (3a) and β-thujaplicin[8] (hinokitiol) (3b) were isolated and characterized some time ago by Nozoe. The conversion of β-dolabrin to β-thujaplicin by catalytic hydrogenation has been reported.[9] Several syntheses of 3b have been



3a R = $CH_2=C(CH_3)-$

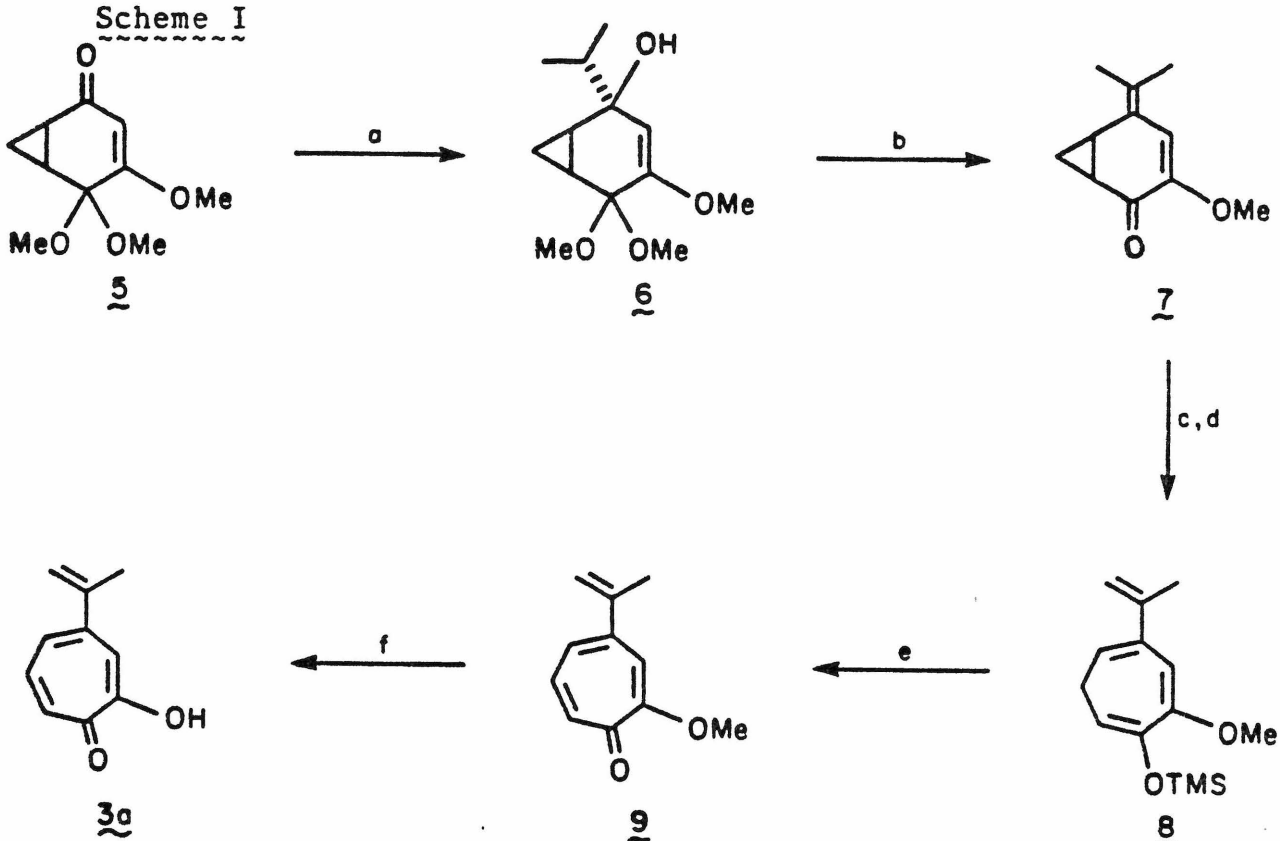
b R = $CH_3-CH(CH_3)-$

carried out.[10] Representative methods for seven-membered ring formation include fragmentation of [3.2.0]-bicycloheptenones and [4.1.0]-bicycloheptenones, and furan-oxallyl cation cycloaddition. Although these procedures led to facile construction of substituted tropolones, manipulation of ring substituents was required to attain the proper oxygenation pattern. In addition, their extension to the synthesis of the more complex polycyclic tropolones might be difficult.

We envisioned that cyclopropanated quinone ketal 5

would contain the appropriate functionality for direct formation of the α-tropolone moiety. This substrate was prepared in high overall yield from commercially available aromatic starting materials, as outlined in our earlier work.[3] The actual synthesis of β-dolabrin then proceeded in five steps, as outlined in Scheme I. The synthetic natural product has been fully characterized, and its melting point corresponds to that reported.[5] Addition of isopropylmagnesium bromide to 5 gave the moderately unstable vinylogous hemiketal 6 in 70-80% yield. This compound was immediately treated with $BF_3 \cdot OEt_2$ in anhydrous nitromethane, resulting in simultaneous dehydration and deketalization to give key dienone 7. The use of anhydrous conditions here was quite crucial, as hydrolysis of the vinylogous hemiketal functionality to afford demethylated products proved to be quite facile. Initially, it was thought that treatment of dienone 7 with acid should result in opening of the 3-membered ring via a cyclopropyl carbinyl-type intermediate. However, exposure of this compound to a variety of acid conditions, both protic and aprotic, resulted in no observable ring fission. It will be seen later, within the context of the imerubrine work, that this type of acid-catalyzed ring opening is indeed facile when the exocyclic olefin

Scheme I



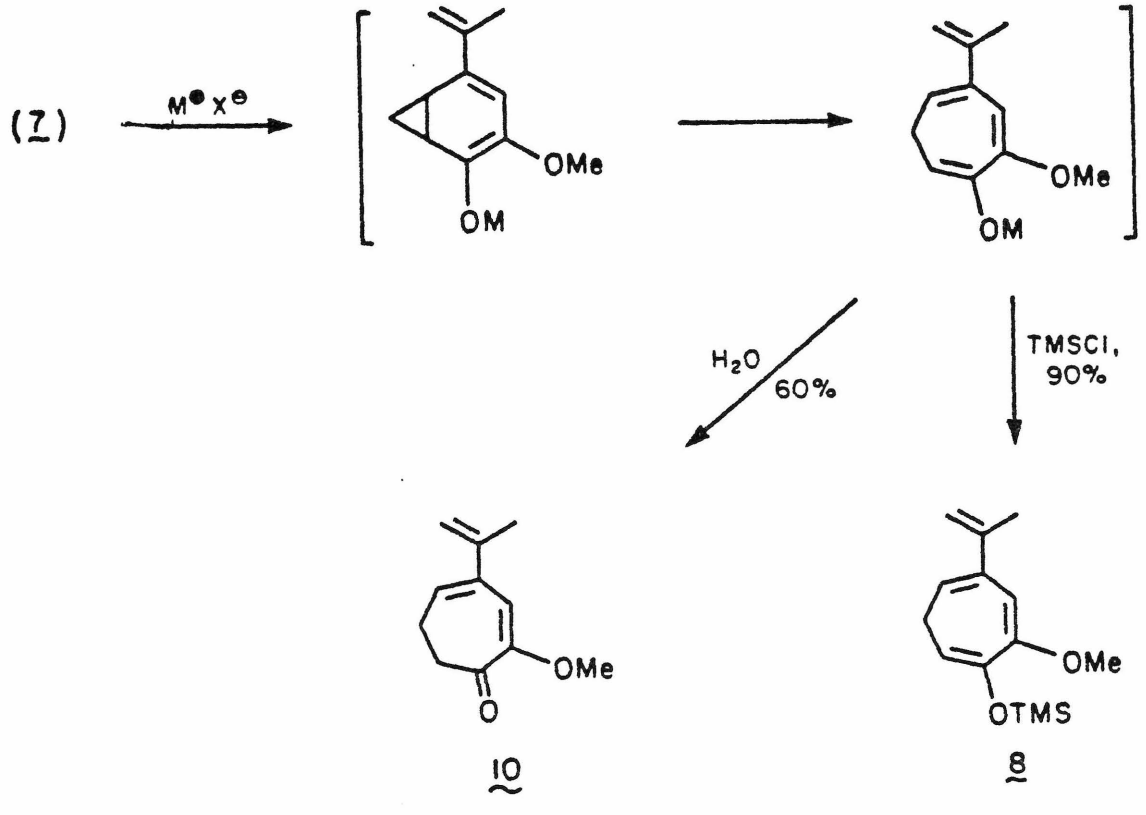
a) i-C_3H_7MgBr, THF, 70-80%; b) $BF_3 \cdot OEt$, CH_3NO_2, 70-80%; c) KH, THF, 0°C → RT; d) $(CH_3)_3SiCl$ (TMSCl), RT, 91%; e) Tetrachloro-p-benzoquinone (p-chloranil), CH_2Cl_2, -78°C → RT, 65-75%; f) BBr_3, CH_2Cl_2, -78°C, 60%.

of a dienone such as 7 is substituted with more strongly electron donating groups than methyl.

Our attention then turned to base-promoted opening, for which there exists some literature precedent.[11] It was gratifying to find that treatment of 7 with strong base, followed by quenching with water after an appropriate time period, gave cycloheptadienone 10 in 60% yield. An

interesting feature of this reaction was the fact that the rate of ring-opening was highly dependent on the nature of the alkali metal counterion and the polarity of the solvent system used. As can be seen in Scheme II, ring-opening of the potassium trienolate proceeds almost instantaneously at RT in dimethyl sulfoxide (DMSO), while 1 h is required in THF for complete reaction. The lithium trienolate, containing the much more covalent Li-O bond, shows no sign of rearrangement after several hours in THF at RT. These results suggest that the reaction proceeds

Scheme II



10 8

Table 1. Effect of cation on base-catalyzed rearrangement of 7

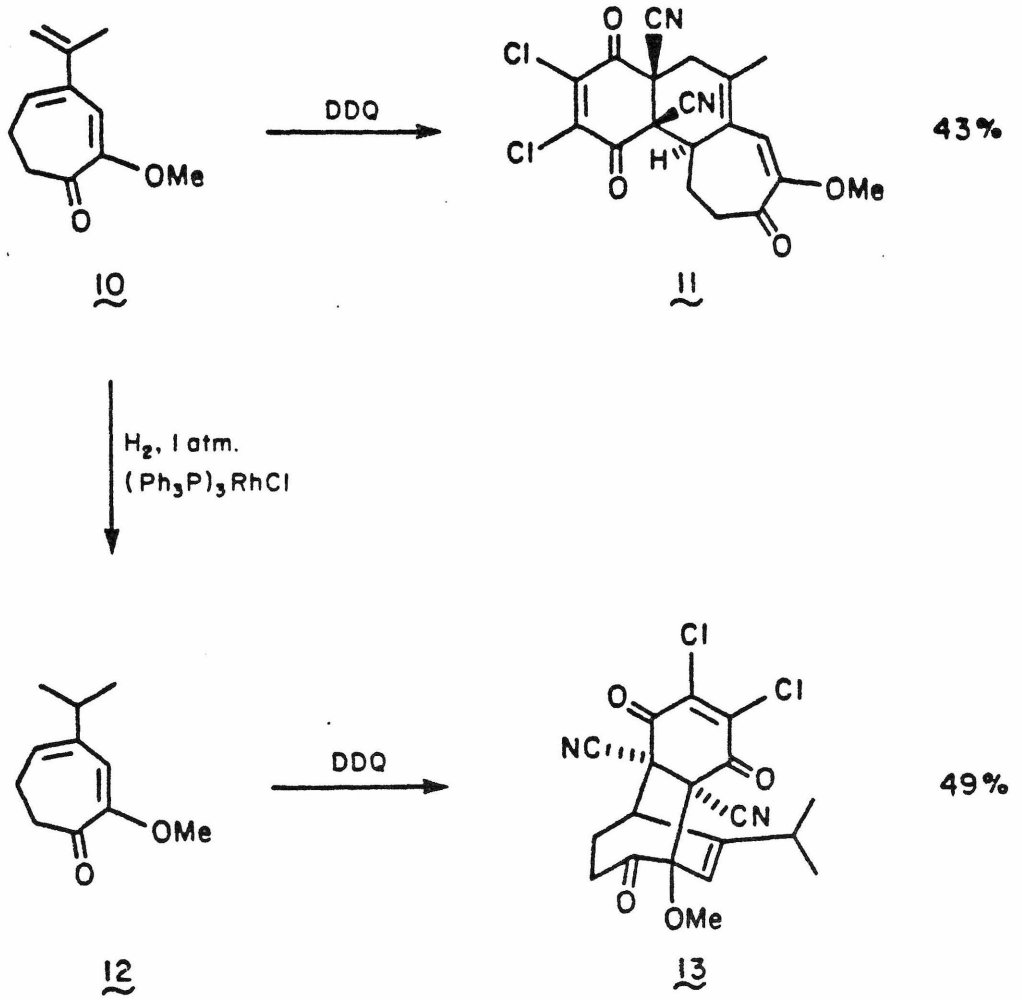
$M^{\oplus}$	$X^{\ominus}$	Solvent	Conditions
K	-O-t-C_4H_9	DMSO	< 2 min, RT
K	-H	THF	1 h, RT
Li	-N(i-C_3H_7)$_2$	THF	4 h, RT, no reaction

through an electrocyclic rearrangement, an analog of the known norcaradiene-cycloheptatriene equilibrium.[12] The effect of varying the nature of the metal-alkoxide bond on the rate of reaction is qualitatively similar to that observed in the oxy-Cope process studied recently in our laboratories.[13]

With cycloheptadienone 10 in hand, it was thought that aromatization to methyl tropolone 9, involving introduction of a single double bond, should proceed quite easily. However, standard methods such as halogenation-dehalogenation and selenylation-oxidative deselenylation gave disappointing yields, perhaps owing to the reactivity of the isopropenyl substituent and the sensitivity of the methyl tropolone nucleus. Another commonly used reagent, 2,3-dichloro-5,6-dicyano-p-benzo-

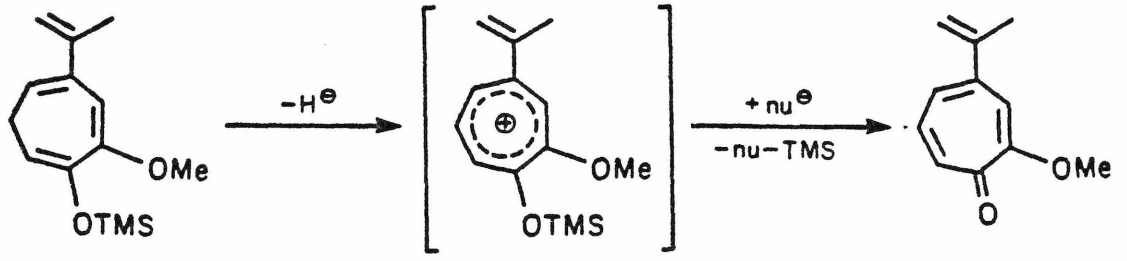
quinone (DDQ), was tried. Although this oxidant was used by us in analogous reactions in our colchicine work, as well as by others,[14] it did not prove useful in the oxidation of 10. As shown in Scheme III, the known propensity of DDQ to act as a Diels-Alder dienophile[15] completely overrode its properties as an oxidant, resulting

Scheme III



in exclusive formation of adduct 11 upon its reaction with 10. Attempt was then made to circumvent this problem by hydrogenation of the terminal double bond [$(Ph_3P)_3$-RhCl, C_6H_6, 80%]. Surprisingly, treatment of the resulting isopropyl cycloheptadienone 12 with DDQ also resulted in the apparently exclusive formation of a Diels-Alder adduct, 13, this time the product of cycloaddition of DDQ with the endocyclic diene.

Alternatively, the fact that cycloheptatriene is known to oxidize smoothly to tropylium cation[16] suggested a promising scheme for carrying out the desired oxidation. Treatment of cycloheptatrienyl trimethylsilyl ether 8 with an appropriate hydride abstracting agent should give an intermediate tropylium salt, which would then be nucleophilically desilylated in situ to give the desired tropolone derivative 9. In practice, silyl ether 8 was



8 9

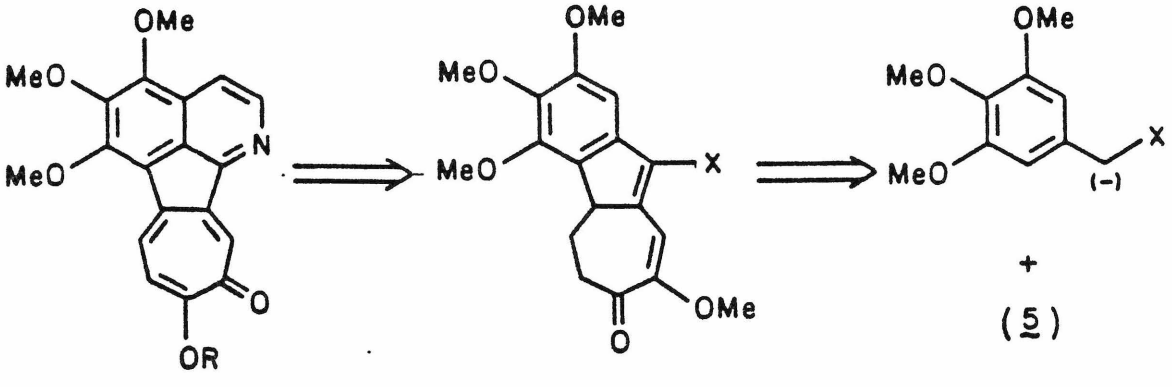
formed in 91% yield by treatment of dienone 7 with KH (THF, RT, 1 h), followed by quenching with TMSCl. Upon

treatment of 8 with p-chloranil, oxidation proceeded as planned to give tropolone methyl ether 9. Subsequent to the completion of this work, other workers reported the oxidation of ketone-derived trimethylsilyl enol ethers to enones with DDQ.[17] Our synthesis of β-dolabrin was then completed by demethylation of 9 under standard conditions.

A Novel Annelation Process: Studies Directed Toward the Synthesis of Imerubrine. Several years ago, the isolation of the alkaloid imerubrine from the tropical American vines Abuta imene and Abuta refescens was reported by Cava and coworkers.[18] At that time an incorrect structure was proposed, based only on spectroscopic evidence. In 1977, after carrying out an X-ray crystallographic analysis, Silverton and Cava reformulated the structure as 4a.[6] This was the first example of such a tropoloisoquinoline structure. Very recently, the isolation of grandirubrine (4b),[8] an analog of imerubrine containing a free tropolone, has been reported. No synthetic work on these compounds has appeared in the literature to date.

We had anticipated that an approach to this class of alkaloids could be found based on our cyclopropanated quinone ketal annelation methodology. However, it was

not immediately apparent how such an annelation would be carried out. The procedure developed in our colchicine synthesis did not seem workable here, due to the necessity of forming a four-membered spirocyclic intermediate (Scheme IV). In order to explore other possible pathways for formation of the required benzhydrazulene nucleus, we chose the tricyclic ketone 14 (VI, X = H) as our initial synthetic objective. It was envisioned that a successful preparation of 14 could be extended or modified so as to append the nitrogen-containing ring contained in the tropoloisoquinolines. A number of methods are known for the elaboration of isoquinolines from appropriately substituted benzenes.[19]



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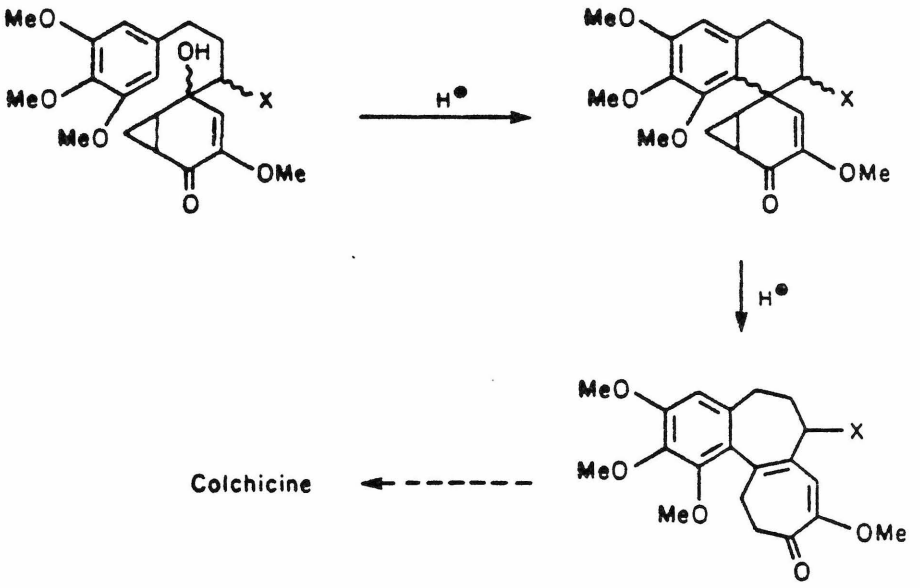
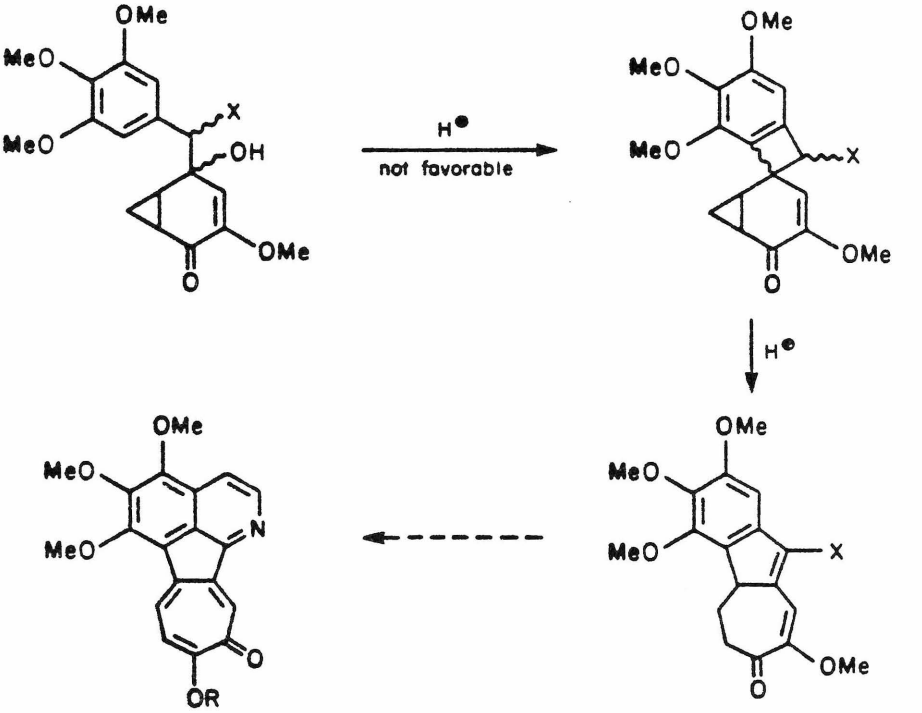
A potentially favorable pathway for preparation of such a tricyclic intermediate is shown in Scheme V. Given that the mixture of dienones IVa and IVb can be

Scheme IV

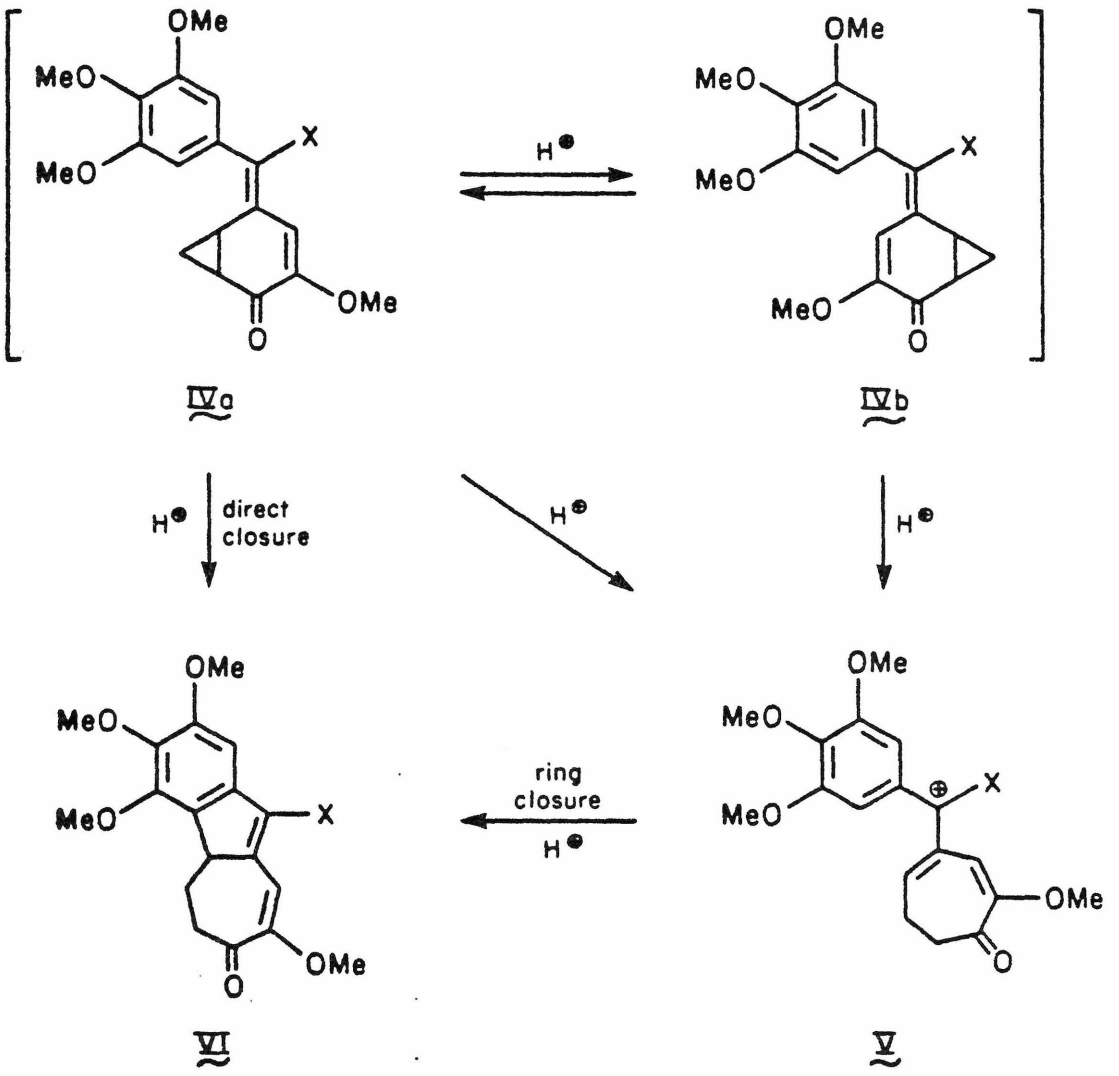
Colchicine series



Imerubrine series



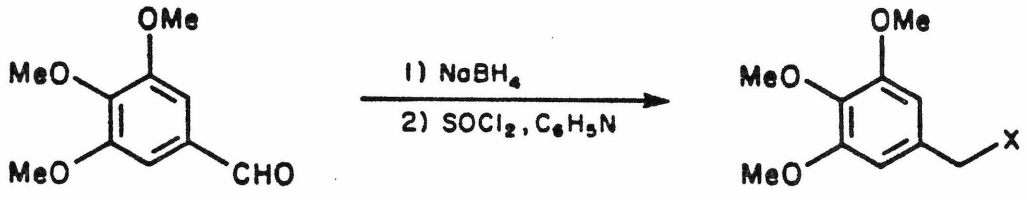
Scheme V



prepared, their exposure to acid could result in formation of VI by one of two mechanistic pathways. Acid-promoted fragmentation of the cyclopropyl ketone moiety would afford the phenyl vinyl carbinyl cation V, which could close to VI via a well precedented Nazarov type cyclization.[20] Alternatively, VI could be formed by direct

aryl-assisted cyclopropyl ketone ring opening of olefin isomers IVa.[21] A presumed equilibrium between the isomeric dienones would allow for complete conversion to VI by this route.

In order to test this hypothesis, we set out to prepare a suitable precursor to dienone 15 (IV, X = H). Trimethoxybenzyl chloride 17a was prepared in 96% yield from aldehyde 16 by standard means. Unfortunately, attempts to prepare the derived Grignard reagent 17b under a variety of conditions failed. The chloride was then converted to phosphonium salt 17c and phosphonate 17d in good yields by treatment with triphenyl phosphine and triethyl phosphate, respectively. However, the anions derived from both 17c and 17d failed to react with cyclopropanated quinone ketal 5, presumably due to insufficient nucleophilicity. It was therefore necessary to prepare



16

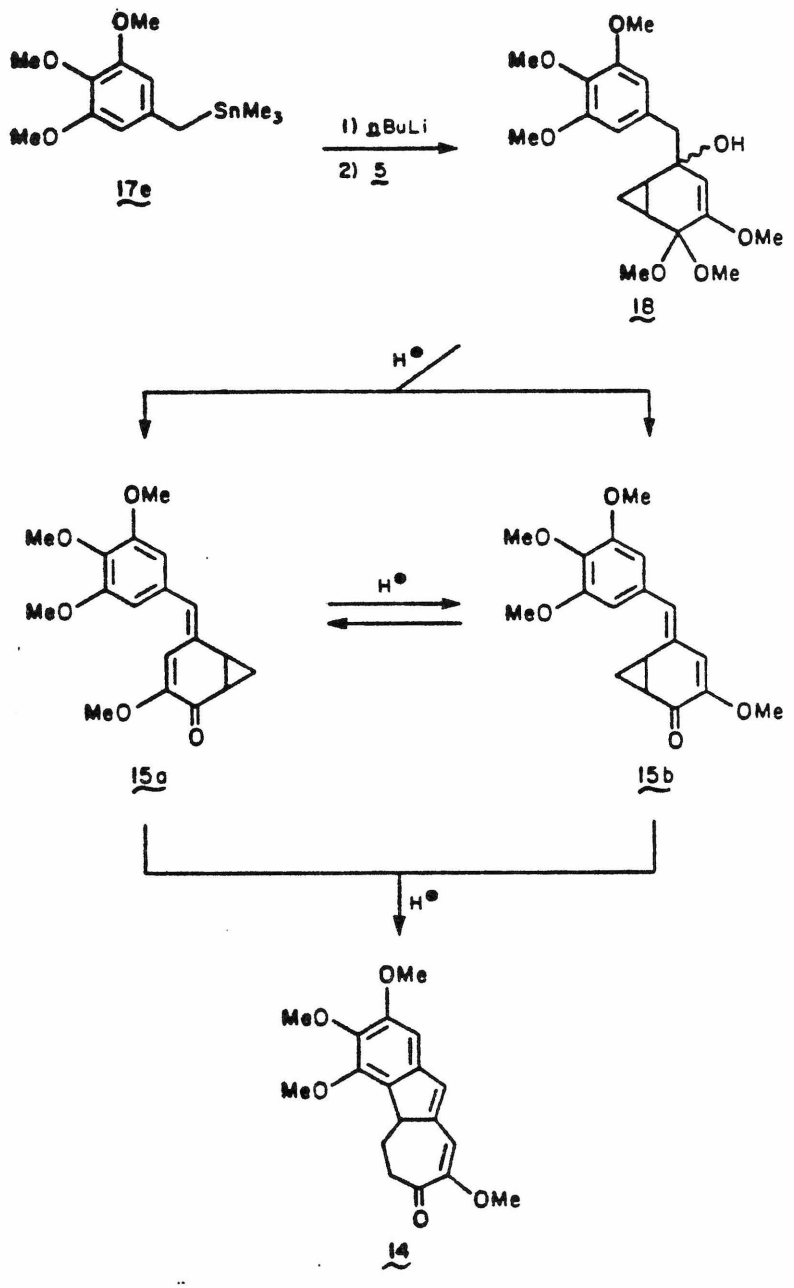
17a X=Cl
b X=MgCl
c X=$PPh_3^{\oplus}$
d X=P(=O)(OEt)$_2$
e X=$SnMe_3$

a sufficiently reactive benzylic anion by indirect means. Chloride 17a was converted to benzylstannane 17e in 94% distilled yield by reaction with $LiSnMe_3$ in THF. Considerable experimentation revealed that tin-lithium exchange could be carried out on 17e (n-BuLi, Et_2O, -78°C) in 75-80% yield, based on D_2O quenching.

The derived benzyllithium reagent reacted smoothly with ketone 5 to give the slightly unstable vinylogous hemiketal 18. This material could be purified by flash silica gel chromatography with moderate loss of material. When 18 was dissolved in triflouroacetic acid (TFA) and allowed to stand at RT for 24 h, the desired tricyclic ketone 14 was isolated; optimization of this procedure allowed for conversion of benzyltin compound 17e to 14 in about 45% overall yield. Greatly encouraged by this initial success, we set out to obtain information on the intermediates and mechanism of this obviously complex process.

Upon very brief exposure of alcohol 18 to either TFA or boron triflouride etherate ($BF_3 \cdot OEt_2$) in nitromethane, a nearly equimolar mixture of dienones 15a and 15b was isolated. The olefin isomers could be separated by chromatography over deactivated alumina. When a pure sample of either isomer was dissolved in neat TFA,

Scheme VI

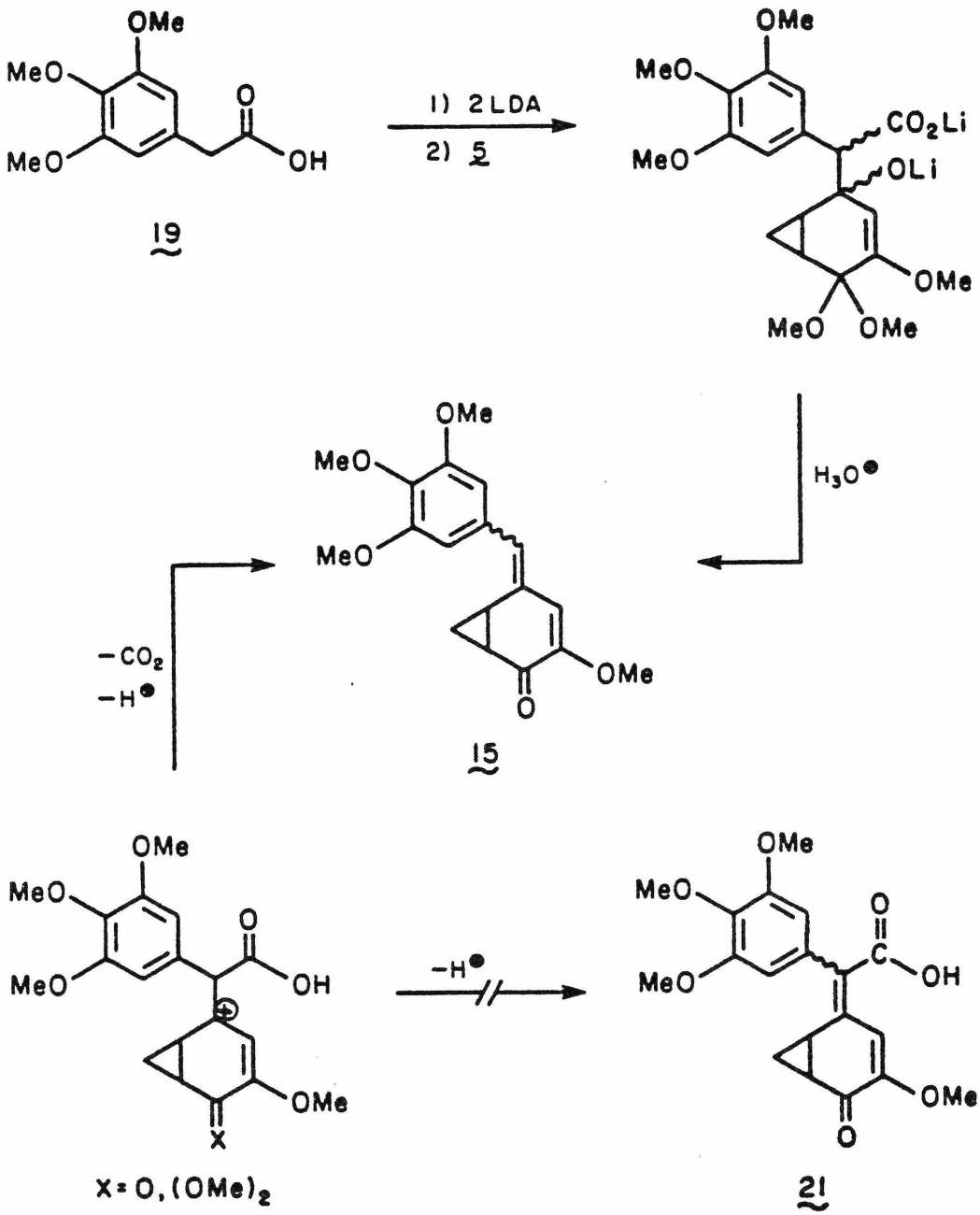


equilibration to an 80:20 mixture of 15a and 15b was observed after 1 h at RT. Continued exposure of this mixture to TFA (24 h, RT) resulted in the isolation of tricyclic 14 in 74% yield. A qualitatively similar process was observed upon treatment of each isomer with $BF_3 \cdot OEt_2$ (CH_3NO_2, RT), except that the overall reaction

time was shorter (70 min) and the yield of 14 was higher (~90%). Careful monitoring of these reactions by ^{1}H NMR and thin-layer chromatography did not reveal the presence of observable quantities of any other intermediate. Although these results do not prove or disprove any mechanism which might be proposed for this process, later results, involving similar rearrangements on substrates with substituents at the benzylic carbon, should provide further mechanistic insight.

Subsequent to the completion of this phase of our work, we developed, quite unintentionally, an alternative preparation of dienones 15 which does not involve the intermediacy of organotin compounds. The starting material, carboxylic acid 19, was prepared in 90% overall yield by conversion of chloride 17a to nitrile 20 (KCN, acetone) followed by basic hydrolysis (KOH, H_2O, MeOH). The dianion of acid 19, formed by treatment with excess lithium diisopropylamide (LDA) in THF, reacted smoothly with cyclopropanated quinone ketal 5. When the reaction was quenched with H_2O, followed by addition of a small amount of acid, the dienones 15 were isolated in 52% yield. None of the expected carboxyl-substituted dienones 21 were observed. Apparently, the reaction is proceeding as in Scheme VII, with the intermediate cation shown

Scheme VII

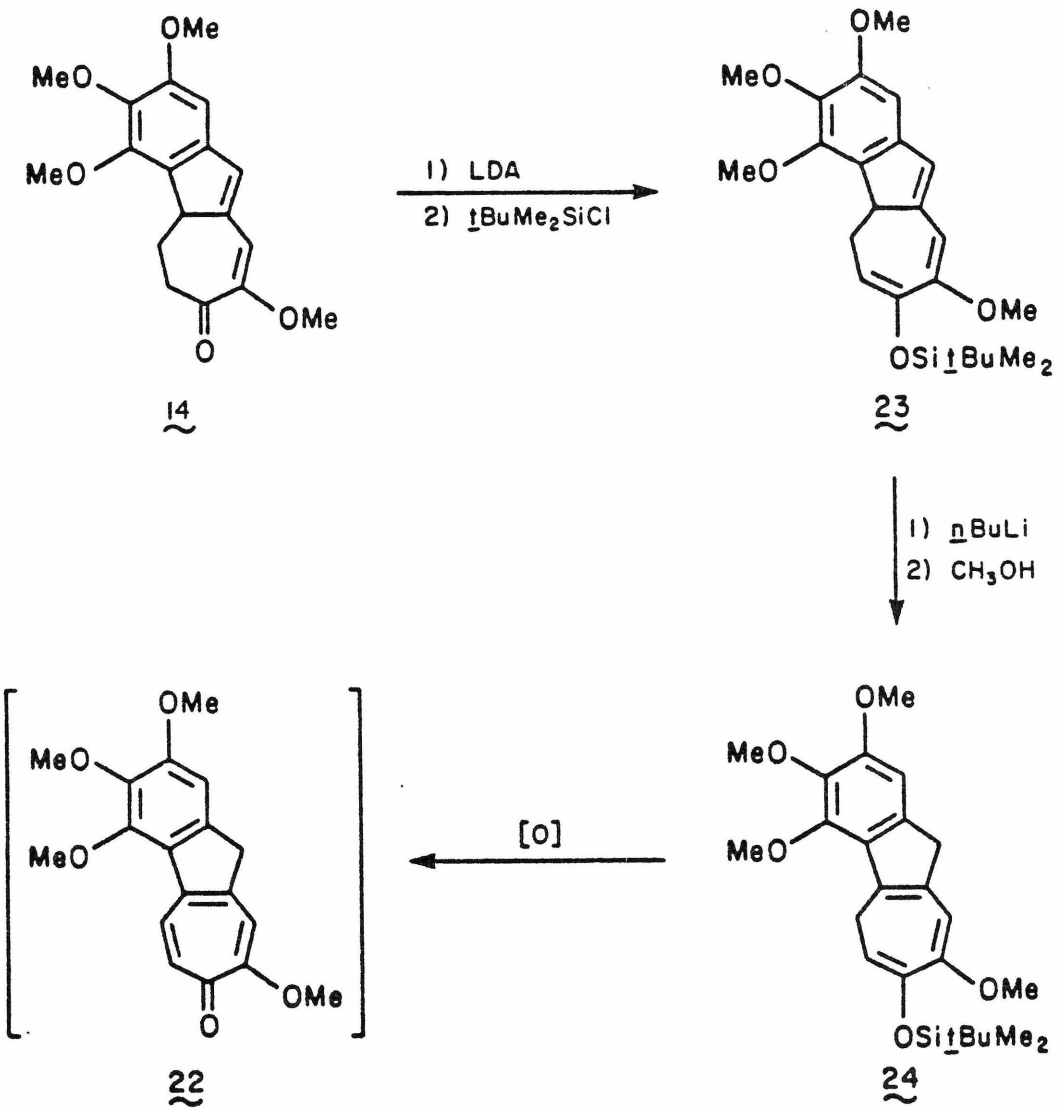


undergoing decarboxylation in preference to the simple proton loss which would have provided acid 21.

With two procedures available for the preparation of tricyclic ketone 14 in 45-50% overall yield from simple precursors, we decided to explore a few of its further transformations in attempts to: 1) determine whether double bond migration and oxidation to the tropolone derivative 22 is feasible; and 2) determine whether a heteroatom (N or O) could be introduced electrophilically at the unsubstituted five-membered ring carbon, thus allowing for construction of the fourth and final ring of the tropoloisoquinoline nucleus. Treatment of ketone 15 with LDA (-78°C, THF), followed by quenching with t-$BuMe_2SiCl$ (-78°C, HMPA), afforded silyl enol ether 23 in 50-60% yield. Use of excess LDA and higher temperatures (-25°C) resulted in indenyl anion formation in addition to enolization, but this dianion could not be trapped regioselectively. When silyl ether 23 was treated with n-BuLi (THF, -78°C) and the resulting indenyl anion was quenched with CH_3OH at -78°C, conversion to cyclohepta-trienyl silyl ether 24 was observed in 90% yield. Unfortunately, attempts to trap the intermediate indenyl anion with representative heteroatom electrophiles (e.g. i-AmONO, MoOPH[22]) were not successful.

Cycloheptatrienyl silyl ether 24 was treated with oxidizing agents such as p-chloranil and DDQ under a

Scheme VIII



14 23 24 22

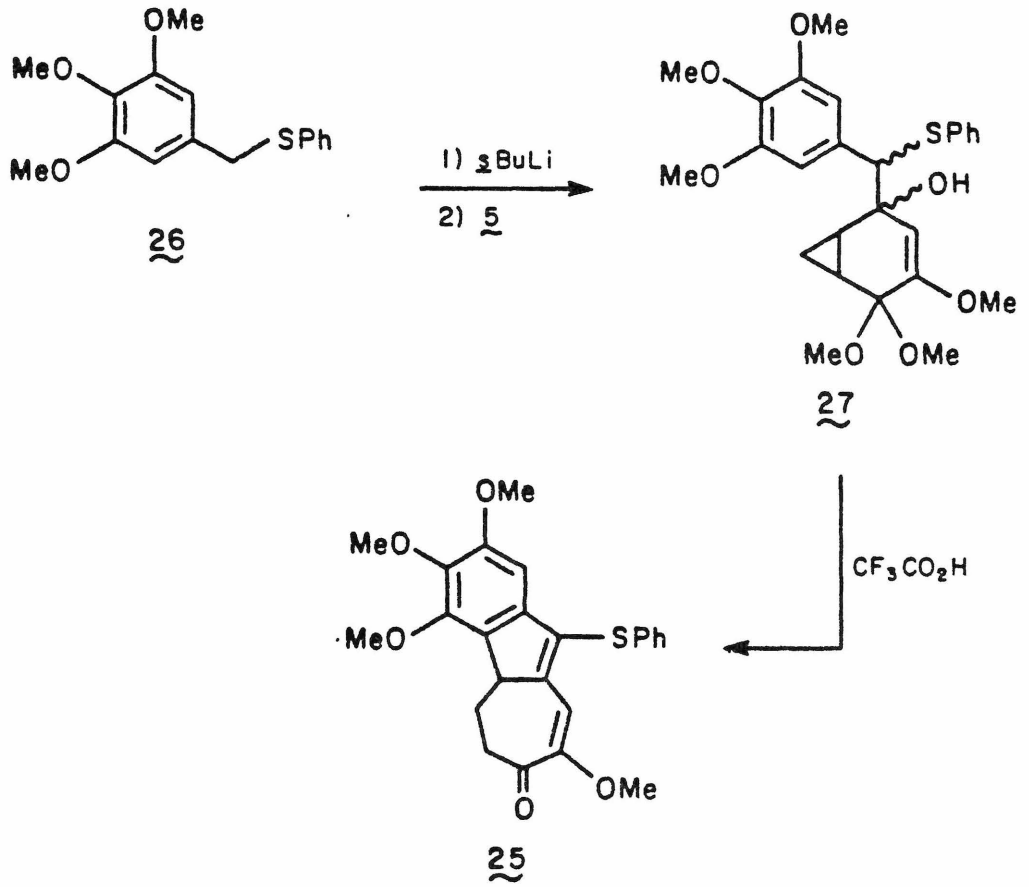
variety of conditions, in analogy to the successful oxidation of the monocyclic substrate 8. However, all of these attempts afforded very little or no desired tricyclic tropolone 22. Similar attempts to dehydrogenate the ketone derived from desilylation of 24 to 22 proved

fruitless. Potential reasons for these difficulties include the hindered "bay region" environment of the hydrogens to be abstracted in such oxidations and the instability of the product tropolone and/or its benzazulene tautomer. In light of these discouraging results, attempts at direct functionalization of ketone 14 were abandoned in favor of approaches which would allow for incorporation of additional functionality within the process of formation of the tricyclic nucleus.

To this end, our attention turned to the preparation of thiophenyl-substituted tricyclic ketone 25. This was viewed as a useful endeavor for a number of reasons, including utility of the new substituent as a mechanistic probe, the potential for its conversion to an oxygen or nitrogen substituent, and its ability to assist in the oxidation of the carbocyclic itself. The starting benzyl phenyl sulfide 26 was prepared in 99% yield by displacement of chloride 17a with sodium thiophenoxide (0°C, CH_3OH). Metallation of 26 at the benzylic position (s-BuLi, HMPA, THF, -78°C), followed by reaction with cyclopropanated quinone ketal 5 afforded vinylogous hemiketal 27, which could be isolated in 72% yield after purification by silica gel chromatography. Exposure of crude 27 to TFA resulted in the formation of tricyclic 25

in 59% overall yield from starting sulfide 26. When carried out at RT, this process required 5 h; alternatively, reaction of alcohol 27 with $BF_3 \cdot OEt$ in CH_3NO_2 at RT resulted in cyclization to 25 within 5 min. Thus, incorporation of the thiophenyl substituent has caused a 5 to 15-fold increase in the rate of this cyclization process, depending on the nature of the acid used. This observation may shed

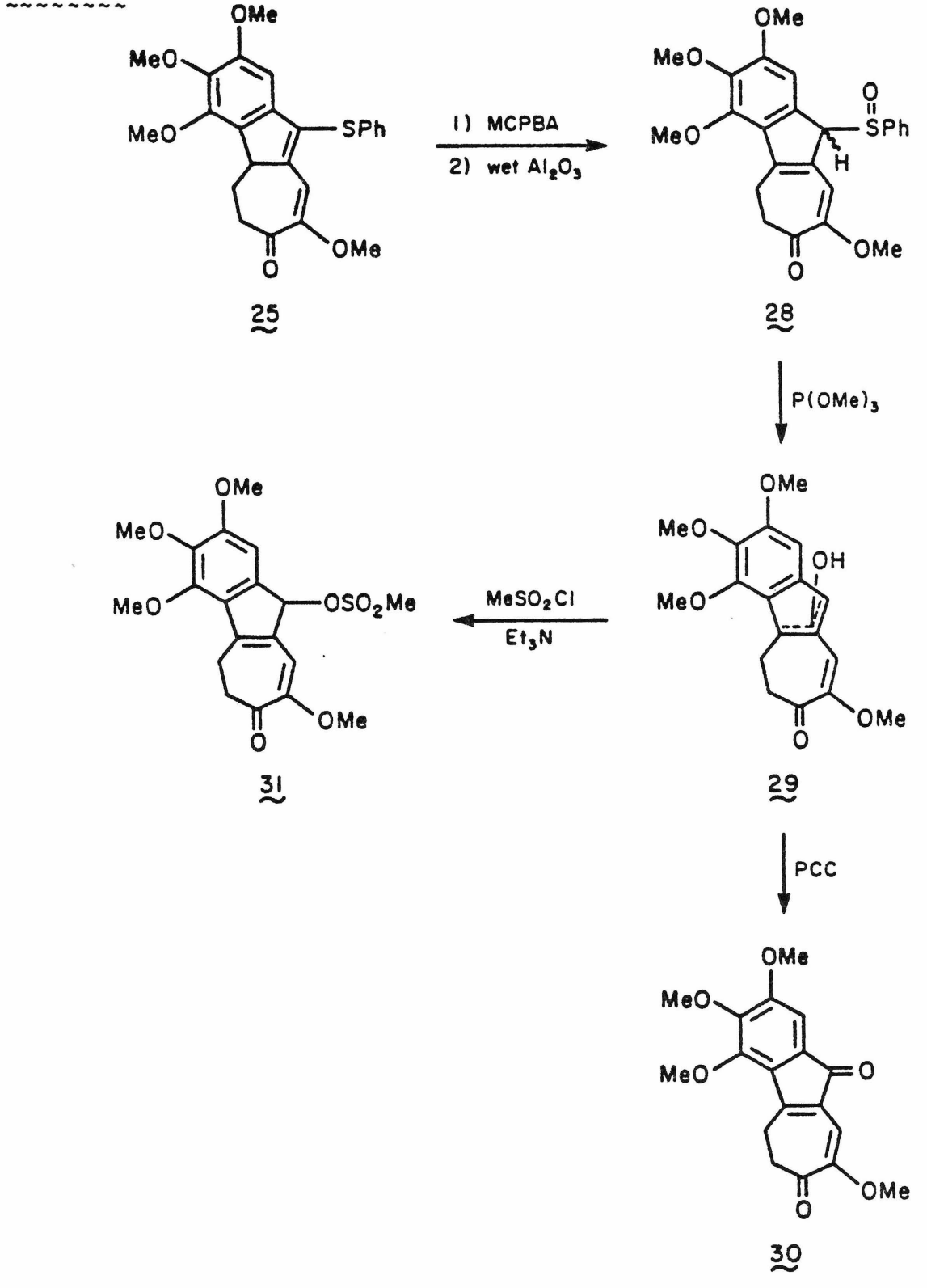
Scheme IX



further light on the mechanism of this process. Of the two most likely pathways, as outlined in Scheme V, the one involving direct aryl-assisted opening of the cyclopropane ring in IVa would not appear to be influenced in rate by variation of substituent X. If the alternative pathway, involving apparently rate-determining formation of cation V, were in operation, a cation-stabilizing substituent X should cause a rate acceleration. This is consistent with the faster reaction observed upon introduction of the thiophenyl group.

With ketone 25 in hand, the manipulation of its five-membered ring functionality was explored. Upon treatment of 25 with m-chloroperbenzoic acid (MCPBA) (1 equiv, CH_2Cl_2, -25°C), a crude diastereomeric mixture of vinyl sulfoxides is formed. When this material was eluted through deactivated alumina, complete isomerization to allylic sulfoxide 28, isolated in 74% yield as a mixture of diastereomers, occurred. Presumably, this isomerization is driven by the fact that the bulky phenylsulfinyl group prefers to orient itself out of the plane of the carbocyclic nucleus. Heating the allylic sulfoxide 28 in methanol for 30 min at 48°C in the presence of the thiophilic trimethyl phosphite resulted in the isolation of an inseparable, approximately equimolar mixture of

Scheme X


OMe
MeO
MeO
SPh
OMe
O
25
1) MCPBA
2) wet Al_2O_3
OMe
MeO
MeO
O
SPh
H
OMe
O
28
$P(OMe)_3$
OMe
MeO
MeO
OH
OMe
O
29
$MeSO_2Cl$
Et_3N
OMe
MeO
MeO
OSO_2Me
OMe
O
31
PCC
OMe
MeO
MeO
O
OMe
O
30

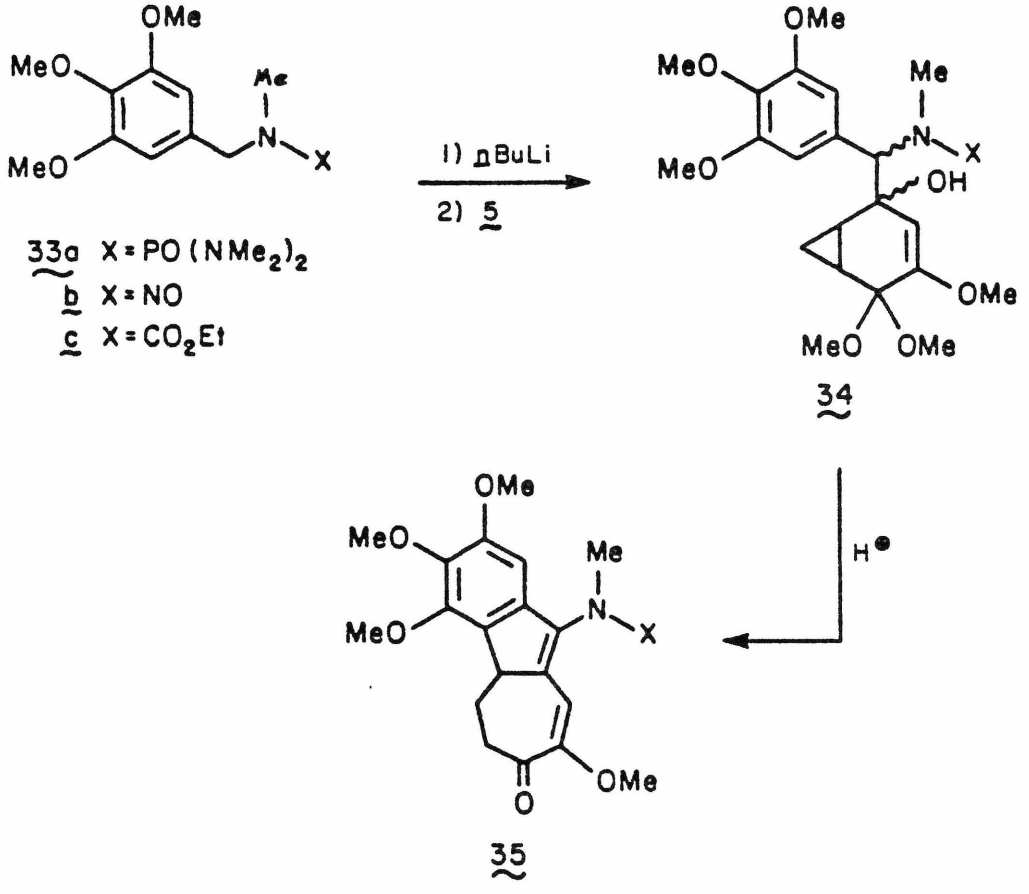
allylic alcohols 29 in 83% yield. This suggests that this rearrangement proceeds *via* initial homolytic C-S bond cleavage, followed by non-regiospecific recombination of the resulting Ph-S-O and allylic radicals, rather than through the anticipated [2,3]-sigmatropic rearrangement.[23]

Oxidation (PCC, CH_2Cl_2) of the mixture of alcohols 29 afforded the dione 30 in 43% yield. Attempts to condense this dione with primary amines resulted only in the formation of intractable tars; in fact, treatment with tertiary amine bases, even at RT or below, caused immediate decomposition. This might result from a facile double enolization of the dione, leading to a probably quite unstable 7,10-dihydroxy benzazulene. Given this seemingly insurmountable difficulty, we sought to introduce a nitrogen functionality by Sn^2 displacement rather than by condensation. Fortuitously, the mixture of allylic alcohols 29, upon exposure to standard mesylation conditions (CH_3SO_2Cl, Et_3N, CH_2Cl_2, -78°C), was converted to *only* the secondary mesylate 31 in quantitative yield. This mesylate proved remarkably stable and unreactive to amine nucleophiles, even at significantly elevated temperatures. As a control experiment, iodide displacement under forcing conditions (KI, 18-crown-6, CH_3CN, 75°C for 24 h) was tried; only starting mesylate was

isolated. Attempts at palladium-mediated allylic displacement[24] also failed. This remarkable degree of unreactivity is apparently due to a surprising amount of anti-aromatic indenyl cation character in the transition state for Sn^2 displacement of 31. In order to decrease the magnitude of this stabilizing effect, the dehydrogenation of 31 to the corresponding tropolone derivative was explored. As in our earlier fruitless attempts to prepare the simpler tricyclic tropolone 22, however, exposure of 31 to similar dehydrogenation procedures gave mainly decomposition products.

In order to circumvent these difficulties, we turned our attention to the inclusion of nitrogen functionality in the initial cyclization process. Trimethoxy benzaldehyde 16 was converted to the corresponding N-methyl amine 32 by standard reductive amination procedure in excellent yield. This amine was elaborated to the respective phosphoramide, nitroso, and carboethoxy derivatives 33a, 33b, and 33c by usual means. The formation of dipole-stabilized carbanions alpha to nitrogen has precedent in each of these cases.[25] Unfortunately, carbamate 33c did not deprotonate substantially even under strongly basic conditions (s-BuLi, HMPA, THF). The three aromatic methoxy groups appear to be rendering the desired benzylic deprotonation kinetically

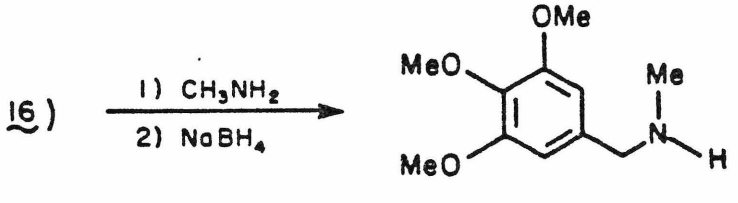
Scheme XI



33a X = PO(NMe$_2$)$_2$
b X = NO
c X = CO$_2$Et

34

35



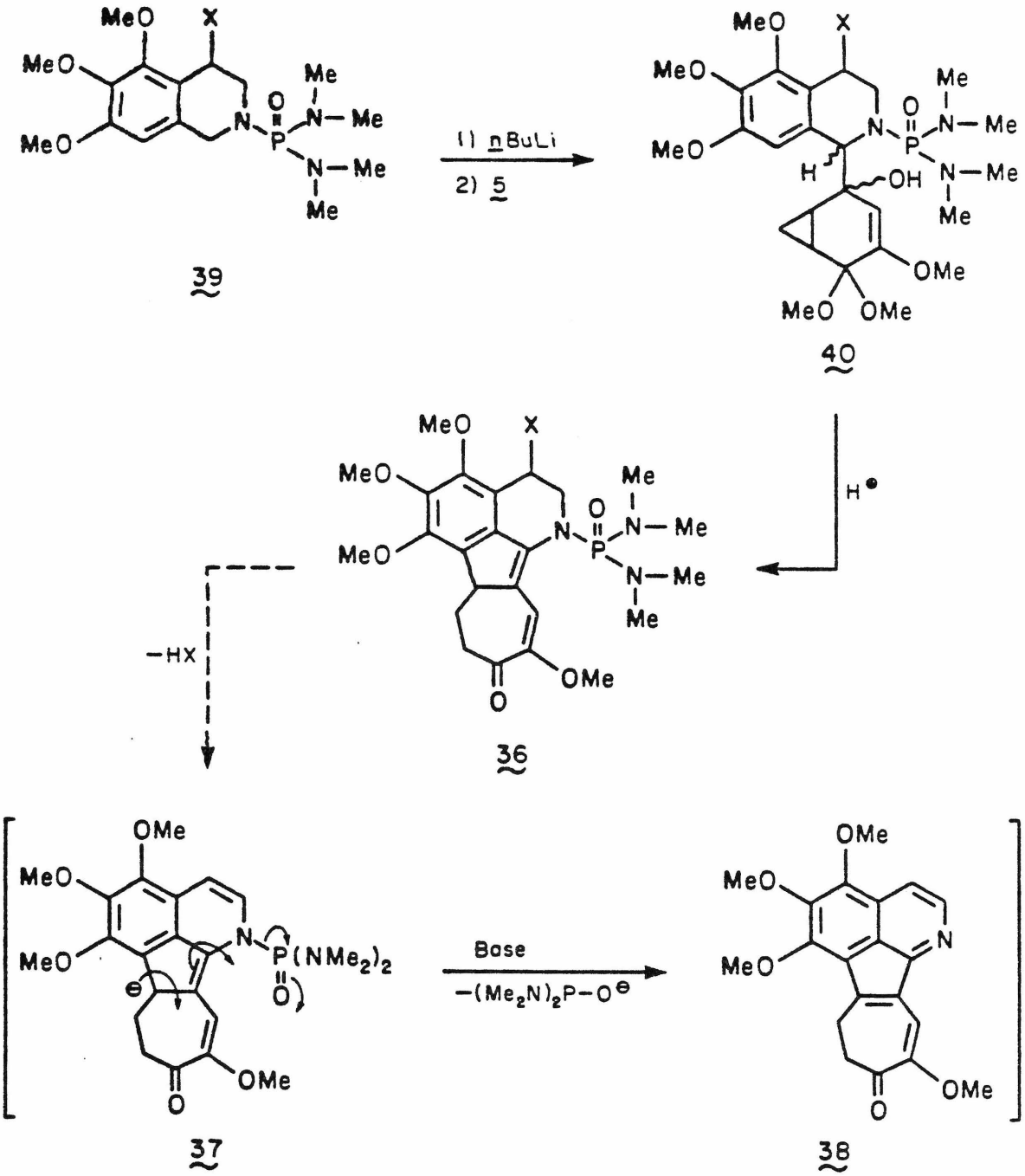
32

difficult. When nitroso compound 33b was treated with LDA in THF at -78°C, deprotonation did indeed occur. The derived anion, however, proved too non-nucleophilic to react with cyclopropanated quinone ketal 5 at temperatures at which the anion is intrinsically stable. The phosphoramide 33a also underwent smooth benzylic deprotonation (n-BuLi, THF, -78°C), and the derived anion in fact reacted with ketone 5 to afford adduct 34a in good yield. Treatment of the crude adduct with with $BF_3 \cdot OEt_2$ (CH_3NO_2, 0°C → RT, 15 min) led to formation of the nitrogen-substituted tricyclic ketone 35a in 57% overall yield from 33a and 5. For this particular cyclization process, the use of TFA proved significantly less efficacious. As in the case of the cyclization to form the thiophenyl-substituted tricyclic 25, a rate acceleration of approximately one order of magnitude was observed versus the cyclization to form unsubstituted tricyclic 15. This is consistent with the moderate cation-stabilizing ability of the phosphoramide substituent [Scheme V, X = $N(Me)P(=O)(NMe_2)_2$].

Although a nitrogen-substituted benzhydrazulene nucleus had at last been synthesized, its further elaboration was not possible due to the unavailability of conditions for dephosphorylation which did not also

destroy the relatively sensitive carbocycle. We therefore decided to look into the possibility of directly preparing tetracyclic compounds such as 36 via similar phosphoramide chemistry (Scheme XII). If such a tetracycle could be prepared where X is some sort of leaving group, elimination of HX would then give 37. If this compound were treated with base, an elimination of phosphorous should occur, given the driving force of aromaticity, to afford dihydroisoimerubrine 38. Such eliminations are precedented,[26] and their ease was confirmed by our own model studies.[27] The parent bicyclic phosphoramide 39b (X = H) was prepared from the corresponding tetrahydroisoquinoline 39a (X = H) using the phosphorylation conditions employed earlier. This tetrahydroisoquinoline, a known compound,[28] was prepared by the Bobbit modification of the Pomeranz-Fritsh reaction.[29] Metallation (n-BuLi, THF) of 39b (X = H) proceeded smoothly, and reaction with 5 provided the vinylogous hemiketal 40 (X = H) in fairly good yield. Unfortunately, exposure of this material to a variety of acid conditions gave yields of tetracyclic 36 (X = H) ranging from 0 to 14%. Attempts to extend this to more highly substituted isoquinolines which could be dephosphorylated according to the sequence shown in

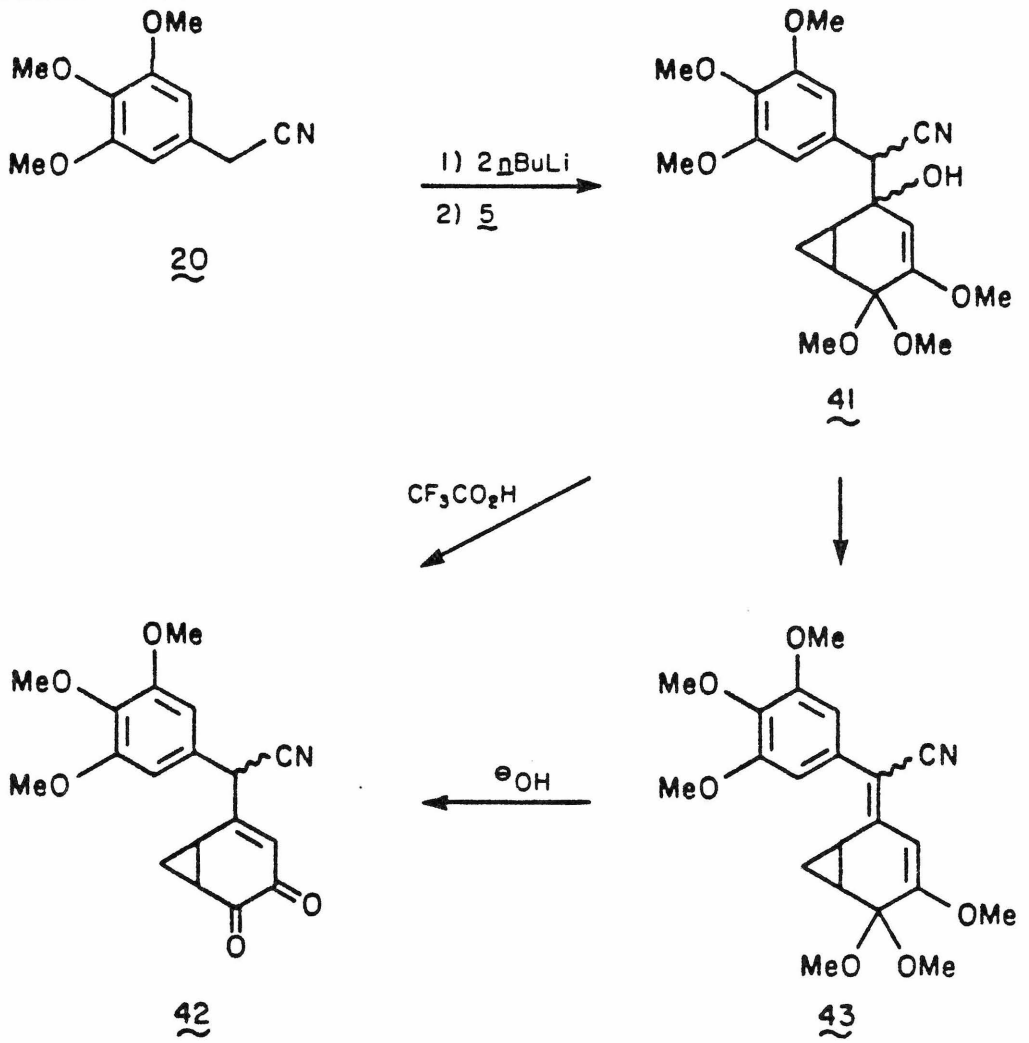
Scheme XII


MeO
X
MeO
MeO
N
O
P
Me
N—Me
N—Me
Me
1) nBuLi
2) 5
H
OH
OMe
MeO
OMe
39
40
H⊕
36
−HX
OMe
O
37
Base
−(Me2N)2P−O⊖
38

Scheme XII, such as 39b (X = SPh) and 39b (X = OR),[30] proved unsuccessful due to difficulty in metallating these substrates. This approach was therefore abandoned.

We next decided to explore the use of carboxylate derivatives in the cyclization process. This would have two purposes: to determine the effect of electron-withdrawing and therefore cation-destabilizing groups on the cyclization, and to provide a vehicle for introduction of a usable nitrogen functionality onto the thus-formed tricyclic via a Curtius-type reaction. Trimethoxyphenylacetic acid 19 was transformed into its methyl ester and dimethylamide derivatives by established procedures. Both of these compounds enolized smoothly upon treatment with LDA (THF, -78°C), but the resulting enolates proved too non-nucleophilic to react with ketone 5. Addition of cosolvents such as HMPA and enolate transmetallation with $ZnCl_2$ failed to increase reactivity enough to carry out these additions.[31] Given these results, it appeared that the only satisfactory carboxylate-type nucleophile would be the nitrile-stabilized α,α-dianion.[32] Trimethoxyphenylacetonitrile 20 was prepared from chloride 17a (NaCN, NaI, acetone) in 95% yield. Treatment with 2.5 equivalents of n-BuLi (THF, HMPA, 0°C) did indeed form the α,α-dianion, and reaction of this dianion with cyclo-

Scheme XIII



propanated quinone ketal 5 furnished the addition product 41 in 61% yield. When this compound was dissolved in TFA-CH_2Cl_2 (75 min, RT), a dienone of type IV (see Scheme V) was not formed. Instead, the only observed product was dione 42, isolated as a mixture of diastereomers. Apparently, the strongly electron-withdrawing cyano group has altered the reactivity of 41 so that vinylogous hemi-

kal-to-enone hydrolysis occurs in preference to the previously observed dehydration. Treatment of alcohol 41 with $BF_3 \cdot OEt_2$ resulted in a mixture of a large number of compounds at short reaction times. Attempt was then made to force dehydration of alcohol 41 by use of basic conditions: exposure to CH_3SO_2Cl and Et_3N in CH_2Cl_2 did indeed afford diene ketal 43 in nearly quantitative yield. However, further treatment of either this diene or the dione 42 with protic or Lewis acid gave mixtures of products which did not contain any of the desired tricyclic rearrangement product. This appears to be due to the strongly electron-withdrawing nitrile group preventing the formation of cation V (Scheme V, X = CN) and thereby blocking formation of the tricyclic. Hydrolysis of nitrile 43 to the somewhat less electronegative carboxy and carboxamide groups was then attempted. Treatment of 43 with refluxing 25% aqueous KOH provided as the major product dione 42, the result of a conjugate addition-elimination process in preference to direct hydrolysis. Conversion of the nitrile 43 to an amide under milder conditions (NaOH, H_2O_2, H_2O, MeOH, RT) gave mainly decomposition product, possibly due to preferential formation of unstable epoxides. At this point, exploration of the chemistry of these cyano compounds was abandoned

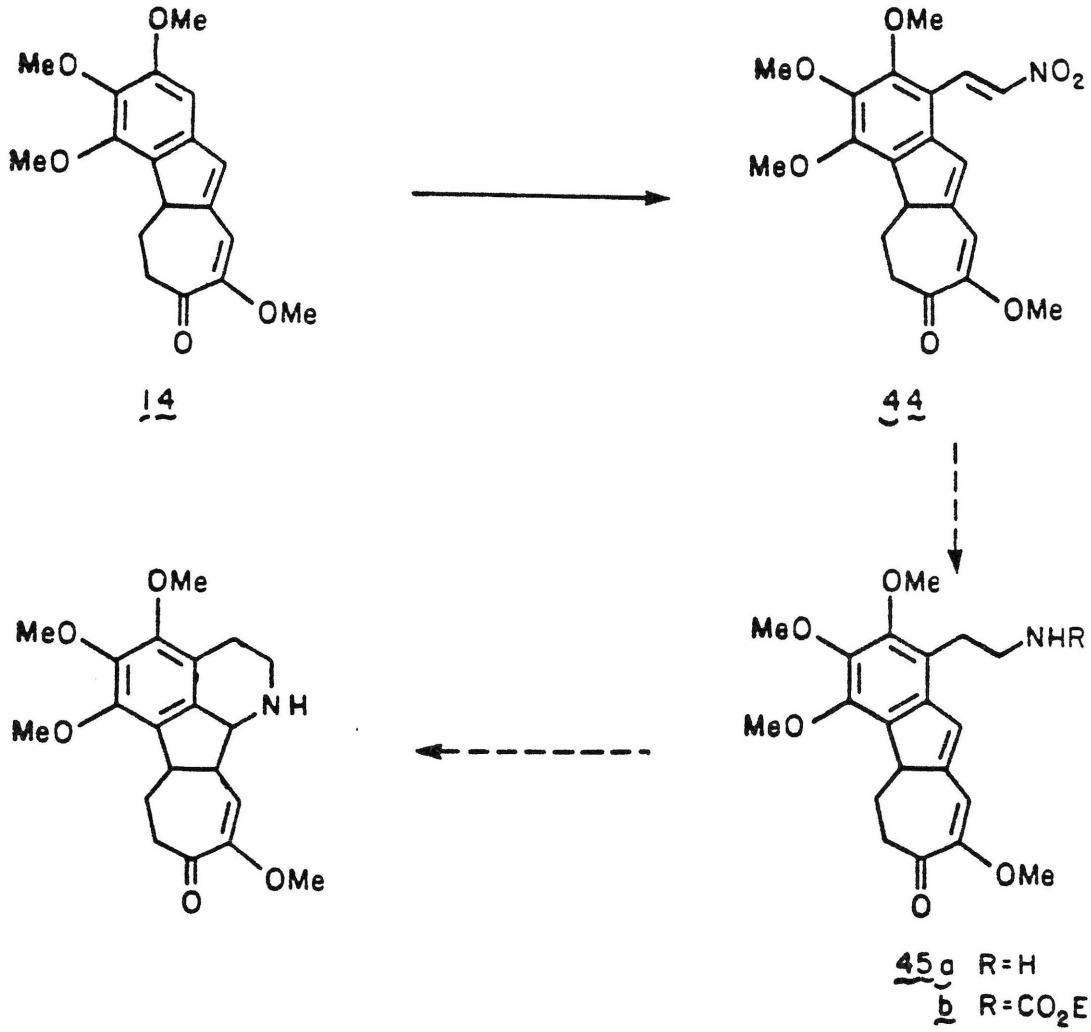
in favor of other approaches.

Another potentially attractive approach to the tetracyclic nucleus involved intramolecular Michael addition of a primary phenethylamine derivative to the conjugated dienone moiety (Scheme XIV). Although attempted intermolecular additions of amines to the tricyclic dienone 14 were not successful, it was considered that intramolecularity might provide the additional driving force necessary to overcome this. Examination of molecular models showed that the phenethylamine substituent in a compound such as 45 could orient itself in such a way as to set up favorable geometry for conjugate addition.

To this end, the nitrostyreneation of tricyclic 14 was carried out according to the procedure of Büchi.[36] Although nitrostyrene derivative 44 was definitely present as the major product by ^{1}H NMR, it proved too unstable to be isolated in pure form. We therefore set out to find conditions for the reduction of crude 44 to phenethylamine 45 which might be compatible with such a high degree of sensitivity.

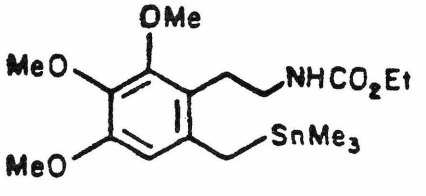
In the reduction of nitrostyrenes to phenethylamines, excesses of harsh reducing agents such as $LiAlH_4$ are commonly used. In the few cases where this conversion has been carried out *via* catalytic reduction, aqueous, acidic

Scheme XIV

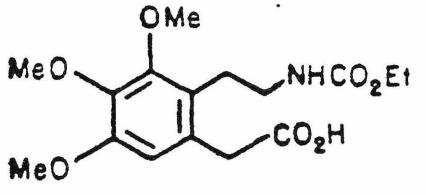


solvent systems and elevated temperatures and pressures were used.[37] Since the use of such methods would not be compatible with the labile substrates 44 and 45, we set out to develop much milder conditions for this reduction. The known nitrostyrene 46[38] was hydrogenated to the corresponding phenethyl nitro-compound [$(Ph_3P)_3RhCl$, toluene-ethanol 1:1, 1 atm, RT],[39] which was subsequently hydrogenated to phenethylamine 47 (Pd-C, ethanol, 1 atm hydrogen, RT). This two-step procedure, involving neutral solvent systems and very mild conditions, proceeded in 54% overall yield (unoptimized). Unfortunately, application of these very gentle conditions to crude nitrostyrene 44 resulted in the formation of intractable tar.

Another approach to 45 was briefly explored, involving the benzyltin-carbamate 48.[40] If this compound were subjected to the general annelation process depicted in Scheme VI, carbamate 45b would result. However, initial



48

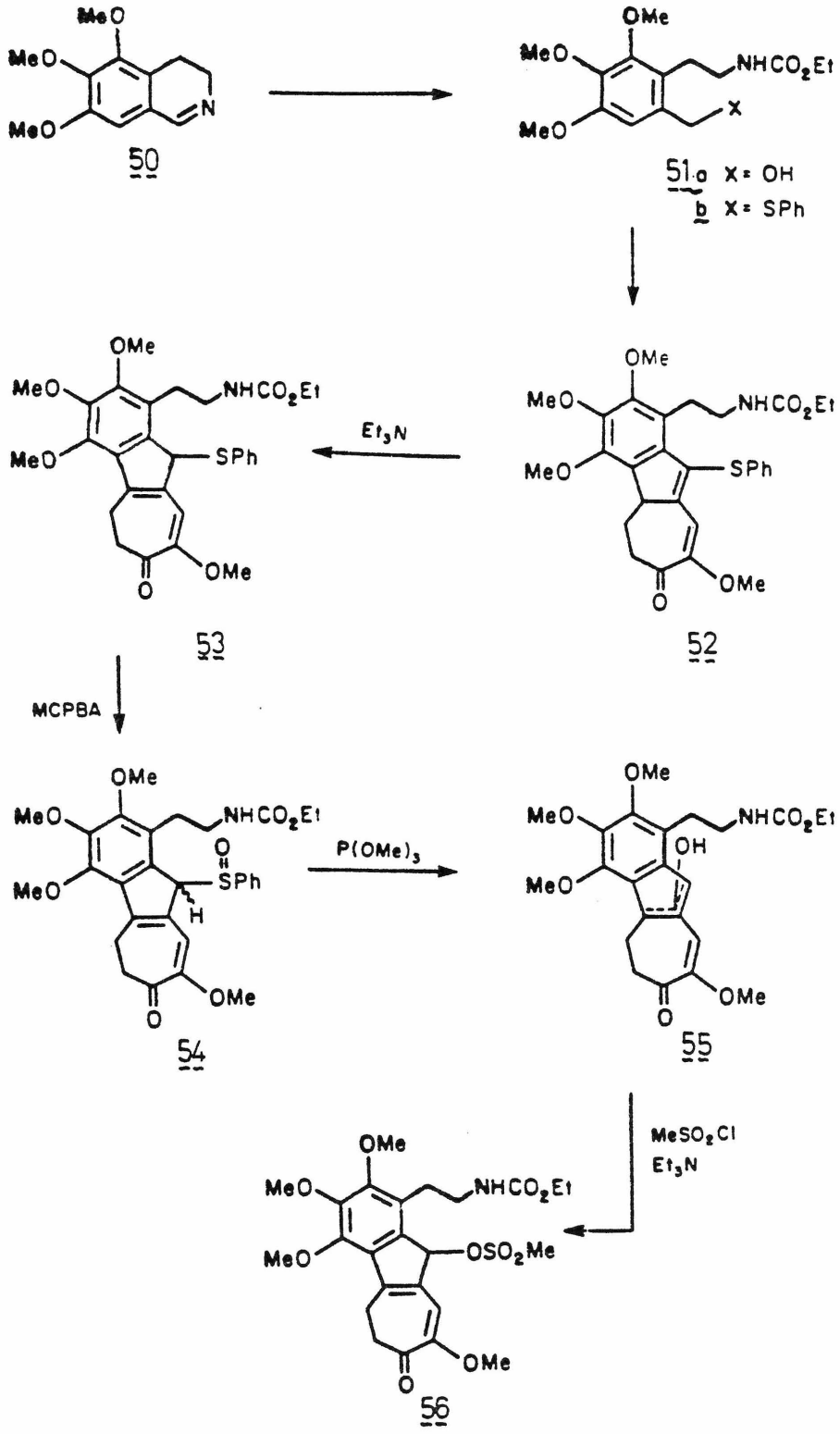


49

attempts at tin-lithium exchange led to the isolation of products resulting from quenching of the benzyllithium moiety by the acidic carbamate hydrogen, even in the presence of excess alkyllithium reagents. Apparently, tin-lithium exchange proceeds faster than carbamate deprotonation in this system. Further modifications, including specific pre-forming of the carbamate anion, did not result in the formation of synthetically useful quantities of the desired benzyllithium derivative. A potential alternative to this somewhat messy tin chemistry would involve formation of the trianion derived from acid 49, followed by annelation as depicted in Scheme VII. This route was not pursued due to lack of time. However, as shall be seen from the results of subsequent work, the success of such an approach, even if carbamate 45b could be made, is somewhat doubtful.

An analogous scheme, based on the preparation of sulfur-substituted tricyclic carbamate 52, was then explored. An intramolecular conjugate addition-elimination process would furnish the desired tetracyclic nucleus in a higher oxidation state. The requisite alcohol 51a (Scheme XV) was prepared from dihydroisoquinoline 50[41] in 84% overall yield [(1) $ClCO_2Et$, THF; (2) 10% aqueous NaOH; (3) $NaBH_4$]. This was converted to the intermediate

Scheme XV


MeO
MeO
MeO
N
50
OMe
MeO
NHCO2Et
MeO
X
51a X = OH
b X = SPh
OMe
MeO
NHCO2Et
MeO
SPh
OMe
O
52
Et3N
OMe
MeO
NHCO2Et
MeO
SPh
OMe
O
53
MCPBA
OMe
MeO
NHCO2Et
O
MeO
SPh
H
OMe
O
54
P(OMe)3
OMe
MeO
NHCO2Et
MeO
OH
OMe
O
55
MeSO2Cl
Et3N
OMe
MeO
NHCO2Et
MeO
OSO2Me
OMe
O
56

benzyl chloride ($SOCl_2$, Et_3N, CH_2Cl_2), which was not purified; it was immediately treated with LiSPh (CH_3OH, RT) to give the key sulfide-carbamate 51b in 80% yield from 51a. This material was converted to its dianion [t-BuLi (2 equiv.), THF-HMPA, -78°C], which reacted smoothly at the benzylic position with cyclopropanated quinone ketal 5. The crude addition product was cyclized as before ($BF_3 \cdot OEt_2$, CH_3NO_2, 0°C , RT) to afford the desired tricyclic carbamate 52, 39% overall from 51b. The use of TFA in this cyclization process furnished 52 in slightly lower yield.

Attempt to cyclize this carbamate directly under basic, protic conditions (e.g. $NaOCH_3$, CH_3OH) resulted in immediate decomposition. Even if such a direct cyclization could be rendered successful, however, it is not clear whether the resulting N,N-disubstituted carbamate could be hydrolyzed without destroying the sensitive carbocyclic nucleus. It was therefore necessary to find a way to cleave the N-monosubstituted carbamate in 52. The silanolysis procedure of Pirkle,[42] specific for the cleavage of N-monosubstituted carbamates to isocyanates, seemed to be an appealing solution. In fact, application of this procedure (Cl_3SiH, Et_3N, 40°C) to both carbamate-sulfide 51b and the ethyl carbamate derived from amine 47

gave the derived isocyanates very cleanly. Exposure of the isocyanates to very mild hydrolysis conditions [(1) 5 equiv. TFA, CH_2Cl_2; (2) 10% aqueous Na_2CO_3][43] gave the primary amines in very good yield.

This procedure was then applied to tricyclic carbamate 52. Instead of the expected isocyanate, however, a crude material was isolated which contained the isocyanate derived from tricyclic carbamate 53, in which the five-membered ring olefin had been isomerized. As a control experiment, 52 was exposed to triethylamine (benzene, RT, 30 min), resulting in virtually quantitative conversion to 53. No 52 could be detected by NMR, but TLC showed that a trace amount of 52 might still be present in equilibrium with 53. The driving force for this isomerization appears to be that, when the sulfur-bearing carbon becomes Sp^3-hybridized in 53, the severe steric interaction present between the benzenesulfenyl group and the $-CH_2CH_2N$ substituent in 52 is greatly relieved. Since a small equilibrium concentration of 52 possibly exists in the presence of base, we attempted to free the amine for intramolecular conjugate addition. Treatment of the isocyanate prepared above from 52 with the reagents used in the earlier isocyanate hydrolyses gave rise to a dark, gummy product which contained a gross mixture of compounds.

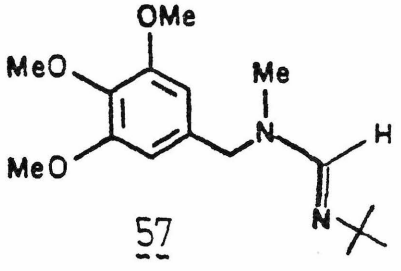
This negative result was quite surprising, since the carbocyclic nucleus itself has previously been demonstrated to be stable to such mild conditions. This led us to abandon the concept of intramolecular conjugate addition.

In light of our earlier success at manipulating sulfur and oxygen functionality (Scheme X), the analogous preparation of mesylate-carbamate 56 from 52 was attempted. Although a re-examination of molecular models showed that the transition state for intramolecular mesylate displacement by nitrogen in 56 would be a strained one, it appeared that some of the problems encountered in the intramolecular Michael approaches would be circumvented and that this displacement approach would be worth a try. Attempted conversion of sulfide 52 to its derived sulfoxide (MCPBA, CH_2Cl_2) failed; a large number of products were formed. However, after isomerization to allylic sulfide 53, oxidation under the same conditions gave rise to sulfoxide 54 in 88% overall yield. This difference in reactivity is probably due to the more sterically accessible sulfur atom in 53 relative to 52. The rearrangement-trapping procedure [$P(OMe)_3$, MeOH, RT -48°C], when carried out on 54, afforded a 59% yield of a 3:2 mixture of alcohols 55 under slightly milder conditions than were required for the similar conversion of 28 to 29. This

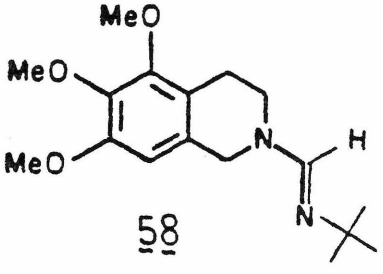
mixture of alcohols was then converted to the desired secondary mesylate 56 under standard conditions ($MeSO_2Cl$, Et_3N, CH_2Cl_2, -78°C → RT, 77%).

The direct cyclization of this substrate proved unsuccessful. Base treatment of 56 at high temperature under aprotic conditions (DBU, 2 equiv., toluene, 115°C) led to recovery of starting mesylate, surprisingly free of decomposition product. Reaction of 56 with base under protic conditions also led to recovery of starting material; when sufficiently vigorous conditions (KOtBu, tBuOH, 55°C) were tried, only decomposition resulted. Since these results seemed to indicate that intramolecular Sn^2 reaction was indeed impractical in this system, the conversion of the carbamate functionality in 56 to the corresponding amine was not pursued, and this entire approach was abandoned.

Toward the end of this work, we were encouraged by a report that formamidines derived from secondary amines could be metallated at an alkyl carbon alpha to nitrogen, and that the resulting anion could readily be added to carbonyls.[44] In order to apply these results to our synthetic program, the substrates 57 and 58 were prepared according to the procedure outlined in that report. Deprotonation of 57 was attempted with both s-BuLi and



57



58

t-BuLi in THF and THF-HMPA solvent systems. In no case was the desired benzylic anion formed in greater than 20% yield, as determined by CH_3I quenching; no indication of competing methyl or aryl lithiation was seen. Besides recovered starting material, the remaining (30-50%) mass balance from each reaction consisted of 3,4,5-trimethoxybenzaldehyde 16. Although this type of oxidative decomposition appears to be a general minor side reaction in these formamidine metallations,[45] the high yield of such product derived from 57 is quite surprising.

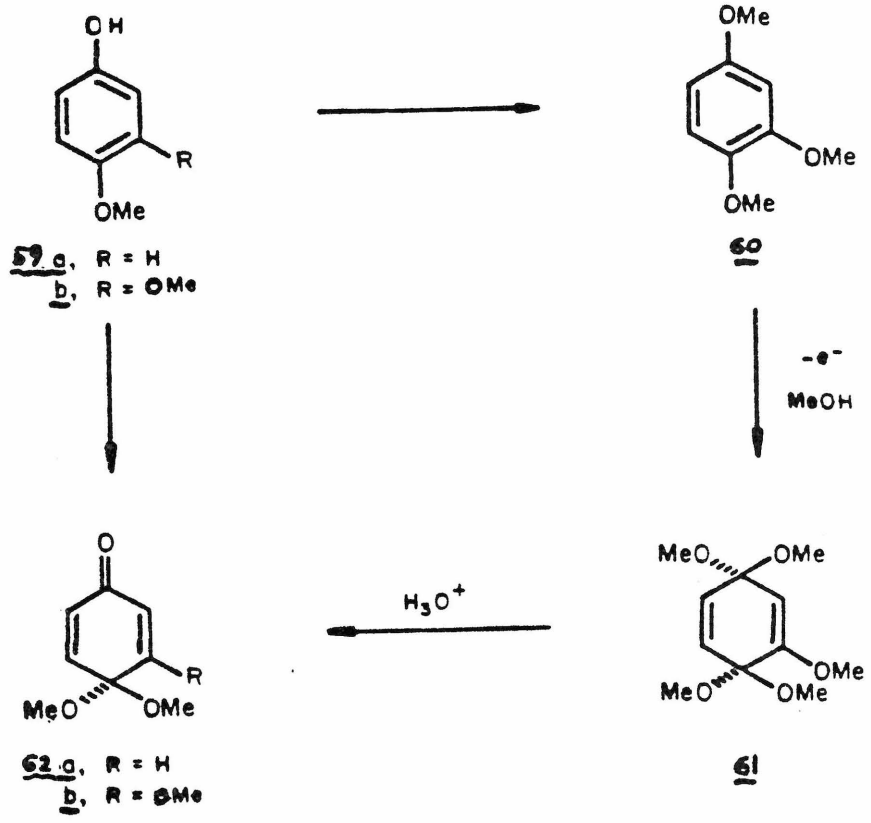
Considerable experimentation with tetrahydroisoquinoline formamidine 58 revealed that the desired benzylic anion could indeed be formed upon exposure to an excess of t-BuLi (THF, -25°C). Quenching with CH_3I demonstrated that this anion had been formed quantitatively. However, application of

this procedure to addition to cyclopropanated quinone ketal 5 failed, due to the presence of excess alkyllithium. When 58 was treated with one equivalent of t-BuLi, only partial metallation took place; addition of 5 to this reaction mixture resulted only in the isolation of numerous decomposition products and unreacted 5. It therefore became necessary to abandon the lithiated formamidine approach.

In closing, it is appropriate to review the methods of preparation of quinone ketal 62b, which has been used extensively during the course of the Evans group's work with masked quinones and their derivatives. The oxidations of p-methoxy phenols 59a and 59b were initially carried out using the excellent $Tl(NO_3)_3$ procedure described by McKillop and Taylor,[46] which proceeded in 65-85% yields to afford quinone ketals 62a and 62b. However, as increasingly large quantities of 62b were required as a precursor to cyclopropanated quinone ketal 5, some of the drawbacks of this oxidation procedure became apparent.

In our experience, commercially supplied $Tl(NO_3)_3$ proved unreliable for use in these reactions, due to the presence of substantial amounts of Tl(I) impurities. It was thus necessary to prepare this reagent from increasingly expensive Tl_2O_3 by a procedure (HNO_3, 85°C) which gave only

Scheme XVI



a 50% yield. Although the oxidation procedure itself is quite convenient on less than 0.10 mol of substrate, its application to larger-scale reactions is very inconvenient due to the voluminous quantities of solvents used in the workup. In addition, the handling of very large quantities of thallium salts, some of which are soluble in water and/or organic solvents, presents obvious health hazards.

These and other difficulties led to the examination of other oxidation procedures.[47]

The most attractive alternative proved to be anodic electrochemical oxidation. In fact, 59a had previously been converted directly to 62a in 65% yield by such a procedure.[48] Our attempts to extend this to dimethoxyphenol 59b led to extensive polymerization, presumably due to the increased ability of the more electron-rich aromatic nucleus to react bimolecularly with aryl radical cation electrolysis intermediates. Fortunately, there existed a report[49] of anodic oxidation of trimethoxybenzene 60 to quinone bis-ketal 61 in 61% yield. Further modification of this procedure allowed for the production of 100 g quantities of 61 in much-improved (88-95%) yields. This bis-ketal could be selectively deblocked to afford quinone monoketal 62b *via* mild acid hydrolysis.[50] The overall yield for the sequence leading from 59b to 62b was 60-65%.

The blocked quinone 62b could subsequently be converted to cyclopropanated quinone ketal 5 in 92% yield upon treatment with dimethyl oxosulfonium methylide.[51,52]

Experimental Section

Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates EM-390 spectrometer (90 MHz) and are reported in ppm from internal tetramethylsilane (TMS) on the δ-scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant, and interpretation. ^{13}C magnetic resonance spectra were recorded on a Varian Associates XL-100 (25.2 MHz) spectrometer and are reported in ppm from TMS using the abbreviations given above. Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. Mass spectra were recorded on a Dupont 21-492B spectrometer by the Caltech Microanalytical Laboratory. Combustion analyses were performed by the Caltech Microanalytical Laboratory and by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Flash chromatography was performed according to the general procedure of Still.[33] When necessary, solvents and reagents were dried prior to use. Dichloromethane, hexamethylphosphoroustriamide (HMPA), and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Benzene and

tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl. Nitromethane was passed through a column of activity I alumina. Butyllithium reagents were titrated by the procedure of Watson and Eastham.[34]

Lithium diisopropylamide (LDA) was always prepared by the following procedure. A solution of diisopropylamine in THF was cooled to -78°C, followed by the addition of n-BuLi in hexane solution. The mixture was allowed to stir for 15 min at -78°C and the resulting solution of LDA was used immediately for subsequent operations. Both flash and normal gravity column chromatography were always carried out using Merck Silica Gel 60 (60-230 mesh) unless otherwise specified, eluting with the solvents mentioned.

4,5,5-Trimethoxybicyclo[4.1.0]hept-3-ene-2-one (5). Sodium hydride (2.40 g, 100 mmol) was washed with hexane and combined with trimethyloxosulfonium iodide (22.1 g, 100 mmol, recrystallized from water) in a three-necked flask equipped with a mechanical stirrer and nitrogen intake. The apparatus was cooled to 0°C (ice-bath), and 150 mL of anhydrous DMSO was added over a 15-min period. The mixture was then allowed to warm to RT and was stirred for 35 min. A solution of 3,4,4-trimethoxycyclohexa-2,5-diene-1-one (9.13 g, 50.0 mmol) in 50 mL of anhydrous

DMSO was then introduced over a 5-min period. The resulting tan solution was stirred at RT for 2 h, then warmed to 55°C and stirred for an additional 1 h. After cooling to RT, the reaction mixture was poured into 900 mL of water. This mixture was extracted with 4 x 400 mL of dichloromethane, and the combined organic layers were dried over Na_2SO_4 and filtered. Removal of all solvents in vacuo afforded 10.46 g of yellow oil. This material was chromatographed on silica gel (100 g, ethyl acetate eluant) to give 5 as a white, crystalline solid, 9.02 g (92%), m.p. 92-93°C: IR (CCl_4) 2860-3010, 2820, 1655, 1610, 1450, 1365, 1210, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (s, 1, vinyl H), 3.69 (s, 3, vinyl -OCH_3), 3.50 (s, 3, ketal -OCH_3), 3.30 (s, 3, ketal -OCH_3), 1.98 (m, 2, cyclopropyl H), 1.25 (m, 1, cyclopropyl H), 0.90 (m, 1, cyclopropyl H).

Anal. calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.65; H, 6.98.

4,4,5-Trimethoxybicyclo[4.1.0]hept-3-ene-isopropyl-2-ol (6). Magnesium shavings (1.23 g, 50.0 mmol) were placed in a three-necked flask equipped with a magnetic stirrer under a nitrogen atmosphere and covered with 50 mL of anhydrous THF. A solution of 4.70 mL (50.0 mmol) of 2-bromopropane in 15 mL of THF was added over a 45-min period. The mixture was stirred at RT for 1 h. Meanwhile,

4.00 g (20.2 mmol) of cyclopropyl ketone 5 was dissolved in 25 mL of anhydrous THF in a separate three-necked flask, equipped with magnetic stirrer and addition funnel, and cooled to 0°C under nitrogen. The solution of 2-propyl-magnesium bromide was transferred to this addition funnel, and then added dropwise to the solution of 5 over a 20-min period. The mixture was then allowed to warm to RT and stir for 2 h. Water was carefully added until all gas evolution ceased, and the resulting mixture was filtered through glass wool into a separatory funnel. The emulsion which collected in the funnel was washed with 250 mL of dichloromethane. The organic layer was separated from the combined filtrates, and the aqueous layer was washed with dichloromethane (2 x 40 mL). The combined organic layers were washed with 100 mL of half-saturated aqueous NaCl, dried over Na_2SO_4, filtered, and freed of solvents *in vacuo* to afford a light yellow oil, 3.85 g (79%), of reasonable purity by ^1H NMR. This material is too unstable for further characterization, and should be used immediately in subsequent experiments: ^1H NMR (CCl_4) δ 4.23 (s, 1, vinylic H), 3.44 (s, 3, vinylic -OCH_3), 3.26 (s, 3, ketal -OCH_3), 3.14 (s, 3, ketal -OCH_3), 1.22-1.90 (m, 3, two cyclopropyl H and isopropyl H), 0.93 (d, 3, J = 4 Hz, isopropyl -CH_3), 0.86 (d, 3, J = 4 Hz,

isopropyl -CH_3).

4-Methoxy-5-isopropylidene[4.1.0]cyclohept-3-ene-2-one (7). The freshly prepared Grignard adduct 6 (704.6 mg, 2.91 mmol) was dissolved in 20 mL of anhydrous nitromethane at RT under a nitrogen atmosphere. Immediately, boron trifluoride etherate (0.36 mL, 2.9 mmol) was added via syringe, and the red solution was stirred for 10 min. Saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture was layered between 20 mL of water and 15 mL of dichloromethane. The organic layer was separated, and the aqueous layer was extracted with 15 mL of dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and freed of solvents in vacuo to afford a deep red oil. This material was distilled (180°C, 0.1 mm) to afford a nearly colorless oil, homogeneous by TLC and NMR, 371.2 mg (72%): IR (CCl_4) 2810-3000, 1665, 1610, 1580, 1450, 1205 cm^{-1}; ^1H NMR (CCl_4) δ 6.06 (s, 1, vinylic -H), 3.56 (s, 3, -OCH_3), 2.33 (m, 1, cyclopropyl -N), 1.92 (s, 3, vinylic -CH_3), 1.85 (s, 3, vinylic -CH_3), 1.10-1.43 (m, 2, cyclopropyl -H), 0.76 (m, 1, cyclopropyl -H).

Exact mass calcd. for $C_{11}H_{14}O_2$: 178.100. Found: 178.099.

2-Methoxy, 4-Isopropylene-2,4-cycloheptadienone (10). Into a three-necked flask under argon equipped with a

magnetic stirrer was placed 22% potassium hydride-oil dispersion (1.46 g, 8.00 mmol). This dispersion was washed successively with 5-8 mL portions of n-pentane and dried over a stream of argon, then covered with 2 mL of anhydrous THF. The flask and contents were cooled to 0°C, and a solution of 931 mg (5.22 mmol) of dienone 7 in 2.5 mL of THF was added over a 2-min period; hydrogen evolution began almost immediately. After 10 min, gas evolution had nearly stopped. The mixture was then allowed to warm to RT. After 50 min, conversion to the enolate of 10 was nearly complete (monitored by TLC, 7→10) The reaction was quenched by careful addition of water under argon, and poured into a vessel containing 40 mL of dichloromethane and 20 mL of water. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 10 mL). All organic phases were combined, washed with 30 mL of half-saturated aqueous NaCl, dried over Na_2SO_4, filtered, and freed of solvents in vacuo to afford a dark red oil. The material was chromatographed on activity III alumina (60 g, solvent: 8% ethyl acetate, 92% n-hexane), giving a yellow oil. Bulb-to-bulb distillation (135°C, 0.1 mm) gave pure 10, 536 mg (58%) as a colorless, free-flowing oil: IR (CCl_4) 2890-3000, 2820, 1678, 1618, 1598, 1450, 1430, 1365, 1225,

1130, 885 cm^{-1}; ^1H NMR (CCl_4) δ 6.29 (1, t, J = 7 Hz, cyclic vinyl -H), 5.90 (1, s, cyclic vinyl ethyl -H), (1, s, cyclic vinyl ether -H), 5.02 (1, s, terminal methylene -H), 4.88 (1, s, terminal methylene -H), 3.65 (3, s, $-OCH_3$), 2.19-2.62 (4, m, cyclic $-CH_2CH_2-$), 1.92 (s, 3, vinylic $-CH_3$).

Exact mass calcd. for $C_{10}H_{14}O_2$: 178.100. Found: 178.098.

1-Trimethylsilyloxy-2-methoxy-4-isopropenyl-2,4,7-cycloheptatriene (8). Dienone 7 (207.0 mg, 1.162 mmol) was deprotonated as in the previous preparation, and the resulting enolate was rearranged exactly as in the preparation of cycloheptadienone 10. However, once monitoring had shown that the rearrangement was complete, the reaction was quenched with chlorotrimethylsilane (0.30 mL, 2.4 mmol, freed of HCl by pretreatment with triethylamine) and allowed to stir at RT for 3 min. Triethylamine (0.2 mL) was added to the reaction mixture, and it was poured into a vessel containing 18 mL of ether and 12 mL of water. The organic layer was removed, dried over Na_2SO_4, and freed of volatiles in vacuo, leaving a yellow oil, nearly pure 8 by NMR, 255.9 mg (91%): IR (CCl_4) 2900-3010, 1620, 1590, 1555, 1445, 1430, 1405, 1368, 1335, 1245, 1210, 1155, 1070, 885, 840 cm^{-1}; ^1H NMR (CCl_4) δ 5.85

(s, 1, cyclic vinyl ether -H), 5.56 (t, 1, J = 7 Hz, cyclic vinyl -H), 4.94 (t, 1, J = 7 Hz, cyclic TMS-enol-vinyl -H), 4.92 (s, 1, terminal methylene -H), 4.80 (s, 1, terminal methylene -H), 3.65 (s, 3, $-OCH_3$), 2.13 (t, 2, J = 7 Hz, cyclic $-CH_2-$), 0.11 [s, 9, $-Si(CH_3)_3$].

2-Methoxy-4-isopropenyl-2,4,6-cycloheptatriene-1-one (9). The trimethylsilyl enol ether 8 (88.1 mg, 0.364 mmol), without purification, was dissolved in 1.4 mL of anhydrous dichloromethane under nitrogen, and cooled to -78°C. p-Chloranil (134.1 mg, 0.545 mmol) was then added directly, and the reaction mixture was allowed to warm up to RT, then stirred for 70 min. Solvents were removed in vacuo, and the dark residue was immediately chromatographed on silica gel, 8 g (eluants: 30% ethyl acetate, 70% n-hexane for first 70 mL, then ethyl acetate). This afforded a light yellow oil, 45.1 mg (70% from TMS enol ether 8, 64% overall from dienone 7): IR ($CHCl_3$) 2880-3000, 1600, 1585, 1560, 1450, 1430, 1380, 1290, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90-7.30 (m, 3, tropolone ring -H's), 6.80 (s, 1, tropolone ring -H), 5.30 (s, 1, terminal vinyl -H), 5.22 (s, 1, terminal vinyl -H), 3.96 (s, 3, $-OCH_3$), 2.13 (s, 3, isopropenyl $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 179.5, 163.4, 146.7, 136.0, 135.0, 124.5, 116.2, 112.4, 56.0, 22.5.

Exact mass calcd. for $C_{11}H_{12}O_2$: 176.084. Found:

176.085.

β-Dolabrin (3a). To a solution of 357.8 mg (2.032 mmol) of 9 in 8.0 mL of anhydrous dichloromethane, cooled to -78°C under a stream of argon, was added boron tribromide (0.20 mL, 2.1 mmol). After stirring at -78°C for 20 min, the reaction mixture was added to 40 mL of 10% aqueous NaOH. The resulting mixture was stirred vigorously at RT for 15 min. Additional water was added to dissolve the insoluble material formed, and the dichloromethane layer was drained off. The aqueous layer was carefully acidified with concentrated HCl to pH ≈ 4. This mixture was extracted with dichloromethane (3 x 20 mL), and the organic layers were combined. After washing with 30 mL of brine, drying over Na_2SO_4, and filtration, removal of solvents in vacuo gave 210 mg of a yellow semisolid. Sublimation (75°C, 0.02 mm) afforded yellow crystals, 199.3 mg (60%), m.p. 57.5-58.5°C (lit.[5] 58-59°C): IR ($CHCl_3$) 3180, 2880-3020, 1600, 1530, 1470, 1435, 1385, 1300, 1250, 950, 910, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.03 (s, 1, -OH), 6.96-7.44 (m, 4, ring -H's), 5.30 (s, 1, terminal vinylic -H), 5.22 (s, 1, terminal vinylic -H), 2.11 (s, 3, $-OCH_3$); ^{13}C NMR ($CDCl_3$) δ 171.8 (s), 169.1 (s), 151.7 (s), 145.3 (s), 136.7 (d), 126.3 (d), 123.7 (d), 121.0 (d), 117.3 (t), 22.4 (q).

Anal. calcd. for $C_{10}H_{10}O_2$: C, 74.07; H, 6.17. Found: C, 73.77; H, 6.08.

Diels-Alder Adduct (11). Cycloheptadienone 10 (124.6 mg, 0.704 mmol) was dissolved in 3.0 mL of anhydrous benzene, and dichlorodicyano-p-benzoquinone (162 mg) was added at once. The mixture was heated to vigorous reflux for 3 h, then cooled to RT. The reaction was then diluted with 30 mL of dichloromethane, and the resulting solution was washed with 15 mL portions of 10% aqueous Na_2CO_3 and brine. After drying over Na_2SO_4, filtration, and removal of solvents in vacuo, a crude, rust-colored solid was isolated, 207.9 mg. This material was chromatographed on silica gel, 15 g (elution with 65:35 ethyl acetate-hexane) to afford a yellow-orange solid. This was recrystallized (chloroform-hexane) to afford pure 11 as a bright orange, crystalline solid, 121.0 mg (43%), m.p. 204-206°C (decomposition): IR ($CHCl_3$) 2900-3030, 1712, 1680, 1590, 1542, 1450, 1372, 1215, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.22 (s, 1, vinylic -H), 3.69 (s, 3, $-OCH_3$), 2.98 (m, 2, ring $-CH_2-$), 2.67 (m, 2, ring $-CH_2-$), 2.00 (dd, 1, J = 7 Hz, J = 3 Hz, angular -H), 1.90 (s, 3, vinylic $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 195.4 (s), 177.8 (s), 177.4 (s), 114.2 (s), 110.5 (d), 55.8 (q), 55.4 (s), 51.7 (s), 44.9 (d), 41.2 (t), 35.6 (t), 25.8 (t), 20.0 (q).

Exact mass calcd. for $C_{18}H_{14}Cl_2N_2O_4$: 404.034. Found: 404.032.

3,4,5-Trimethoxyphenylchloromethane (17a). To a suspension of 10.23 g (0.052 mol) of 3,4,5-trimethoxybenzylaldehyde 16 in 150 mL of absolute ethanol at RT was added 1.97 g (0.052 mol) of sodium borohydride. The resulting solution was stirred at RT for 60 min, followed by removal of the ethanol under reduced pressure. The residue was then decomposed by careful addition of 200 mL of 1% aqueous HCl. The resulting mixture was extracted with dichloromethane (2 x 100 mL), and the organic extracts were combined, washed with brine (250 mL), and dried over Na_2SO_4. Removal of all volatiles in vacuo left a clear, colorless oil, 10.06 g (98%). This material was dissolved in 250 mL of anhydrous toluene at RT under a nitrogen atmsophere, and 4.62 mL (0.053 mol) of pyridine was added. A solution of 3.81 mL (0.053 mol) of thionyl chloride in 15 mL of anhydrous toluene was then added over 10 min. Once addition was complete, the solution was allowed to stir at RT for 30 min, and then heated to reflux for 30 min. The reaction was then allowed to cool back to RT, and the resulting mixture was washed with water (200 mL), 5% HCl (200 mL), and brine (200 mL). After drying over Na_2SO_4, solvents were removed in vacuo

to afford a white, crystalline solid, 10.68 g (95% overall from 16), m.p. 61.5-62.5°C: ^{1}H NMR ($CHCl_3$) δ 6.60 (s, 2, aromatic -H), 4.50 (s, 2, Ar-CH_2-Cl), 3.85 (s, 9, AR-OCH_3).

Exact mass calcd. for $C_{10}H_{13}O_3Cl$: 216.055. Found: 216.055.

(3,4,5-Trimethoxyphenyl)-acetonitrile (20). To a solution of 4.40 g (20.3 mmol) of chloride 17a in 20 mL of acetone was added 1.50 g (30.5 mmol) of sodium cyanide and 0.20 g (1.3 mmol) of sodium iodide. The resulting suspension was heated at reflux for 15 h with vigorous stirring. It was then allowed to cool down to RT, and the suspended solid was removed by filtration. The filter cake was washed with additional portions of acetone, and the washings were combined with the filtrate. The acetone was removed under reduced pressure, and the resulting white, semisolid residue was partitioned between 40 mL of dichloromethane and 40 mL of water. The organic layer was removed and washed with 40 mL portions of water and brine, then dried over $MgSO_4$. Concentration in vacuo afforded a white solid, 3.98 g (95%), of sufficient purity to be used directly in further operations, m.p. 73-75°C. Subsequent recrystallization from ether-hexane afforded analytically pure 20 as white needles, m.p. 75.5-

76.5°C: IR ($CHCl_3$) 3030-2820, 2250, 1595, 1465, 1425, 1335, 1130, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (s, 2, aromatic -H), 3.87 (s, 6, $-OCH_3$), 3.84 (s, 3, $-OCH_3$), 3.67 (s, 2, $Ar-CH_2-$).

Anal. calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.69; H, 6.29; N, 6.64.

(3,4,5-Trimethoxyphenyl)-acetic acid (19). A suspension of 1.89 g (9.12 mmol) of (3,4,5-trimethoxyphenyl)-acetonitrile 20 in 10 mL of 30% aqueous KOH was heated to reflux for 5 h. After cooling down to RT, the mixture was washed with ether (2 x 12 mL). The remaining aqueous layer was rendered slightly acidic by addition of 6 N aqueous HCl, then extracted with dichloromethane (3 x 15 mL). The organic extracts were combined and washed with 25 mL portions of water and brine, then dried over $MgSO_4$. Removal of solvents in vacuo afforded a white, crystalline solid, 1.95 g (95%), m.p. 111-113°C, suitable for use in future operations. Recrystallization from Et_2O gave analytically pure 20 as white prisms, m.p. 114-116°C: IR ($CHCl_3$) 3300-2500, 3100-2820, 1710, 1595, 1460, 1330, 1210, 1130, 1000, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (s, 2, aromatic -H), 3.84 (s, 9, $-OCH_3$), 3.58 (s, 2, $Ar-CH_2-$).

Exact mass calcd. for $C_{11}H_{14}O_5$: 226.084. Found: 226.086.

Anal. calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.34; H, 6.15.

3,4,5-Trimethoxyphenyl-(trimethylstannyl)-methane (17e). Lithium wire (0.49 g, 71 mmol) was washed with anhydrous hexane and covered with 4.0 mL of anhydrous THF under nitrogen. The mixture was cooled to -5°C, and a solution of 1.40 g (7.0 mmol) of chlorotrimethylstannane in 2.0 mL of anhydrous THF was added over 2 min. The resulting mixture was stirred at -5°C for 2 h. At this time, the mixture was filtered under nitrogen through glass wool. The filtrate was then added to a solution of 870.2 mg (4.02 mmol) of 3,4,5-trimethoxybenzylchloride 17a in 2.5 mL anhydrous THF, also at -5°C. The reaction was maintained at this temperature for 5 min, and then allowed to warm to RT. Upon reaching RT, the mixture was carefully quenched by dropwise addition of water, and added to 50 mL of dichloromethane. The resulting organic layer was washed with 40 mL portions of water and brine, and dried over Na_2SO_4. Removal of volatiles in vacuo left a cloudy, yellow oil. This material was immediately distilled (135°C/0.005 mm) to afford a clear, colorless, free-flowing liquid, 1.307 g (94%): IR ($CHCl_3$) 3120-2810, 1585, 1500, 1460, 1450, 1335, 1220, 1125, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.16 (s, 2, aromatic -H), 3.70 (s, 9,

-OCH_3), 2.20 (s, 2, Ar-CH_2-Sn), 0.07 (s, 9, CH_3-Sn).

Exact mass calcd. for $C_{13}H_{22}O_3Sn$: 346.059. Found: 346.058.

Anal. calcd. for $C_{13}H_{22}O_3Sn$: C, 45.26; H, 6.43. Found: C, 45.42; H, 6.38.

4,5,5-Trimethoxy-2-[(3,4,5-trimethoxyphenyl)-methyl]-bicyclo [4.1.0]hept-3-en-2-ol (18). The 3,4,5-trimethoxybenzylstannane 17e (348.3 mg, 1.01 mmol) was dissolved in 8.0 mL of anhydrous ether under a nitrogen atmosphere, and the solution was cooled to -78°C. A solution of n-BuLi in hexane (1.29 M, 0.84 mL) was added at a moderate rate, and the resulting slurry was stirred for 35 min at -78°C. Cyclopropanated quinone ketal 5 (200.2 mg, 1.01 mmol) was dissolved in 2.0 mL of anhydrous THF, and the solution was added to the above slurry. The reaction was maintained at -78°C for 30 min, then allowed to warm to RT. Upon reaching RT, the reaction was quenched by careful, dropwise addition of saturated, aqueous NH_4Cl, and then washed with 10 mL portions of 5% aqueous $NaHCO_3$, water, and brine. After drying over Na_2SO_4, removal of all solvents in vacuo left a slightly yellow, viscous oil. This material was immediately rapidly eluted with ethyl acetate through 32 g of silica gel. The product appeared to be only moderately stable to the chromatography medium.

This afforded the desired adduct as an oily, equimolar mixture of two diastereomers, 180 mg (47%). The material decomposes upon standing within days: IR (CCl_4) 3500, 2830-3020, 1670, 1650, 1585, 1455, 1370, 1240, 1125 cm^{-1}; ^1H NMR (CCl_4) δ 6.43 (s, 2, aromatic -H), 6.35 (s, 2, aromatic -H), 4.49 (s, 1, vinyl -H), 4.22 (s, 1, vinyl -H), 3.75 (s, 12, aromatic $-OCH_3$), 3.63 (s, 6, aromatic $-OCH_3$), 3.39 (s, 3, vinyl $-OCH_3$), 3.32 (s, 3, vinyl $-OCH_3$), 3.26 (s, 6, ketal $-OCH_3$), 3.17 (s, 3, ketal $-OCH_3$), 3.12 (s, 3, ketal $-OCH_3$), 2.76 (s, 2, Ar-CH_2-), 2.69 (s, 2, Ar-CH_2-), 0.05-1.85 (m, 8, cyclopropyl -H).

5-[(3,4,5-Trimethoxyphenyl)methylidene]-3-methoxybicyclo[4.1.0]hept-3-en-2-one (15). The crude, oily carbinol 18, prepared as before from 1.130 g (3.28 mmol) of trimethoxybenzylstannane 17e and 0.64 g (3.28 mmol) of cyclopropanated quinone ketal 5, was dissolved in 18 mL of anhydrous nitromethane under a nitrogen atmosphere. The solution was cooled to 0°C, and boron triflouride etherate (0.30 mL, 3.3 mmol) was added. After stirring for 10 min at 0°C, the reaction was quenched with saturated, aqueous $NaHCO_3$. The resulting mixture was partitioned between 30 mL of dichloromethane and 25 mL of water. The organic layer was washed with 30 mL of brine, dried over Na_2SO_4, and freed of all solvents in vacuo to afford a

deeply yellow oil. This material was chromatographed over 100 g of activity III neutral alumina (3:7 ethyl acetate-hexane), affording three sets of fractions, listed in order of increasing polarity. Set 1 gave a yellow solid, dienone 15b,[35] (19%), m.p. 126.5-127.5°C: IR ($CHCl_3$) 3060-2810, 1670, 1575, 1500, 1460, 1350, 1240, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 (s, 1, vinyl -H), 6.52 (s, 2, aromatic -H), 6.40 (s, 1, vinyl -H), 3.85 (s, 9, aromatic $-OCH_3$), 3.62 (s, 3, vinyl $-OCH_3$), 2.21-2.46 (m, 2, cyclopropyl -H), 1.34-1.62 (m, 1, cyclopropyl -H), 0.99-1.18 (m, 1, cyclopropyl -H).

Exact mass calcd. for $C_{18}H_{20}O_5$: 316.131. Found: 316.130.

Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.26; H, 6.29.

Set 2 gave a yellow solid mixture of dienones 15a and 15b, 43.1 mg (4%). Set 3 gave a yellow solid, dienone 15a, 206.2 mg (20%), m.p. 122-123°C: IR ($CHCl_3$) 3060-2810, 1665, 1590, 1575, 1500, 1460, 1335, 1260, 1240, 1130, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.71 (s, 2, aromatic -H), 6.63 (s, 1, vinyl -H), 6.08 (s, 1, vinyl -H), 3.87 (s, 9, aromatic $-OCH_3$), 3.68 (s, 3, aromatic $-OCH_3$), 2.60-2.94 (m, 1, cyclopropyl -H), 2.00-2.33 (m, 1, cyclopropyl -H), 1.47-1.71 (m, 1, cyclopropyl -H),

0.97-1.18 (m, 1, cyclopropyl -H).

Exact mass calcd. for $C_{18}H_{20}O_5$: 316.131. Found: 316.130.

Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.21; H, 6.26.

Preparation of Dienones (15) from Carboxylic Acid (19) and Ketone (5). To a solution of 2.1 mmol of LDA, prepared as usual in 4.0 mL of THF at -78°C under nitrogen, was added a solution of carboxylic acid 19 (219 mg, 0.97 mmol) in 3.0 mL of anhydrous THF. The reaction mixture was then allowed to warm to RT and stir for 3 h, then cooled to -78°C. A solution of cyclopropanated quinone ketal 5 (198 mg, 1.00 mmol) in 2.0 mL of THF was added, and the reaction was maintained at -78°C for 10 min. It was then allowed to warm to RT and stir for 30 min, and was then quenched by the slow addition of a pH 7 phosphate buffer solution. The resulting solution was washed with 8 mL of dichloromethane. To the remaining aqueous layer was added 0.5 mL of trifluoroacetic acid; the resulting yellow suspension was immediately extracted with dichloromethane (3 x 8 mL). The combined extracts were washed with 15 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to afford 318.2 mg of a crude, yellow oil. Purification (no attempt was made to separate isomers 15a and 15b) by

chromatography on silica gel (25 g, 3:2 ethyl acetate-hexane) gave 155.2 mg (52%) of dienones 15 as a yellow solid, as characterized previously.

2,3,4,8-Tetramethoxy-5,5a-dihydrobenz[a]azulene-7-(6H)-one (14). The crude, oily carbinol 18, prepared as before from 9.84 g (28.5 mmol) of benzylstannane 17e and 5.65 g (28.5 mmol) of cyclopropanated quinone ketal 5, was dissolved in 100 g of triflouroacetic acid at 0°C. The resulting deeply red solution was allowed to warm to RT and stir for a total of 30 h. It was then dissolved in 500 mL of diethyl ether, and the resulting solution was washed with saturated aqueous $NaHCO_3$ until gas evolution ceased. The remaining organic layer was washed with 500 mL of brine, dried over Na_2SO_4, and freed of solvents *in vacuo* to afford a viscous oil, 11.13 g. This material was flash chromatographed on 300 g of silica gel (ethyl acetate-hexane, 3:7). Lower yields are obtained if contact time with silica gel is not minimized. Evaporation *in vacuo* of appropriate fractions afforded 15 as a yellow solid, 4.22 g (47%), m.p. 113-114°C: IR ($CHCl_3$) 3100-2820, 1655, 1610, 1470, 1370, 1350, 1225, 1125, 1095, 1040, 995, 885 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64 (s, 1, vinyl -H), 6.63 (s, 1, aromatic -H), 6.40 (s, 1, aromatic -H), 3.92 (s, 3, aromatic -OCH_3), 3.63 (m, 1, Ar-CH-), 2.57-

3.10 (m, 4, -CH_2); ^{13}C NMR ($CDCl_3$) δ 195.8 (s), 153.6 (s), 151.2 (s), 149.6 (s), 146.2 (s), 140.1 (s), 138.7 (s), 131.7 (d), 130.1 (s), 110.8 (d), 100.5 (d), 60.9 (q), 60.4 (q), 56.1 (q), 55.9 (q), 50.5 (d), 43.8 (t), 23.4 (t).

Exact mass calcd. for $C_{18}H_{20}O_5$: 316.131. Found: 316.131.

Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.25. Found: C, 68.30; H, 6.42.

2,3,4,8-Tetramethoxy-7-tert-butyldimethylsilyloxy-5,5a-dihydrobenz[a]azulene (23). To a solution of 0.80 mmol LDA, prepared at -78°C under argon in 1.0 mL of anhydrous THF was added a solution of tricyclic ketone 15 in 1.5 mL of THF. After stirring at -78°C for 30 min, 0.45 mL of a 2.0 M solution of t-$BuMe_2SiCl$ in HMPA was added. The reaction was then allowed to warm to RT and then quenched with saturated aqueous NH_4Cl. This mixture was diluted with 12 mL of ether and washed with water (4 x 12 mL) and brine (1 x 12 mL). After drying over $MgSO_4$, concentration in vacuo afforded crude 23 as a yellow oil, 266.1 mg. Purification by flash chromatography on silica gel (10 g, 3:1 ethyl acetate-hexane) gave a yellow, amorphous solid, 126.1 mg (51%): IR ($CHCl_3$) 3040-2820, 1585, 1460, 1380, 1215, 1115, 865, 835 cm^{-1}; ^1H NMR

($CDCl_3$) δ 6.37 (s, 1, aromatic -H), 6.16 (s, 1, vinyl -H), 5.73 (s, 1, vinyl -H), 5.51 (dd, 1, J = 10.5 Hz, J = 4.5 Hz, SiO-C=C-H), 3.87 (s, 3, Ar-OCH_3), 3.77 (s, 3, Ar-OCH_3), 3.71 Ar-OCH_3), 3.58 Ar-OCH_3), 2.67-3.00 (m, 1, Ar-CH-), 1.77-2.20 (m, 2, -CH_2-), 0.95 [s, 9, $(CH_3)_3C$-Si), 0.09 [s, 6, $(CH_3)_2Si$-).

Exact mass calcd. for $C_{24}H_{34}O_5Si$: 430.217. Found: 430.218.

2,3,4,8-Tetramethoxy-7-tert-butyldimethylsilyloxy-5,10-dihydrobenz[a]azulene (24). The silyl enol ether 23 (98.4 mg, 0.229 mmol) was dissolved in 2.0 mL of anhydrous THF under nitrogen at -78°C, and 0.20 mL of n-BuLi solution (1.27 M in hexane, 0.25 mmol) was added. After stirring at -78°C for 15 min, two drops of methanol were added, and the reaction was quenched with saturated aqueous NH_4Cl and allowed to warm to RT. It was diluted with 10 mL of dichloromethane and washed with 10 mL portions of water and brine. After drying over Na_2SO_4, removal of solvent in vacuo gave a crude, yellow oil, 96.8 mg. After filtration through a 1" x 20 mm plug of silica gel with 4:1 ethyl acetate-hexane, a yellow, amorphous solid was isolated, 89.5 mg (90%): IR (CCl_4) 3020-2820, 1565, 1460, 1360, 1235, 1215, 1155, 1090, 865, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (s, 1, aromatic -H), 5.88

(s, 1, vinyl -H), 4.99 (t, 3, J = 8 Hz, SiO-C=C-H), 3.87 (s, 3, Ar-OCH_3), 3.76 (s, 3, Ar-OCH_3), 3.75 (s, 3, Ar-OCH_3), 3.67 (s, 3, vinyl -OCH_3), 3.19 (s, 2, -CH_2 in 5-membered ring), 2.92 (d, 2, J = 8 Hz, -CH_2- in 7-membered ring), 0.93 [s, 9, $(CH_3)_3CSi$), 0.05 [s, 6, $(CH_3)_2Si$).

Exact mass calcd. for $C_{24}H_{34}O_5Si$: 430.217. Found: 430.218.

Phenylsulfenyl-(3,4,5-trimethoxyphenyl)-methane (26). Sodium methoxide (0.84 g, 15.5 mmol) was dissolved in 25 mL of methanol, and the resulting solution was cooled to 0°C. Benzenethiol (1.52 mL, 14.8 mmol) was added dropwise via syringe, and the reaction was stirred at 0°C for 15 min. At this time, a solution of 3.03 g (14.0 mmol) of 3,4,5-trimethoxybenzylchloride 17a in 35 mL of methanol was added. The reaction was stirred at 0°C for 10 min. Upon warming to RT, a white solid precipitated. After standing at RT for 15 min, solvent was removed in vacuo and the white residue was layered between 150 mL of dichloromethane and 100 mL of water. The resulting organic layer was washed with 150 mL portions of 10% aqueous NaOH and brine, and dried over Na_2SO_4. Removal of all solvents in vacuo afforded 26 as a white, crystalline solid, 4.01 g (99%), mp 77-78.5°C: IR ($CHCl_3$) 3040-2819, 1590, 1500, 1460, 1330, 1225, 1125, 1000 cm^{-1}; ^1H NMR

($CDCl_3$) δ 7.16-7.40 (m, 5, S-aromatic -H's), 6.47 (s, 2, aromatic -H), 4.03 (s, 2, Ar-CH_2-), 3.80 (s, 3, -OCH_3), 3.78 (s, 6, -OCH_3).

Exact mass calcd. for $C_{16}H_{18}O_3S$: 290.098. Found: 290.098.

Anal. calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.45; H, 6.18.

2,3,4,8-Tetramethoxy-10-phenylsulfenyl-5,5a-dihydro-benz[a]azulene-7(6H)-one (25). To a solution of 2.7 mL of anhydrous HMPA in 11.0 mL of anhydrous THF was added 1.57 g (5.41 mmol) of benzyl sulfide 26. The solution was cooled down to -78°C under argon, and 5.0 mL of s-butyllithium solution (1.18 M in cyclohexane, 5.90 mmol) was added over a 4-min period. The reaction was allowed to warm up to 0°C and stir for 15 min, then was cooled back down to -78°C. A solution of 1.10 g (5.55 mmol) of cyclopropanated quinone ketal 5 in 7.0 mL of THF was then added. The reaction was allowed to warm slowly to RT, and then quenched by dropwise addition of 2.0 mL of saturated aqueous NH_4Cl. The resulting mixture was diluted with 50 mL of ether and washed with water (3 x 75 mL) and brine (1 x 75 mL). The remaining organic layer was dried over Na_2SO_4 and freed of all volatiles in vacuo to afford crude 27 as a white, foamy solid, 2.83 g. This material

was virtually homogeneous by TLC (silica gel, ethyl acetate eluant), and was used for further operations without further purification: ^{1}H NMR ($CDCl_3$) major diastereomer δ 6.98-7.28 (m, 5, S-aromatic -H), 6.59 (s, 2, aromatic -H), 4.58 (s, 1, vinyl -H), 4.09 (s, 1, Ar-CH-S), 3.72 (s, 3, Ar-OCH_3), 3.70 (s, 6, Ar-OCH_3), 3.26 (s, 3, vinyl -OCH_3), 3.24 (s, 3, ketal -OCH_3), 3.15 (s, 3, ketal -OCH_3), 2.53 (broad s, 1, -OH), 0.22-1.72 (m, 4, cyclopropyl -H's); minor diastereomer δ 6.98-7.28 (m, 5, S-aromatic -H), 6.45 (s, 2, aromatic -H), 4.74 (s, 1, vinyl -H), 4.05 (s, 1, Ar-CH-S), 3.68 (s, 9, Ar-OCH_3), 3.34 (s, 3, vinyl -OCH_3), 3.12 (s, 3, ketal -OCH_3), 3.06 (s, 3, ketal -OCH_3), 2.62 (broad s, 1, -OH), 0.22-1.72 (m, 4, cyclopropyl -H).

The 2.83 g of crude 27 was dissolved in 25 mL of triflouroacetic acid, resulting in formation of an extremely dark solution. This was allowed to stir for 5 h at RT. At that time, the solution was diluted with 120 mL of ether, and slowly added to 200 mL of saturated aqueous $NaHCO_3$. Once addition was complete, the remaining organic phase was removed and washed with saturated aqueous $NaHCO_3$ (2 x 150 mL), water (1 x 150 mL), and brine (1 x 150 mL). After drying over Na_2SO_4, removal of solvents in vacuo gave a crude, brown, tarry residue.

This material was chromatographed over 100 g of silica gel, using the flash technique. Elution was first carried out with hexane-ethyl acetate, 8:3, 550 mL, and then with hexane-ethyl acetate, 1:1, 600 mL. Concentration of appropriate fractions *in vacuo* afforded spectrally pure tricyclic sulfide **25** as a highly viscous, deeply yellow gum, 1.36 g (59% overall from benzyl sulfide **26**). This material is slightly unstable, and is best stored at low temperature, under an inert atmosphere, and away from light: IR ($CHCl_3$) 3100-2820, 1655, 1590, 1465, 1435, 1340, 1215, 1135, 1005, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03-7.31 (m, 5, S-aromatic -H's), 6.79 (s, 1, aromatic -H), 6.47 (s, 1, vinyl -H), 3.93 (s, 3, $-OCH_3$), 3.80 (s, 3, $-OCH_3$), 3.67 (m, 1, Ar-C-H), 3.64 (s, 3, $-OCH_3$), 3.63 (s, 3, $-OCH_3$), 2.65-3.12 (m, 4, $-CH_2$).

Exact mass calcd. for $C_{24}H_{24}O_5S$: 424.134. Found: 424.136.

2,3,4,8-Tetramethoxy-10-phenylsulfinyl-5,10-dihydrobenz[a]azulene-7(6H)-one (28). A solution of 755.8 mg (1.780 mmol) of tricyclic sulfide **25** in 12.0 mL of anhydrous dichloromethane was cooled to -25°C under an argon atmosphere, and 384 mg (1.78 mmol, assuming 80% purity) of *m*-chloroperbenzoic acid was added as a solid at once. The resulting mixture was stirred at -25°C for 15 min, and then

quenched by dropwise addition of saturated aqueous $NaHCO_3$. The mixture was then washed with saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine (1 x 30 mL). After drying over Na_2SO_4, removal of solvents *in vacuo* left a crude, viscous, green oil, 790 mg. This material was immediately chromatographed over 35 g of neutral, activity III alumina. Elution was carried out first with 120 mL of ethyl acetate-hexane, 1:1, and then with pure ethyl acetate thereafter. Concentration of appropriate fractions *in vacuo* afforded the allylic sulfoxide **28**, a mixture of diastereomers, as a yellow, amorphous solid, 580 mg (74%). This material is slightly unstable and should be stored in the cold, away from light, and under an inert atmosphere. Subsequent recrystallization from ethyl acetate-petroleum ether gave an analytical sample of **28** as a yellow solid, m.p. 125.5-126.5°C (decomposition): IR ($CHCl_3$) 3030-2920, 1660, 1600, 1465, 1410, 1370, 1330, 1220, 1135, 1045, 995 cm^{-1}; ^1H NMR ($CDCl_3$), for equimolar mixture of diastereomers, δ 6.84-7.38 (12, m, S-aromatic H's and aromatic -H), 6.53 (s, 1, vinyl -H), 6.34 (s, 1, vinyl -H), 4.90 (s, 1, Ar-CH-S), 4.87 (s, 1, Ar-CH-S), 3.95 (s, 3, Ar-OCH_3), 3.93 (s, 3, Ar-OCH_3), 3.84 (s, 3, Ar-OCH_3), 3.80 (s, 3, Ar-OCH_3), 3.78 (s, 3, Ar-OCH_3), 3.74 (s, 3, Ar-OCH_3), 3.66 (s, 3, vinyl -OCH_3), 3.54 (s, 3, vinyl -OCH_3),

2.40-2.87 (m, 8, $-CH_2-$).

Anal. calcd. for $C_{24}H_{24}O_6S$: C, 65.44; H, 5.49. Found: C, 65.00; H, 5.40

2,3,4,8-Tetramethoxy-10-hydroxy-5,10-dihydrobenz[a]-azulene-7(6H)one and 2,3,4,8-tetramethoxy-5a-hydroxy-5,5a-dihydrobenz[a]azulene-7(6H)one (29). To a suspension of 600 mg (1.36 mmol) of allylic sulfoxide 28 in 16.0 mL of methanol under nitrogen was added 0.66 mL (5.0 mmol) of trimethylphosphite. The resulting mixture was heated to 48°C for 45 min. It was then cooled to RT, and the methanol was removed in vacuo. The residue was taken up in 25 mL of dichloromethane, and this solution was washed with 25 mL portions of water and brine. After drying over Na_2SO_4, removal of all solvents in vacuo afforded a crude, viscous, tan-brown oil. This material was chromatographed on 40 g of silica gel, using the flash technique. Elution was carried out with the following solvent mixtures: 1) ethyl acetate-hexane, 3:7, 300 mL; 2) ethyl acetate-hexane, 2:3, 200 mL; and 3) ethyl acetate-hexane, 1:1, 200 mL. Concentration of appropriate fractions afforded the mixture of alcohols 29 as a yellow, amorphous solid, 376 mg (83%). Subsequent recrystallization from ether gave an analytical sample, m.p. 153-154°C: IR ($CHCl_3$) 3600-3300, 3030-2820, 1680, 1650, 1600, 1460, 1350,

1285, 1230, 1130, 1090, 995, 905 cm^{-1}; ^1H NMR ($CDCl_3$), 1:1 mixture of regioisomers, δ 6.50 (s, 1, aromatic -H), 6.47 (s, 1, aromatic -H), 6.39 (s, 1, vinyl -H), 6.09 (s, 1, vinyl -H), 5.93 (s, 1, vinyl -H), 5.47 (s, 1, Ar-CH-OH), 3.95 (s, 3, Ar-OCH_3), 3.93 (s, 3, Ar-OCH_3), 3.81 (s, 6, Ar-OCH_3), 3.80 (s, 6, Ar-OCH_3), 3.67 (s, 6, vinyl -OCH_3), 1.63-3.23 (m, 8, -CH_2-).

Exact mass calcd. for $C_{18}H_{20}O_6$: 332.126. Found: 332.125.

Anal. calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.93; H, 6.07.

2,3,4,8-Tetramethoxybenz[a]azulen-7(6H)-10(5H)-dione (30). The mixture of alcohols 29 (375.6 mg, 1.130 mmol) was dissolved in 12.0 mL of anhydrous dichloromethane at RT and under nitrogen. To this solution was added 487.2 mg (2.26 mmol) of pyridinium chlorochromate. The dark reaction mixture was stirred for 2 h at RT, then filtered to remove remaining suspended material. The filtrate was then rapidly eluted through a plug of silica gel, and the eluant was concentrated in vacuo to afford a crude, brown gum, 260 mg. This material was chromatographed on 25 g of silica gel, using the flash technique (1:1 ethyl acetate-hexane) to afford a yellow, amorphous solid, 161.1 mg (43%). Recrystallization gave 30 as yellow needles,

m.p. 158-160°C: IR (CHCl) 3020-2810, 1770, 1705, 1655, 1595, 1470, 1430, 1330, 1230, 1180, 1100, 1040, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (s, 1, aromatic -H), 6.78 (s, 1, vinylic -H), 3.96 (s, 6, aromatic $-OCH_3$), 3.90 (s, 3, aromatic $-OCH_3$), 3.78 (s, 3, vinyl $-OCH_3$), 2.42-3.80 (m, 4, $-CH_2-$). Material was not stable enough to obtain anal. data.

2,3,4,8-Tetramethoxy-5,10-dihydrobenz[a]azulen-7(6H)-one-10-methanesulfonate (31). The mixture of alcohols 29 (49.2 mg, 0.148 mmol) was dissolved in 1.0 mL of anhydrous dichloromethane, and the solution was cooled to -78°C under an argon atmosphere. To this was added triethylamine (30 μL, 0.21 mmol), followed by methanesulfonyl chloride (14 μL, 0.18 mmol). The resulting solution was stirred at -78°C for 10 min, then allowed to warm to 0°C and stir for 25 min. It was then quenched by addition of 1 mL of saturated aqueous NH_4Cl, and the mixture was partitioned between 10 mL of water and 10 mL of dichloromethane. The organic layer was removed and washed with 10 mL portions of water and brine, then dried over Na_2SO_4. Removal of all solvents in vacuo afforded the mesylate 31 as a yellow, foamy solid, 61.5 mg (quantitative). By NMR, this material is of excellent purity, satisfactory as is for subsequent operations. Further purification can be carried out by rapid filtration through a short column

of silica gel, using ethyl acetate as eluant. An analytical sample was prepared by recrystallization from ether-petroleum ether, m.p. 138-140°C (decomposition): IR ($CHCl_3$) 3100-2820, 1605, 1465, 1410, 1365, 1215, 1115, 1075, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.58 (s, 1, aromatic -H), 6.00 (s, 1, vinylic -H), 5.58 (s, 1, Ar-CH-O), 3.96 (s, 3, Ar-OCH_3), 3.85 (s, 6, Ar-OCH_3), 3.75 (s, 3, Ar-OCH_3), 3.10 (s, 3, -OSO_2CH_3), 1.60-3.10 (m, 4, -CH_2-).

Exact mass calcd. for $C_{19}H_{22}O_8S$: 410.103. Found: 410.101.

Anal. calcd. for $C_{19}H_{22}O_8S$: C, 55.60; H, 5.40. Found: C, 55.40; H, 5.40.

N-Methyl-(3,4,5-Trimethoxyphenyl)-methylamine (32). To a suspension of 1.96 g (10.0 mmol) of 3,4,5-trimethoxybenzaldehyde 16 in 8 mL of methanol was added 1.2 mL of 40% aqueous methylamine. The resulting solution was stirred at RT for 1 h, then poured into 20 mL of half-saturated aqueous sodium chloride. The resulting mixture was extracted with dichloromethane (4 x 25 mL), and the combined extracts were dried over Na_2SO_4. Concentration in vacuo afforded the crude N-methyl imine as a colorless oil, 2.07 g.

This material was immediately dissolved in 12 mL of absolute ethanol at RT, and 0.38 g (10 mmol) of sodium

borohydride was added at once. After stirring at RT for 2 h, the reaction mixture was concentrated under reduced pressure and the foamy white residue was partitioned between 40 mL of dichloromethane and 40 mL of water. The organic layer was removed and washed with 40 mL of brine, then dried over Na_2SO_4. Removal of solvents in vacuo afforded the amine as a colorless oil, 2.01 g (96%). Purity adequate for further operations: IR ($CHCl_3$) 3340, 3080-2780, 1590, 1505, 1460, 1325, 1225, 1125, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (s, 2, aromatic -H), 3.86 (s, 6, $-OCH_3$), 3.85 (s, 3, $-OCH_3$), 3.59 (s, 2, $Ar-CH_2-$), 2.43 (s, 3, $N-CH_3$), 1.42 (s, 1, N-H).

Exact mass calcd. for $C_{11}H_{17}NO_3$: 211.121. Found: 211.121.

N-(3,4,5-Trimethoxyphenyl)-methyl-N,N',N',N'',N''-pentamethylphosphoryltriamide (33a). To 20 mL of anhydrous dichloromethane was added 2.00 g (9.47 mmol) of amine 32, 1.53 mL (11.0 mmol) of triethylamine, and, finally, 1.48 mL (10.0 mmol) of bis-dimethylaminophosphochloridate. The resulting solution was heated to reflux for 7 h under a nitrogen atmosphere. It was then allowed to cool to RT, washed with 25 mL portions of water and brine, and dried over Na_2SO_4. After concentration in vacuo, there remained 3.05 g of an impure, colorless oil. This material was

chromatographed over an 8" x 30 mm column of silica gel, using the flash technique. Elution was first carried out with 120 mL of ethyl acetate, then with a 1:9 methanol-ethyl acetate mixture. Concentration of appropriate fractions gave the desired phosphoramide as a white, crystalline solid, 1.92 g (59%), m.p. 55-57°C. A small portion of this material was recrystallized from ether-petroleum ether to give an analytical sample, m.p. 62-63°C: IR ($CHCl_3$) 3030-2800, 1590, 1460, 1415, 1335, 1290, 1220, 1125, 985, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 (s, 2, aromatic-H), 4.05 (d, 2, J = 9 Hz, Ar-CH_2-), 3.84 (s, 6, -OCH_3), 3.83 (s, 3, -OCH_3), 2.67 [d, 12, J = 9 Hz, -$N(CH_3)_2$], 2.52 (d, 3, J = 9 Hz, -N-CH_3).

Exact mass calcd. for $C_{15}H_{28}N_3O_4P$: 345.182. Found: 345.182.

Anal. calcd. for $C_{15}H_{28}N_3O_4P$: C, 52.16; H, 8.17; N, 12.17. Found: C, 52.25; H, 8.30; N, 12.26.

N-[2,3,4,8-Tetramethoxy-5,5a-dihydrobenz[a]azulene-7(6H)one-10yl]-N,N',N',N'',N''-pentamethylphosphoryltriamide (35a). A solution of 537.0 mg (1.559 mmol) of phosphoramide 33a in 5.0 mL of anhydrous THF was cooled to -78°C under a nitrogen atmosphere. A 1.61 M solution of n-butyllithium in hexane (1.10 mL, 1.77 mmol) was added over a 2-min period, and the resulting deeply red solution was stirred

at -78°C for an additional 30 min. At that time, a solution of 318 mg (1.60 mmol) of cyclopropanated quinone ketal 5 in 2.5 mL of THF was added. The reaction was maintained at -78°C for 15 min and then allowed to warm slowly to RT. Upon reaching RT, it was quenched by dropwise addition of saturated aqueous ammonium chloride and diluted with 40 mL of dichloromethane. This mixture was washed with brine (2 x 30 mL) and dried over Na_2SO_4. Removal of solvents in vacuo left a viscous, yellow oil, 848.1 mg. Although all of this material was used immediately in the cyclization reaction to form 35a, a similar crude product from an earlier run was chromatographed on silica gel (flash technique, 8" x 20 mm column for 818 mg of substrate). Elution was carried out first with 150 mL of ethyl acetate and then with 16:84 methanol-ethyl acetate. Concentration of appropriate fractions afforded reasonably pure 34a as a white, foamy solid, apparently one diastereomer: ^1H NMR ($CDCl_3$) δ 7.06 (s, 2, aromatic -H), 5.53 (d, 1, J = 1 Hz, vinyl -H), 4.46 (d, 1, J = 12 Hz, Ar-CH-N), 3.85 (s, 9, Ar-OCH_3), 3.63 (s, 3, vinyl -OCH_3), 3.40 (s, 3, ketal -OCH_3), 3.26 (s, 3, ketal -OCH_3), 2.81 (d, 3, J = 9 Hz, N-CH_3), 2.61 [d, 6, J = 9 Hz, N-$(CH_3)_2$], 2.41 [d, 6, J = 9 Hz, N-$(CH_3)_2$], 2.13-2.40 (m, 1, cyclopropyl -H), 0.33-0.68 (m, 1, cyclopropyl -H).

The 848 mg of crude addition product 34a, as described in the above preparation, was dissolved in 14 mL of anhydrous nitromethane, and the solution was cooled down to 0°C under nitrogen. Boron triflouride etherate (0.65 mL) was then added, and the highly colored solution was stirred at 0°C for 5 min and at RT for 10 min. It was then quenched with saturated aqueous $NaHCO_3$, and partitioned between 25 mL of water and 25 mL of dichloromethane. The organic layer was removed and washed with 30 mL portions of saturated aqueous $NaHCO_3$, water, and brine, and finally dried over Na_2SO_4. Removal of solvents in vacuo left a highly crude, brown residue. This material was chromatographed on 30 g of silica gel, using the flash technique. Elution was carried out first with methanol-ethyl acetate 3:97, 300 mL, and then with methanol-ethyl acetate 15:84, 400 mL. Concentration of appropriate fractions in vacuo afforded the tricyclic phosphoramide 35a in good purity, 423.0 mg (57% overall from 33a), as a red oil: IR ($CHCl_3$) 3100-2800, 1650, 1595, 1460, 1415, 1345, 1220, 1125, 990, 925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (d, 1, J = 2 Hz, aromatic -H), 3.93 (s, 3, $-OCH_3$), 3.85 (s, 3, $-OCH_3$), 3.82 (s, 3, $-OCH_3$), 3.77 (s, 3, $-OCH_3$), 3.63 (m, 1, Ar-C-H), 2.40-3.15 (m, 4, $-CH_2-$), 2.91 (d, 3, J = 9 Hz, $N-CH_3$), 2.62 [d, 12, J = 9 Hz,

$-N(CH_3)_2]$.

Exact mass calcd. for $C_{23}H_{34}N_3O_6P$: 479.218. Found: 479.219.

α-(2-Hydroxy-4,5,5-trimethoxybicyclo[4.1.0]hept-3-en-2-yl)-α-(3,4,5-trimethoxyphenyl)acetonitrile (41). A solution of 655.3 mg (3.16 mmol) of trimethoxyphenylacetonitrile 20 in 5.5 mL of anhydrous THF and 0.9 mL of HMPA was cooled to 0°C under nitrogen, and 5.0 mL of n-BuLi solution (1.40 m in hexane, 7.0 mmol) was added over the next 5 min. The resulting dark solution was stirred at 0°C for 15 min and at RT for 45 min. It was cooled back to 0°C, and a solution of ketone 5 (670 mg, 3.38 mmol) in 3.0 mL of anhydrous THF was added. After stirring at 0°C for 30 min, the reaction was warmed to RT and quenched with saturated aqueous NH_4Cl. This mixture was diluted with 40 mL of dichloromethane, and washed with 40 mL portions of water and brine. After drying over $MgSO_4$, concentration of the remaining organic layer in vacuo left a crude red-brown oil which still contained HMPA, 1.60 g. Purification was carried out by flash chromatography on silica gel (6" x 30 mm column, 3:2 ethyl acetate-petroleum ether). Concentration of appropriate fractions in vacuo afforded 41 as a nearly white solid, 780 mg (61%), m.p. 125-129°C: ^1H NMR ($CDCl_3$) major diastereomer δ 6.57 (s,

2, aromatic -H), 5.94 (s, 1, vinyl -H), 5.03 (s, 1, Ar-CH-CN), 3.85 (s, 6, Ar-OCH_3), 3.83 (s, 3, Ar-OCH_3), 3.56 (s, 3, vinyl -OCH_3), 3.30 (s, 3, ketal -OCH_3), 3.03 (s, 3, ketal -OCH_3), 1.93-2.30 (m, 2, cyclopropyl -H), 0.70-1.53 (m, 2, cyclopropyl -H); minor diastereomer δ 6.37 (s, 2, aromatic -H), 5.90 (s, 1, vinyl -H), 4.96 (s, 1, Ar-CH-CN), 3.85 (s, 9, Ar-OCH_3), 3.60 (s, 3, vinyl -H), 3.27 (s, 3, ketal -OCH_3), 3.03 (s, 3, ketal -OCH_3).

Exact mass calcd. for M-H_2O ($C_{21}H_{25}O_6N$): 387.168. Found: 387.170.

α-(4,5-Dioxobicyclo[4.1.0]hept-2-en-2-yl)-α-(3,4,5-trimethoxyphenyl)acetonitrile (42). Crude vinylogous hemiketal 41, prepared from 208.1 mg (1.00 mmol) of phenylacetonitrile 20, was dissolved in 8 mL of dichloromethane, and 0.8 mL of trifluoroacetic acid was added at RT. The solution was stirred for 75 min, and then washed with 10% aqueous $NaHCO_3$ until gas evolution appeared complete. The remaining organic layer was washed with 10-mL portions of water and brine, then dried over $MgSO_4$. Removal of solvents in vacuo left a dark-yellow, viscous oil, 375 mg. This material was chromatographed at medium pressure (Lobar size B column, 1:1 ethyl acetate-hexane, 15 $mL \cdot min^{-1}$). Concentration of appropriate fractions afforded the dione 42 as a 3:2 mixture of diastereomers,

172.7 mg (53% overall from 20), m.p. 133-135°C. Recrystallization from ethyl acetate-ether-hexane afforded 42 as a slightly yellow solid, m.p. 135-137°C: IR ($CHCl_3$) 3060-2920, 2250, 1690, 1685, 1600, 1465, 1290, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) major diastereomer δ 6.68 (s, 1, vinyl -H), 6.44 (s, 2, aromatic -H), 5.18 (s, 1, -CH-CN), 3.83 (s, 6, $-OCH_3$), 3.81 (s, 3, $-OCH_3$), 2.45-2.70 (m, 2, cyclopropyl -H), 1.22-1.85 (m, 2, cyclopropyl -H); minor diastereomer δ 6.50 (s, 2, aromatic -H), 6.35 (s, 1, vinyl -H), 5.07 (s, 1, -CH-CN), 3.83 (s, 6, $-OCH_3$), 3.81 (s, 3, $-OCH_3$), 2.45-2.70 (m, 2, cyclopropyl -H), 1.22-1.85 (m, 2, cyclopropyl -H).

Exact mass calcd. for $C_{18}H_{19}O_5N$: 341.126. Found: 341.126.

5-[(3,4,5-Trimethoxyphenyl)cyanomethylidene]-2,2,3-trimethoxybicyclo[4.1.0]hept-3-ene (43). The purified cyano-alcohol 41 (535.6 mg, 1.32 mmol) was dissolved in 4.5 mL of anhydrous dichloromethane, 0.40 mL (2.9 mmol) of triethylamine was added, and the solution was cooled to -78°C under nitrogen. After 112 mL (1.45 mmol) of methanesulfonyl chloride had been added, the reaction was stirred at -78°C for 30 min, then warmed to RT and stirred for 30 min. After quenching with 5% aqueous $NaHCO_3$, the mixture was diluted with 5 mL of dichloromethane and washed

with water (2 x 10 mL) and brine (1 x 10 mL). The remaining organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to leave 542 mg of a yellow-orange gum. Purification by flash chromatography on silica gel (40 g, 11:9 ethyl acetate-petroleum ether) afforded 43, a deeply yellow solid, 486.8 mg (95%), m.p. 132-135°C. Recrystallization (ether petroleum ether) gave 43 as a yellow solid, 135-137°C: IR ($CHCl_3$) 3060-2920, 2220, 1675, 1640, 1595, 1470, 1345, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 (s, 2, aromatic -H), 5.95 (d, 1, J = 1.5 Hz, vinyl -H), 3.90 (s, 9, aromatic $-OCH_3$), 3.64 (s, 3, vinyl $-OCH_3$), 3.40 (s, 3, ketal $-OCH_3$), 3.16 (s, 3, ketal $-OCH_3$), 1.90-2.28 (m, 2, cyclopropyl -H), 1.33-1.60 (m, 1, cyclopropyl -H), 0.87-1.05 (m, 1, cyclopropyl -H).

Exact mass calcd. for $C_{21}H_{25}O_6N$: 387.168. Found: 387.170.

Reduction of 2-(2,3,4-trimethoxyphenyl)-nitroethylene (46) to 2-(2,3,4-trimethoxyphenyl)-ethylamine (47). A solution of 153.4 mg (0.641 mmol) of nitrostyrene 46 and 98.2 mg (0.106 mmol) of $(Ph_3P)_3RhCl$ in 4.0 mL of anhydrous toluene and 4.0 mL of absolute ethanol was hydrogenated (1 atm, RT) for 12.5 h. The mixture was then concentrated *in vacuo*, and the residue was eluted through a short column of activity I alumina (3:2 hexane-ethyl acetate),

giving a red-orange oil, 140 mg. Further purification by chromatography on silica gel (15 g, 3:7 ethyl acetate-hexane) afforded the nitro-compound as a slightly yellow oil, 112.4 mg (73%): ^{1}H NMR ($CDCl_3$) δ 6.83 (d, 1, J = 8 Hz, aromatic -H), 6.54 (d, 1, J = 8 Hz, aromatic -H), 4.56 (t, 3, J = 7 Hz, $-CH_2NO_2$), 3.91 (s, 3, Ar-OCH_3), 3.84 (s, 3, Ar-OCH_3), 3.82 (s, 3, Ar-OCH_3), 3.21 (t, 3, J = 7 Hz, Ar-CH_2).

This nitro-compound (55.8 mg, 0.231 mmol) was dissolved in 0.4 mL of absolute ethanol, 24.6 mg of 5% Pd on C was added, and the mixture was hydrogenated (1 atm, RT) for 2 h. The catalyst was removed by vacuum filtration through Celite, and the filtrate was concentrated in vacuo. The residue was taken up in 5 mL of 5% aqueous HCl, and the resulting solution was washed with ether (2 x 5 mL). The remaining aqueous layer was rendered slightly basic by addition of NH_4OH, then extracted with dichloromethane (2 x 5 mL). The extracts were combined, dried over Na_2SO_4, and concentrated in vacuo to afford the known[38] phenylethylamine 47 as a colorless oil, 36.2 mg (74%): ^{1}H NMR ($CDCl_3$) δ 6.81 (d, 2, J = 8 Hz, aromatic -H), 6.56 (d, 2, J = 8 Hz, aromatic -H), 3.86 (s, 6, Ar-OCH_3), 3.83 (s, 3, Ar-OCH_3), 2.56-2.97 (m, 4, $-CH_2CH_2-$), 1.96 (broad s, 2, $-NH_2$). This was identical in all respects to material

prepared by the literature procedure.[38]

N-2-(2,3,4-Trimethoxy-5-hydroxymethylphenyl)-ethylamine ethyl carbamate (51a). A solution of 1.07 g (4.84 mmol) of 5,6,7-trimethoxy-1,2-dihydroisoquinoline in 10 mL of anhydrous THF was cooled to 0°C under a nitrogen atmosphere. Ethyl chloroformate (0.49 mL, 5.2 mmol) was added, and the reaction was stirred at 0°C for 15 min, then allowed to warm to RT and was stirred for an additional 15 min. At this time, 4.0 mL of 10% aqueous NaOH was added, and the resulting two-phased mixture was stirred vigorously until both phases were colorless and free of suspended solid. To this mixture was added 5.0 mL of a 2 M solution of sodium borohydride in 15% aqueous NaOH. Vigorous stirring was continued for 3 h at RT; the reaction was then diluted with 40 mL of ether. The resulting organic layer was removed and washed with 50-mL portions of water and brine and dried over $MgSO_4$. Removal of solvents in vacuo left a crude, white solid, 1.41 g. This was recrystallized (dichloromethane-ether-petroleum ether) to afford pure 51a, 1.27g (84%), m. p. 101-102°C: IR ($CHCl_3$) 3460, 3430, 3030-2820, 1700, 1600, 1510, 1455, 1230, 1120, 1030, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.73 (s, 1, aromatic -H), 5.23 (broad s, 1, -N-H), 4.63 (broad s, 2, Ar-CH_2-OH), 4.05 [q, 2, J = 7 Hz, C(=O)-OCH_2-],

3.87 (s, 3, Ar-OC$\underline{H}_3$), 3.84 (s, 6, Ar-OC$\underline{H}_3$), 3.31 (q, 2, J = 7 Hz, -C$\underline{H}_2$-NH-), 2.82 (t, 2, J = 7 Hz, Ar-C$\underline{H}_2$-C), 1.20 [t, 3, J = 7 Hz, C(=O)-CH_2-C$\underline{H}_3$].

Exact mass calcd. for $C_{15}H_{23}NO_6$: 313.152. Found: 313.154.

Anal. calcd. for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.36; H, 7.37; N, 4.49.

N-2-[2,3,4-Trimethoxy-5-(α-phenylsulfenylmethyl)-phenyl]-ethylamine ethyl carbamate (51b). To a suspension of 1.25 g (3.99 mmol) of benzylic alcohol 51a in 28 mL of anhydrous toluene was added 1.12 mL (8.0 mmol) of triethylamine. The mixture was cooled to 0°C under a nitrogen atmosphere, and 0.32 mL (4.4 mmol) of thionyl chloride was added. The reaction was stirred at 0°C for 20 min, then allowed to warm up to RT and stir for an additional 30 min. The mixture was then diluted with 30 mL of ether and freed of suspended solid by filtration. The filtrate was washed with 50-mL portions of water and brine, then dried over $MgSO_4$. Concentration in vacuo left a colorless oil, 1.39 g. Although this crude chloride was carried on to the sulfide immediately and without further purification, a sample from an earlier run was purified by chromatography on silica gel 60 (flash technique, elution with 2:3 ethyl acetate-hexane) to afford reasonably pure

chloride as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.59 (s, 1, aromatic -H), 5.02 (broad s, 1, N-H), 4.51 (s, 2, Ar-CH_2-Cl), 4.01 [q, 2, C(=O)OCH_2-], 3.85 (s, 3, Ar-OCH_3), 3.80 (s, 3, Ar-OCH_3), 3.77 (s, 3, Ar-OCH_3), 3.21 (q, 2, J = 7 Hz, -CH_2N), 2.79 (dd, 2, J = 7 Hz, J = 6 Hz, Ar-CH_2-CH_2), 1.19 [t, 3, J = 7 Hz, C(=O)OCH_2CH_3).

The crude chloride was converted to sulfide 51b as follows. Sodium methoxide (0.25 g, 4.6 mmol) was dissolved in 7 mL of methanol at 0°C under a nitrogen atmosphere, and 0.48 mL (4.6 mmol) of benzenethiol was added. The solution was stirred at 0°C for 15 min, at which time a solution of all 1.39 g of crude chloride in 8 mL of methanol was added dropwise. The reaction was stirred at 0°C for 15 min, then allowed to warm to RT and stir for 45 min. The resulting mixture was concentrated *in vacuo*, and the residue was partitioned between 30 mL of methylene chloride and 30 mL of water. The resulting organic layer was removed and washed with 30-mL portions of water and brine, then dried over $MgSO_4$. Removal of solvents *in vacuo* gave a nearly colorless oil, 1.66 g. This material was chromatographed over 60 g of silica gel (11:9 petroleum ether-ethyl acetate) to afford the sulfide as a colorless, viscous oil, 1.29 g (80%). Distillation (215°C/0.2 mm) gave analytically pure 51b: IR ($CHCl_3$) 3460, 3040-2820,

1705, 1600, 1575, 1510, 1490, 1455, 1405, 1355, 1225, 1055, 985, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14-7.47 (m, 5, -S-aromatic -H), 6.47 (s, 1, aromatic -H), 5.07 (broad s, 1, -N-H), 4.06 (s, 2, Ar-CH_2-S), 4.04 [q, 2, J = 7 Hz, C(=O)-OCH_2), 3.87 (s, 3, Ar-OCH_3), 3.82 (s, 3, Ar-OCH_3), 3.69 (s, 3, Ar-OCH_3), 3.31 (q, 2, J = 7 Hz, -CH_2-NH-), 2.81 (t, 2, J = 7 Hz, Ar-CH_2-C), 1.19 [t, 3, J = 7 Hz, $C(=O)OCH_2CH_3$.

Exact mass calcd. for $C_{21}H_{27}NO_5S$: 405.161. Found: 405.161.

Anal. calcd. for $C_{21}H_{27}NO_5S$: C, 62.20; H, 6.71; N, 3.45. Found: C, 62.19; H, 6.67; N, 3.52.

N-2-[2,3,4,8-Tetramethoxy-10-phenylsulfenyl-5,5a-dihydrobenz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate (52). A solution of carbamate-sulfide 51b (614 mg, 1.51 mmol) in 9.0 mL of anhydrous THF and 1.0 mL of anhydrous HMPA was cooled to -78°C under an argon atmosphere. To this was added 2.60 mL of t-butyllithium solution (1.3 M in pentane, 3.38 mmol) over a 3-min period. The reaction mixture was maintained at -78°C for 45 min, at which time a solution of 317 mg (1.60 mmol) of cyclopropanated quinone ketal 5 in 3.0 mL of THF was added. After stirring at -78°C for an additional 20 min, the solution was allowed to warm up to 0°C and stir for

20 min. Quenching was then carried out by dropwise addition of saturated aqueous NH_4Cl, and the mixture was diluted with 40 mL of ether. After washing with water (3 x 40 mL) and brine (1 x 40 mL), the remaining organic phase was dried over $MgSO_4$. Removal of all volatiles *in vacuo* afforded a white, foamy semisolid, 903 mg (99% mass balance). This material was carried on without further purification. The 903 mg of crude addition product was dissolved in 20 mL of anhydrous nitromethane at 0°C, and 0.90 mL of boron trifluoride etherate was added. The deeply colored solution was stirred at 0°C for 20 min, then allowed to warm to RT and stir for 30 min. Saturated aqueous $NaHCO_3$ was added to quench, and the resulting mixture was partitioned between 50 mL of ether and 50 mL of water. The organic layer was removed and washed with 10% aqueous $NaHCO_3$ (2 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL). After drying over $MgSO_4$, concentration *in vacuo* left a highly viscous, red-brown oil. This material was chromatographed over 70 g of silica gel, using the flash technique. Elution with ethyl acetate-petroleum ether, 9:11, and concentration of appropriate fractions *in vacuo* afforded 328 mg (39% overall from 51b) of tricyclic ketone 52 as a deeply yellow, foamy solid: IR ($CHCl_3$) 3440, 3050-2900, 1700, 1675, 1500, 1470, 1460, 1400, 1335,

1220, 1130, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03-7.33 (m, 5, S-aromatic -H's), 6.86 (s, 1, vinyl -H), 4.87 (broad s, 1, -N-H), 4.02 [q, 2, J = 7 Hz, -C(=O)-OCH_2-], 3.95 (s, 3, Ar-OCH_3), 3.87 (s, 3, Ar-OCH_3), 3.83 (s, 3, Ar-OCH_3), 3.60 (s, 3, vinyl -OCH_3), 2.60-3.80 (m, 7, Ar-CH_2-CH_2-N, ring H's), 1.30-1.90 (m, 2, ring -CH_2-), 1.16 [t, 3, J = 7 Hz, C(=O)-OCH_2CH_3].

Exact mass calcd. for $C_{29}H_{33}NO_7S$: 539.198. Found: 539.198.

N-2-[2,3,4,8-Tetramethoxy-10-phenylsulfenyl-5,10-dihydrobenz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate (53). To a solution of 154.6 mg (0.287 mmol) of vinyl sulfide 52 in 2.5 mL of anhydrous benzene at RT and under nitrogen was added 0.15 mL of triethylamine. The solution was stirred for 30 min, then freed of all volatiles in vacuo to afford allyl sulfide 53 as a yellow-orange foam, 149.6 mg: IR ($CHCl_3$) 3470, 3080-2810, 1720, 1675, 1500, 1465, 1370, 1260, 1230, 1120, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.84-7.30 (m, 5, S-aromatic -H), 6.34 (s, 1, vinyl -H), 4.99 (broad s, 1, -N-H), 4.59 (s, 1, Ar-CH-S), 4.09 [q, 2, J = 7 Hz, C(=O)-OCH_2), 3.93 (s, 3, Ar-OCH_3), 3.87 (s, 3, Ar-OCH_3), 3.73 (s, 3, Ar-OCH_3), 3.63 (s, 3, vinyl -OCH_3), 2.32-3.75 (m, 8, four -CH_2-S), 1.23 [t, 3, J = 7 Hz, C(=O)OCH_2CH_3).

Exact mass calcd. for $C_{29}H_{33}O_7NS$: 539.198. Found: 539.198.

N-2-[2,3,4,8-Tetramethoxy-10-phenylsulfinyl-5,10-dihydrobenz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate (54). A solution of 149.6 mg (0.277 mmol) of allylic sulfide 53 in 5.0 mL of anhydrous dichloromethane cooled to -25°C under nitrogen, and 60.4 mg (0.28 mmol) of 80% m-chloroperbenzoic acid was added at once. The mixture was stirred at -25°C for 30 min, then slowly allowed to warm to RT. Upon reaching RT, it was diluted with 8 mL of dichloromethane and washed with 10% aqueous $NaHCO_3$ (3 x 12 mL), water (1 x 12 mL), and brine (1 x 12 mL). The remaining organic layer was dried over $MgSO_4$ and concentrated in vacuo to leave 169.1 mg of a yellow-orange foam. Elution through a 3" x 20 mm column of silica gel (100% ethyl acetate) gave 54 as a deeply yellow foam, 136.2 mg (88%): ^1H NMR ($CDCl_3$) δ 7.04-7.55 (m, 4, S-aromatic -H's), 6.78 (dd, 1, J = 8 Hz, J = 1 Hz, S-aromatic -H), 5.20 (s, 1, Ar-CH-S), 5.20 (broad s, 1, -NH), 4.10 [q, 2, J = 7 Hz, C(=O)OCH_2-], 3.97 (s, 3, Ar-OCH_3), 3.87 (s, 3, Ar-OCH_3), 3.81 (s, 3, Ar-OCH_3), 3.60 (s, 3, vinyl -OCH_3), 2.00-3.80 (m, 8, four -CH_2-S), 1.23 [t, 3, J = 7 Hz, -C(=O)OCH_2CH_3].

N-2-[2,3,4,8-Tetramethoxy-10-hydroxy-5,10-dihydro-

benz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate and N-2-[2,3,4,8-tetramethoxy-5a-hydroxy-5,5a-dihydro-benz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate (55). Allylic sulfoxide 54 (136.2 mg, 0.245 mmol) was dissolved in 5.0 mL of methanol at RT under argon, and 0.12 mL (0.97 mmol) of trimethyl phosphite was added. The solution was stirred for 10 min at RT, then warmed briefly to 48°C. At this point, TLC monitoring showed that reaction was complete. The solution was allowed to cool to RT, and all volatiles were removed in vacuo. The resulting oil was taken up in 12 mL of ether, and this solution was washed with aqueous Na_2CO_3 (2 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL). After drying over $MgSO_4$, concentration of the remaining organic layer in vacuo left a viscous, orange oil, 99.3 mg. This material was flash chromatographed on a 12" x 10 mm column of silica gel, using the following eluants: 1:1 ethyl acetate-hexane, 170 mL; 13:7 ethyl acetate-hexane; 3:1 ethyl acetate-hexane, thereafter. Concentration of appropriate fractions in vacuo afforded 55 as a nearly 3:2 mixture of allylic alcohol regioisomers, a yellow, foamy solid, 64.8 mg (59%): ^1H NMR ($CDCl_3$) major regio-isomer δ 6.14 (s, 1, vinyl -H), 5.52 (s, 1, Ar-CH-OH), 4.97 (broad s, 1, N-H), 4.07 [q, w, J = 7 Hz, C(=O)OCH$_2$-],

3.96 (s, 3, Ar-OC$\underline{H}_3$), 3.86 (s, 6, Ar-OC$\underline{H}_3$), 3.69 (s, 3, vinyl -OC$\underline{H}_3$), 3.29 (q, 2, J = 7 Hz, C$\underline{H}_2$-N), 2.81 (q, 2, J = 7 Hz, Ar-C$\underline{H}_2$CH_2N), 1.22 [t, 3, J = 7 Hz, (C=O)OCH_2C$\underline{H}_3$], both regioisomers share a set of multiplets, δ 1.62-3.43 (4 each, ring -C$\underline{H}_2$C$\underline{H}_2$-); minor regioisomer δ 6.63 (s, 1, vinyl -$\underline{H}$), 6.11 (s, 1, vinyl -$\underline{H}$), 4.92 (broad, 1, -N-$\underline{H}$), 4.07 [q, 2, J = 7 Hz, C(=O)OC$\underline{H}_2$], 3.95 (s, 3, Ar-OC$\underline{H}_3$), 3.86 (s, 6, Ar-OC$\underline{H}_3$), 3.69 (s, 3, vinyl -OC$\underline{H}_3$), 3.29 (q, 2, J = 7 Hz, -C$\underline{H}_2$N), 2.81 (t, 2, J = 7 Hz, ArC$\underline{H}_2$CH_2N), 1.22 [t, 3, J = 7 Hz, N(C=O)OCH_2C$\underline{H}_3$].

N-2-[2,3,4,8-Tetramethoxy-10-methansulfonyloxy-5,10-dihydrobenz[a]azulene-7(6H)-one-1-yl]-ethylamine ethyl carbamate (56). The mixture of alcohols 55 (64.2 mg, 0.143 mmol) was dissolved in 1.8 mL of anhydrous dichloromethane, and the solution was cooled to -78°C under nitrogen. Triethylamine (25 μL, 0.18 mmol) was added, followed by 13.2 μL (0.170 mmol) of methanesulfonyl chloride. The resulting solution was stirred at -78°C for 10 min, then allowed to warm to RT and stir for 25 min. The reaction was then quenched with saturated aqueous NH_4Cl and diluted with 8 mL of dichloromethane. After washing with 10 mL portions of 10% aqueous $NaHCO_3$, water, and brine, the remaining organic phase was dried over $MgSO_4$. Concentration in vacuo afforded crude mesylate as a yellow foam.

Purification by flash chromatography on a 6" x 10 mm column of silica gel (3:1 ethyl acetate-hexane) gave 56 as a light yellow foam, 57.7 mg (77%): IR ($CHCl_3$) 3460, 3080-2110, 1715, 1620, 1575, 1475, 1455, 1370, 1240, 1115, 1075, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.14 (s, 1, vinyl -H), 5.57 (s, 1, Ar-CH-O), 4.88 (broad s, 1, -NH), 4.08 [q, 2, J = 7 Hz, C(=O)OCH_2], 3.94 (s, 3, Ar-OCH_3), 3.86 (s, 6, Ar-OCH_3), 3.75 (s, 3, vinyl -OCH_3), 3.29 (q, 2, J = 7 Hz, CH_2-N), 3.15 (s, 3, SO_2CH_3), 2.90 (t, 2, J = 7 Hz, Ar-CH_2-C), 2.64-2.95 (m, 1, ring -CH), 2.27-2.50 (m, 2, ring -CH_2), 1.55-1.90 (m, 1, ring -CH), 1.22 [t, 3, J = 7 Hz, NC(=O)CH_2CH_3].

Exact mass calcd for $C_{24}H_{31}NO_{10}S$: 525.167. Found: 525.169.

1,2,5-Trimethoxybenzene (60). Dimethoxyphenol 59b[53] (29.5 g, 0.19 mmol) was placed in a three-neck flask and heated to 105°C. To the resulting melt was added, simultaneously, a solution of 16 g (0.28 mol) of KOH in 25 mL of water and 30.2 g (0.25 mol) of dimethyl sulfate at such a rate that the reaction mixture remained basic and at a gentle reflux. After addition was complete, the mixture was then heated at reflux for 1.5 h, cooled, and quenched with 150 mL of 30% NH_4OH. The resulting mixture was diluted with 500 mL of dichloromethane, and the

organic phase was removed. The aqueous layer was extracted with dichloromethane (150 mL), and the combined organic layers were washed with water (750 mL) and 20% ammonium hydroxide (500 mL), and dried over Na_2SO_4. Concentration *in vacuo* afforded a yellow liquid, which was purified by elution with dichloromethane through 150 g of silica gel to provide 28.84 g (90%) of **60**[54] as a colorless liquid.

1,1,2,4,4-Pentamethoxycyclohexa-2,5-diene (61). A solution of 1,2,4-trimethoxybenzene **60** (37.61 g, 0.224 mol) in 220 mL of 3% methanolic KOH was placed in a 400 mL beaker equipped with a magnetic stirrer and an ice-water bath. Into the solution was inserted a platinum anode and cathode, along with a potassium chloride reference electrode. Electrolysis was then carried out at 0°C for 25 h (initial potential, 4.0 V; initial current, 1.03 amp), using a P.A.R. 173 potentiostat/galvanostat as power source. Methanol was periodically added in order to keep the reaction at its original volume. Completion of electrolysis was confirmed both by observation of a substantial drop in the amount of current being passed through the solution (1.03 amp → 0.40 amp) and by examination of aliquots. The power source and electrodes were removed, and the reaction mixture was freed of solvents *in vacuo* to leave a tan residue. This material was layered between

300 mL of dichloromethane and 250 mL of half-saturated aqueous NaCl. The resulting organic layer was removed, and the aqueous layer was extracted with 100 mL of dichloromethane. The extract was combined with the initial organic phase, and the solution was washed with 300 mL of brine and dried over Na_2SO_4. Removal of all solvents in vacuo afforded the crude bis-ketal as an amber oil, of sufficient purity to be used directly in the next reaction, 46.71 g (91%): ^{1}H NMR ($CDCl_3$) δ 6.18 (dd, 1, J = 11 Hz, J = 2 Hz), 5.89 (d, 1, J = 11 Hz), 5.10 (d, 1, J = 2 Hz), 3.68 (s, 3), 3.30 (s, 6), 3.27 (s, 6).

3,4,4-Trimethoxycyclohexa-2,5-diene-1-one (62b). The crude bis-ketal 61 (46.71 g, 0.203 mol) was dissolved in 250 mL of THF and 60 mL of water at RT, and oxalic acid (1.0 g, 0.01 mol) was added at once. The solution was allowed to stir at RT for 12 min, and then was quenched with 5% aqueous Na_2CO_3. After dilution with 400 mL of ether, an organic layer separated. This was removed, and the remaining aqueous layer was extracted with ether (2 x 150 mL). All ether layers were combined and washed with 400 mL of brine, then dried over Na_2SO_4. After removal of solvents in vacuo, the orange residue was eluted rapidly with dichloromethane through a 7" column

of activity III alumina. This afforded 34.61 g of a crude, yellow solid, which was recyrstallized (chloroform-hexane) to afford 62b as a white solid, m.p. 62-64°C (lit.[55] 63.5-64.5°C), 26.86 g (72% from crude bis-ketal, 65% overall from trimethoxybenzene): IR ($CHCl_3$) 2880-3050, 2825, 1660, 1625, 1600, 1450, 1365, 1350, 1305, 1225, 1170, 1115, 1000, 990, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (d, 1, J = 11 Hz), 6.26 (dd, 1, J = 11 Hz, J = 1.5 Hz), 5.60 (d, 1, J = 1.5 Hz), 3.79 (s, 3), 3.32 (s, 6).

References and Notes

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(9) See Ref. 5.

(10) (a) Takaya, H.; Hayakawa, Y.; Makimo, S.; Noyori, R. J. Am. Chem. Soc. 1977, 100, 1778-1785; (b) Macdonald, T. L. J. Org. Chem. 1978, 43, 3621-3624; (c) Tanaka, K.; Yoshikoshi, A. Tetrahedron 1971, 27, 4889-4899; (d) For a review including some

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(13) (a) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. J. Am. Chem. Soc. 1978, 100, 2242-2244; (b) Baillargeon, D. J. Ph.D. Thesis, California Institute of Technology, 1979, and references therein.

(14) For an example of such a dehydrogenation, see Ref. 10a.

(15) Kuroda, S.; Funamizu, M.; Kitahara, Y.; Asao, T. Tetrahedron Lett. 1975, 1973-1974.

(16) For an example involving DDQ, see Reid, D. H.; Fraser, M.; Molloy, B. B.; Payne, H. A. S.; Sutherland, R. G. Tetrahedron Lett. 1961, 530-535.

(17) (a) Fleming, I.; Paterson, I. Synthesis 1979, 736-738; (b) Ryn, I.; Murai, S.; Hatayama, Y.; Sonoda, N. Tetrahedron Lett. 1978, 3455-3458.

(18) Cava, M. P.; Buck, K. T.; Noguchi, I.; Srinivassan, M.; DeRocha, A. I. Tetrahedron 1975, 31, 1667-1669.

(19) For a review of isoquinoline synthesis, see Shamma, M. "The Isoquinoline Alkaloids: Chemistry and

and Pharmacology"; Academic Press: New York, 1972.

(20) (a) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/ Bergstr., Germany, 1971. (b) For a more recent discussion, see Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. J. Org. Chem. 1980, 45, 3017-3028.

(21) Such an aryl-assisted ring-opening process is analogous to that which occurs during the aryl migration to form the colchicine nucleus (Scheme IV).

(22) Vedejs, E.; Engles, D. A.; Telschow, J. E. J. Org. Chem. 1978, 43, 188-196.

(23) For a review of this rearrangement, see Evans, D. A.; Andrews, G. C.. Accts. Chem. Res. 1974, 7, 147-155.

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(25) (a) For phosphoramides, Savignac, P.; Leroux, Y. J. Organomet. Chem. 1973, 57, C47-C50; (b) For a review of nitrosamine anion chemistry, see Seebach, D.; Enders, D. Angew. Chem. Int. Ed. 1975, 14, 15-32; (c) For lithiation of N-allyl carboxamides, see Tischler, A. N.; Tischler, M. N. Tetrahedron Lett. 1978, 3407-3410.

(26) For an example of such an E^1cb elimination which

proceeds at -78°C, see Ref. 25a.

(27) Treatment of 39 (X = OMs) with triethylamine at RT for only a short time gave rise to some aromatized isoquinoline in addition to phosphorylated 1,2-dihydroisoquinoline. Elimination of phosphorous is apparently very facile in this system.

(28) This material has recently been isolated as a natural product, Nortehuanine. Mata, R.; McLaughlin, J. L. Phytochem. 1980, 19, 673.

(29) Bobbit, J. M.; Kiely, J. M.; Khanna, K. L.; Ebermann, R. J. Org. Chem. 1965, 30, 2247-2250.

(30) The amino-alcohol 39 (X = OH) was prepared as in Ref. 29. This could be converted to 3a (X = SPh) by BF_3-catalyzed exchange of the alcohol with benzenthiol.

(31) Although attempts were also made to quench the addition product of the dianion of carboxylic acid 19 and 5 (Scheme VII) in such a way as to avoid decarboxylation, a practical method could not be developed.

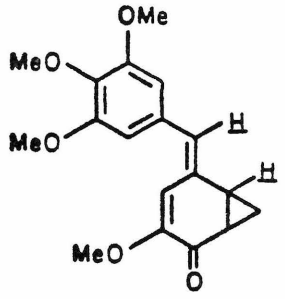
(32) Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. J. Am. Chem. Soc. 1971, 93, 4327-4346.

(33) Still, W. C.; Khan, M.; Mitra, A. J. Org. Chem.

1978, 43, 2923-2925.

(34) Watson, S. L.; Eastham, J. F. J. Organomet. Chem. 1967, 9, 165-168.

(35) These two isomeric olefin structures have been assigned based on cyclopropyl and vinylic proton chemical shifts, as well as by the fact that 500 MHz ^1H decoupling experiments have shown a slight allylic coupling between the vinyl and cyclopropyl protons shown in isomer 15a.



15a

(36) Büchi, G.; Mak, C.-P. J. Org. Chem. 1977, 42, 1784-1786.

(37) (a) Teitel, S.; Brossi, A. J. Heterocyclic Chem. 1968, 5, 825-829; (b) Wagner, D. P.; Rachlin, A. I.; Teitel, S. Synthetic Commun. 1971, 1, 47-50.

(38) Kubota, S.; Masui, T.; Fujita, E.; Kupchan, S. M. J. Org. Chem. 1966, 31, 516-520.

(39) The reduction of nitroalkenes to nitroalkanes with Wilkenson's catalyst under more severe conditions

been reported: Harmon, R. E.; Parsons, J. L.; Cooke, D. W.; Gupta, S. K.; Schoolenberg, J. J. Org. Chem. 1969, 34, 3684-3685.

(40) This compound was prepared from alcohol-carbamate 51a by a procedure similar to that used to convert aldehyde 16 to benzylstannane 17e.

(41) This dihydroisoquinoline was prepared by N-chlorination (t-butylhypochlorite) of tetrahydroisoquinoline 39a (X = H), followed by base-promoted elimination of HCl.

(42) Pirkle, W. H.; Hauske, J. R. J. Org. Chem. 1977, 42, 2781-2782.

(43) This reaction probably proceeds via addition of triflouroacetic acid to the isocyanate to form a mixed anhydride, followed by disproportionation to triflouroacetic anhydride and the unstable carbamic acid, which loses carbon dioxide to afford the amine. For a review of isocyanate addition chemistry, see: Satchell, D. P. N.; Satchell, R. S. Chem. Soc. Rev. 1975, 4, 231-250.

(44) Meyers, A. I.; Ten Hoeve, W. J. Am. Chem. Soc. 1980, 102, 7125-7126.

(45) Meyers, A. I. Personal communication.

(46) McKillop, A.; Perry, D. H.; Edwards, M.; Antus,

S.; Farkas, L.; Nogradi, M.; Taylor, E. C. J. Org. Chem. 1976, 41, 282-287.

(47) Although a variety of inorganic oxidants have been used for the conversion of methoxy phenols to quinone ketals, the $Tl(NO_3)_3$ procedure proved to be the best for the substrates mentioned here. For a discussion of these other methods, see: (a) Ref. 1a; (b) Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. J. Org. Chem. 1978, 43, 3983-3985; (c) Ref. 50.

(48) Nillson, A.; Ronlan, A.; Parker, V. D. Tetrahedron Lett. 1975, 1107-1110.

(49) Bellau, B.; Weinberg, N. L. J. Am. Chem. Soc. 1963, 85, 2525-2526.

(50) Recently, a similar procedure for carrying out this oxidation-deblocking sequence has been reported: Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. J. Org. Chem. 1980, 45, 3422-3433, and references therein.

(51) Corey, E. J.; Chaykovsky, M. J. Am. Chem. Soc. 1965, 87, 1353-1364.

(52) For a relevant study, see: Heller, J. E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, G. L.; Buchanan, G. L.; Raphael, R. A.; Taylor, R. Helv. Chim.

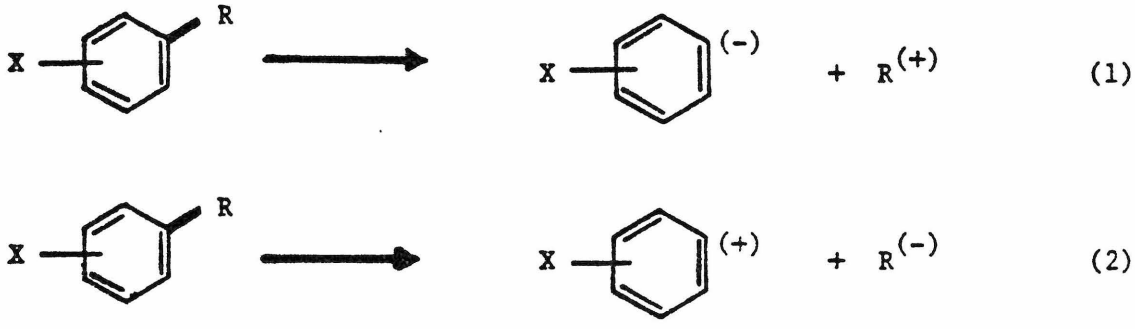
Acta 1973, 56, 272-280.

APPENDIX I

A Brief Review of Quinone Ketal Chemistry in the Evans Group

Introduction

The presence of aromatic rings as structural subunits of many naturally occurring organic compounds has led to the development of a plethora of methods for the construction of aryl-carbon bonds. Assuming the synthetic objective to be the union of an aromatic synthon with an aliphatic moiety, these methods might be assigned to one of two different schemes of "polar disconnection" (eq. 1 and 2). Often, electrophilic aromatic substitution (eq.



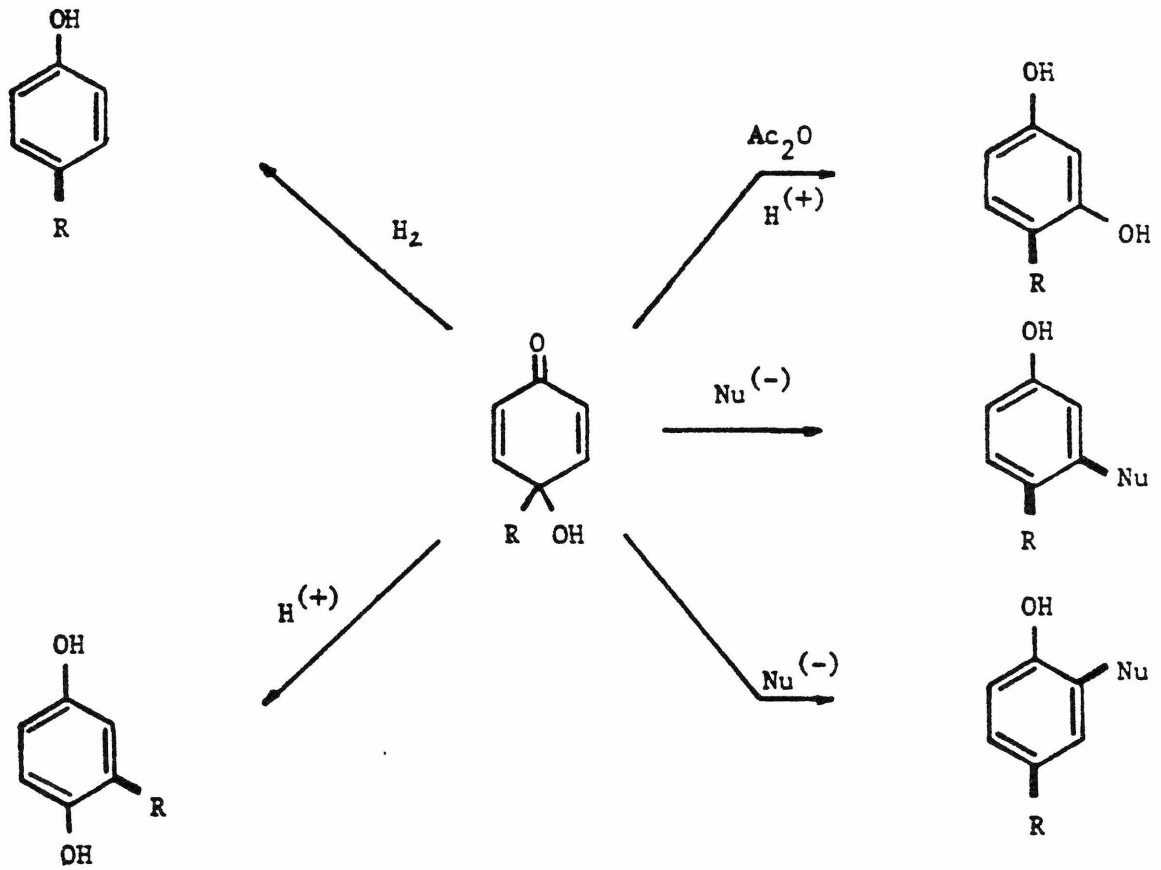
1), wherein the aromatic ring serves as the nucleophilic partner in the coupling process, provides the more expedient solution. Nonetheless, the alternate mode of disconnection (eq. 2), where an electrophilic aromatic ring is attacked by a nucleophile, is a potentially

powerful synthetic tool. In addition to some often impractical classical methods,[1] some interesting transition metal-mediated[2] and photochemical methods[3] have appeared during the past decade.

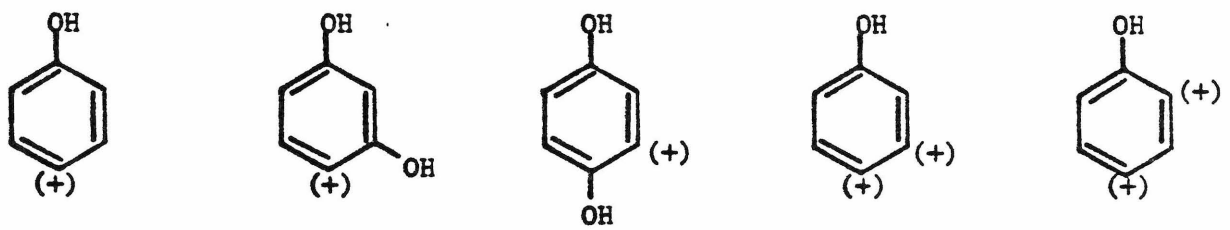
The purpose of this discussion will be to review the body of work recently completed within the Evans group directed towards the utilization of quinonoid substrates as synthetic equivalents for nucleophilic aromatic substitution.[4,5] It was initially envisioned that such methodology would lead to a number of schemes for bond formation to aromatic rings; consider, for example, the various possible modes of bond construction resulting from the initial 1,2-addition of an organometallic reagent (R^-M^+) to p-benzoquinone (Scheme I). Such refunctionalization reactions would define a family of electrophilic aryl cation and dication synthetic equivalents.

The reduction of this hypothetical chemistry to practice required a general method for the synthesis of p-quinols. Unfortunately, the direct reaction of p-quinones with "hard" organometallic reagents has often provided poor yields of p-quinols due both to intervening quinone redox chemistry and non-specific modes of addition.[6] Such problems have been largely circum-

Scheme I



Equivalents

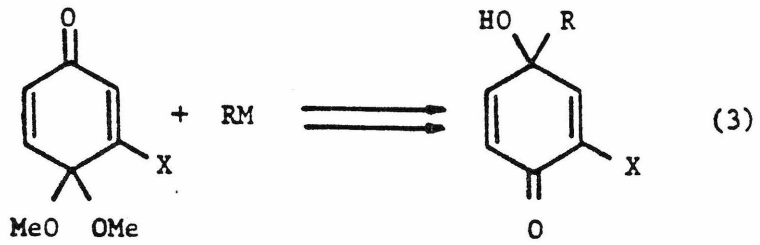


vented by the use of quinone monoketals in such reactions.[7] Results in our laboratories have demonstrated that quinone monoketals indeed serve as useful building blocks in the construction of complex aromatic molecules, as well as various tropolonoids. Several such applications will be discussed in this chapter.

Synthesis of Quinone Monoketals. A wide range of chemical oxidants has been reported to convert substituted 4-methoxyphenols to the corresponding quinone ketals. Good compilations of these procedures are available elsewhere.[8] The yields of quinone ketals appear to be highly dependent both upon the structure of the phenolic substrate and the nature of the oxidizing agent. To date, the only uniformly high yield oxidant for this procedure has been thallium trinitrate, as described by McKillop and Taylor.[9] In our work, we have utilized either this procedure or a sequence involving electrochemical oxidation of substituted hydroquinone dimethyl ethers followed by selective mono-hydrolysis of the resulting bis-ketal.[10] We have found the electrochemical procedure to be preferable for larger scale preparations due to difficulties with the thallium procedure such as need for massive quantities of solvent, severe reagent and byproduct toxicity, and expense. The versatility of

the electrochemical procedure has been highlighted by its recent application to the synthesis of a large number of quinone ketals by Swenton et al.[11]

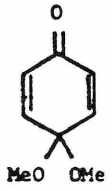
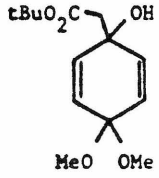
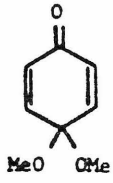
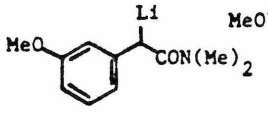
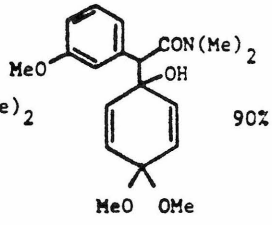
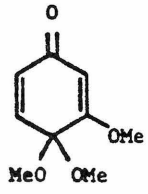
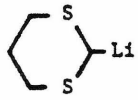
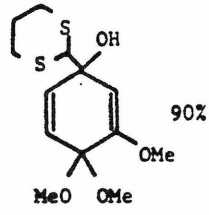
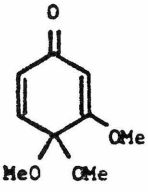
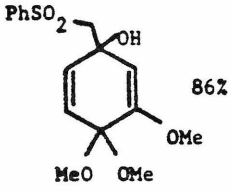
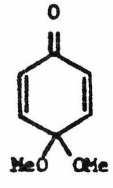
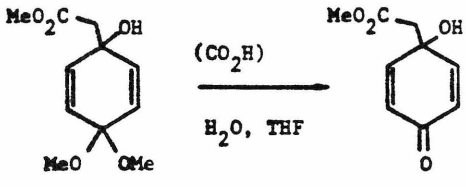
The Synthesis and Transformation of p-Quinols. In contrast to the often poor yields encountered in 1,2-carbonyl addition reactions of organometallic nucleophiles to quinones, we have found that the addition of such reagents to quinone monoketals proceeds in excellent yields (eq. 3). A representative summary of nucleophiles



(3)

which have been employed in such additions is shown in Table 1. In general, it was found that Grignard and organolithium reagents add in very high yields, as do nucleophilic ester and amide enolates, sulfur-stabilized carbanions, and Wittig reagents. The somewhat less nucleophilic ketone enolates and metalloenamines are not sufficiently reactive to afford high yields of addition products. As illustrated in the table, the p-quinol

Table 1

Quinone	R-M	Product (yield)
	$LiCH_2CO_2tBu$	 85%
		 90%
		 90%
	$PhSO_2CH_2Li$	 86%
	$LiCH_2CO_3Me$	 Jaccarone 54%

ketal adducts can be hydrolyzed to the corresponding p-quinols under mild aqueous acidic conditions. This was illustrated by preparation of the naturally occurring p-quinol jacarone. This overall procedure serves as an excellent complement to the somewhat less general preparation of p-quinol derivatives by oxidation of p-alkyl phenols, as illustated by the work of Umezawa.[12]

As suggested earlier (Scheme I), the high level of functionality and reactivity of these p-quinol intermediates can readily be exploited in further bond construction reactions. An annelation concept which we have recently reduced to practice is depicted below wherein the quinone nucleus is used for the construction of biaryls (Scheme II). In general, this procedure involves addition of an appropriately substituted carbanion to a quinone ketal, followed by acid-promoted cyclization to afford dihydrophenanthrene and flourene derivatives. This overall process defines quinone ketals as aryl dication equivalents; the tricyclic nucleus has been assembled by two successive nucleophilic attacks on the quinonoid moiety. This annelation method has been explored in some detail by us and the results of a representative set of such sequences are enumerated in Table 2.[13] In addition, fully aromatic phenanthrenes

Scheme II

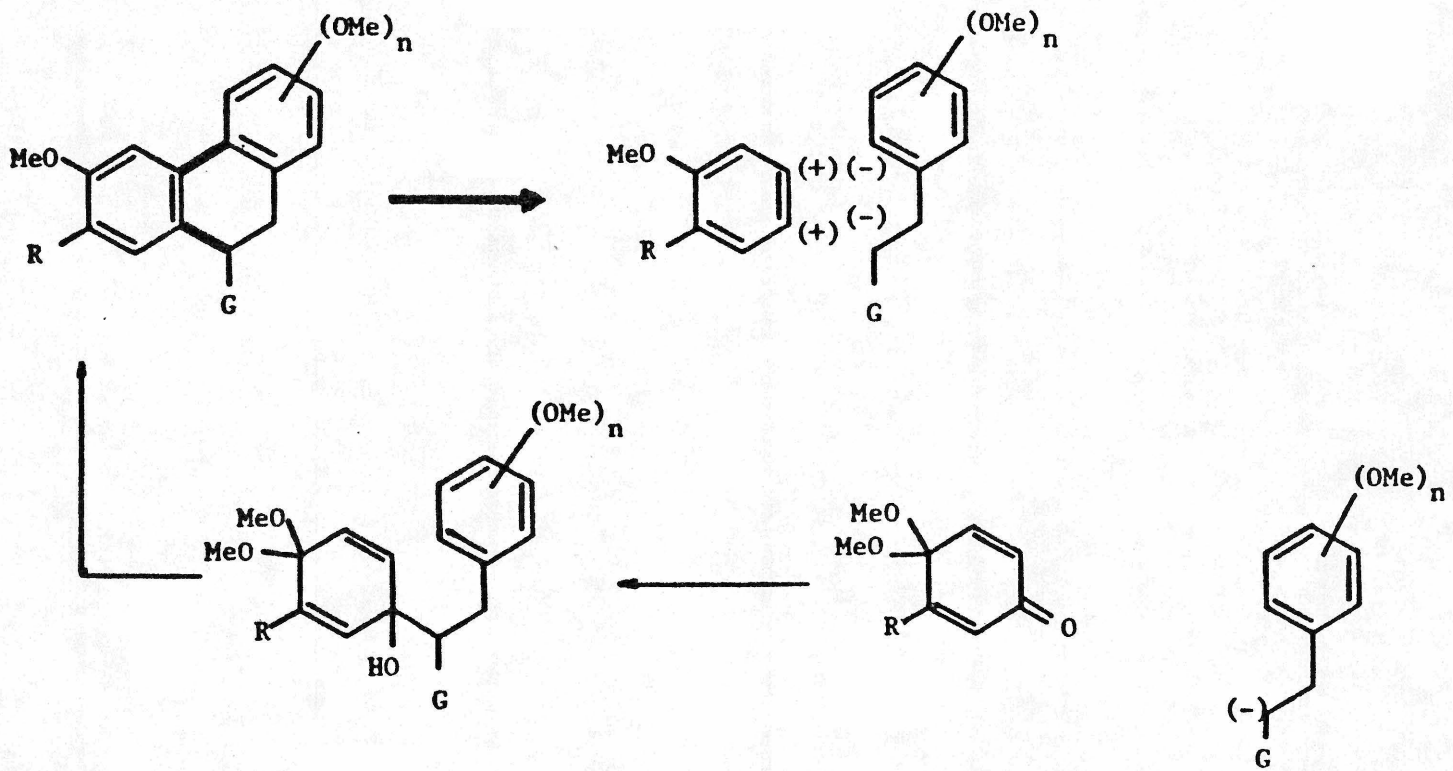
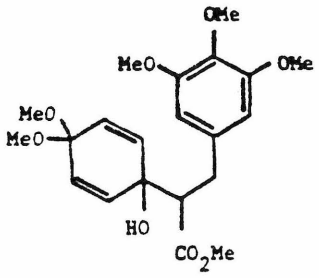
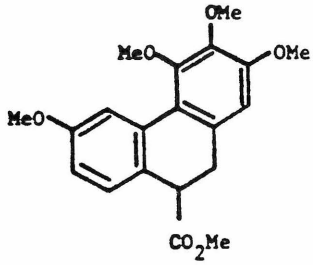
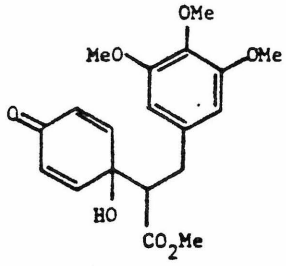
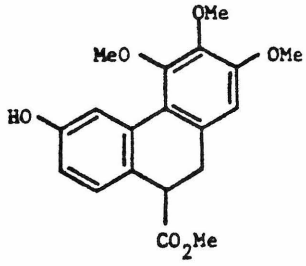
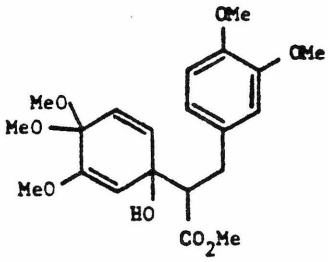
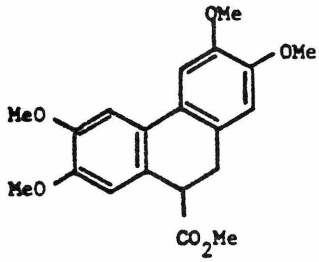
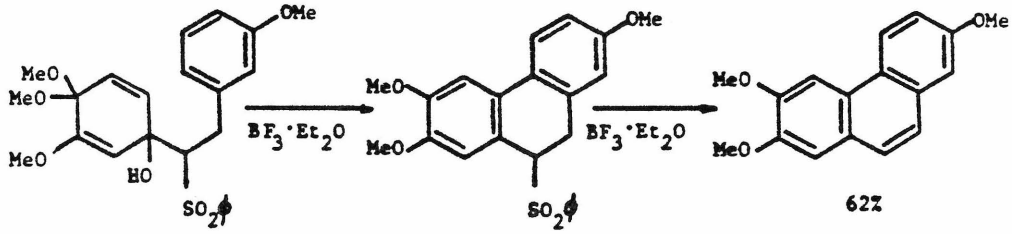


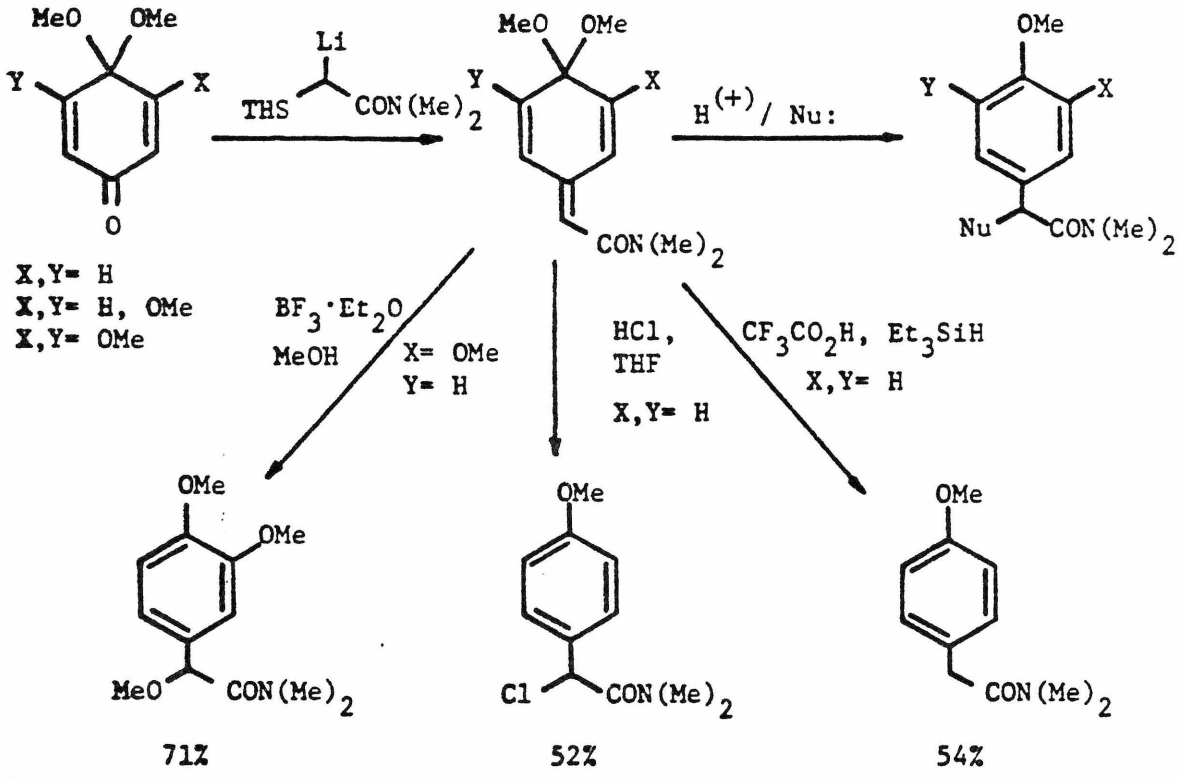
Table 2.

p-Quinol	Product	Yield (%)	Acid
		77	P_2O_5-$MeSO_3H$
		78	P_2O_5-$MeSO_3H$
		74	$SnCl_4$
		62%	

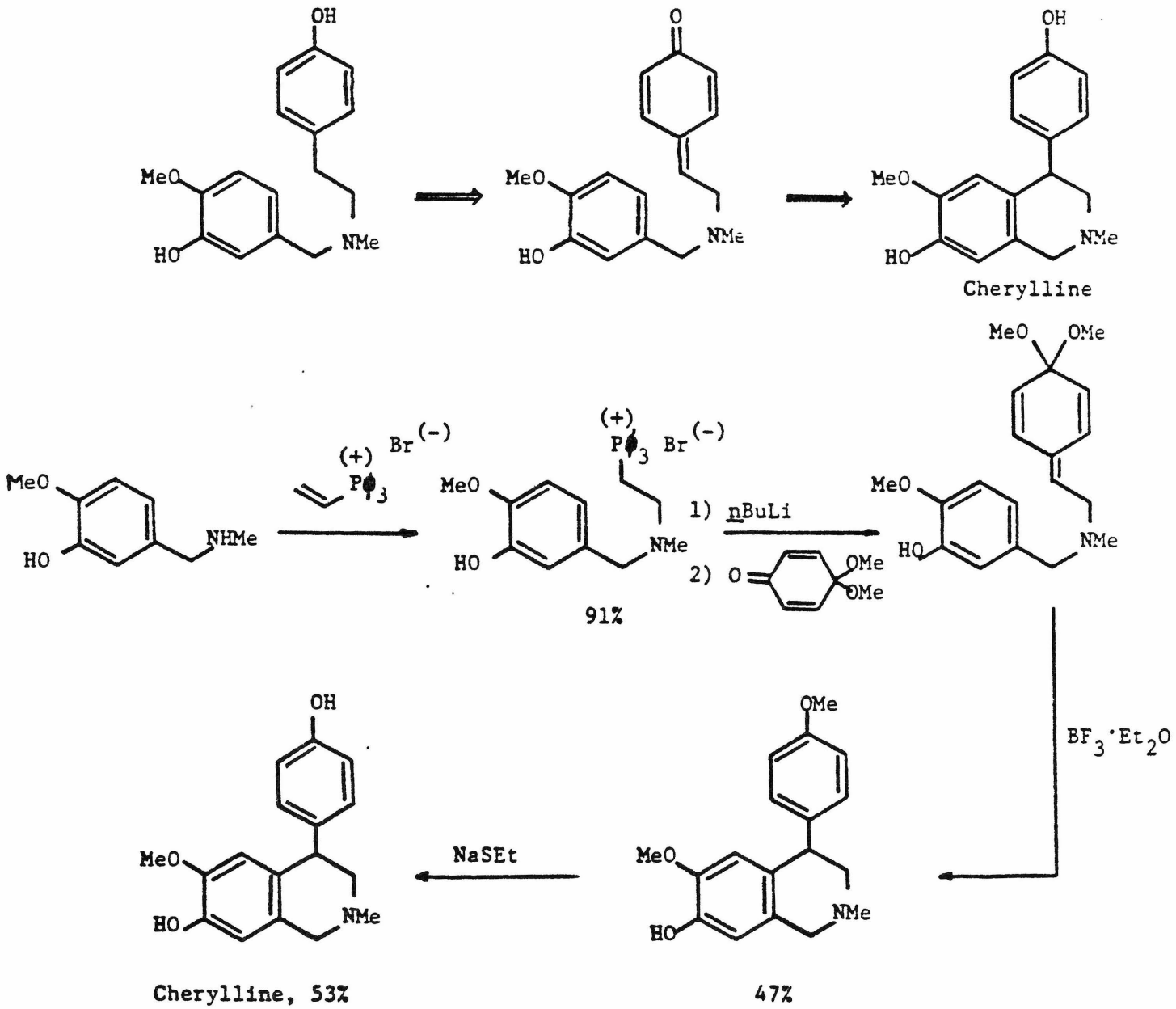
have been obtained either by use of activating groups G which can undergo subsequent *in situ* 1,2-elimination (e.g. phenylsulfonyl, phenylsulfinyl[14]) or by subsequent oxidation of dihydrophenthrenes with DDQ.[15] Although a number of interesting observations have been made, the mechanistic intricacies of these cyclizations have yet to be firmly established.[13,16]

Synthesis and Application of *p*-Quinone Methides. In addition to developing chemistry based on the 1,2-addition of nucleophiles to quinone ketals, we have found that these substrates are also excellent partners in olefination reactions. The intrinsic reactivity of the resultant *p*-quinone methide derivatives may then be exploited, as in the case of *p*-quinols. A series of such olefination reactions, including some transformations of the resultant quinone methide ketals, is presented in Table 3. In addition, such intermediates have been obtained by the dehydration of *p*-quinols under non-acidic conditions.[14] These concepts have been applied to a biogenetically modeled synthesis of the benzylisoquinoline alkaloid cherylline *via* the short sequence outlined in Scheme III.[17] Since both *p*-quinone methides and *p*-quinols are ubiquitous intermediates in the biosynthesis of many phenolic natural products, it is not unexpected

Table 3.

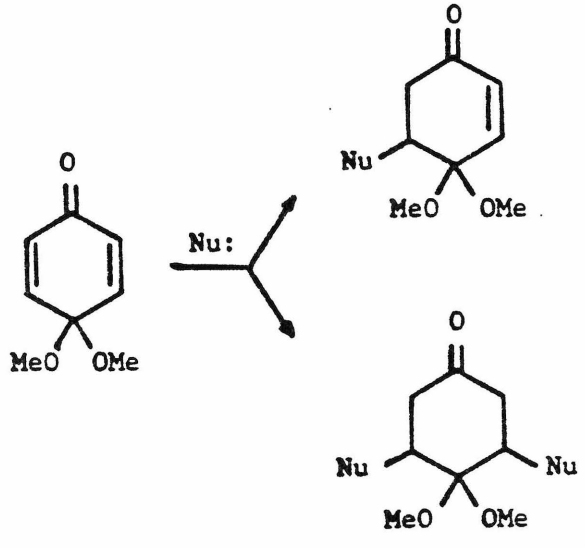

MeO
OMe
Y
X
O
X,Y= H
X,Y= H, OMe
X,Y= OMe
Li
THS
CON(Me)2
H(+) / Nu:
Nu
BF3·Et2O
MeOH
X= OMe
Y= H
HCl,
THF
X,Y= H
CF3CO2H, Et3SiH
X,Y= H
Cl
71%
52%
54%

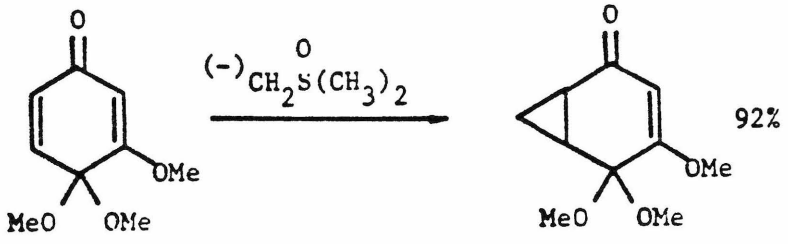
Scheme III


OH
MeO
HO
NMe
O
Cherylline
OMe
NHMe
Br(-)
(+)
Pϕ_3
1) nBuLi
2) O
91%
47%
$BF_3 \cdot Et_2O$
NaSEt
Cherylline, 53%

that their application to natural product total synthesis will continue to be a fruitful area of research.

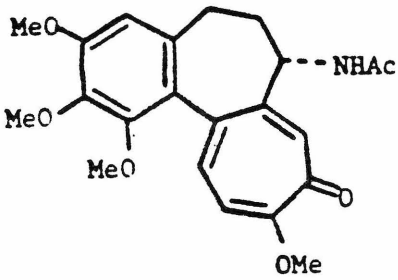
Conjugate Addition Reactions of Quinone Monoketals. In the 1,2-addition reactions of "hard", reactive nucleophiles mentioned earlier, products resulting from competitive 1,4-addition to the quinone ketal substrate were not observed. However, reports have recently appeared of successful 1,4-additions of "softer", less-reactive nucleophiles such as malonate carbanions[18] as well as alkoxides and thiolates.[19] An attempt at alkyl conjugate addition via lithium dialkyl cuprates failed due to the intervention of redox chemistry.[20] We were gratified to find that the conjugate attack on quinone ketals by sulfur ylids is also quite facile, affording



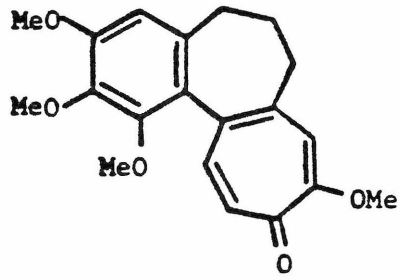


cyclopropanated quinone ketals such as the one shown above in excellent yield. In our hands, this substrate proved to be a versatile precursor for tropolonoid molecules.

The Synthesis of Tropolonoid Natural Products from Quinone Ketal Precursors. Very few general strategies currently exist for the synthesis of substituted tropolones. In this regard, we have undertaken studies to define the equivalency between the quinone-derived cyclopropyl ketone just mentioned and the hypothetical tropolone dication synthon illustrated below. Our initial investigations in this area were directed towards the total synthesis of the alkaloid colchicine, a deceptively simple molecule which has attracted the attention of numerous investigators.[21] Desacetamidoisocolchicine was chosen as a preliminary synthetic target; this molecule is in fact an intermediate in seven of the ten published syntheses



Colchicine

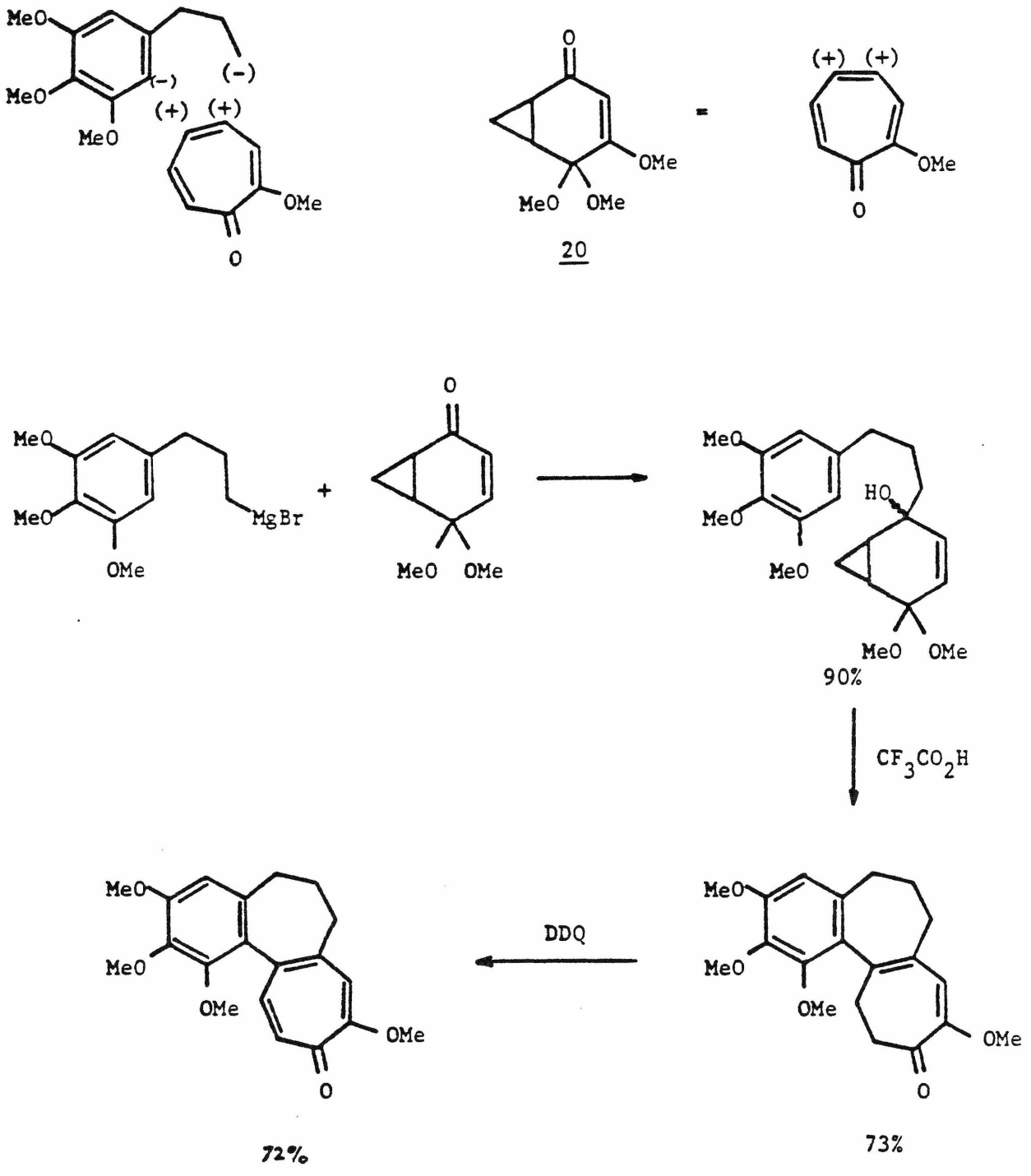


Desacetamidoisocolchicine

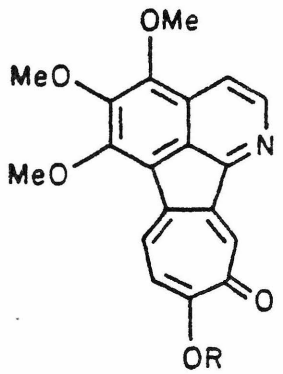
of colchicine. The basic disconnection perceived in the construction of this tricyclic involves annelation of bis-nucleophile II with the quinone-derived tropolone dication III. This strategy is illustrated in Scheme IV, along with the rapid, high-yield, and convergent synthesis of desacetamidoisocolchicine which resulted. Further investigation revealed the somewhat complex mechanism of the acid-promoted cyclization process.[22] More recently, we have succeeded in carrying out a direct synthesis of colchicine itself via a similar scheme of bond formation.[23]

In parallel studies, similar concepts have been applied to the total synthesis of β-dolabrin[22] and

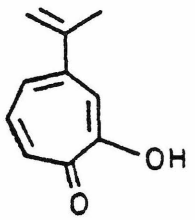
Scheme IV


MeO
MeO
MeO
(-)
(-)
(+) (+)
OMe
O
O
OMe
MeO OMe
20
=
(+) (+)
OMe
O
MeO
MeO
OMe
MgBr
+
O
MeO OMe
HO
MeO
MeO OMe
90%
CF_3CO_2H
DDQ
73%
72%

towards the total synthesis of the recently-isolated alkaloid imerubrine.[24] The retrosynthetic disconnections shown below illustrate the utility of the quinone-derived tropolone cation equivalent as a key building block in the synthesis of these molecules as well. In practice, the utilization of these equivalencies proceed via different mechanisms than in the colchicine case, despite the conceptual similarity. Synthetic work and mechanistic conclusions pertaining to the β-dolabrin and imerubrine work are discussed in detail elsewhere in this thesis, and will therefore not be included here.



R=H, Grandirubrine
R=Me, Imerubrine



β-Dolabrin

Conclusion

This report has discussed some of the chemistry of quinone ketals and their application as useful building blocks in the synthesis of complex chemical structures. Convergent, high yield total syntheses of several natural products have resulted from these investigations, and greatly increased interest in the chemistry of these substrates has been observed in the form of recent publications from other research groups. Further exploitation of these building blocks in synthesis design should be fruitful and will be limited only by the imagination of the investigator.

References and Notes

(1) Some examples of these methods include: (a) electron deficient aryl halide substrates, Bunnett, J. F. Q. Rev. Chem. Soc. 1958, 12, 1-16; (b) benzyne intermediates, Hoffman, H. M. R. "Dehydrobenzene and Cycloarynes"; Academic Press: New York, 1967; (c) diazonium salts.

(2) Some representative methods involve: (a) π-aryl chromium complexes, Semmelhack, M. F.; Clark, G. J. Am. Chem. Soc. 1977, 99, 1675-1676; (b) aryl-nickel (II) species, Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. Tetrahedron Lett. 1973, 4519-4522.

(3) A number of photochemically and reductively initiated Srn^1 reactions have been reported. For a recent reference, see Tremelling, M. J.; Bunnett, J. F. J. Am. Chem. Soc. 1980, 102, 7375-7377.

(4) Collaborators in this venture, in addition to Professor D. A. Evans, included P. A. Cain, D. J. Hart, P. M. Koelsch, and S. P. Tanis.

(5) For earlier reviews, see: (a) Koelsch, P. M.; Tanis, S. P. Kodak Laboratory Chemicals Bulletin 1980, 52, 1-7; (b) Evans, D. A.; Hart, D. J.;

Koelsch, P. M.; Cain, P. A. Pure & Appl. Chem. 1979, 51, 1285-1300.

(6) For a preliminary study on circumventing these problems, see Evans, D. A.; Wong, R. Y. J. Org. Chem. 1977, 42, 350-352.

(7) Some additional applications of quinone monoketals are discussed in Ref. 5a.

(8) (a) Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. J. Org. Chem. 1978, 43, 3983-3985; (b) Ref. 5a.

(9) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. J. Org. Chem. 1976, 41, 282-287.

(10) Some scattered early reports of such electrochemical oxidations had appeared: (a) Nillson, A.; Ronlan, A.; Parker, V. D. Tetrahedron Lett. 1975, 1107-1110; (b) Bellau, B.; Weinberg, N. L. J. Am. Chem. Soc. 1963, 85, 2525-2526.

(11) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. J. Org. Chem. 1980, 45, 3422-3433, and references therein.

(12) (a) Umezawa, B.; Hoshino, O.; Terayama, Y.; Ohyama, K.; Yamanashi, Y.; Inoue, T.; Toshioka, T. Chem. Pharm. Bull. (Tokyo) 1971, 19, 2138-2146;

(b) Hoshino, O.; Toshioka, T.; Umezawa, B. J. Chem. Soc., Chem. Commun. 1972, 740-741; (c) Hoshino, O.; Toshioka, T.; Ohyama, K.; Umezawa, B. Chem. Pharm. Bull. (Tokyo) 1974, 22, 1307-1312.

(13) Evans, D. A.; Cain, P. A.; Wong, R. Y. J. Am. Chem. Soc. 1977, 99, 7083-7085.

(14) Koelsch, P. M. Unpublished results.

(15) Cain, P. A. Unpublished results.

(16) For discussions of alternative procedures for fused biaryl construction based on oxidative coupling, see: (a) Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnurvajjala. J. Am. Chem. Soc. 1977, 99, 2571-2578; (b) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. J. Org. Chem. 1978, 43, 4076-4081.

(17) Hart, D. J.; Cain, P. A.; Evans, D. A. J. Am. Chem. Soc. 1978, 100, 1548-1557.

(18) Parker, K. A.; Kang, S.-K. J. Org. Chem. 1980, 45, 1218-1224.

(19) Foster, C. H.; Payne, D. A. J. Am. Chem. Soc. 1978, 100, 2834-2837.

(20) See Ref. 10a.

(21) For a compilation of prior syntheses, see Refs. 2 and 3 in Ref. 22.

(22) Evans, D. A.; Hart, D. J.; Koelsch, P. M. J. Am. Chem. Soc. 1978, 100, 4593-4594.

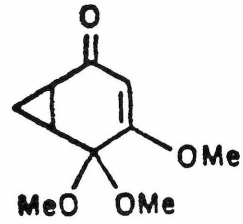
(23) Evans, D. A.; Tanis, S. P.; Hart, D. J. J. Am. Chem. Soc. 1981, 103, 0000.

(24) Silverton, J. C.; Kabuto, C.; Buck, K. T.; Cava, M. P. J. Am. Chem. Soc. 1977, 99, 6708-6712.

APPENDIX II

IR and ^{1}H NMR Spectral Catalog

Page 50



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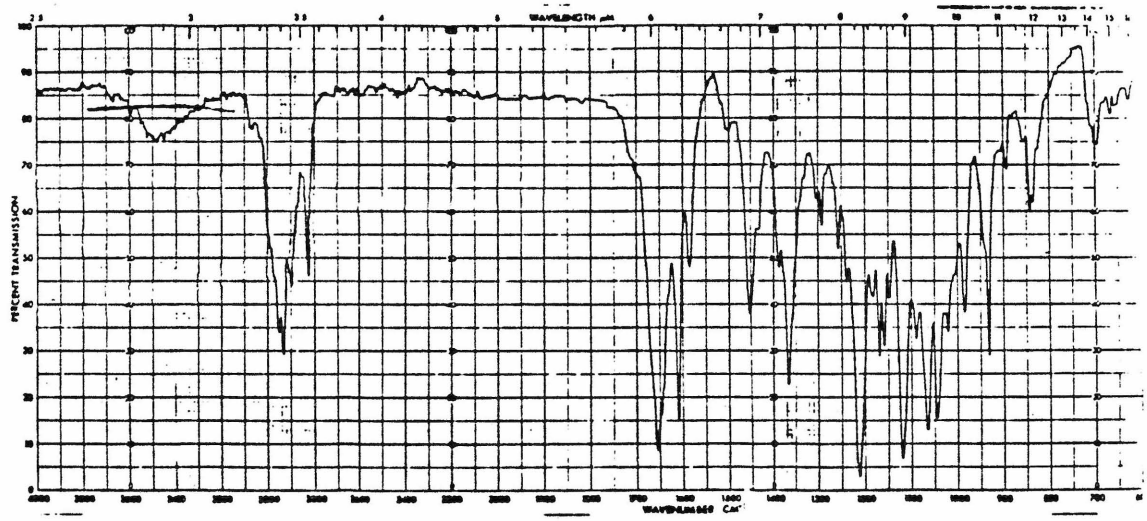

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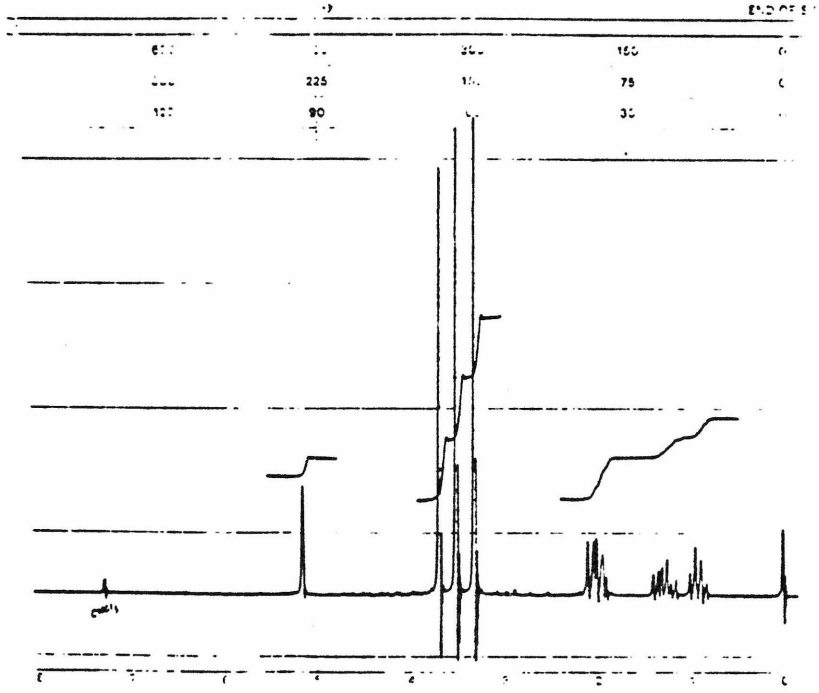

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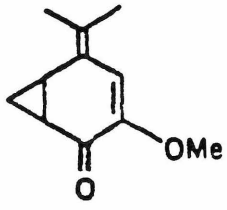

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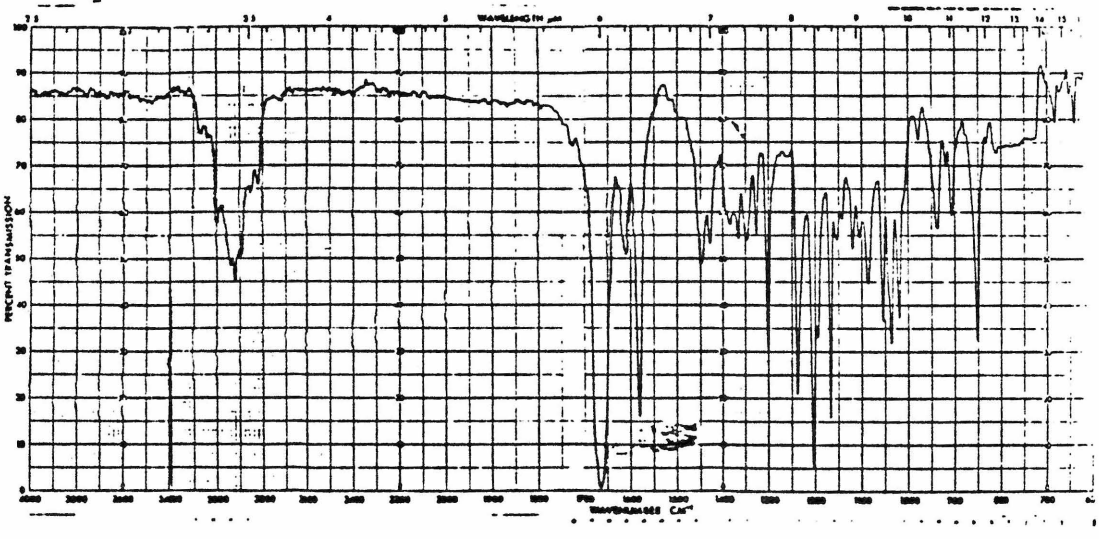

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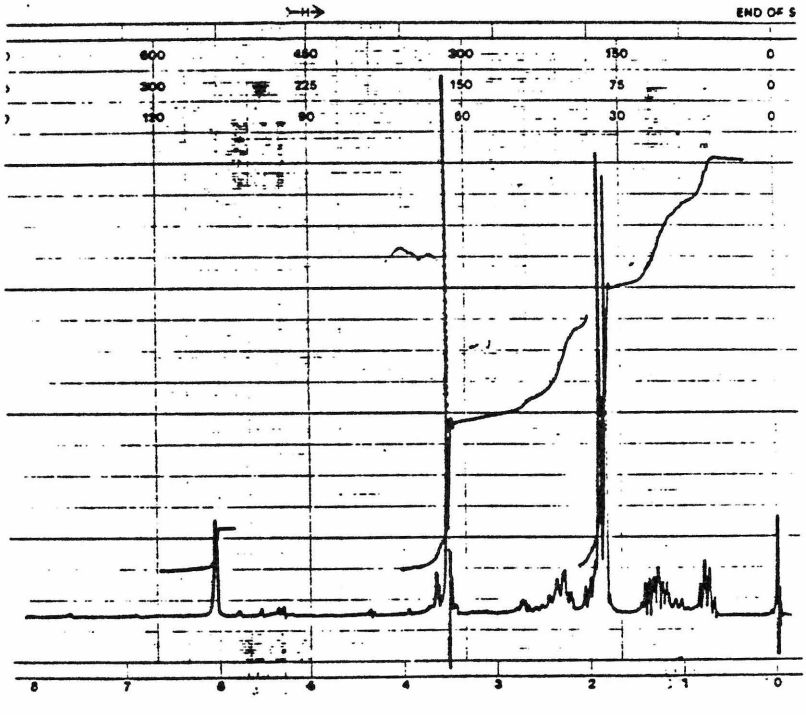

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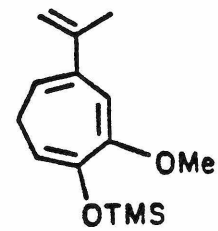

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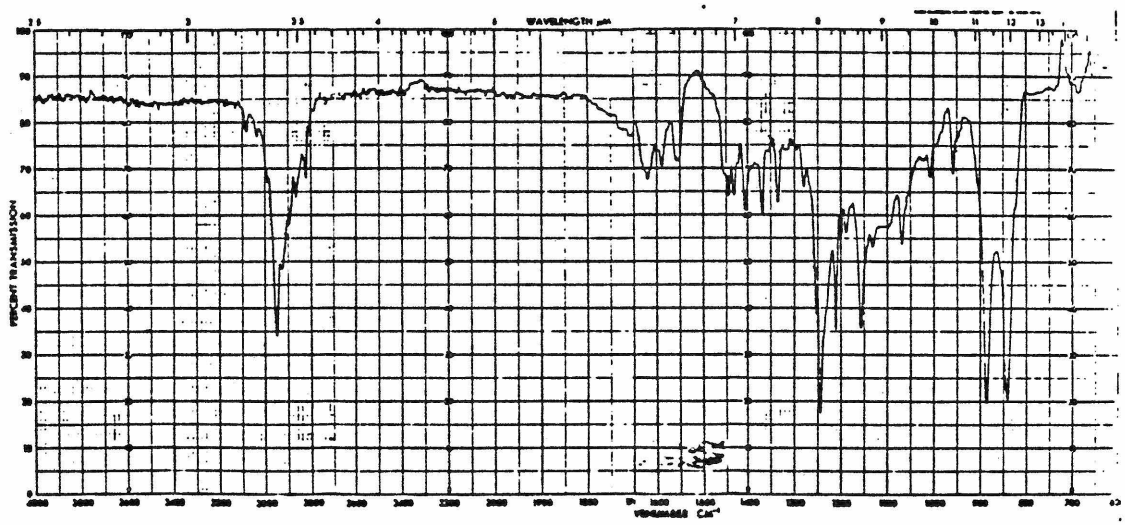

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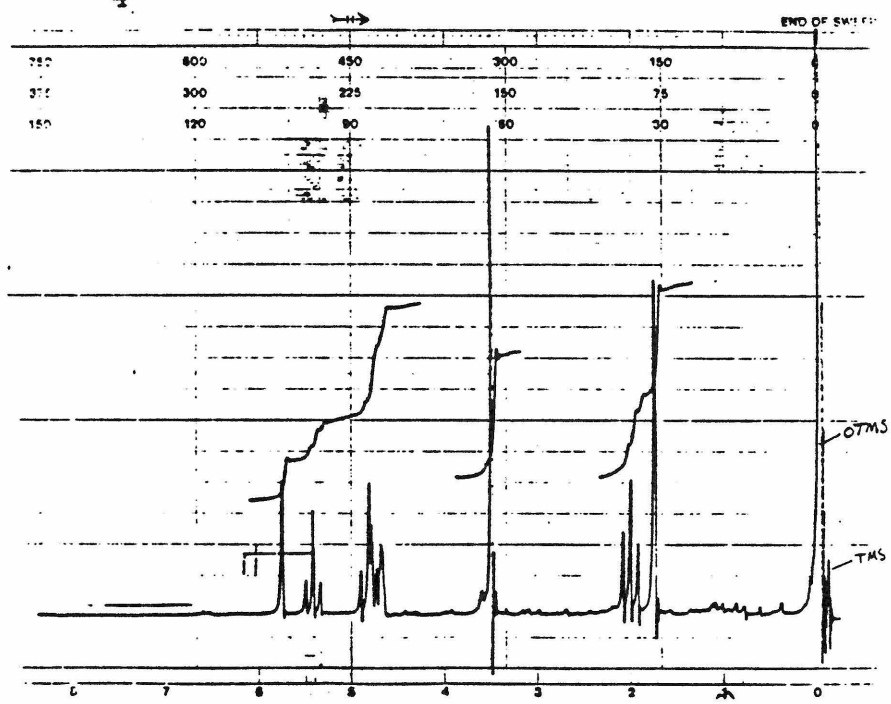

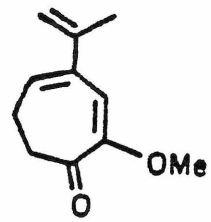

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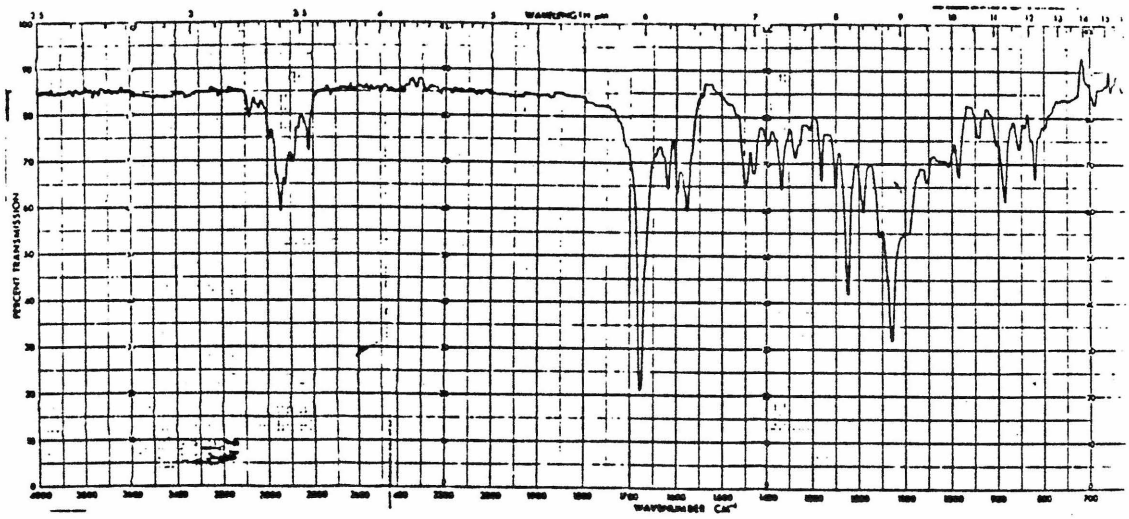

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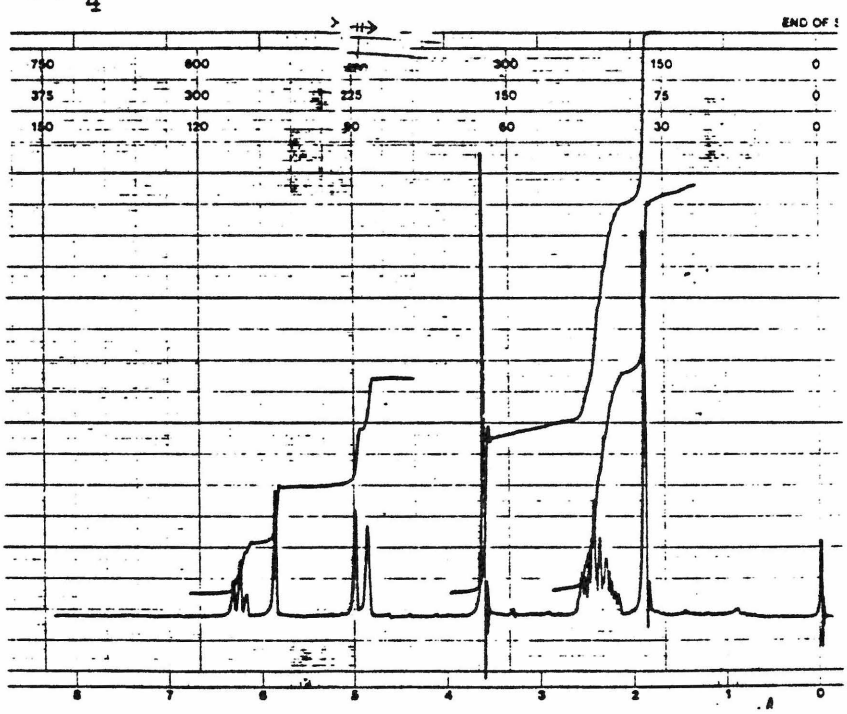

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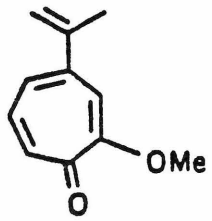

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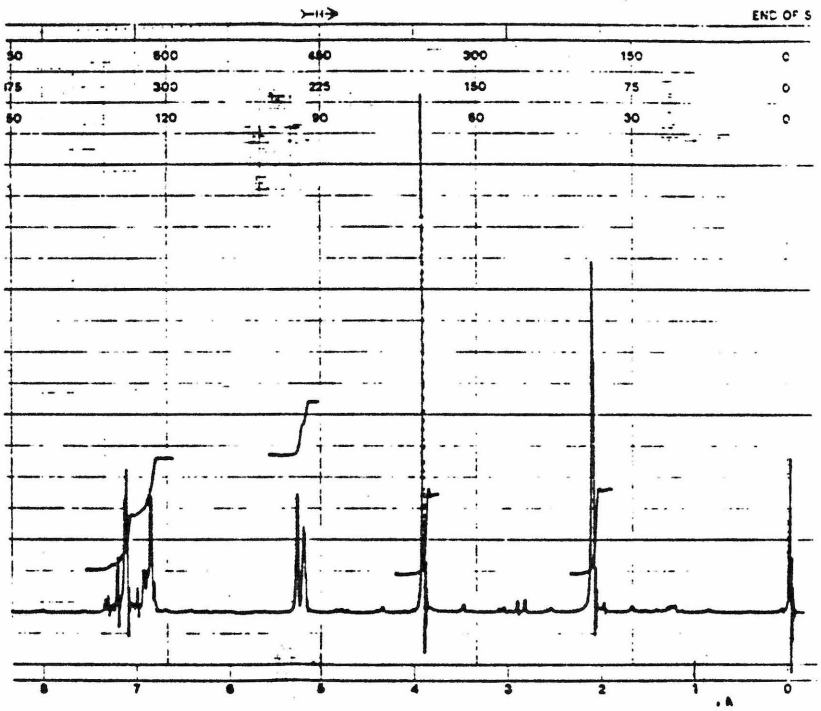

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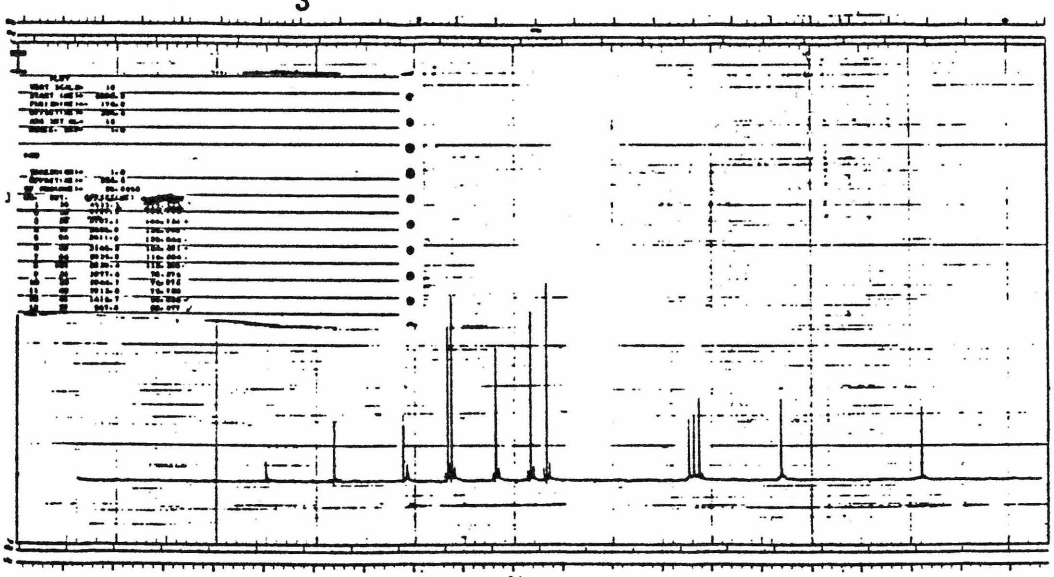

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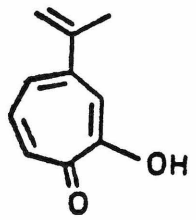

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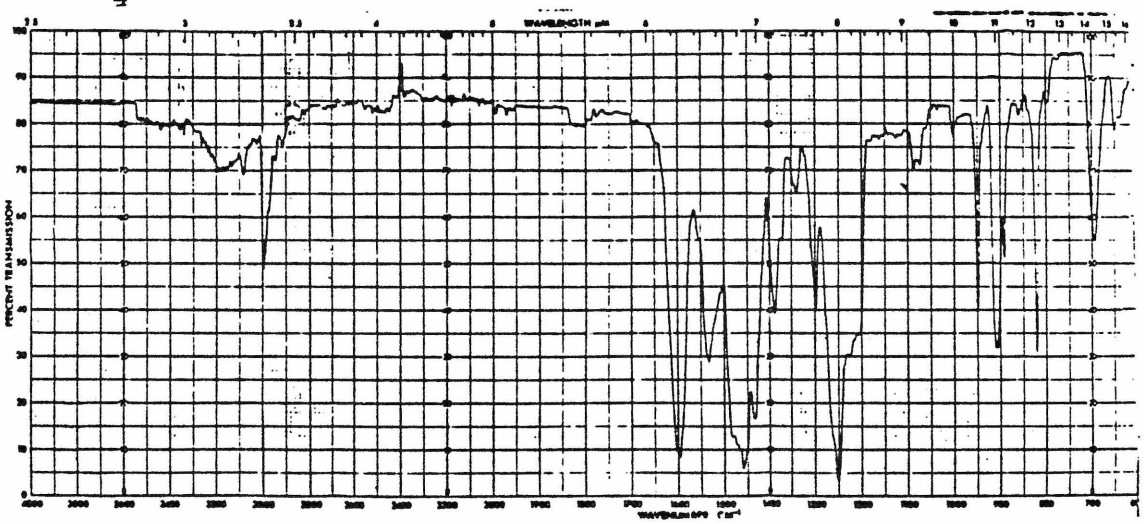

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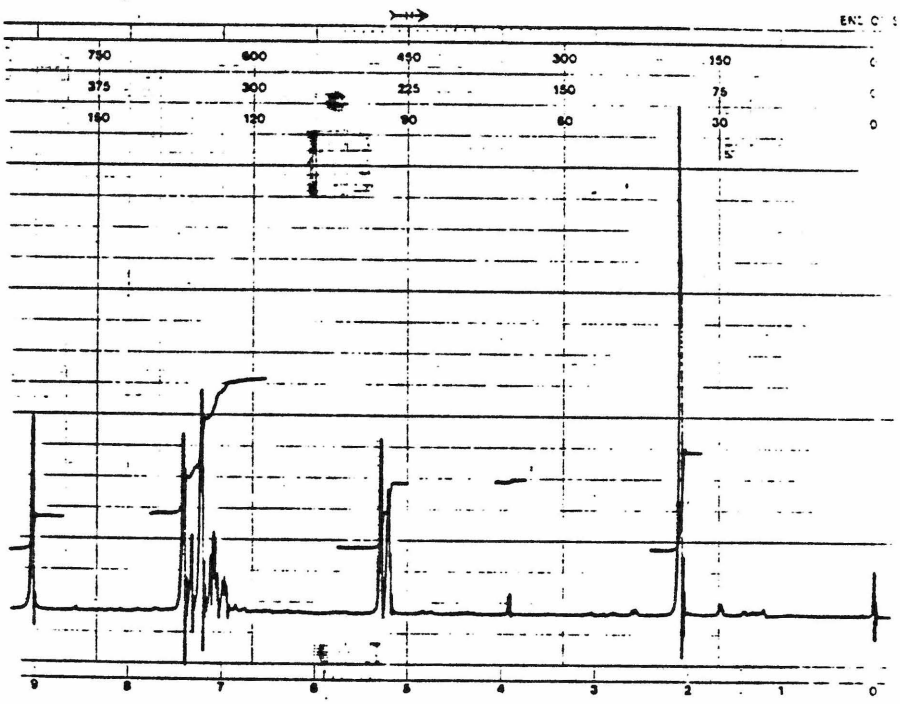

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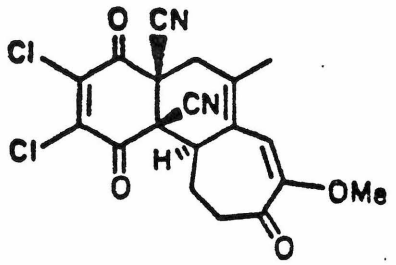

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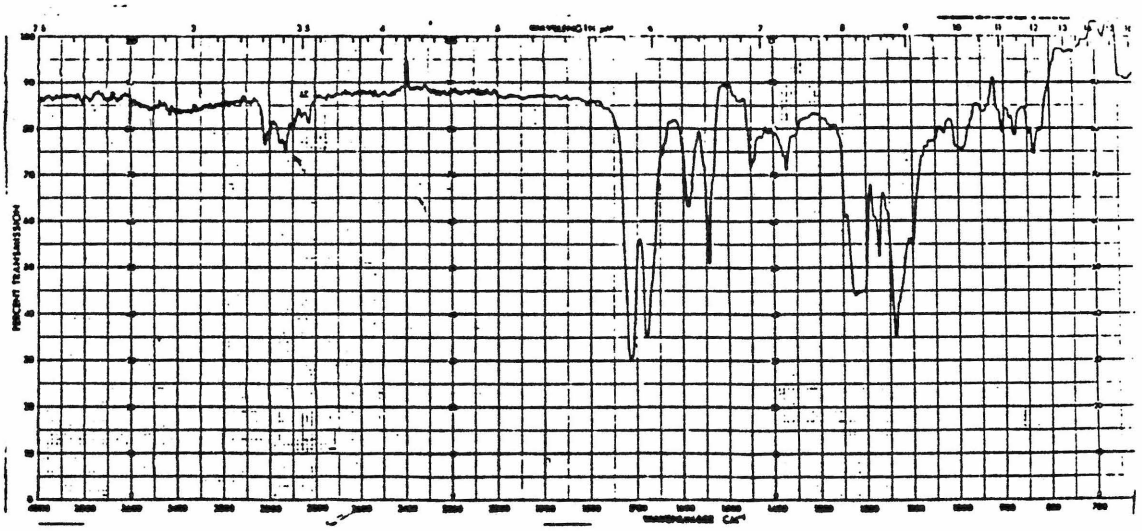

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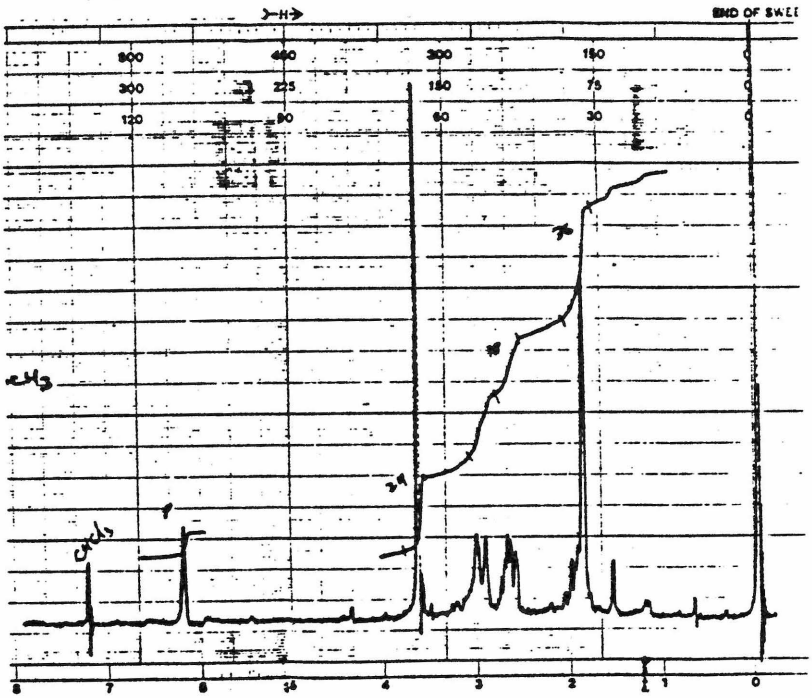

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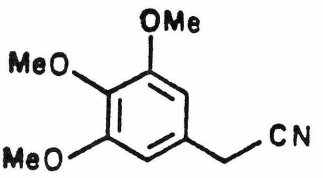

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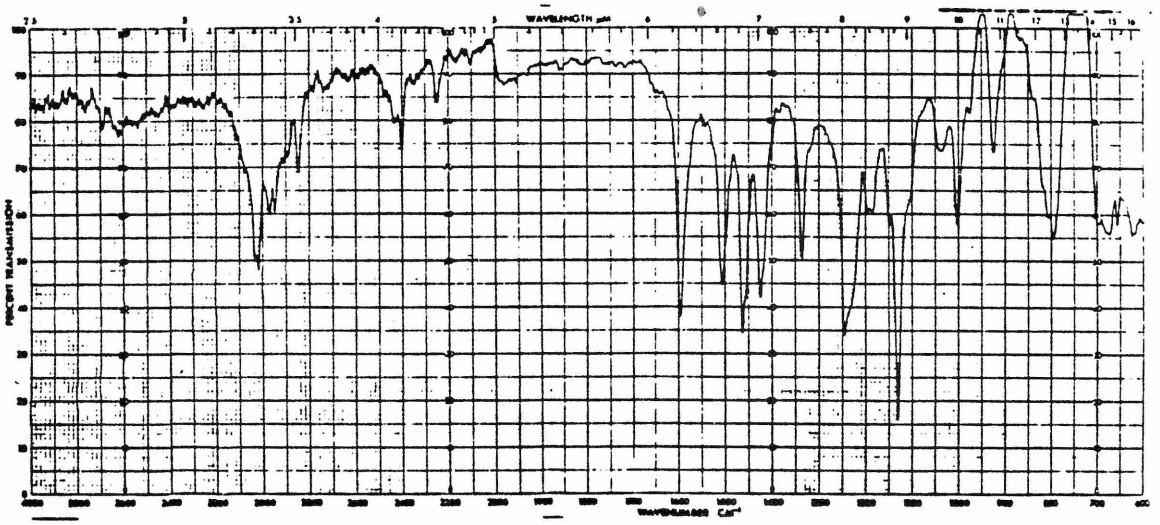

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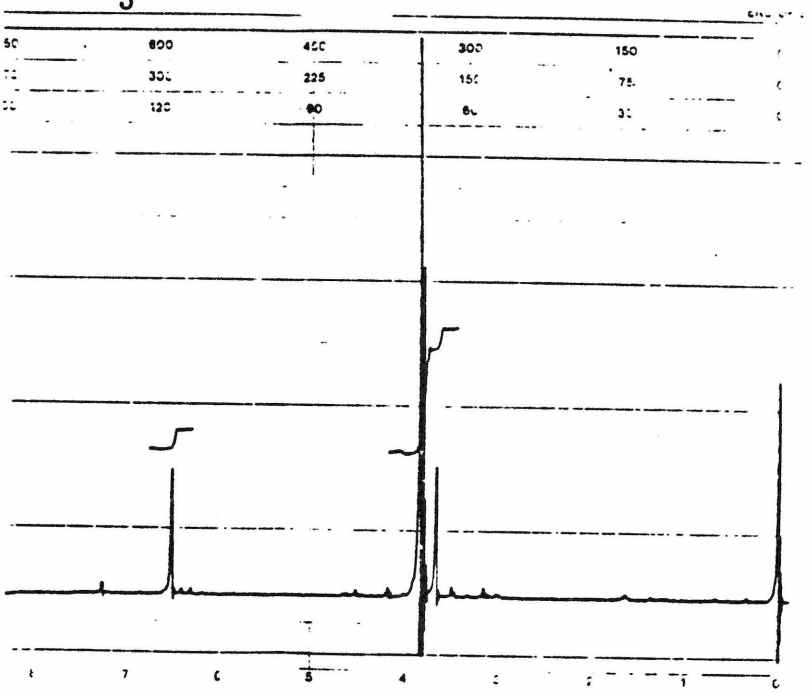

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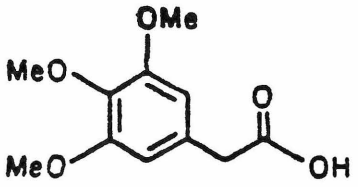

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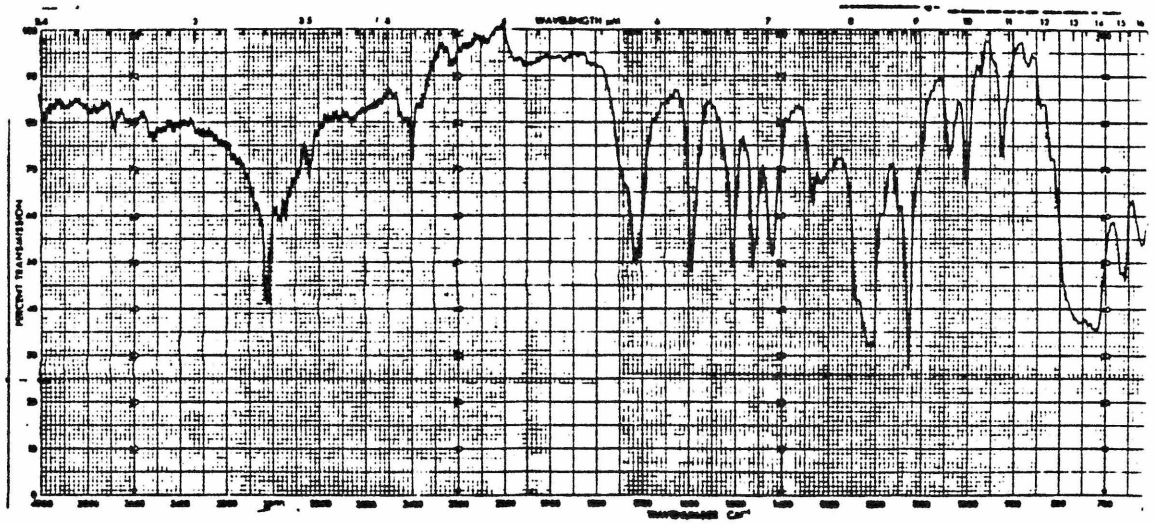

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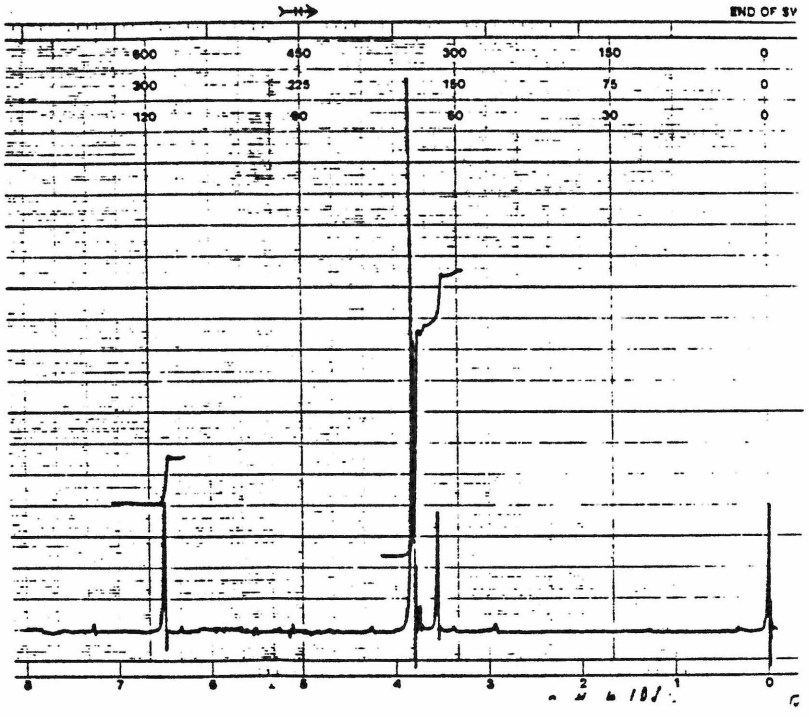

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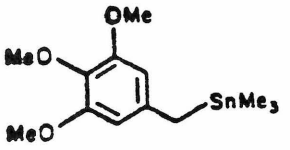

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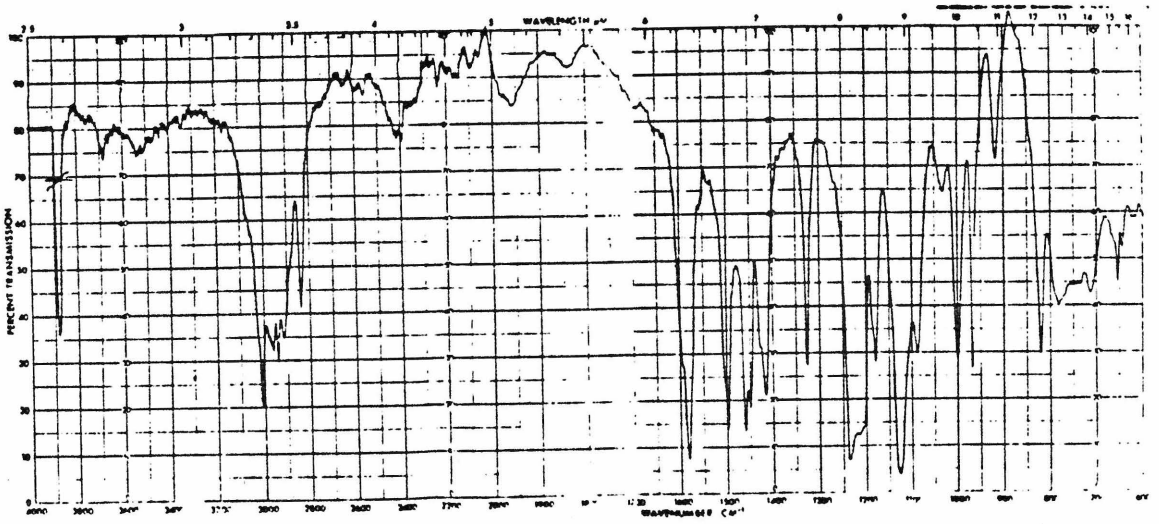

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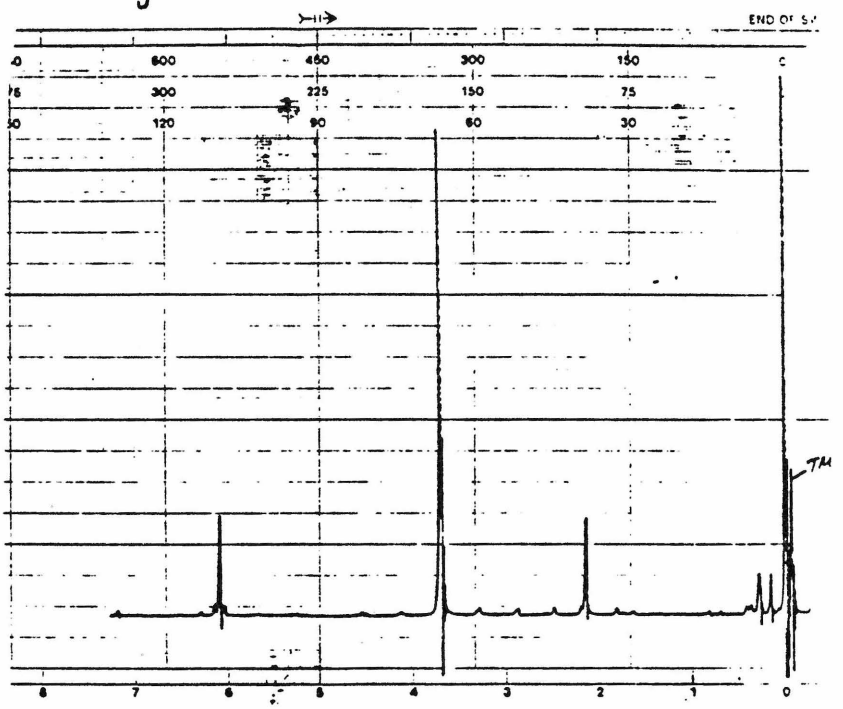

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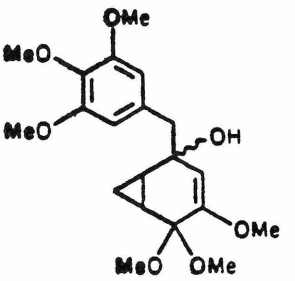

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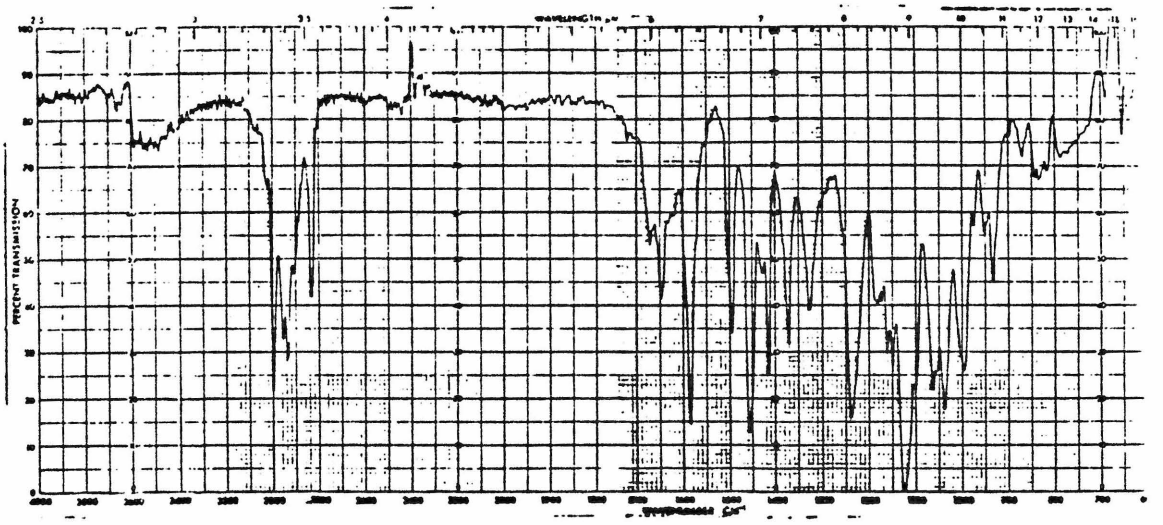

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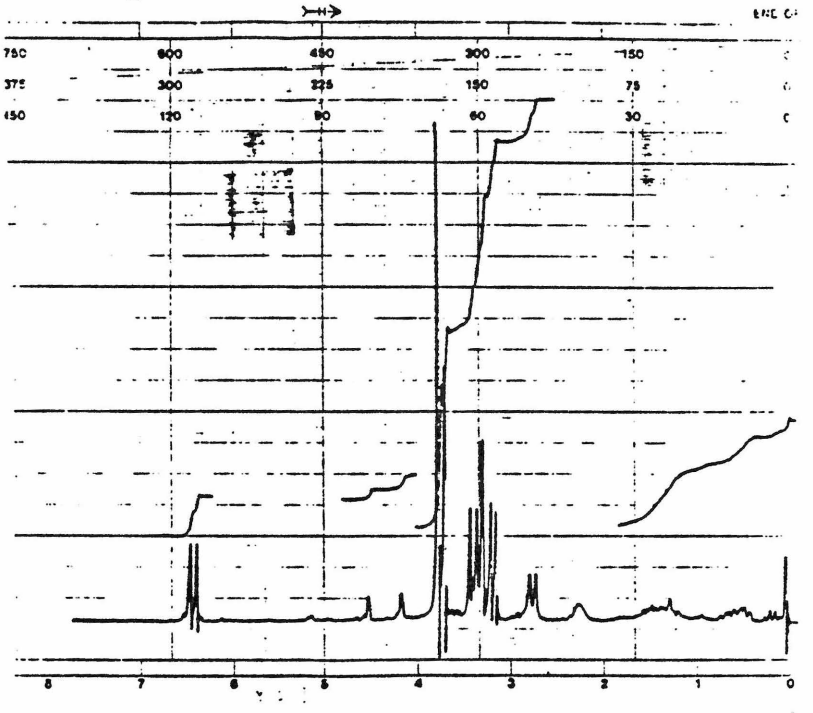

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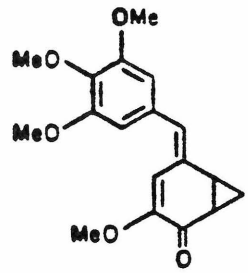

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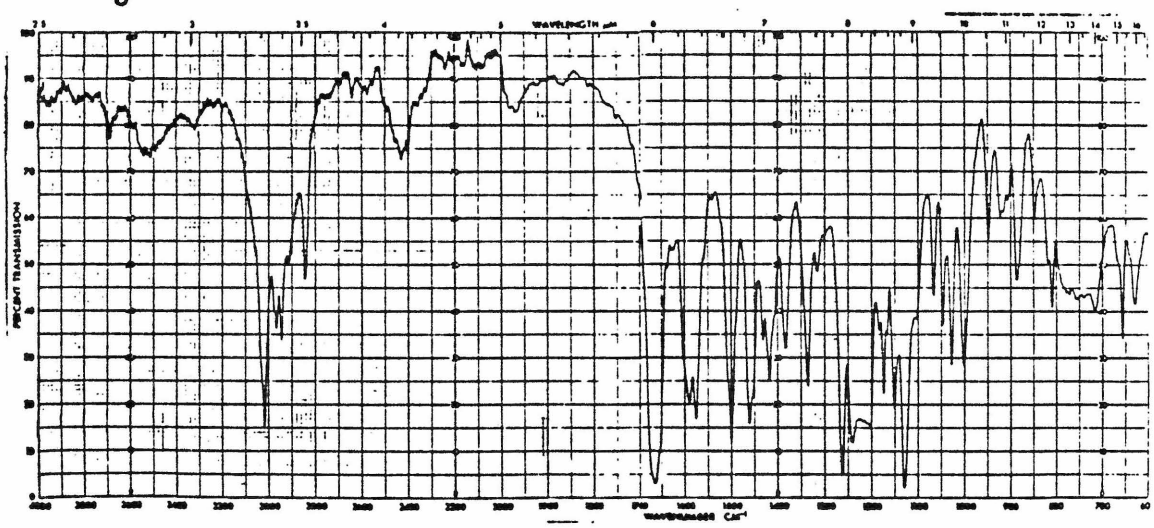

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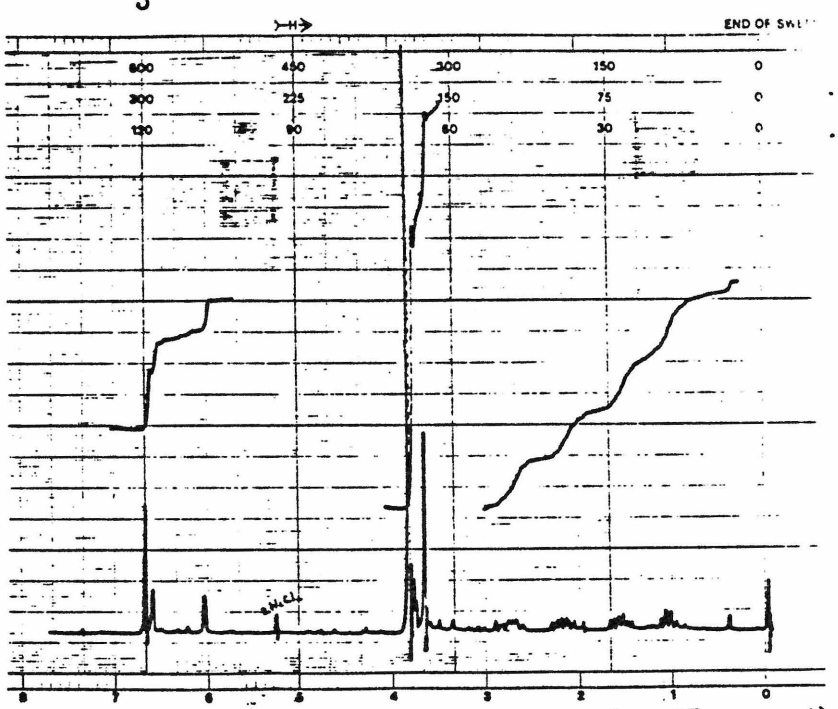

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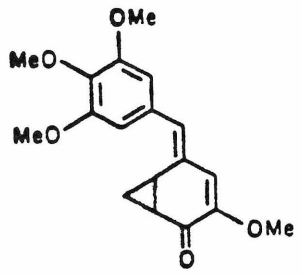

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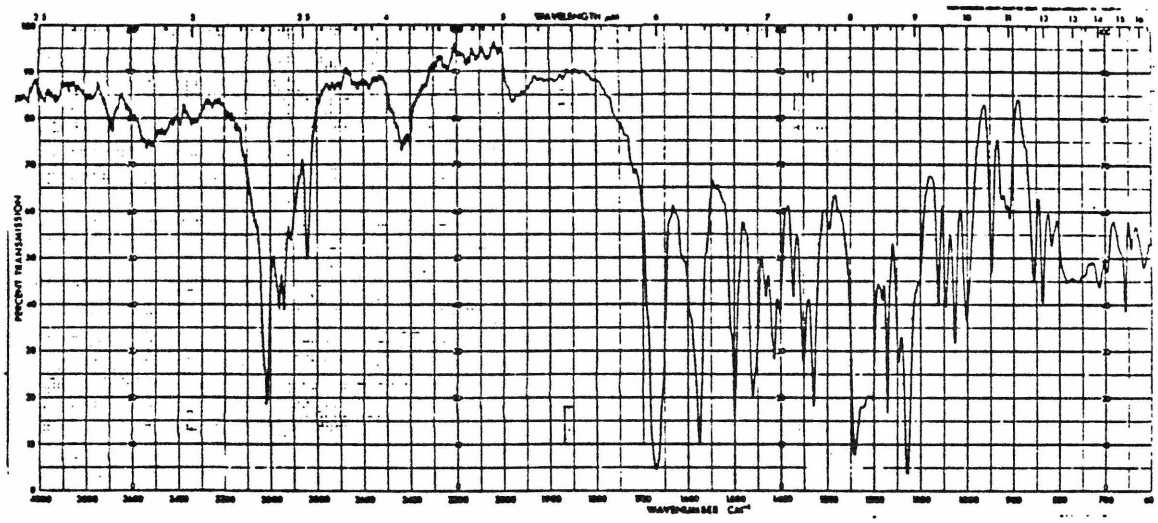

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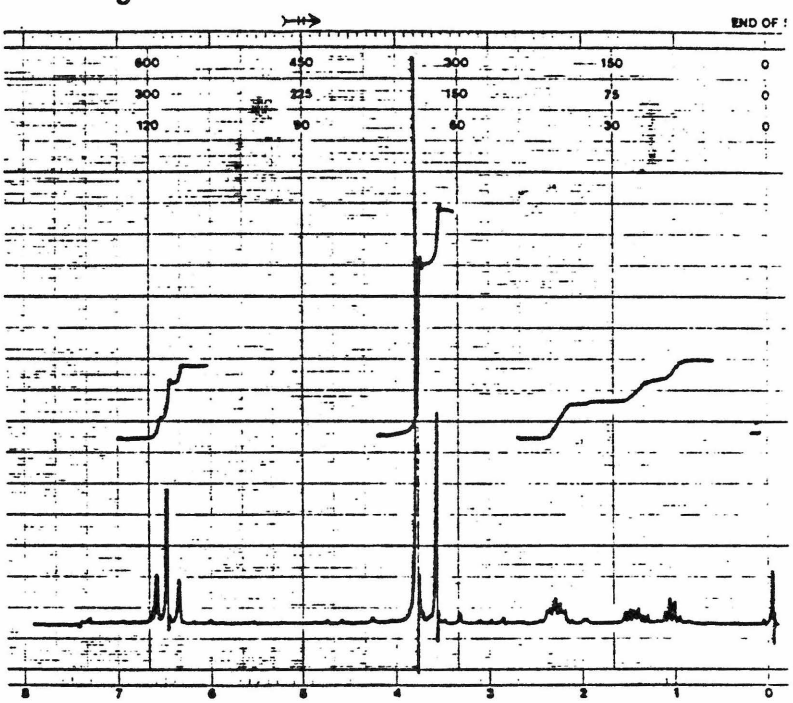

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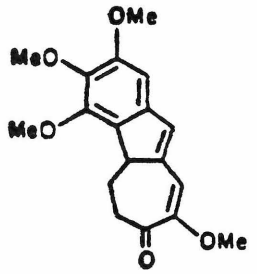

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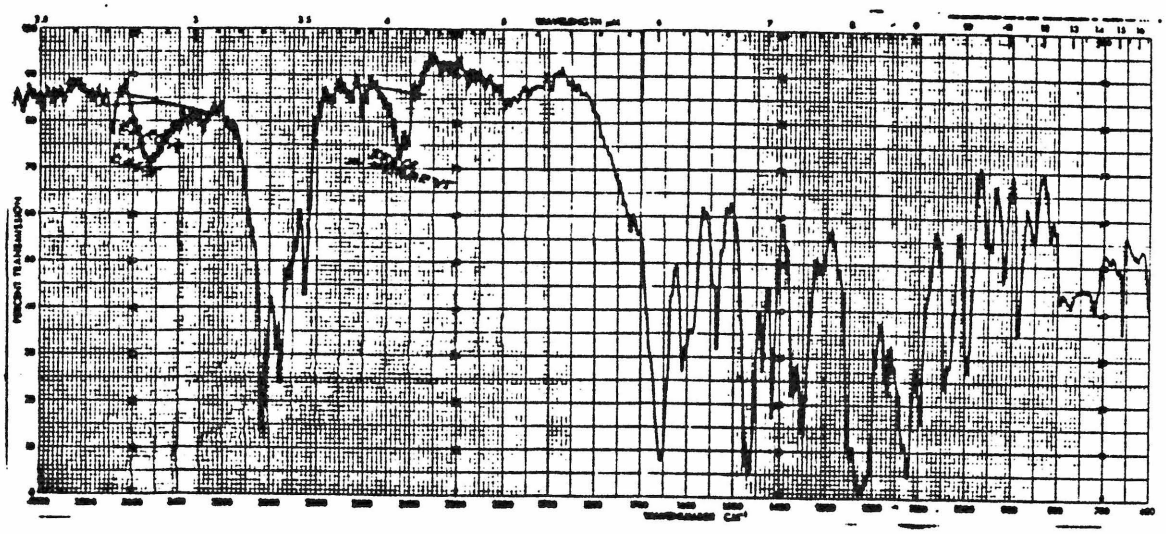

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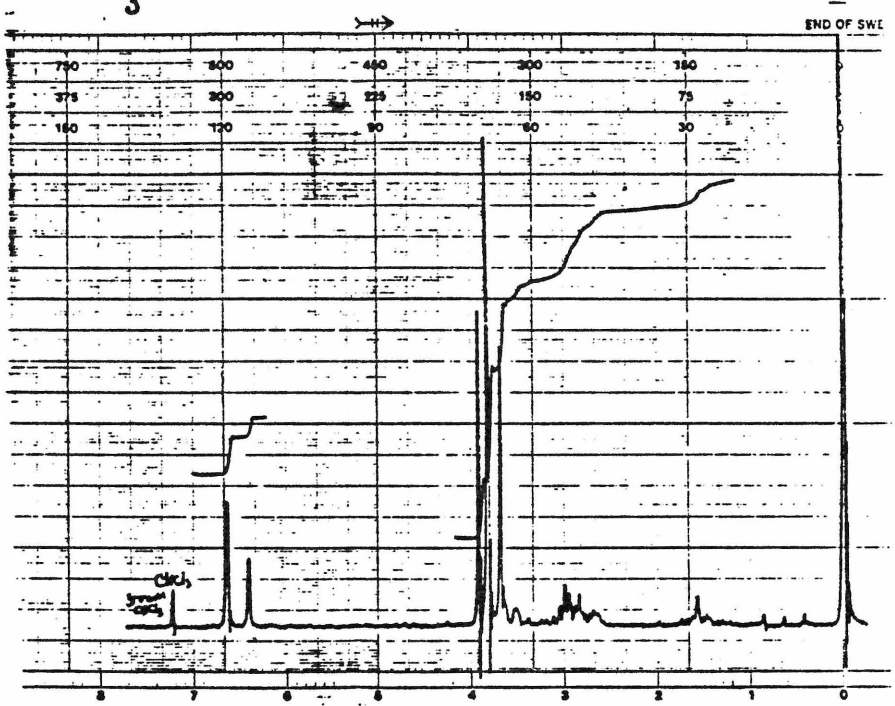

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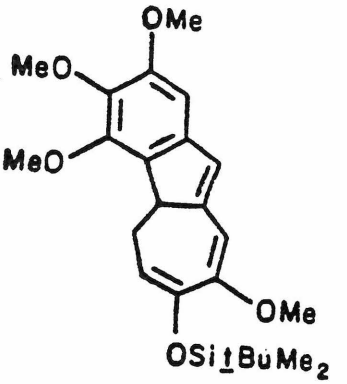

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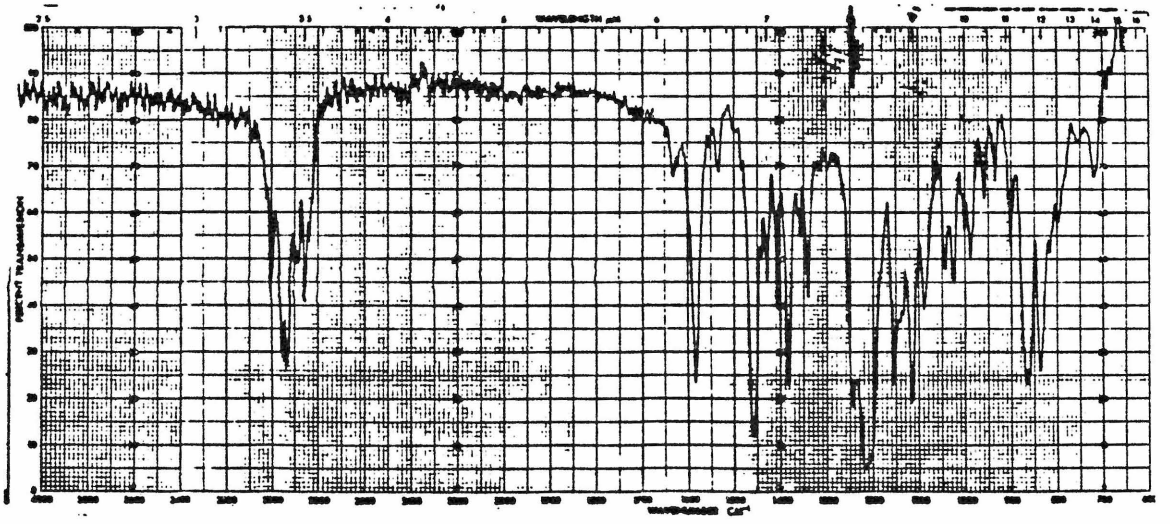

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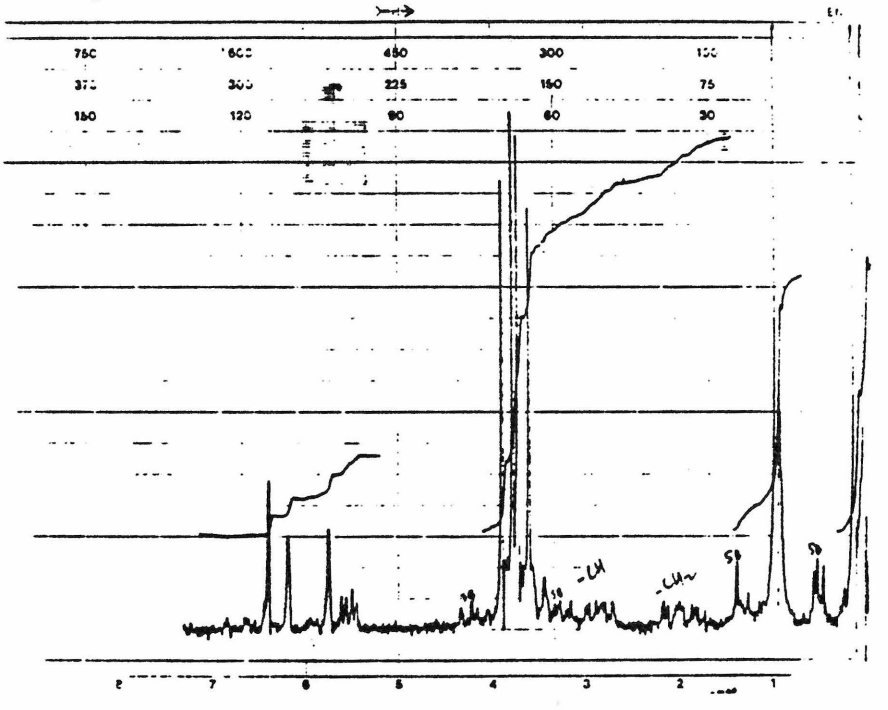

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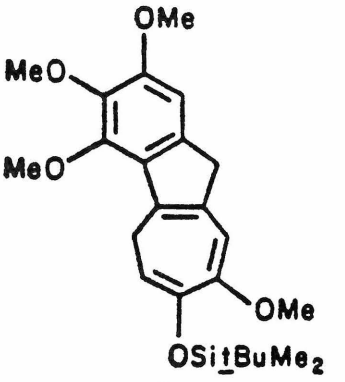

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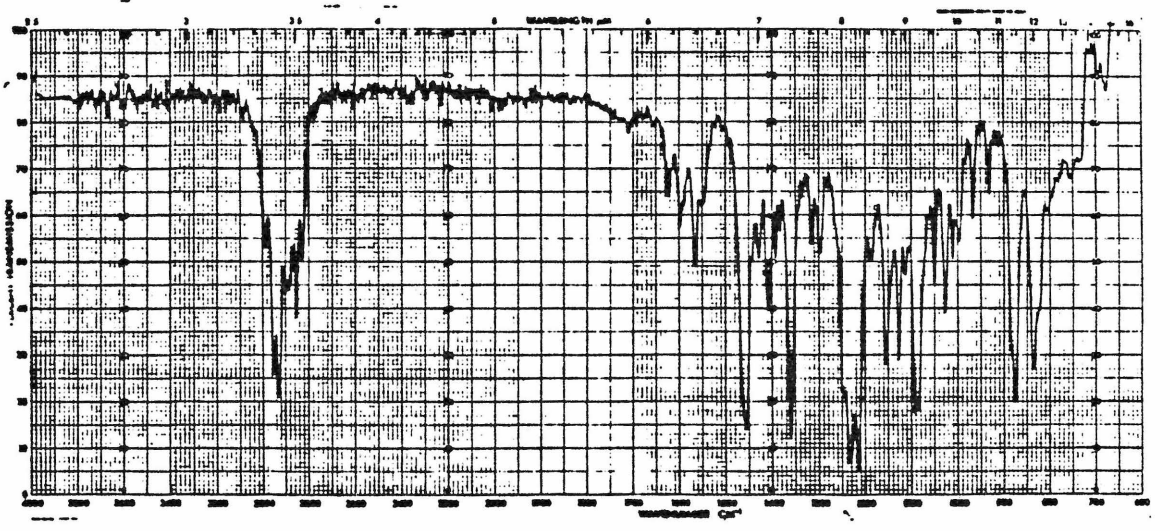

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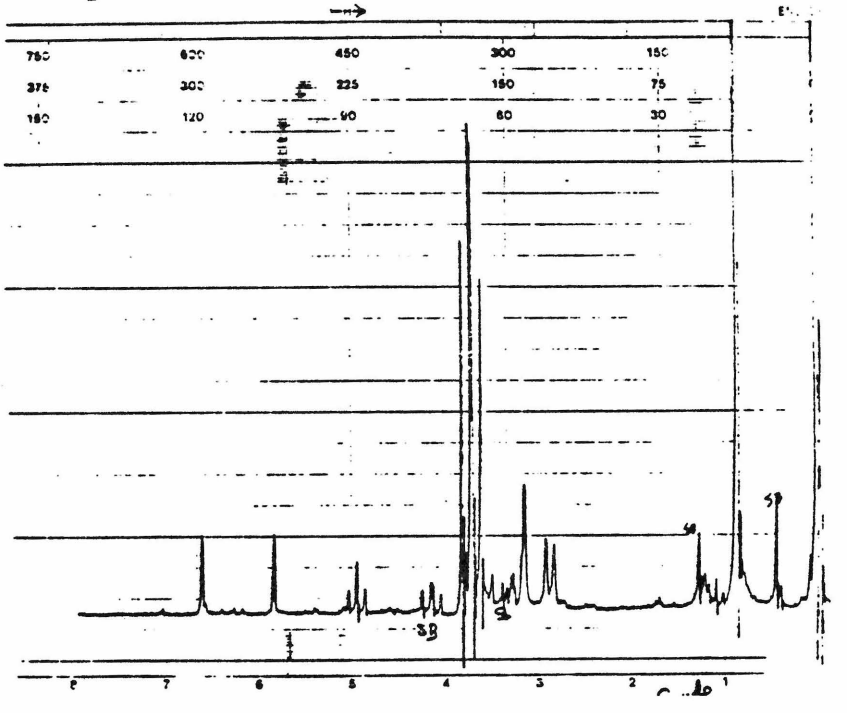

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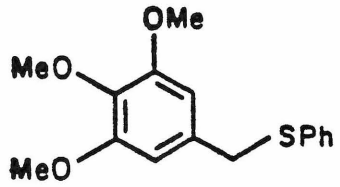

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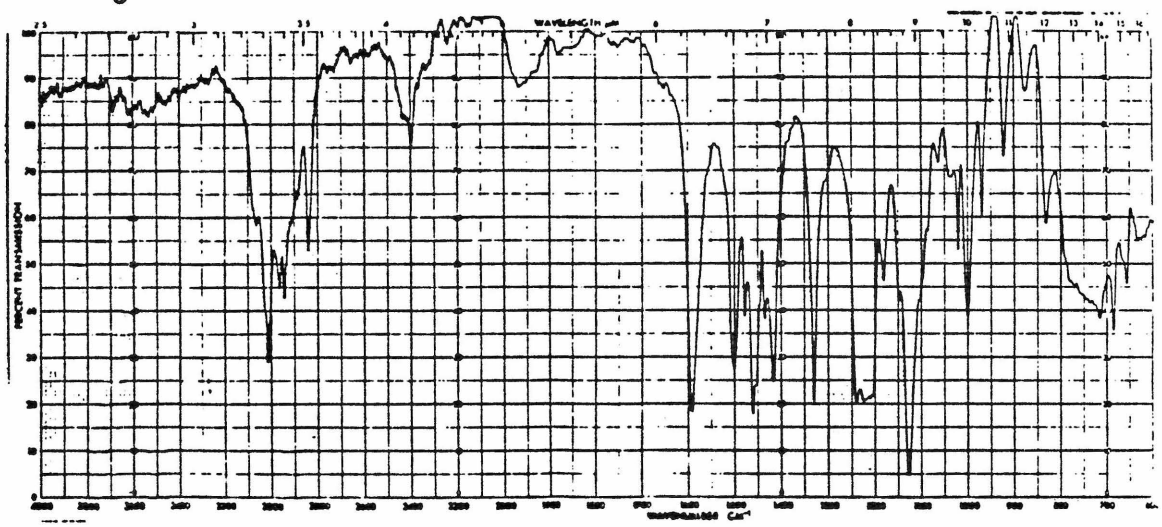

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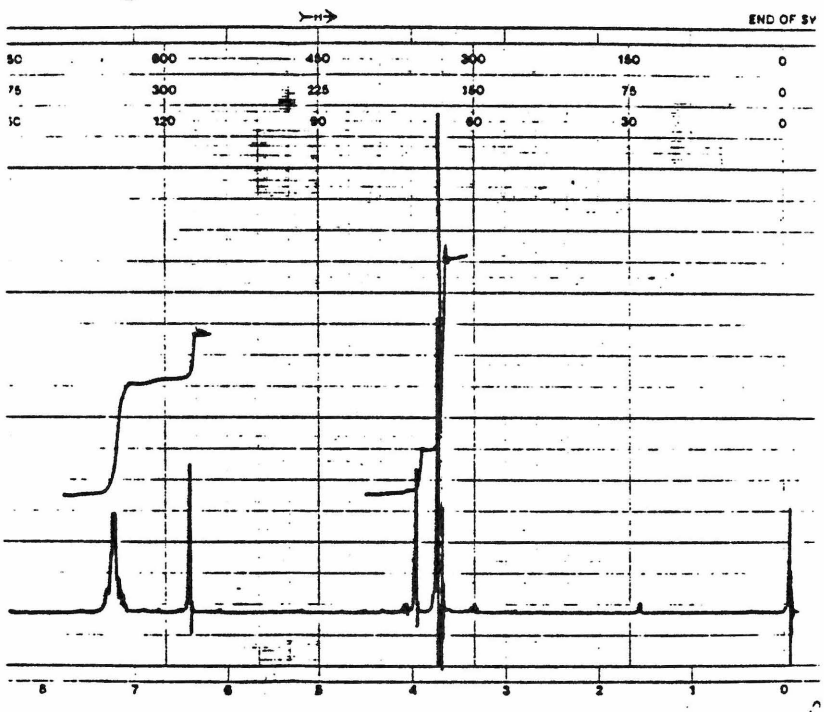

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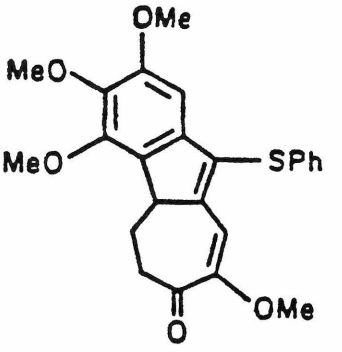

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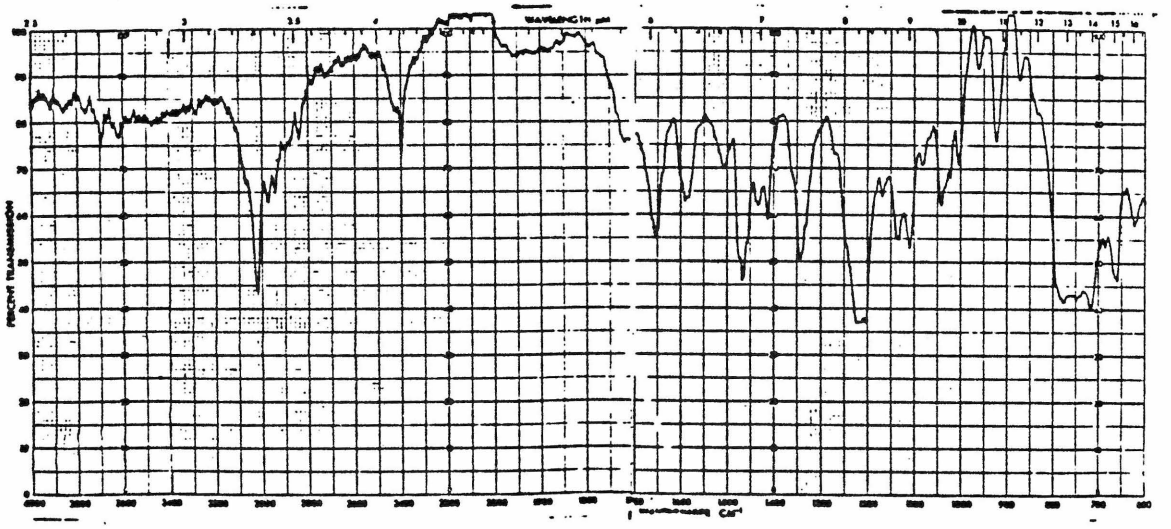

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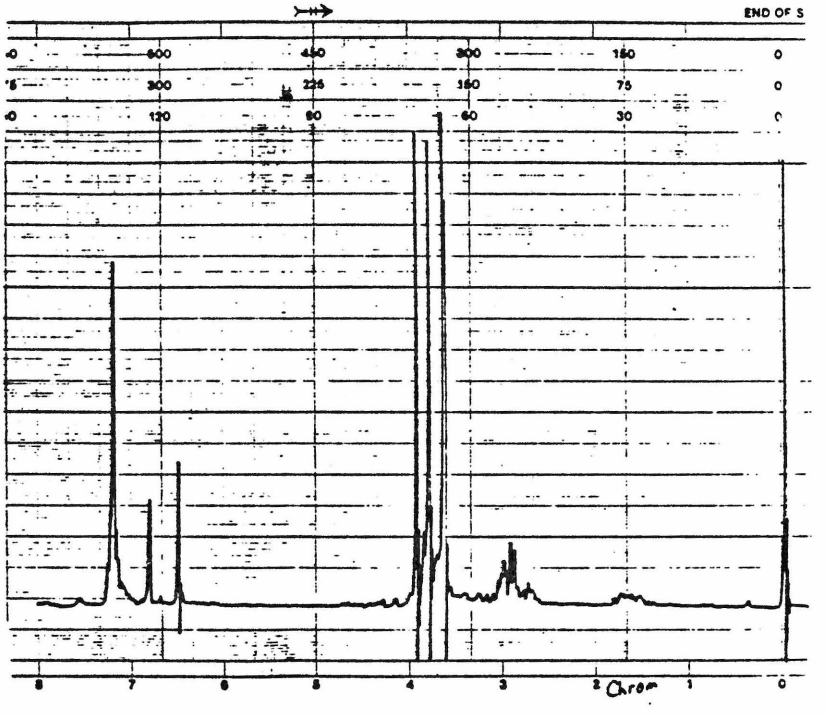

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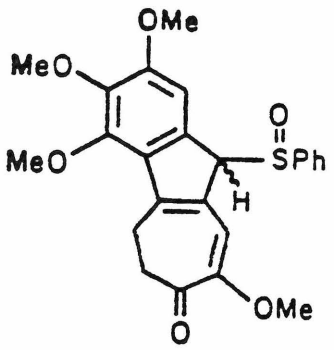

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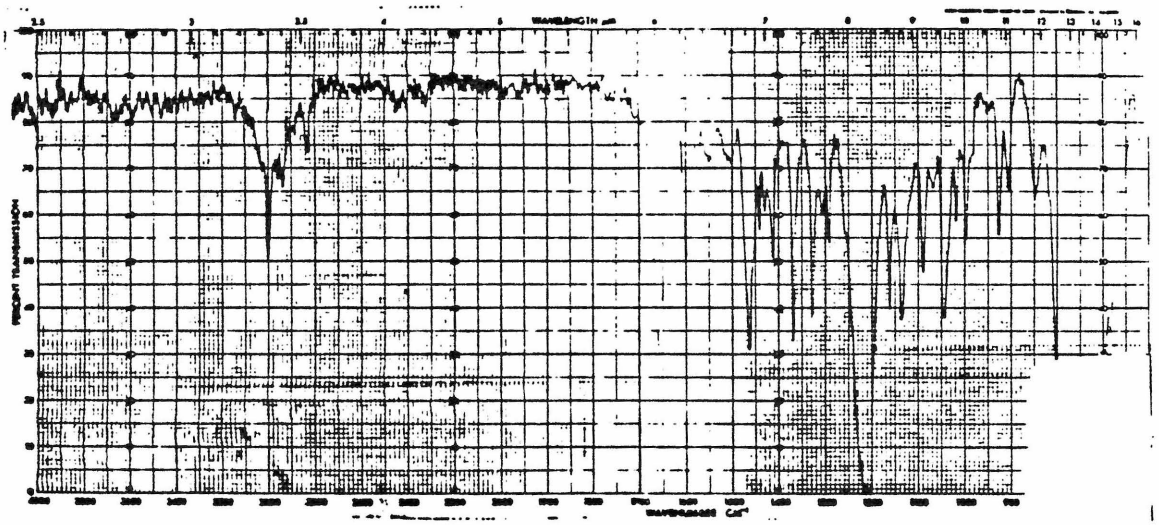

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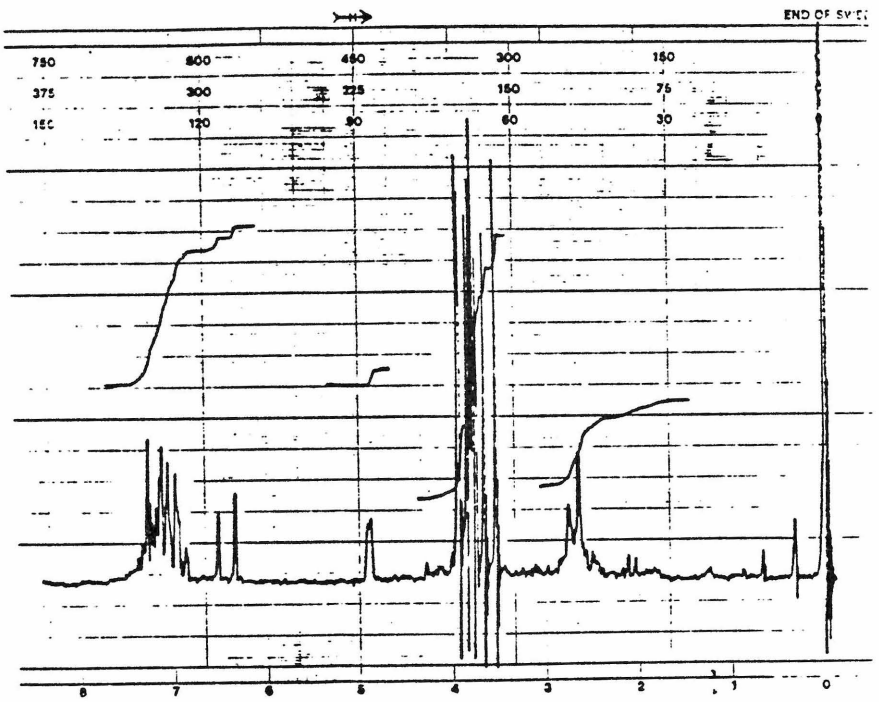

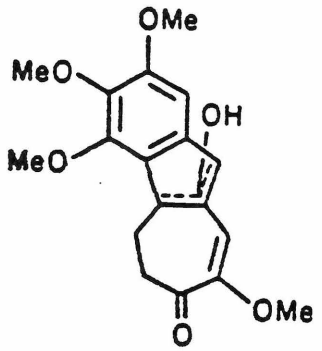

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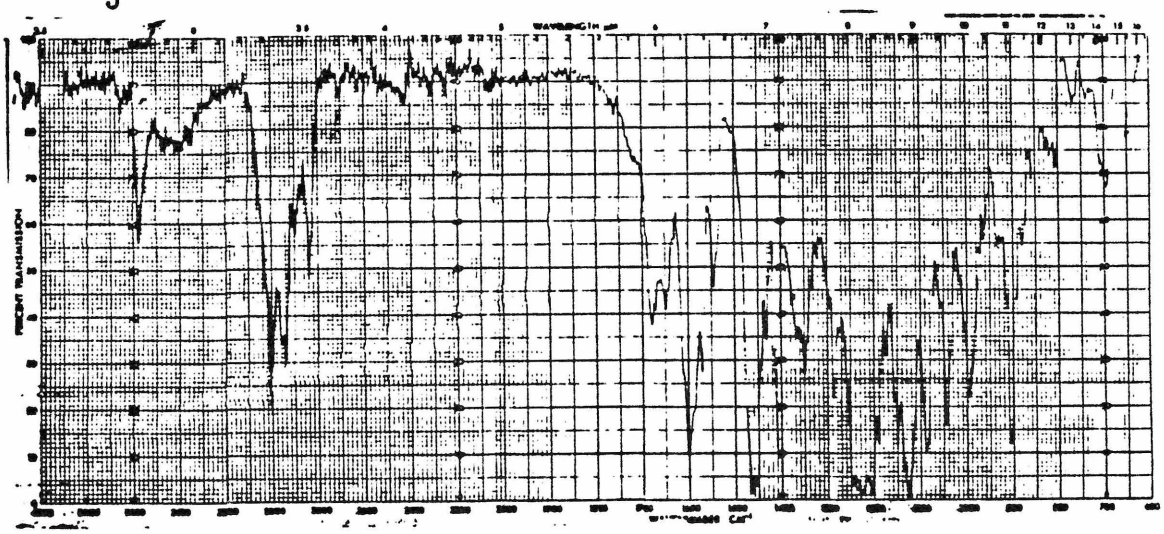

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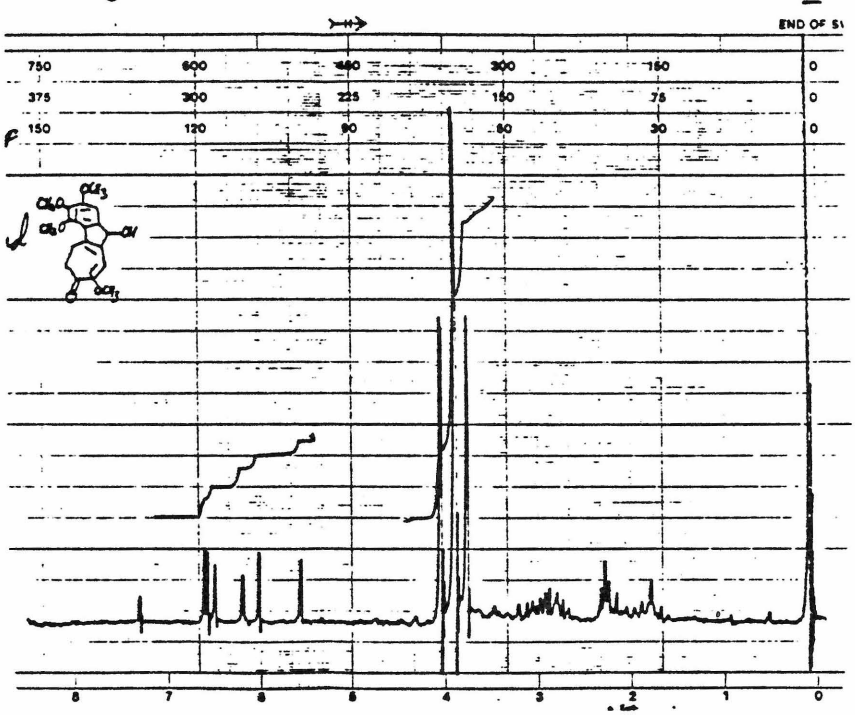

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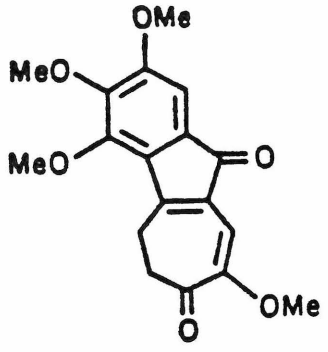

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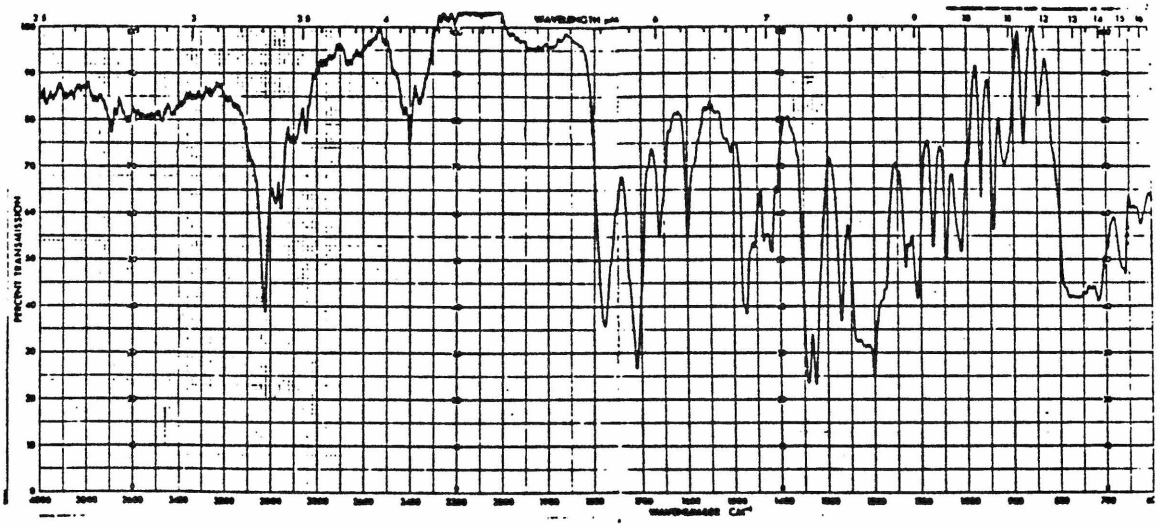

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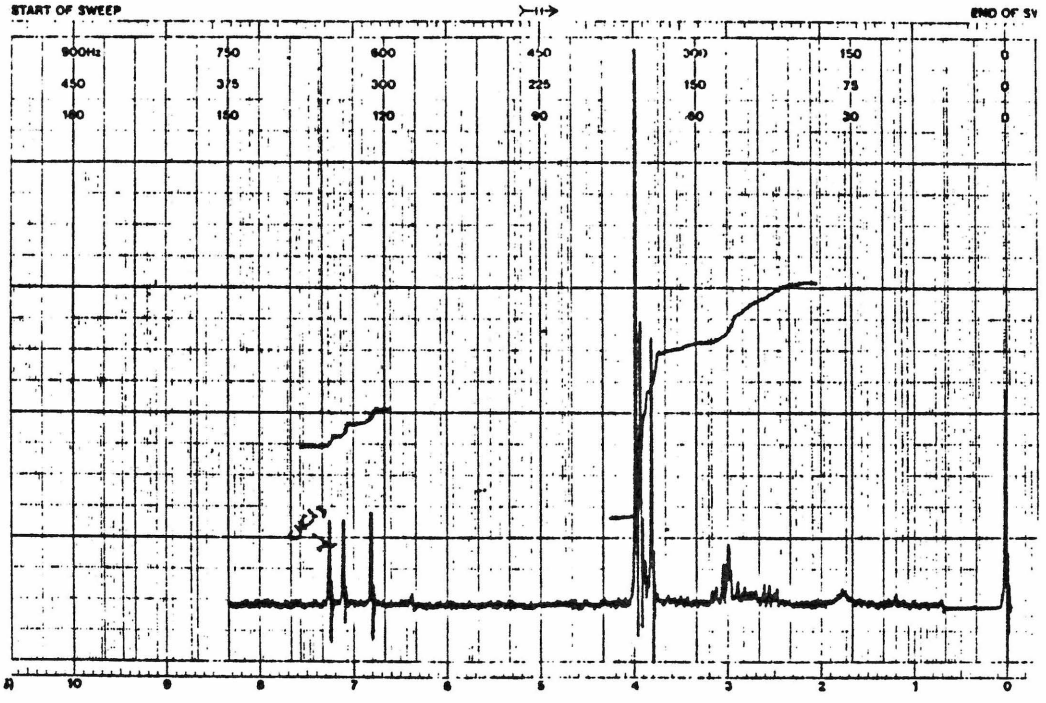

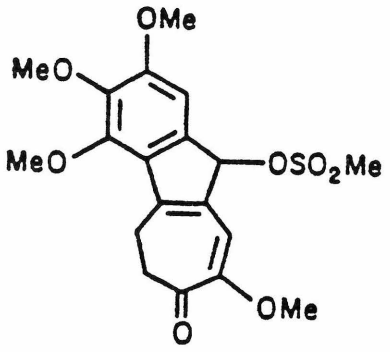

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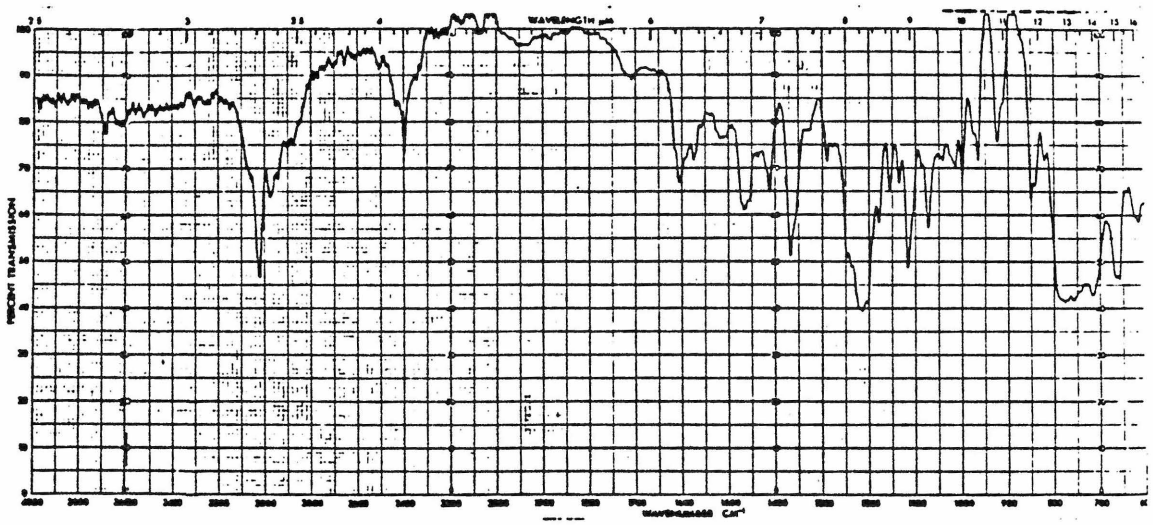

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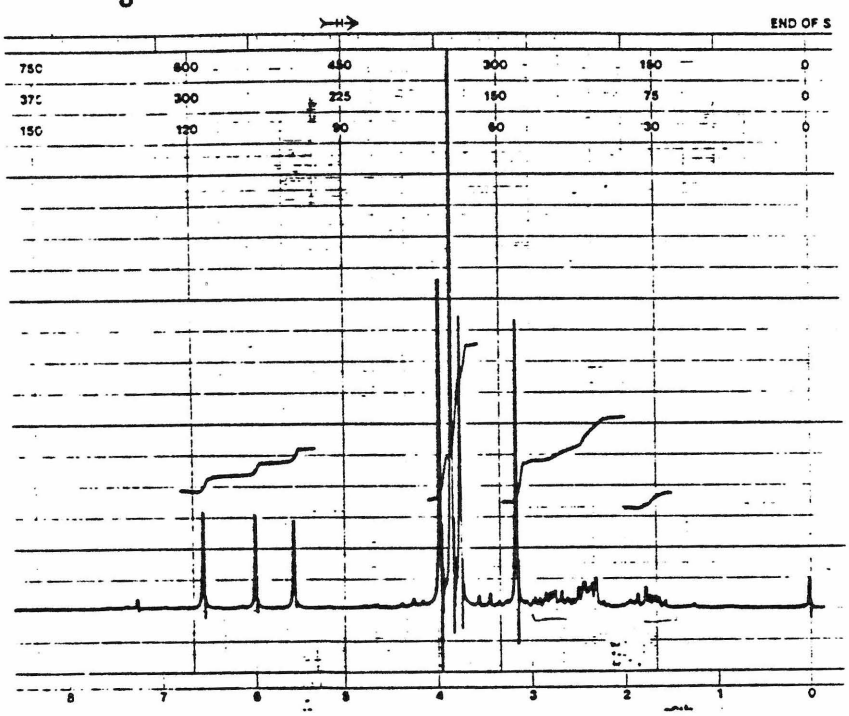

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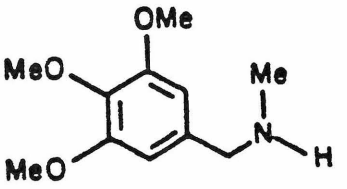

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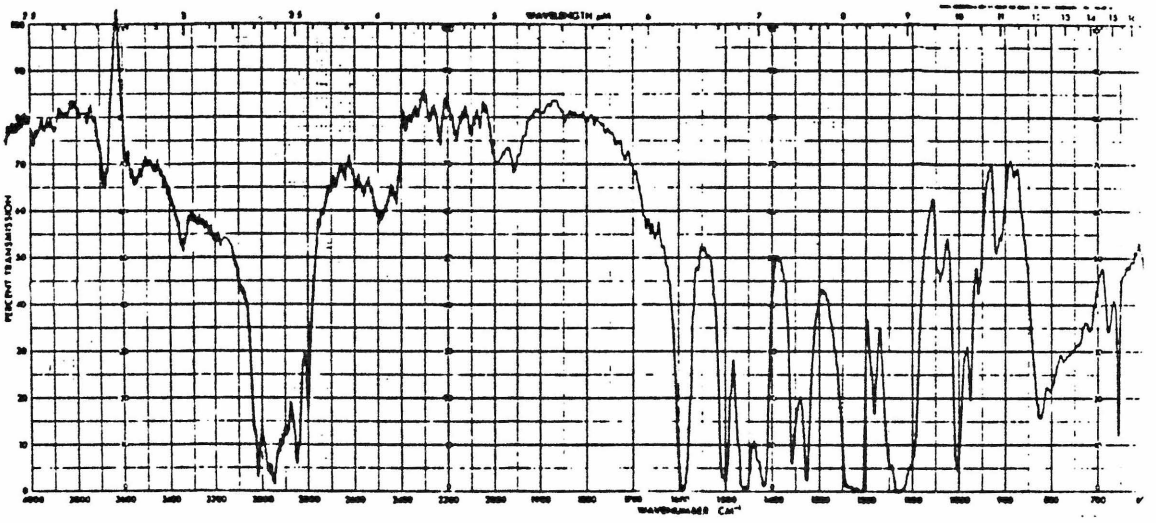

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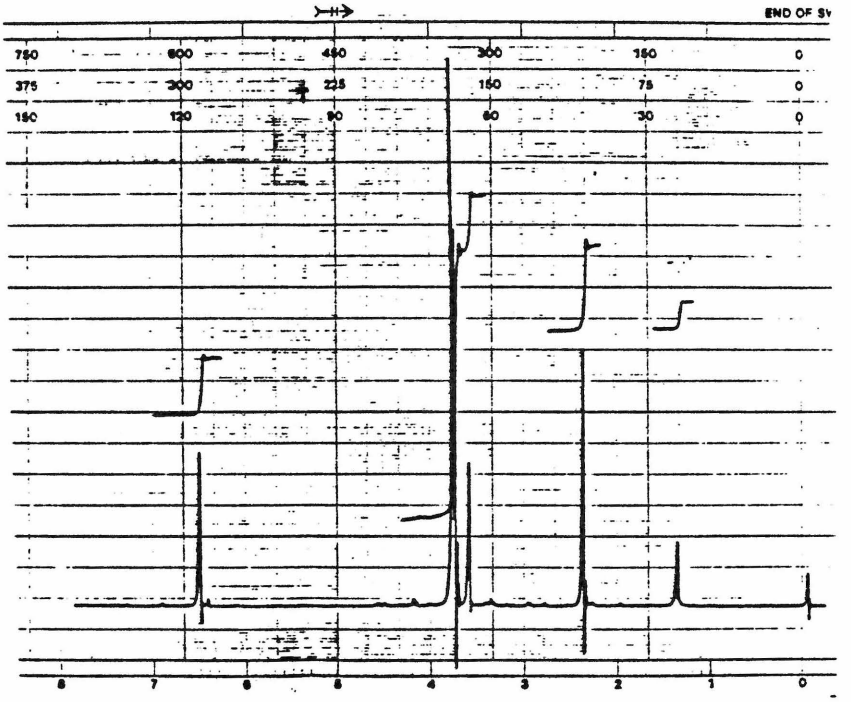

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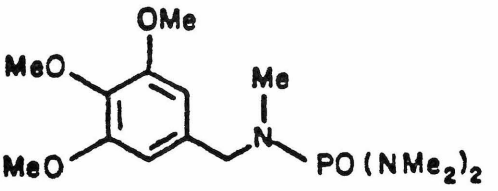

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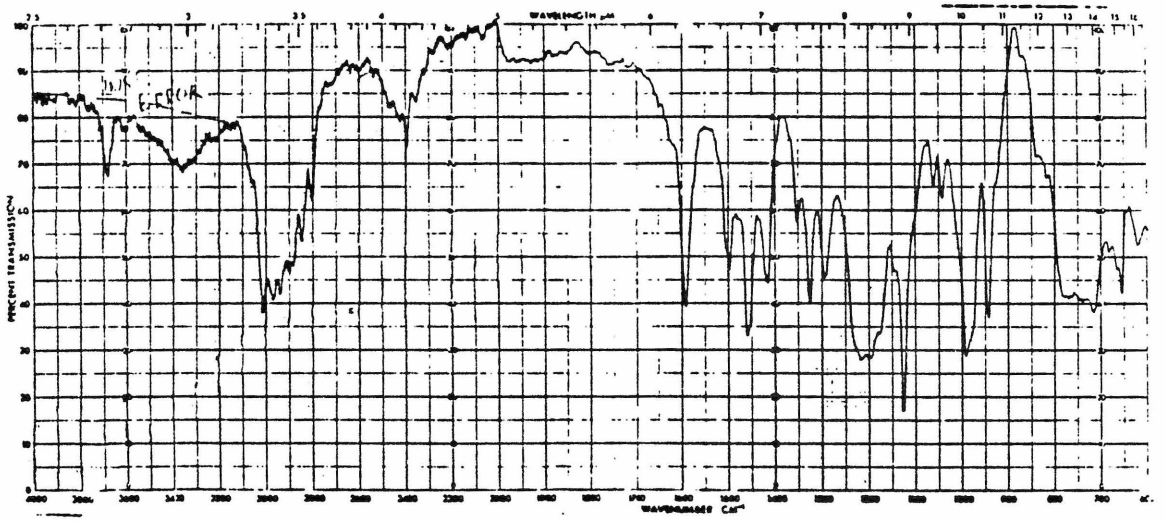

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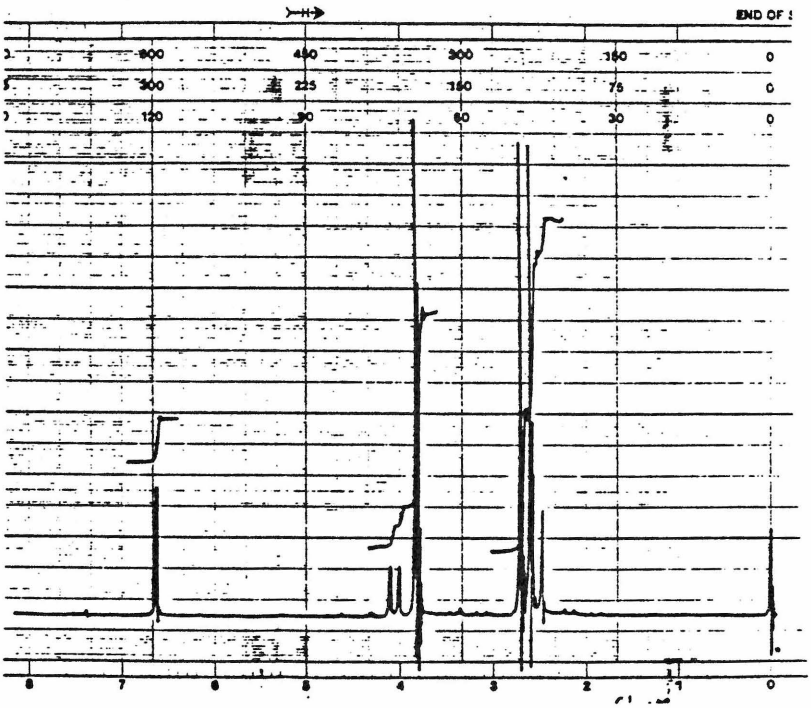

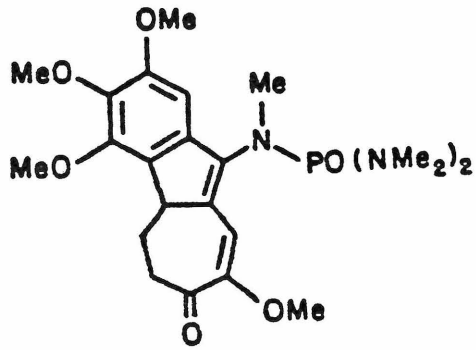

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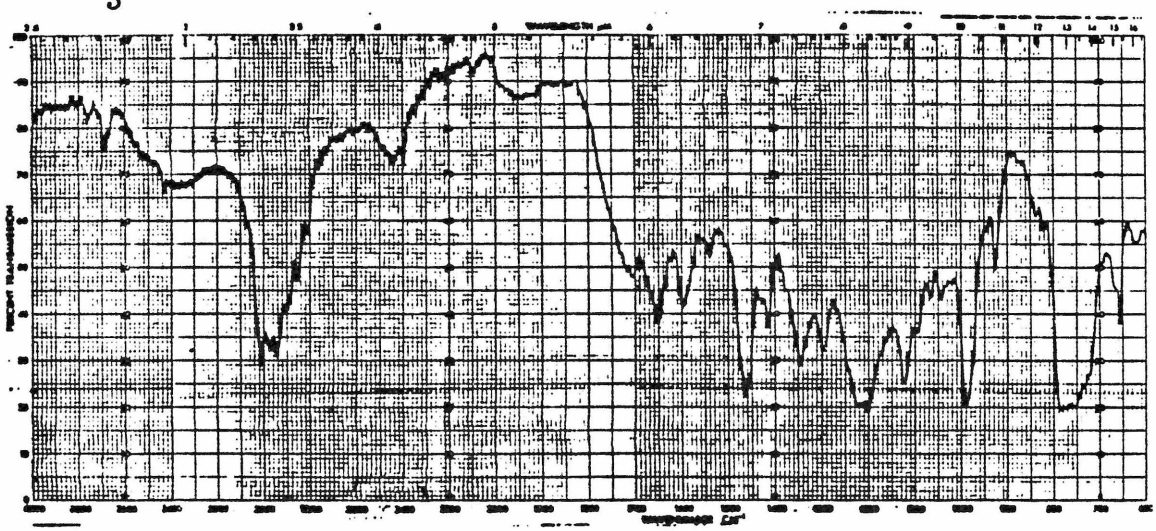

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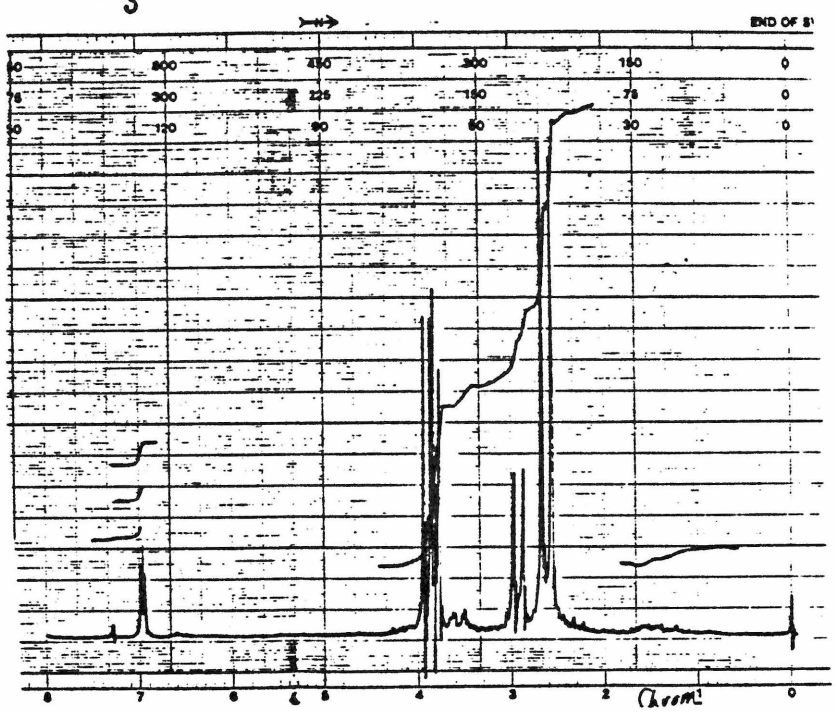

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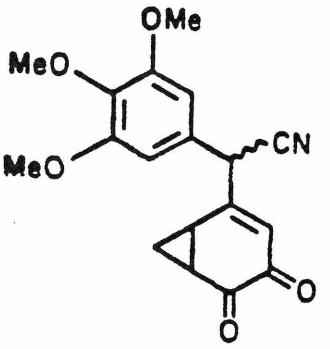

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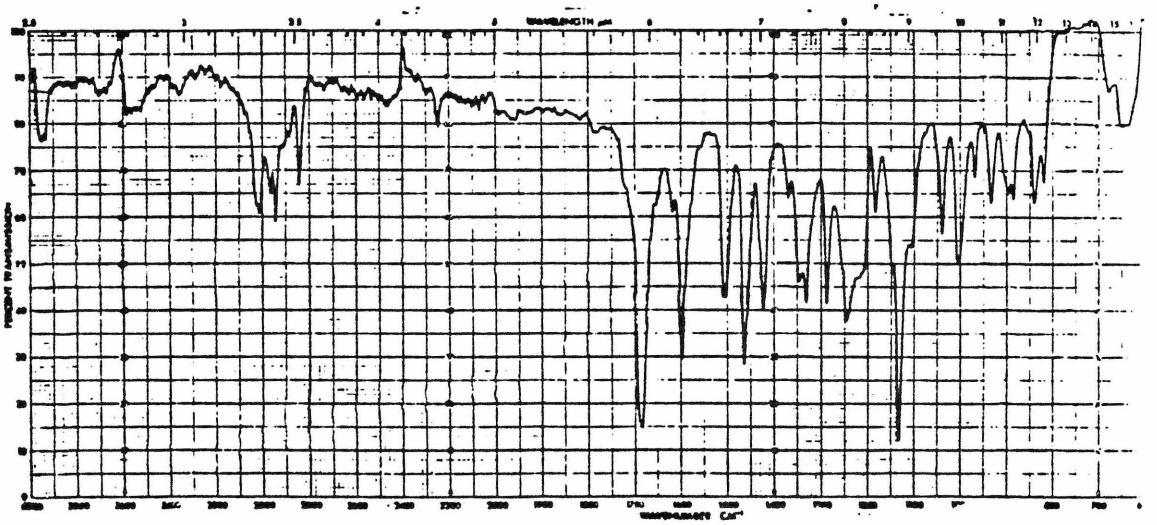

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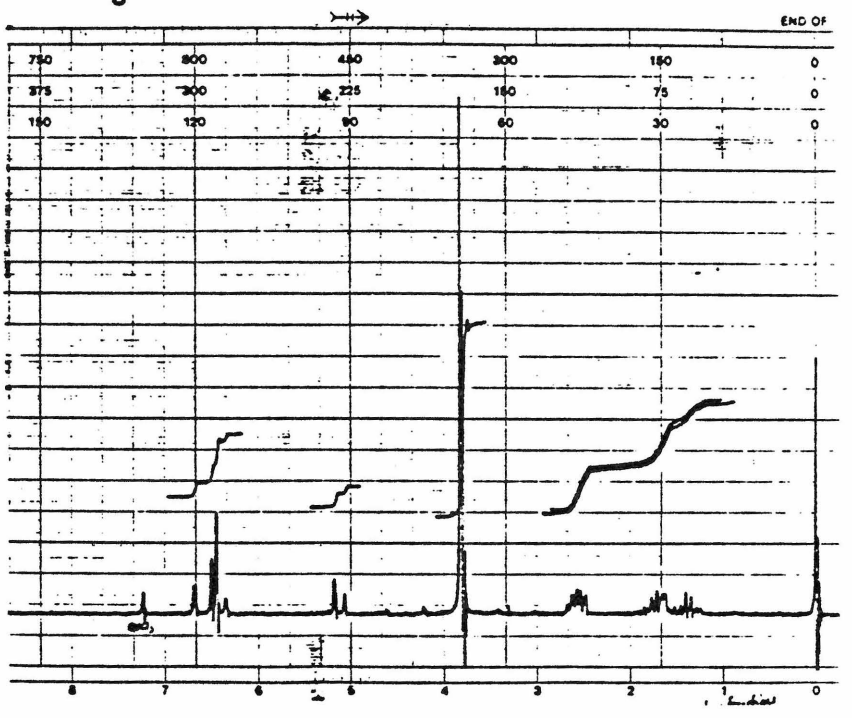

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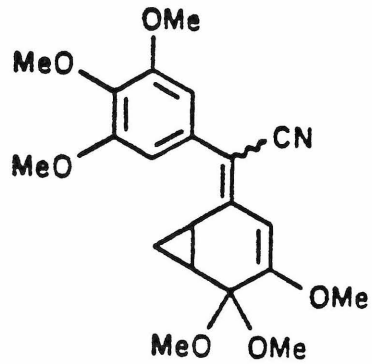

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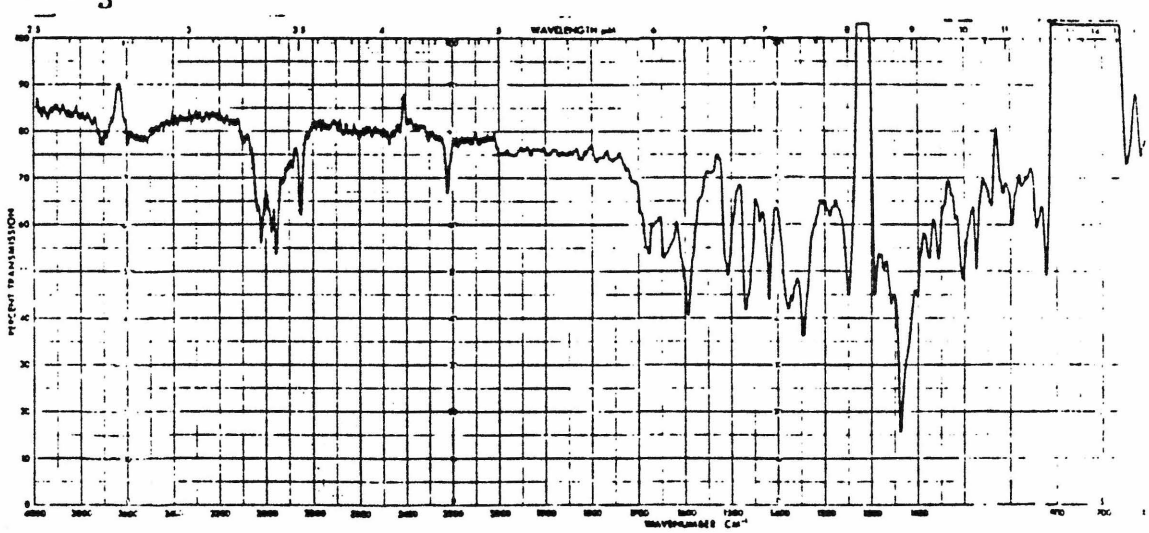

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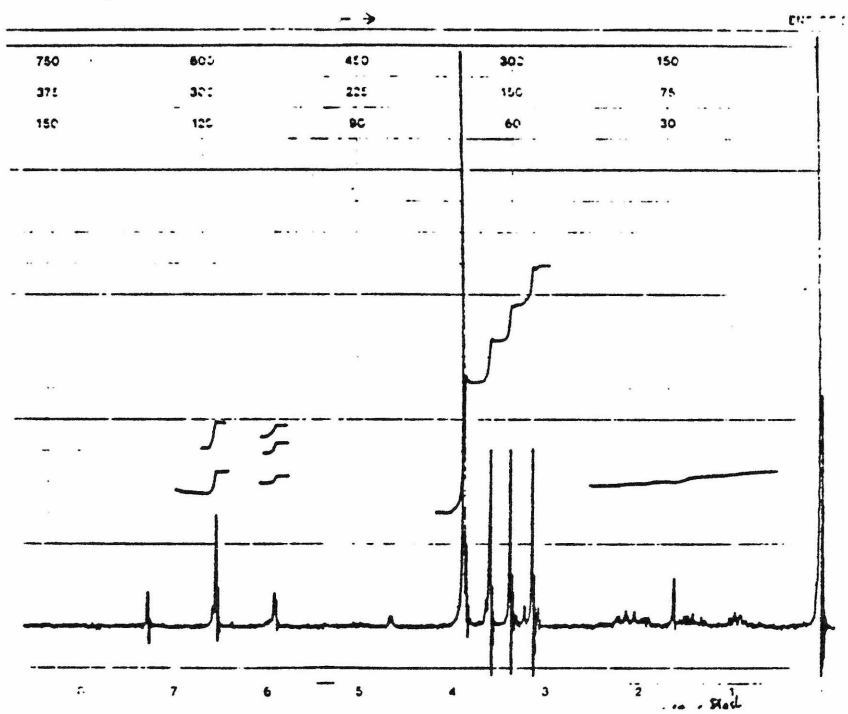

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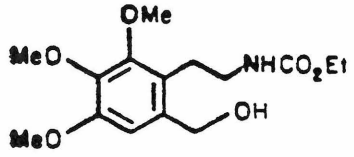

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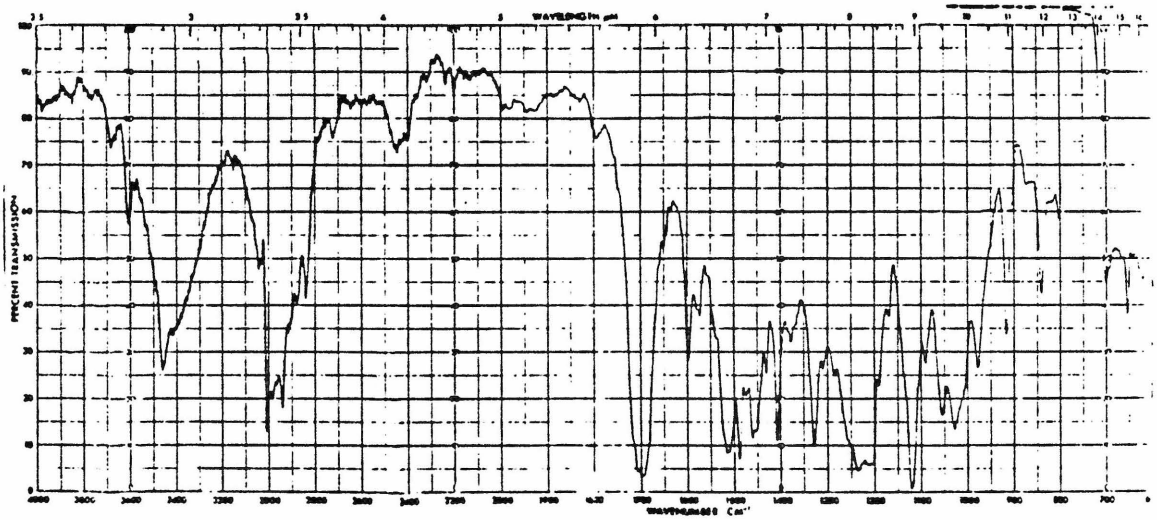

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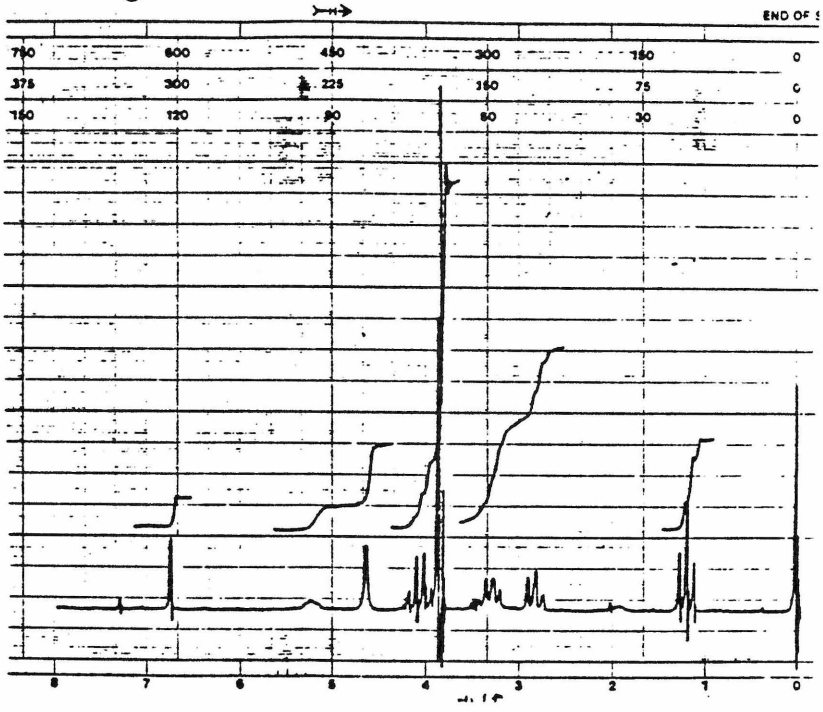

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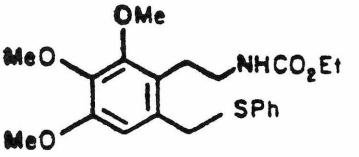

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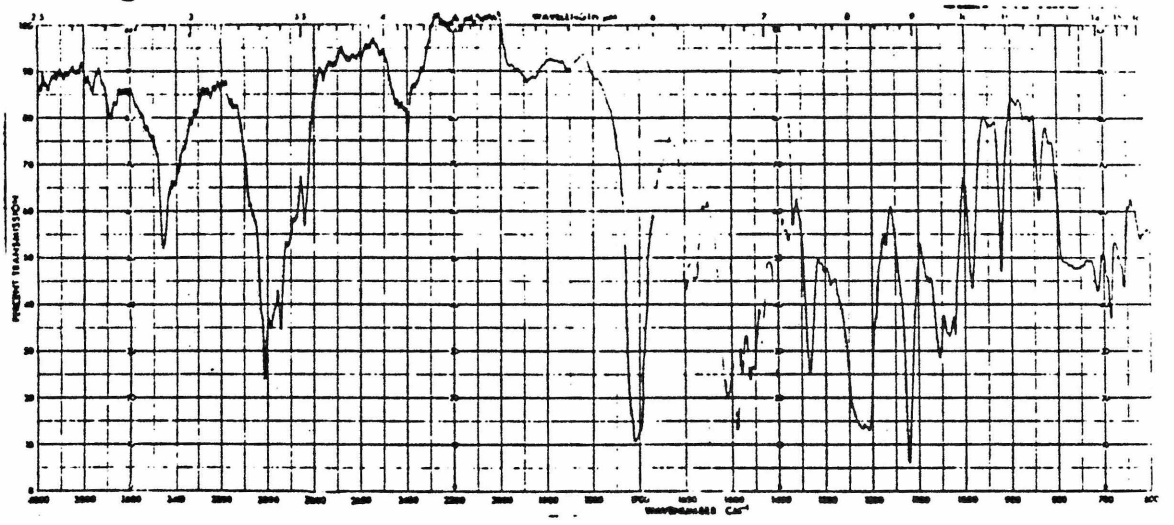

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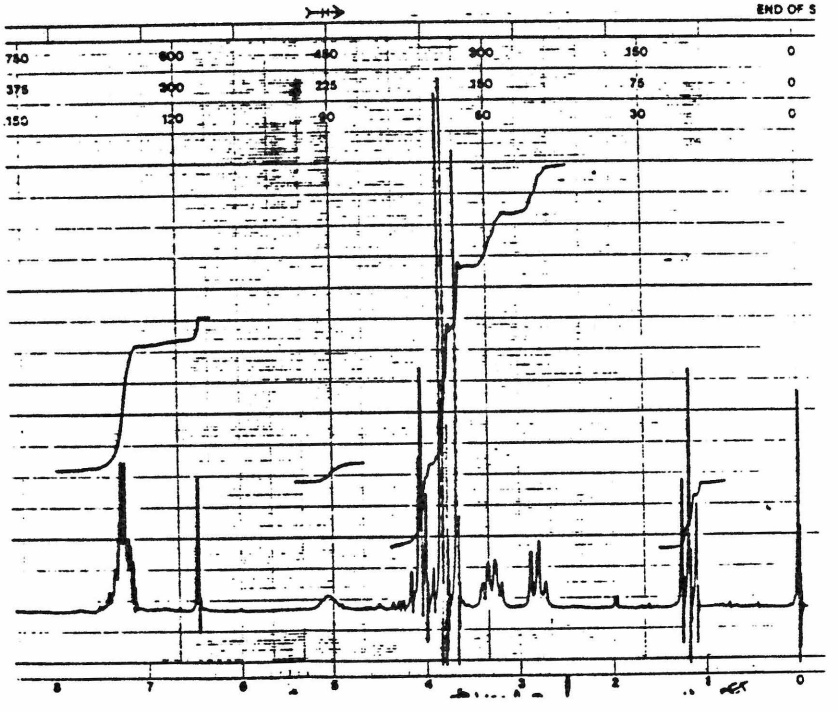

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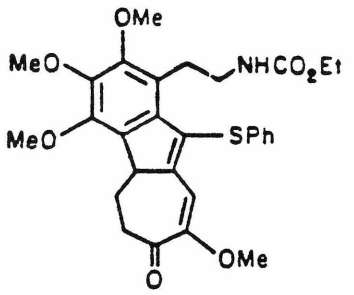

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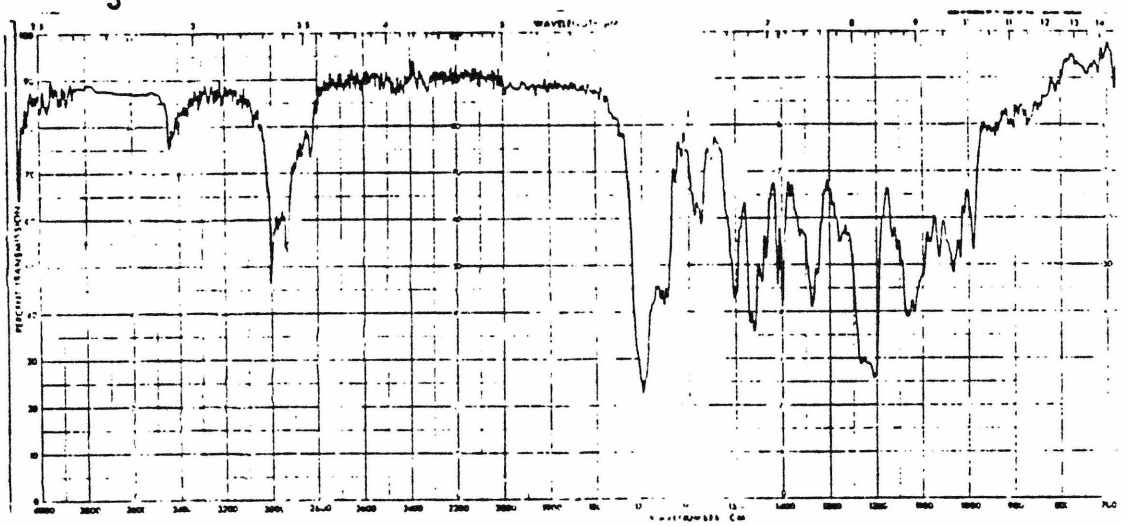

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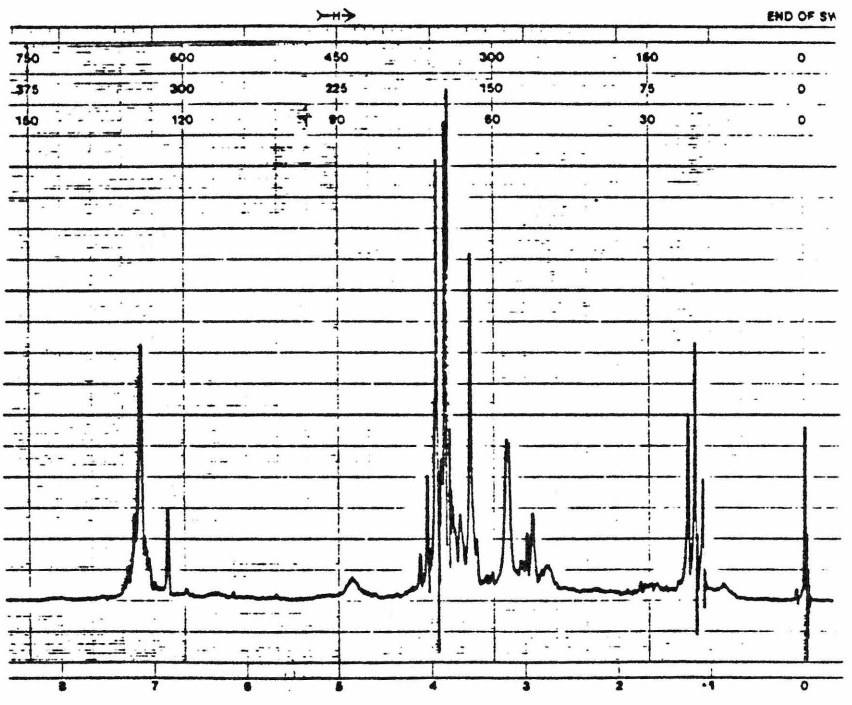

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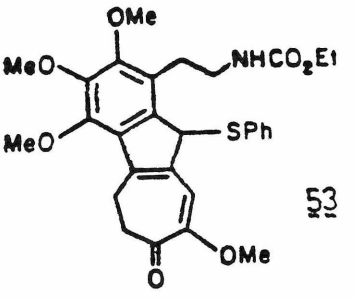

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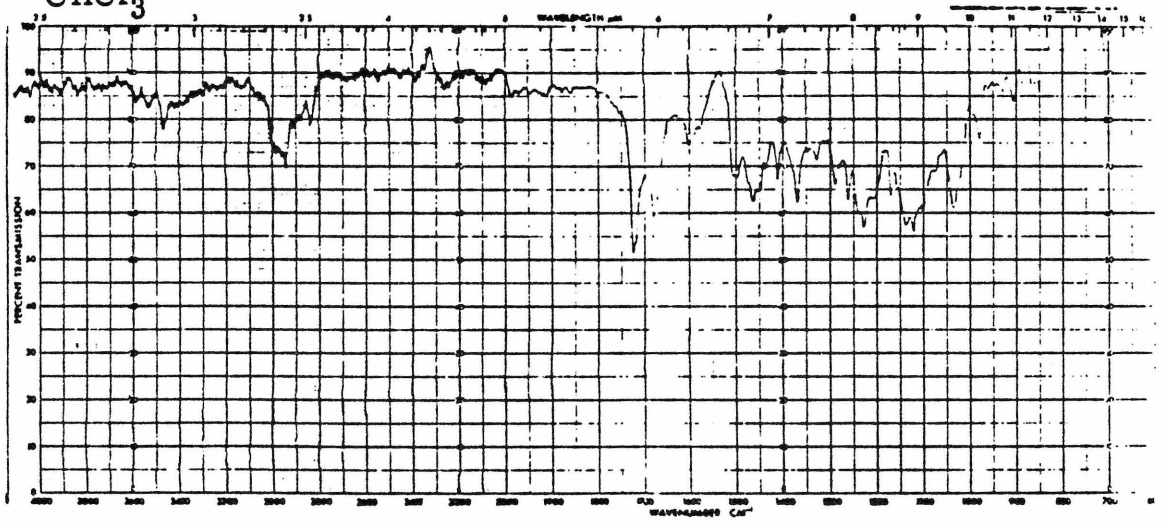

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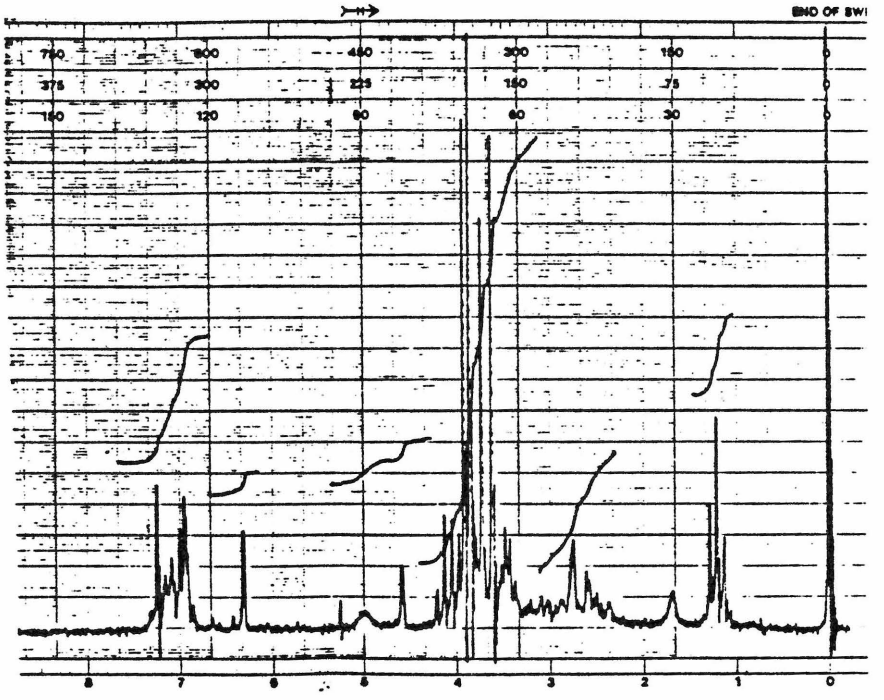
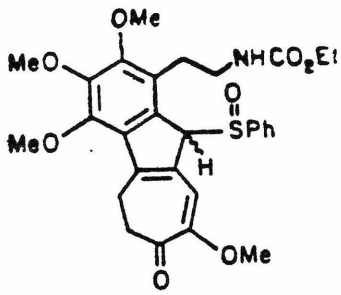


Page 94 $CDCl_3$



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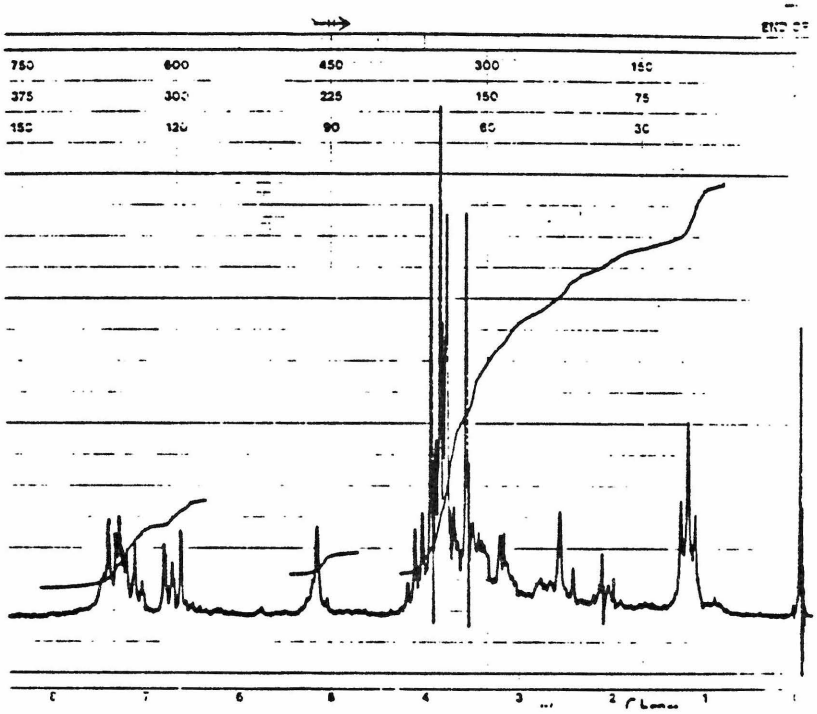
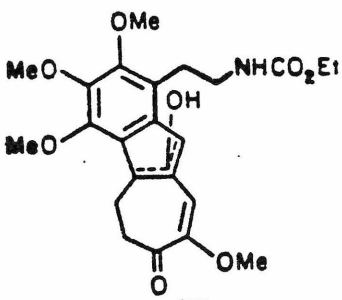


Page 94 $CDCl_3$



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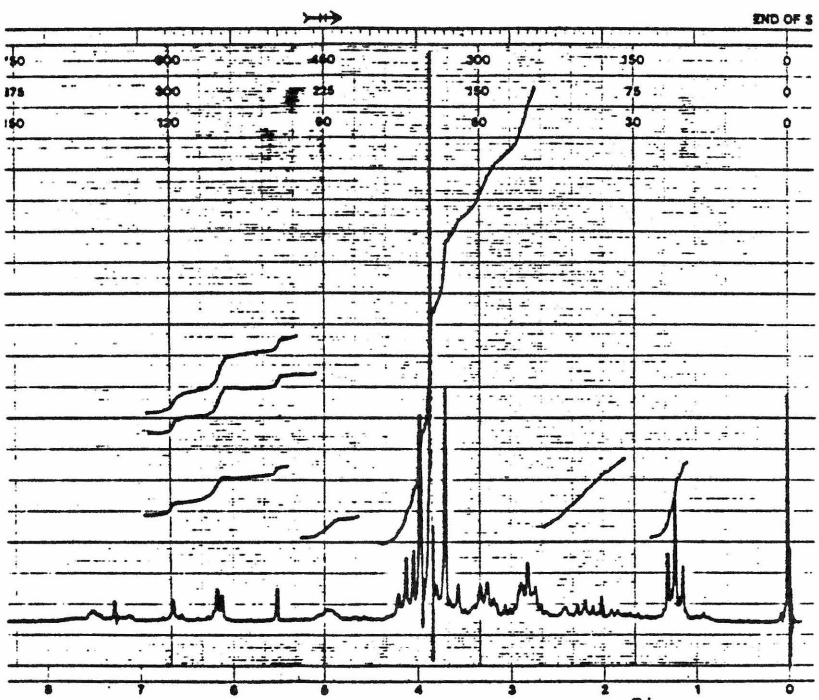

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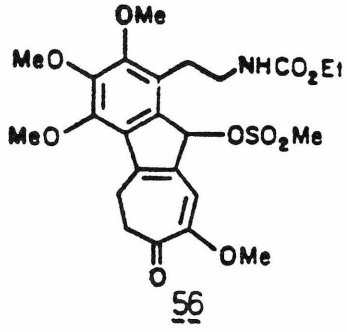

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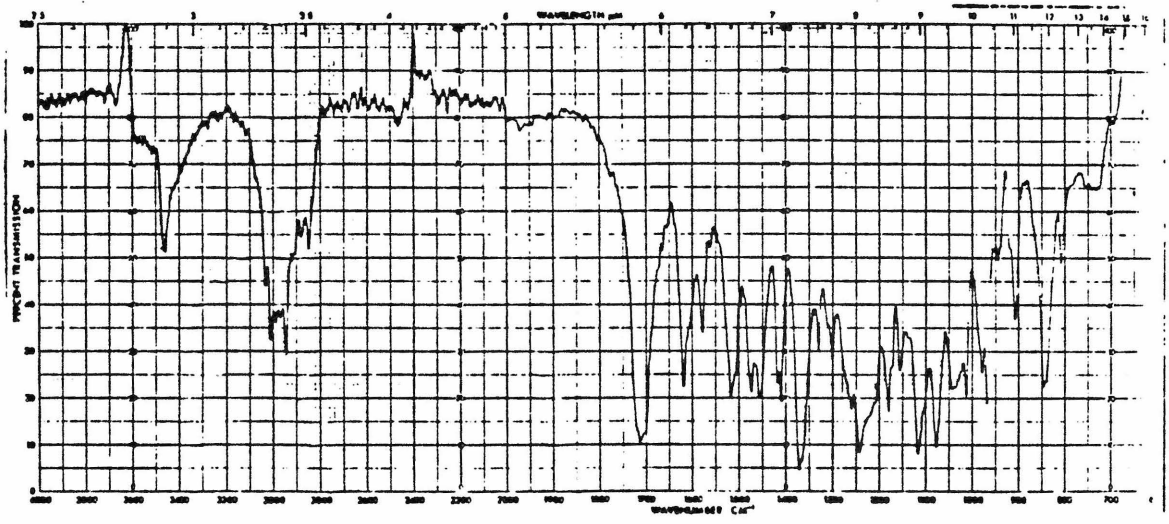

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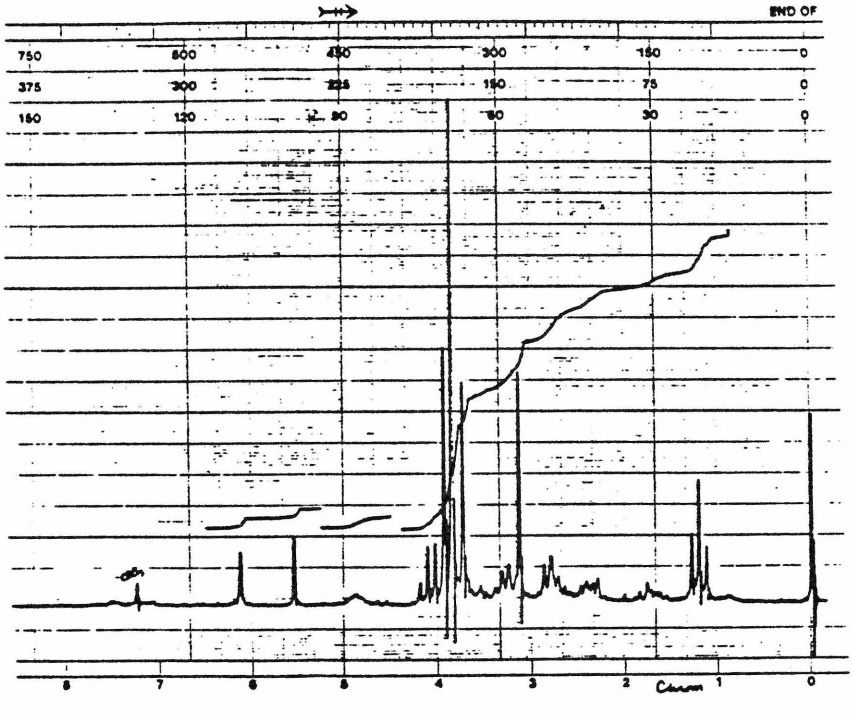

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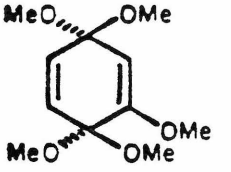

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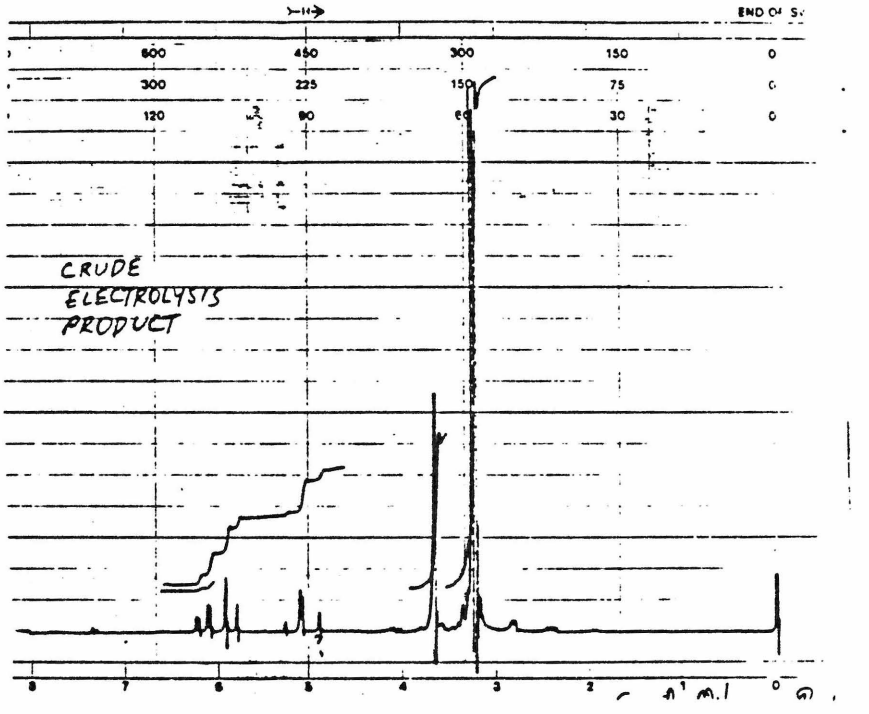


PROPOSITIONS

ABSTRACTS

PROPOSITION I: The total synthesis of two Rhazya Stricta alkaloids is proposed, incorporating an intramolecular imine aldol-alkyl migration sequence.

PROPOSITION II: The preparation and investigation of a new class of asymmetric bifunctional heterogeneous catalysts is proposed.

PROPOSITION III: The enantioselective alkylation of chiral nitrosamine anions is proposed as a method of generating asymmetry alpha to an amine.

PROPOSITION IV: A series of experiments involving measurement of the kinetic parameter "volume of activation" is suggested to resolve questions about the mechanism of an induced free radical decomposition.

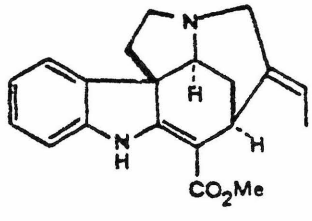
PROPOSITION V: A new application of π-allyl palladium chemistry is proposed, and its utility is demonstrated both as a method of resolving a conformational mechanistic question and as the key step in a chiral total synthesis of pseudomonic acid C.

PROPOSITION I

The total synthesis of two Rhazya Stricta alkaloids is proposed, incorporating an intramolecular imine aldol-alkyl migration sequence.

* * * * * * *

A structurally interesting class of alkaloids has been isolated form the Rhazya Stricta plant.[1] Among these are the indole bases akuammicine (1) and strictamine (2). Recently, the structure and both relative and



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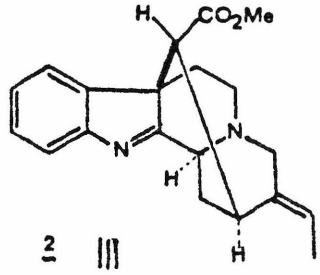

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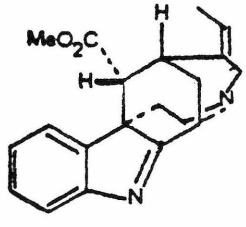
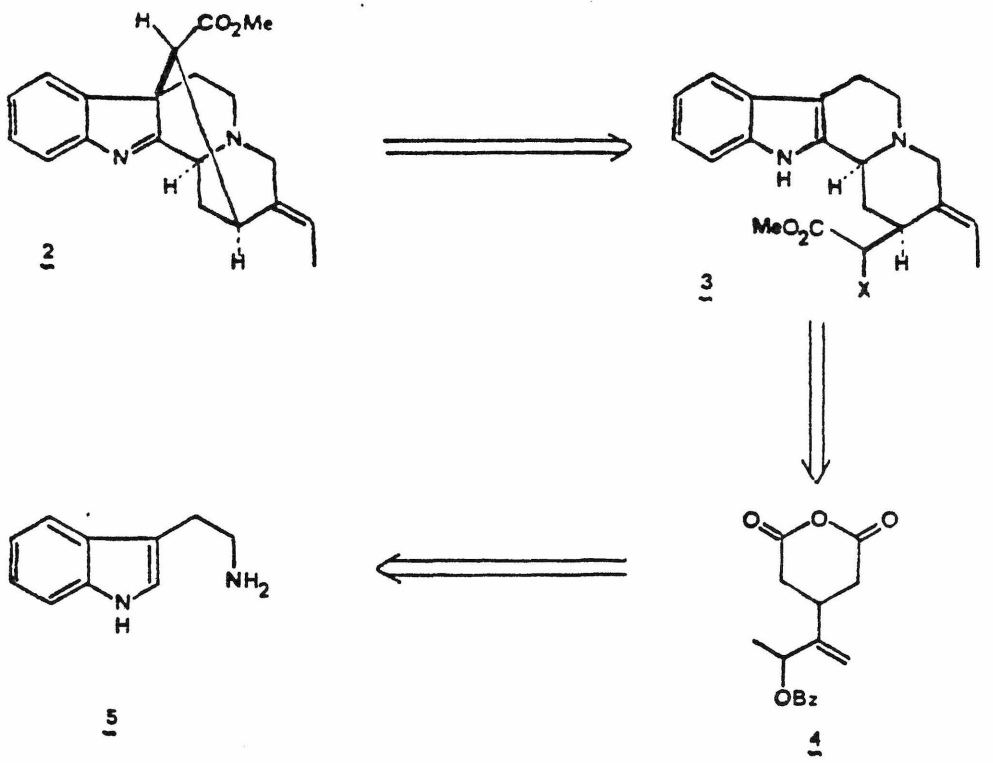


absolute stereochemistry of strictamine have been unequivocally established by X-ray crystallographic studies.[2] Derivatives of both 1 and 2, containing only minor structural alterations, have also been isolated,[3] and 2 has been converted to 1 chemically.[4] Despite the synthetically challenging skeleta of such compounds, very little actual work has been done on their total synthesis. A rapid, convergent synthesis of strictamine (2) will be discussed here.

A proposed retrosynthetic plan is shown for strictamine in Scheme I. A key intermediate is envisioned to

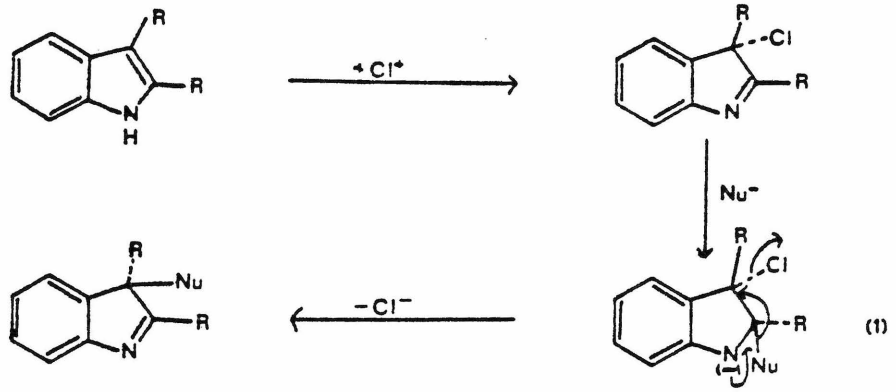
Scheme I

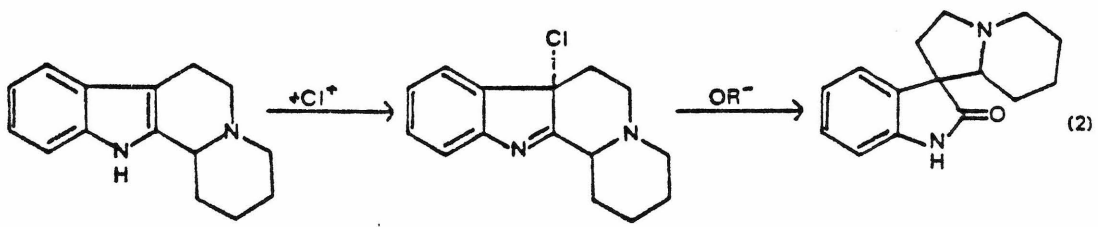


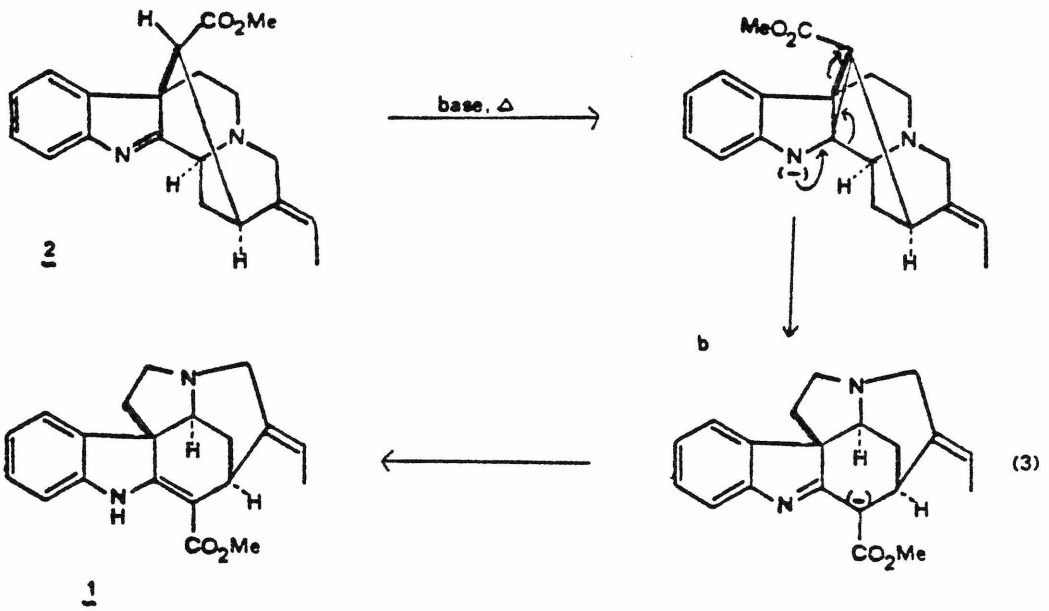
be the tetracyclic monoester 3a (X = H) or diester 3b (X = CO_2Me). This might be prepared by combination and appropriate refunctionalization of anhydride 4 and tryptamine (5).[5] Clearly, a major problem, besides the formation of intermediate 3 with the proper relative stereochemistry, will be its conversion to the strictamine skeleton.

However, a number of known reaction types in the area of indole alkaloid chemistry suggest the general route shown in Scheme II, equation 1. That treatment of indoles with a positive halogenating agent (e.g. (t-BuOCl) affords isolable chloroindolenines is well-known. Addition of a nucleophile to the imino moeity anti to the chlorine would allow for a subsequent rearrangement involving 1,2-migration of the nucleophile concomitant with expulsion of the chloride, giving an indolenine such as the one shown. Since there exists a stereoelectronic requirement for antiperiplanarity of the migrating group with the leaving group for such a rearrangement, Nu should migrate in preference to R_2 (eq. 1). The strategy proposed here, which will be discussed more fully later, will therefore involve the conversion of intermediate 3 to its derived chloro-indolenine, followed by acid or base-promoted nucleophilic

Scheme II


R
R
N
H
+Cl⁺
R
Cl
R
N
Nu⁻
R
Cl
R
N
Nu
(-)
Nu
R
R
N
-Cl⁻
(1)


N
H
+Cl⁺
Cl
N
OR⁻
N
O
N
H
(2)

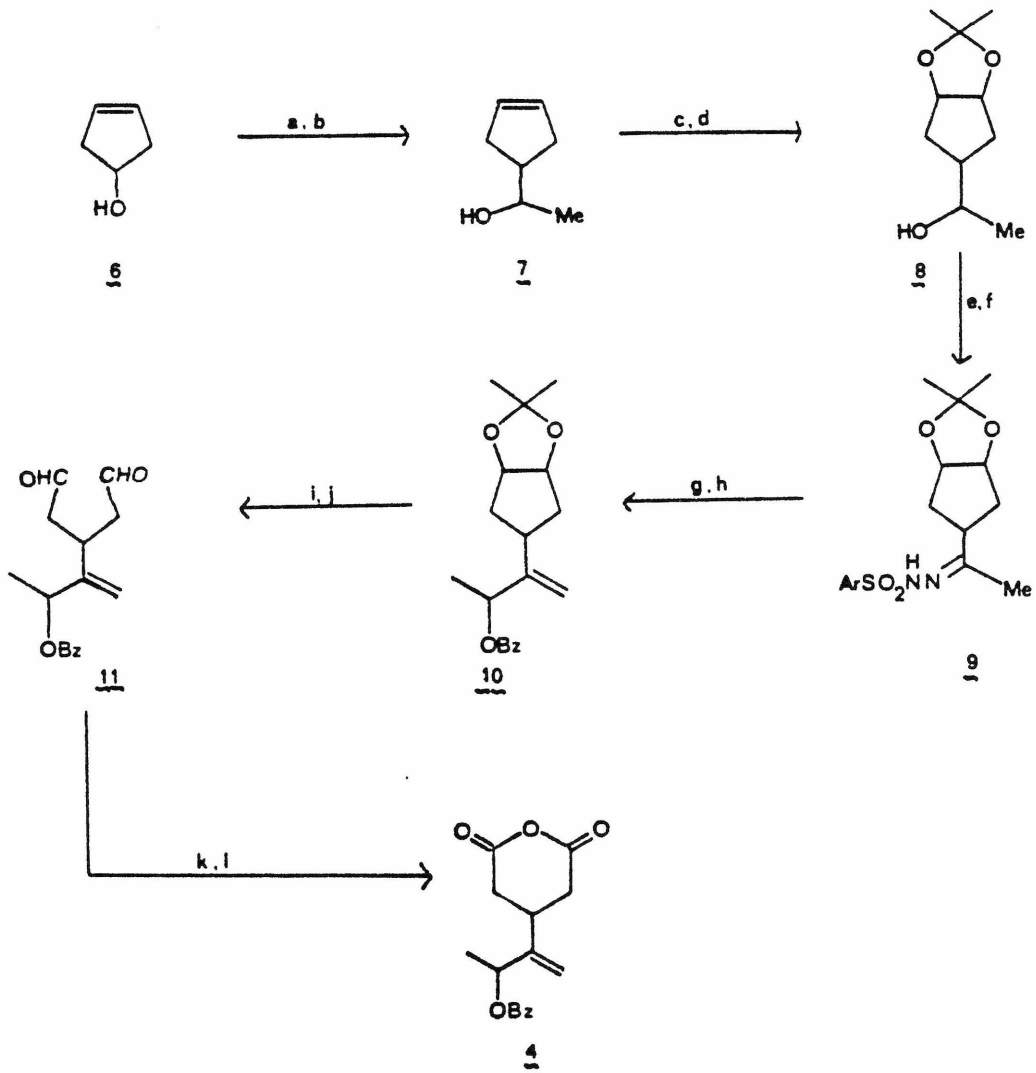

H
CO₂Me
N
N
H
H
2
base, Δ
MeO₂C
N
(-)
N
H
H
b
N
H
N
H
H
CO₂Me
1
N
H
N
(-)
H
CO₂Me
(3)

addition of the ester or malonate to the imine, followed by 1,2-rearrangement. This would furnish the strictamine skeleton directly.

Some precedents for such a route are also shown in Scheme II. The widely used yohimbine to oxindole conversion (eq. 2) proceeds via addition of alkoxide to the chloroindolenine followed by alkyl migration.[6] In fact, the aforementioned conversion of 2 to 1 (eq. 3) is thought to involve a similar alkyl migration,[7] concomitant with the opening of an activated cyclopropane. The feasibility of intramolecular nucleophilic addition to an indolenine is further demonstrated within the context of the sporidesmin A synthesis of Kishi et al.[8]

A proposed route for the preparation of the intermediate anhydride 4 can be seen in Scheme III. This route involves a reasonably straightforward sequence of reactions. Hydroboration-oxidation of cyclopentadiene is known to give cyclopentenol 6.[9] Sequential conversion of the alcohol to bromide and Grignard reagent, followed by addition to acetaldehyde, should afford secondary alcohol 7. The olefin would then be treated with OsO_4, and the resulting vic-diol would be protected as its acetonide, giving 8. After oxidation of the secondary alcohol to ketone and conversion to its trisylhydrazone

Scheme III

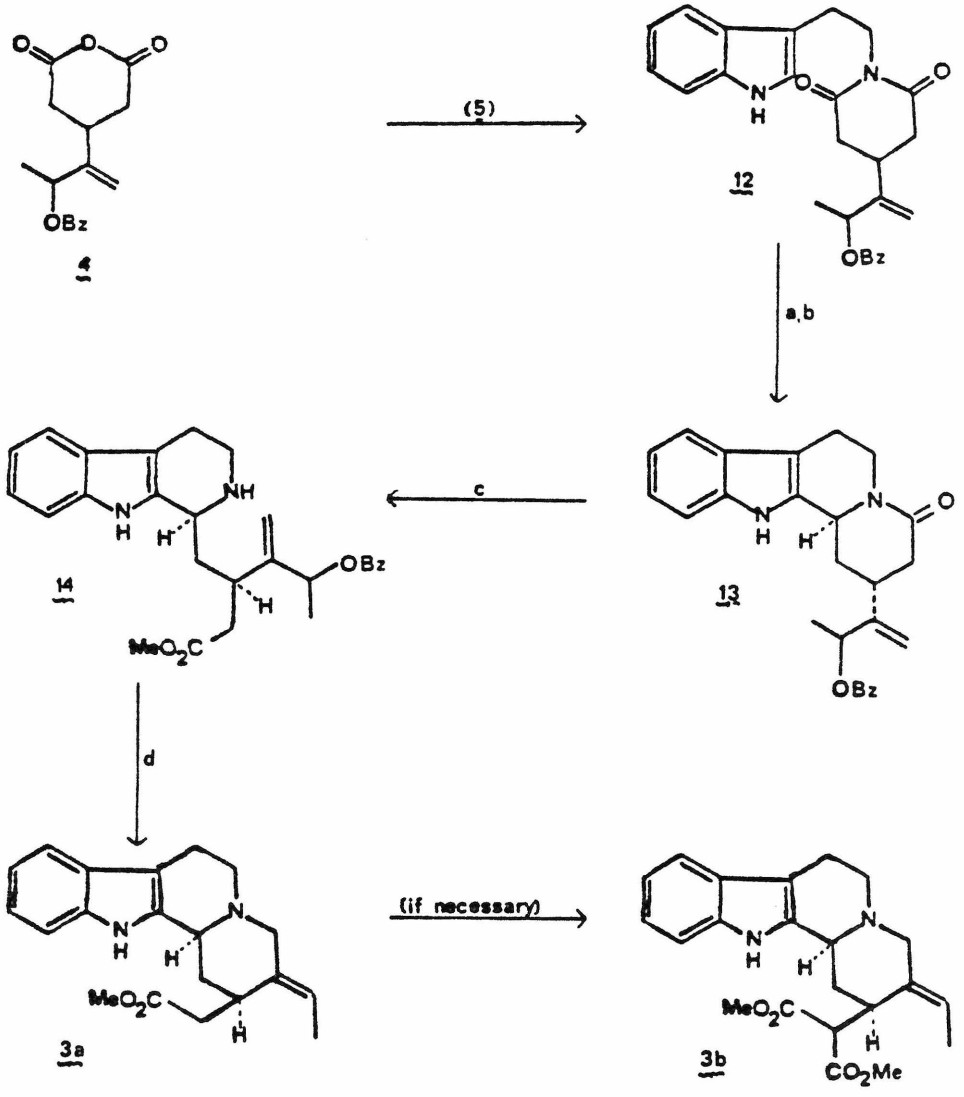


a) PBr_3. b) Mg, MeCHO. c) OsO_4. d) Me_2CO, H^+. e) [0]. f) triisopropylphenylsulfonyl hydrazone. g) 2 equiv n-BuLi, MeCHO. h) $PhCH_2Br$(BZBr). i) H^+, H_2O. j) $NaIO_4$. k) [0]. l) $(CF_3CO)_2O$, Et_3N.

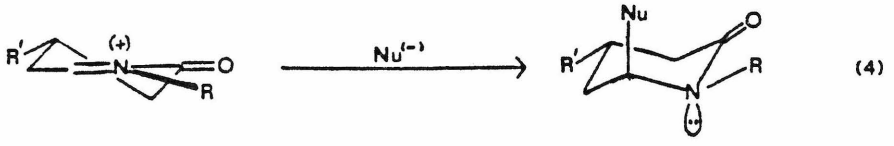
derivative 9, decomposition with n-BuLi[10] and addition of the resulting vinyllithium species to acetaldehyde followed by benzylation of the secondary alkoxide should afford the allyl ether 10. At this point, the acetonide would then be removed hydrolytically, and the exposed vic-diol would be cleaved by the action of $NaIO_4$, giving dialdehyde 11. Subsequent oxidation to the corresponding diacid and dehydrative cyclization will then furnish the key anhydride 4.

With this intermediate in hand, pathways for its stereospecific conversion to tetracyclic ester derivative 3 can be explored. A promising and very rapid route is presented in Scheme IV. Condensation of anhydride 4 with tryptamine (5) will give cyclic imide 12; note that, ignoring the inconsequential relative stereochemistry about the allyl ether moiety, the cyclic imide is symmetrical. Therefore, subsequent DIBAL-H reduction of 12, followed by acid-promoted *in situ* acylimmonium ion formation[11] can be carried out without regard to carbonly regiochemistry. This acylimmonium ion should be attacked by the indole to give the relative stereochemistry shown about the cyclic lactam 13. Due to stereoelectronic factors, a nucleophile (i.e. indole) will prefer to attack an immonium salt so that it and the

Scheme IV



a) DIBAl-H. b) HCO_2H. c) NaOMe, MeOH. d) $Pd(PPh_3)_4$ (cat.), Δ.

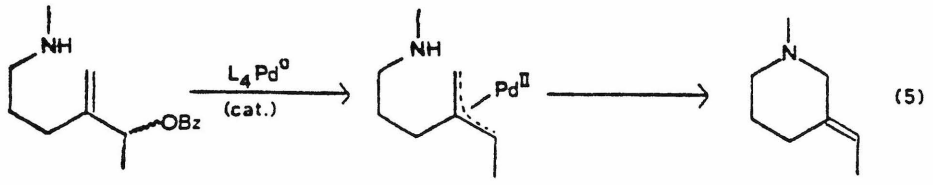


(4)

nitrogen lone pair in the initially formed adduct are oriented in a trans-diaxial configuration (eq. 4). In the case of addition to an acylimmonium ion such as the one shown, an even greater driving force for the formation of an adduct having an axial nitrogen lone pair should be provided due to its overlap with the carbonyl group. During the addition process, of course, the bulky ring substituent (R', eq. 4) should prefer an equatorial configuration so as not to interfere 1,3-diaxially with the incoming nucleophile and to provide a more stable addition product. An analogy for such a stereospecific acylimmonium cyclization can be found in the classic yohimbine synthesis of van Tamelin.[12]

With lactam 13 in hand, its methanolysis should give the ring-opened compound 14. Treatment of 14 with the appropriate L_4Pd° species should then furnish the crucial intermediate 3a via formation of an intermediate

π-allyl palladium complex, followed by intramolecular attack by nitrogen (eq. 5). The formation of allylic



(5)

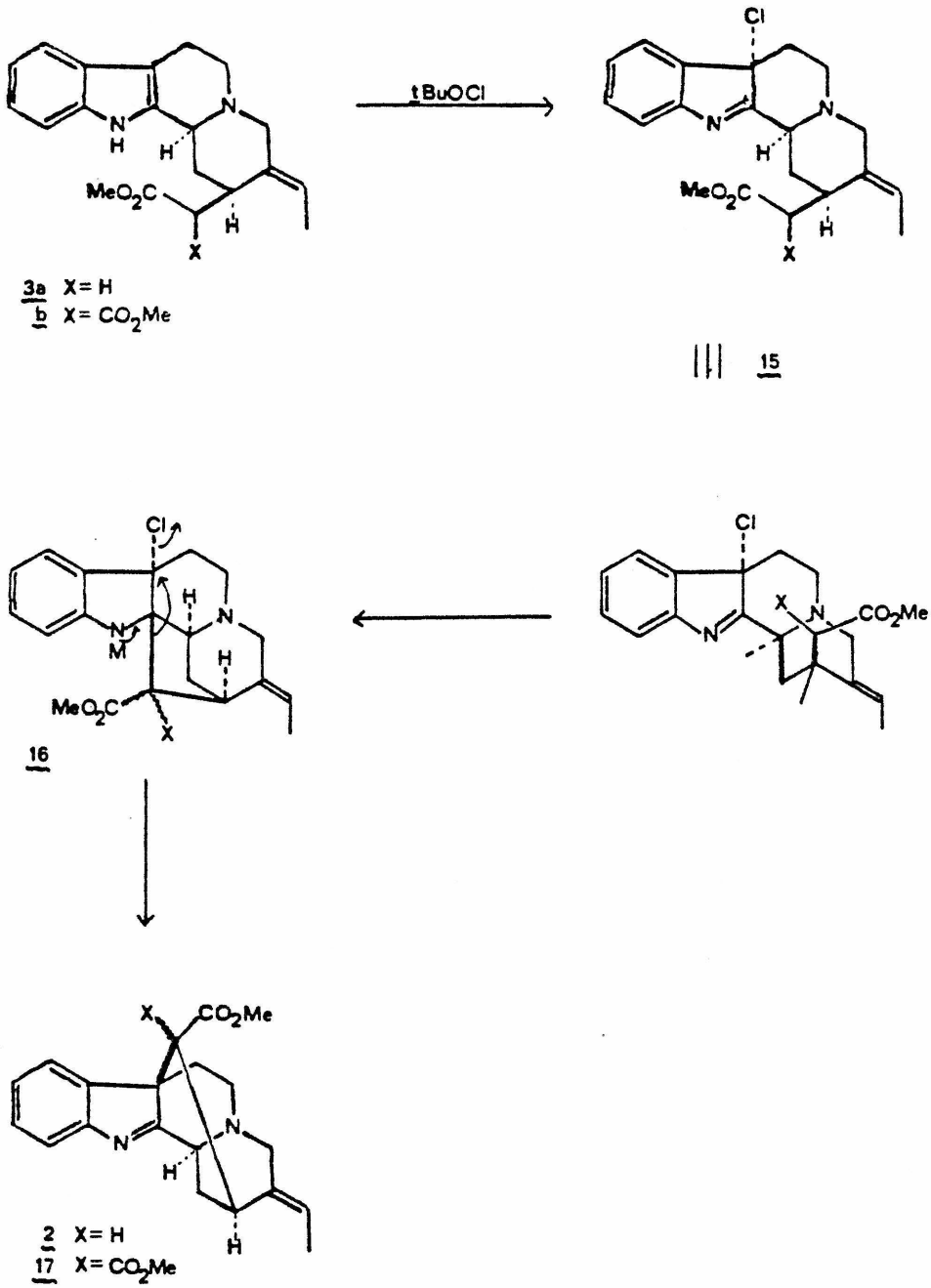
amines by the intermolecular palladium-catalyzed reaction of amines and allyl benzyl ethers is known;[13] products resulting from the possibly competing scission of the benzyl-oxygen bond are not observed. Intramolecular amine attack on an allyl palladium complex has in fact been used in a successful ibogamine synthesis.[14] The stereochemistry and regiochemistry of the conversion of 14 to 3a should be dictated by the thermodynamic preference for formation of an allyl complex having w-configuration versus sickle-configuration and by the preference for nucleophilic attack on the less-substituted side of an alkyl-substituted allyl complex, respectively. Several examples of both of these tendencies can be found in a recent review.[15] It should be noted that this procedure allows for exclusive formation of the configuration about the exocyclic double bond required for the natural

product.[16]

Several procedures can be explored for conversion of 3 to the target compounds 2 and 1 along the strategic lines discussed earlier. First, treatment of 3 with t-BuOCl would furnish chloroindolenine 15. The chlorinating reagent should react exclusively on the α-face due to the fact that this is the less-hindered face of the C-ring boat. According to models, 15 should exist in the conformation shown. Due to severe $A_{1,3}$ strain between the ethylidene methyl group and the $-CH_2CO_2Me$ substituent, a D-ring chair conformation should be significantly destabilized. This effect should force the molecule towards the conformation drawn, where the D-ring exists more as a half-chair or boat. As can be seen, such an orientation should substantially lower the activation energy for subsequent intramolecular reaction between the carbon alpha to the ester and the imine.

Substantial literature precedent exists for the intermolecular addition of ester enolates and enols to imines, perhaps owing to the utility of the resulting adducts as intermediates in the synthesis of pharmacologically important β-lactams. The first attempts to carry out such an addition in the case of compound 15a would involve enolization of the ester with 1 equivalent

Scheme V



of $LiN(\underline{i}\text{-}Pr)_2$ at -78°C.[17] Although ester enolization might be kinetically preferred over abstraction of the 3° proton alpha to the imine carbon, this is by no means certain. If ester enolization did in fact proceed cleanly, one could then envision a one-pot process involving imine addition and 1,2-migration to afford 2 as a mixture of epimers at C-16. Alternatively, the ester enolate could be trapped immediately upon its formation with Me_3SiCl at -78°C (assuming that imine addition is not very rapid), and the resulting silyl ketene acetal could be added intramolecularly to the imine under Lewis acidic ($TiCl_4$) conditions to afford intermediate 16a.[18] Exposure of 16a to an appropriate base would result in deprotonation of the aniline-type nitrogen and rearrangement to 2. If either of these routes were to prove workable, an intriguing possibility would involve an exploration of the ester enolization with respect to the geometry of the enolate formed. Ireland *et al*[19] have shown that either possible enolate geometry could be obtained specifically by varying enolization conditions in the case of propionate derivatives. Generation of an enolate with appropriate geometry might result in a stereospecific addition to the imine, eventually resulting in the formation of 2 with only the natural C-16

stereochemistry.

If direct generation of an ester enolate does not prove practical, other alternatives are available. Esters have in fact been added to N-aryl imines with α-hydrogens intramolecularly *via* Lewis acid catalysis ($AlCl_3$, Et_2O).[20] Such a procedure might be useful for the conversion of 15a to 16a. Subsequent base treatment would in turn furnish 2 with indefinite C-16 stereochemistry. In addition, problems involving ester enolate formation might be circumvented by the use of malonate derivative 15b. Treatment with 1 equivalent of an appropriate base should give the malonate anion selectively. Upon warming, an equilibrium with the amide anion of 16b might be set up, which would then be driven in the desired direction by its rearrangement to 17. This diester would then be converted to 2 by exposure to standard malonate decarboxylation conditions in a protic system. In this case, as in some of the procedures mentioned earlier, the stereochemistry at C-16 needs to be adjusted upon formation of the strictamine skeleton. It appears that, from examination of models, a kinetic protonation of the ester enolate of 2 should afford predominantly the correct C-16 stereochemistry due to hinderance of protonation of the other side of the enolate

by the exocyclic ethylidene group. Thus, no matter which method is eventually used for the imine addition-rearrangement sequence, there exists a way to obtain the correct natural stereochemistry. Of course, a synthesis of strictamine also constitutes a formal total synthesis of akuammicine (1) *via* the base-catalyzed rearrangement mentioned earlier.

In summary, routes for the total synthesis of *Rhazya Stricta* alkaloids have been discussed which involve some very interesting chemical transformations.

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PROPOSITION II

The preparation and investigation of a new class of asymmetric bifunctional heterogeneous catalysts is proposed.

* * * * * * * *

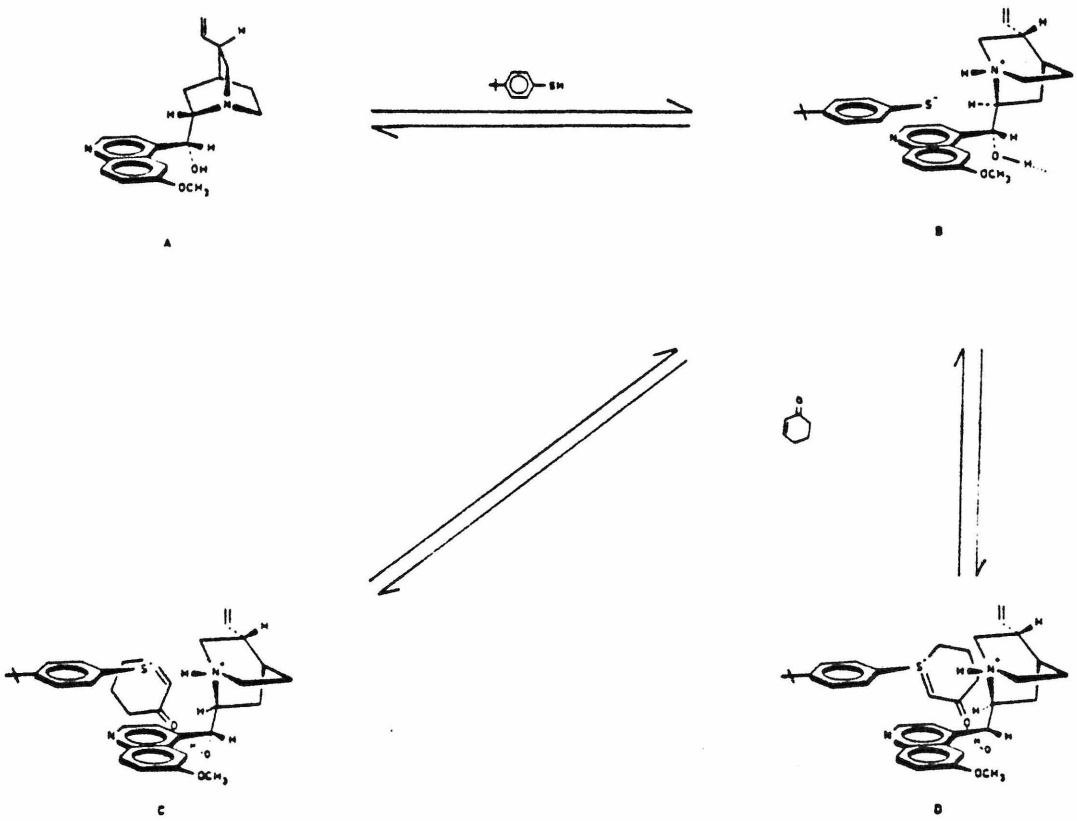
Bifunctional homogeneous catalysts have been used to promote a variety of chemical transformations. Such catalysts contain functional groups capable of binding both a substrate and a reactant in a conformation leading to a favorable transition state. A potentially important application of this involves the use of chiral catalysts to obtain chiral products from achiral starting material; such a procedure is advantageous due to the fact that no chiral auxiliaries need to be attached and removed, and that only a small amount of catalyst is required. Recent examples have appeared in the areas of hydrogenation,[1] Michael additions with both heteroatom[2] and carbon[3] nucleophiles, and intramolecular aldol condensations.[4]

Wynberg and Hiemstra[5] have very recently published a detailed study of the conjugate addition of sulfur nucleophiles to cyclic enones with the purpose of better

defining the factors involved in bifunctional catalysis by chiral amino alcohols. The major reaction studied was the addition of aryl thiols to cyclohexanone catalyzed by the cinchona alkaloid quinine. Based on kinetic studies, it was determined that these additions proceed *via* a rapid, reversible formation of a "complex" between the amine catalyst and thiol, followed by a rate-determining attack of this complex on the cycloalkenone substrate. It is in this rate-determining step that the bond is formed and chirality of the product is determined.

Based on a variety of experiments using chemically modified catalysts, thiols, and substrates, Wynberg postulated the geometry for the catalyst-arylthiol complex and the two diastereomeric transition states for conjugate addition shown in Scheme I. The conformation of quinine and the position of the thiolate in the catalyst-thiol complex is thought to be influenced both by electrostatic interaction between the positively charged nitrogen and negatively charged sulfur atoms and by a stabilizing interaction between the thiolate anion and the aromatic π-electron cloud.[6] Given such a conformation, the incoming cyclohexenone substrate should be hydrogen bonded by the catalyst hydroxyl group as seen in transition states C and D (Scheme I). That

Scheme I

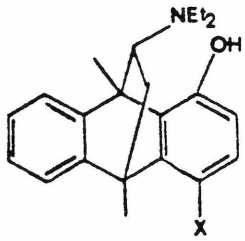


this hydrogen bonding is necessary for efficient catalysis is illustrated by the drastic rate decrease observed upon substitution of O-acetyl quinine as the catalyst.[5] Of the two transition states, C should be of lowest energy due to the unfavorable steric interaction between

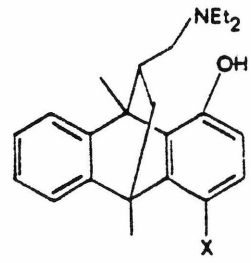
the alkyl portion of the cycloalkenone and the quinuclidine portion of the catalyst seen in D. Conjugate addition products obtained *via* transition states C and D are in fact obtained in an 81:19 ratio.

These results and conclusions suggest the design of further bifunctional chiral catalysts. Such compounds might incorporate the following features: 1) few or no rotational degrees of freedom, allowing for the formation of a rigid and well-defined catalyst-nucleophile complex; 2) an aromatic ring located in close proximity to the basic nitrogen, allowing for binding of a charged nucleophile such as a thiolate anion in a bidentate fashion; 3) a phenolic rather than an alcoholic hydroxyl group, resulting in a stronger hydrogen bond to the enone substrate and greater stabilization of the enolate character present in the transition state for conjugate addition; 4) the ability to introduce various aromatic substituents on the catalyst, thereby allowing one to study their electronic influences both on the interaction between the charged nucleophile and the aromatic ring and on the hydrogen bonding of the phenolic hydroxyl; and 5) the ability to slightly vary the location of the basic nitrogen functionality on the catalyst, thereby slightly varying the position of the

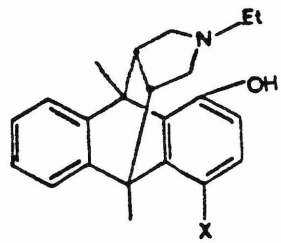
charged nucleophile in the catalyst-substrate complex. In addition, the preparation of such catalysts should not present a major synthetic challenge. The results of such a study would provide additional mechanistic information on this type of catalyst and might either directly provide a superior catalyst or suggest additional design parameters. It is therefore proposed that the chiral compounds 1a-c, 2a-c, and 3a-c be prepared, and their catalytic activity in the conjugate addition of thiophenols to cycloalkenones be investigated with respect to both reaction rate and chiral induction.



1a X = H
b X = OMe
c X = NO_2



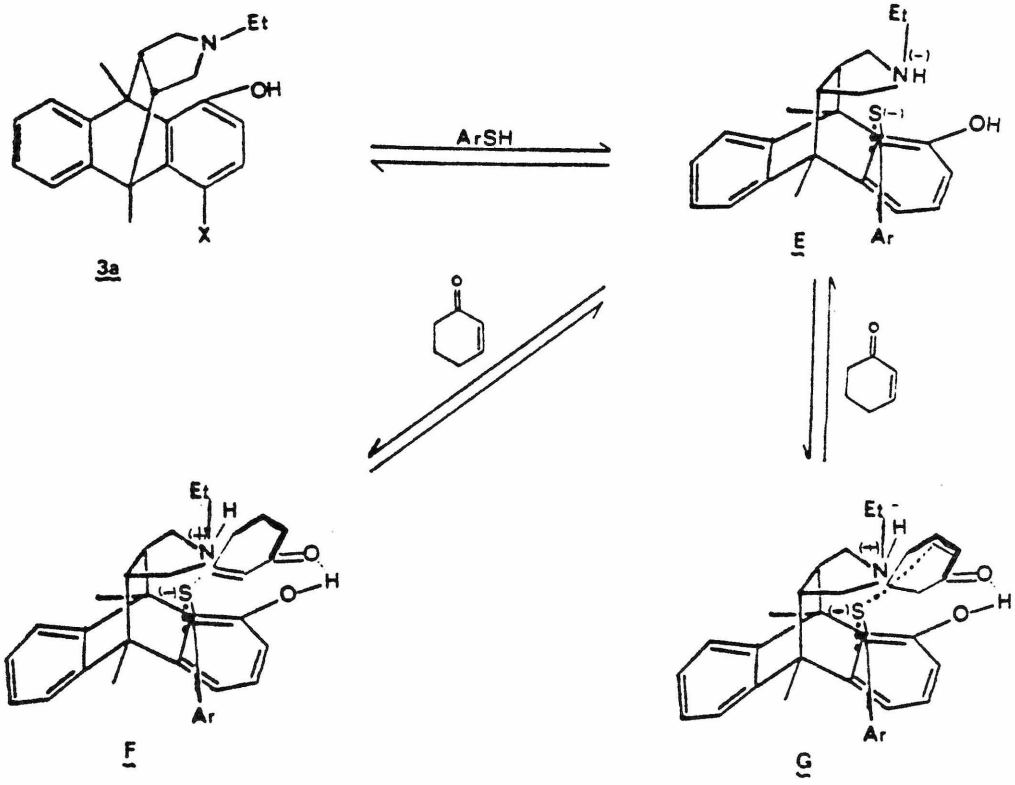
2a X = H
b X = OMe
c X = NO_2



3a X = H
b X = OMe
c X = NO_2

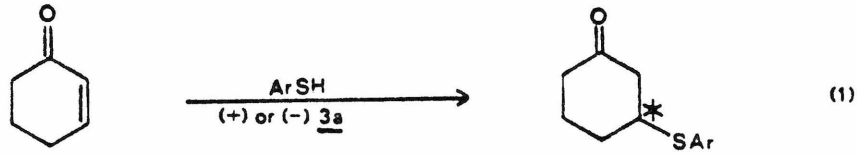
The preparation of the catalysts is reasonably straightforward, and suggested methods will be presented later. The proposed mode of action of these catalysts is illustrated in Scheme II, with compound 3a used as an example. The other catalysts of types 1 and 2 should behave analogously, except that their basic nitrogens should be located slightly differently, along with the thiolate anion in the transition states for addition. The conformations and interactions shown here can be seen even better with the aid of molecular models. The complex E should have the structure shown, with the negatively charged sulfur atom stabilized both by electrostatic interaction with the nitrogen and by interaction with the aromatic ring. Such a complex should be additionally stabilized by the fact that

Scheme II



the charged interior is well separated from the aprotic, non-polar solvent system (i.e. toluene)[7] by its hydrocarbon-type exterior. Diastereomeric complexes F and G would then result from the exposure E to cyclohexenone. Of these two, F should be considerably more stable due to the fact that the cyclohexenone alkyl carbons are

located in free space while in G they are suffering unfavorable interactions with the framework of the catalyst. Therefore, we should see a considerable preference for conjugate addition product derived from F; substantial enantiomeric excess, as well as catalytic rate acceleration, should be observed in this process, summarized in equation 1.



(1)

Once this reaction has been explored, comparison with the results derived from exposure of the same reactants to catalysts 1a and 2a might provide useful information on catalyst design as well as optimization within this particular type of system.

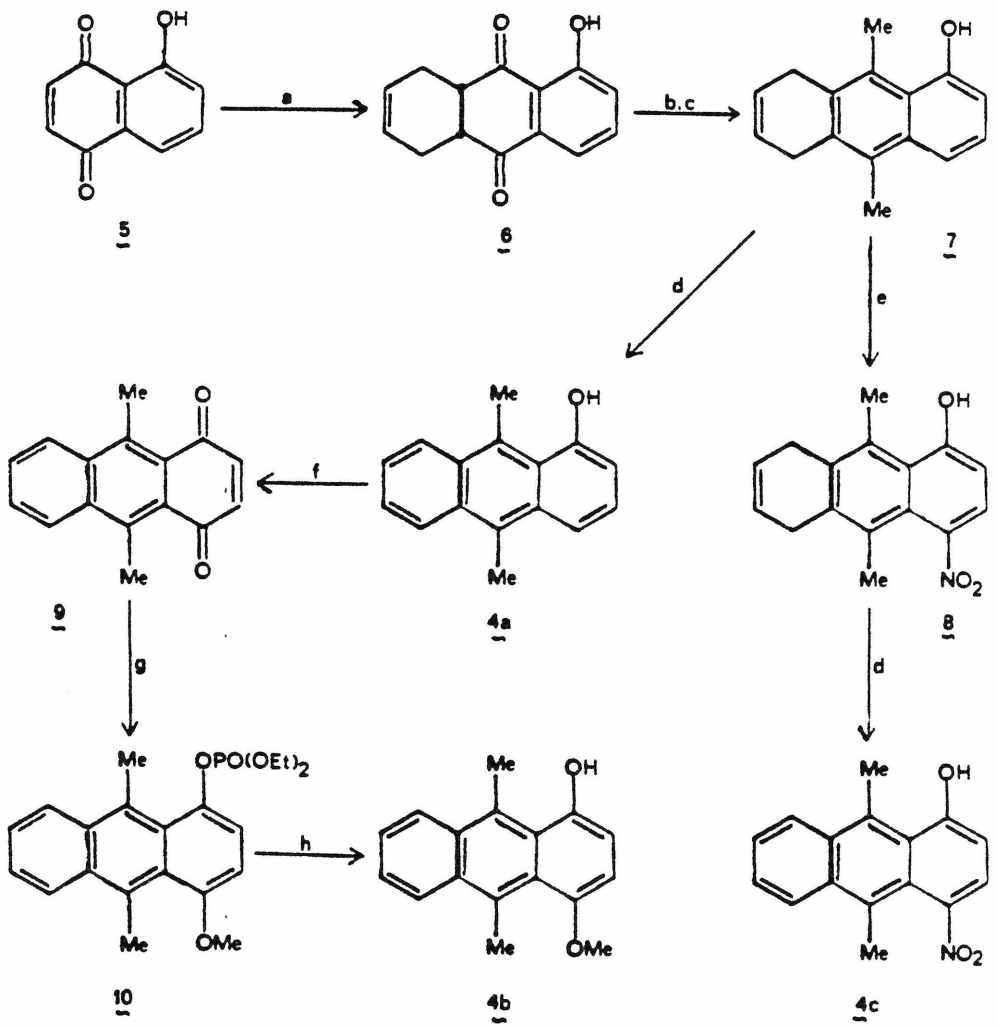
In addition to this, the study of modified catalysts 1b, 1c, 2b, 2c, 3b, and 3c should also be of interest. The presence of either an electron-donating (OMe) or an electron-withdrawing (NO_2) group on the phenolic ring should influence factors such as the degree of interaction between the thiolate anion and the ring π-cloud

and the acidity of the crucial phenolic hydrogen. Comparison of results obtained from these catalysts with those obtained from 1a, 2a, and 3a should afford quantitative data regarding the degree of importance of these effects in bifunctional catalysis.

As mentioned previously, the preparation of these catalysts should not prove difficult. Since they will be used only in small amounts and are recoverable, large quantities would not be required. The key step in this preparation involves Diels-Alder cycloaddition of an appropriate anthracene derivative with an electron poor olefin. Such processes have been carried out both intermolecularly[8] and intramolecularly.[9] Routes for the synthesis of anthracene intermediates 4a, 4b, and 4c are outlined in Scheme III. These are derived from a common, commercially available starting material [juglone, (5)].[10] The reactions involved require little explanation; references are included with the scheme where appropriate.

With the intermediates 4a-4c in hand, Diels-Alder reactions can be explored. Given the usual factors controlling the regiochemistry of Diels-Alder cycloadditions, one would expect the product of reaction of 4a-4c with an acrylate ester to have the regiochemistry

Scheme III

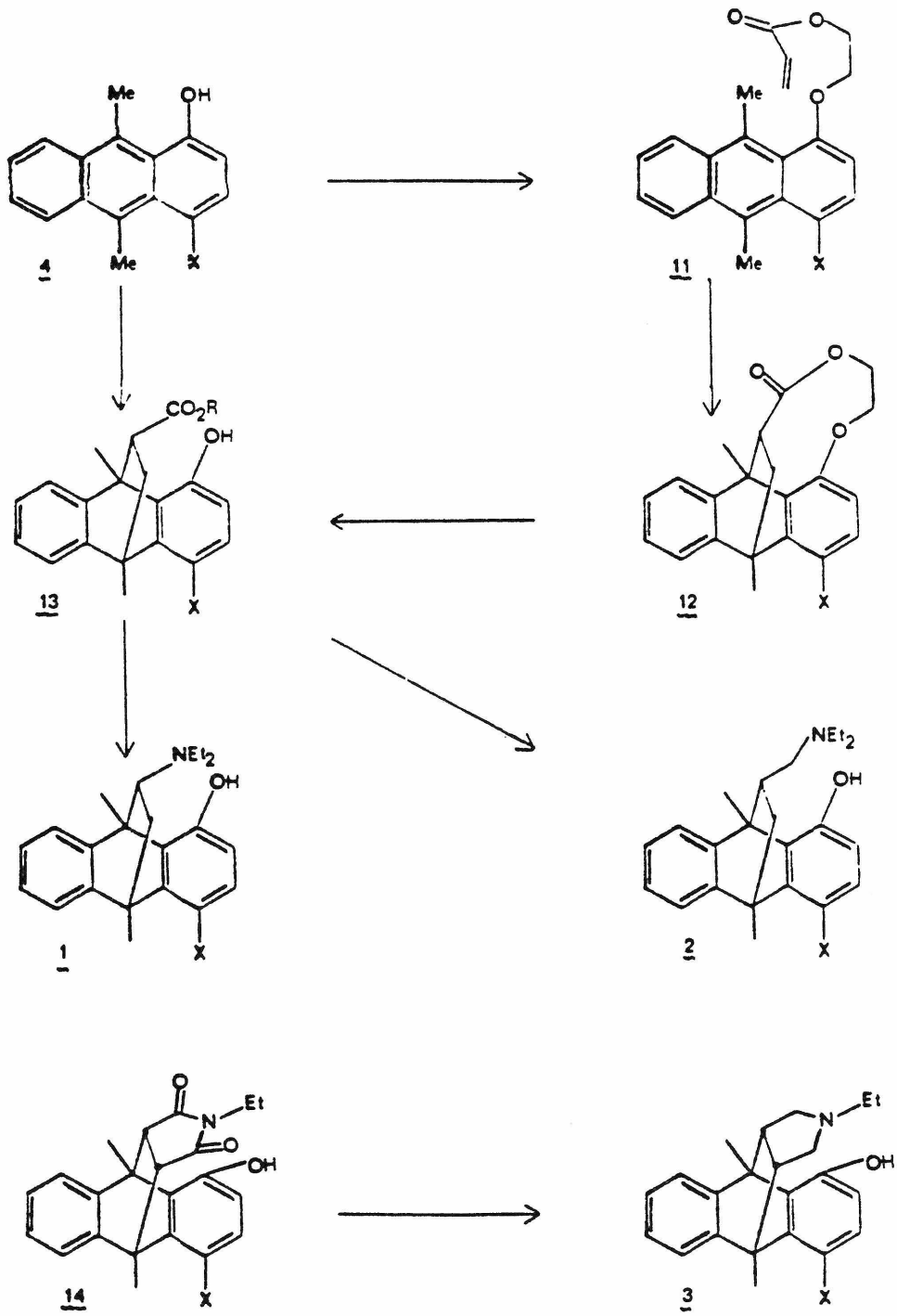


a) Butadiene, Δ. B) MeLi. c) Dehydration. d) DDQ or Pd-C. e) $NO_2^+BF_4^-$.[11] f) Fremys salt.[12] g) $P(OMe)_3$[13]. h) ^-OH, H_2O.

shown for 13. However, the stereochemistry of the ester group in 13, with respect to its disposition syn or anti to the phenol, would probably not be controlled in an intermolecular cycloaddition. If isolation of significant amounts of the desired syn-13 were to prove difficult, the alternate route 4 → 11 → 12 → 13, involving intramolecular cycloaddition, would provide the desired isomer exclusively. Intermediates 13a-13c would then be converted to 1a-1c by a Curtius-type reaction[14] followed by bis-alkylation of the resulting primary amine. Catalysts 2a-2c would be formed by derivativization of 13a-13c to the appropriate carboxamide followed by reduction.

In order to prepare 3a-3c, phenanthrenes 4a-4c could be reacted with the excellent dienophile N-ethyl-maleimide, affording, after separation of diastereomers, 14a-14c. Reduction would then afford the desired catalysts.[15] Since functional groups such as amines, carboxylic acids, and phenols are present throughout each of these sequences, a variety of options are available for optical resolution in order to obtain enantiomerically pure catalysts. If 1-3 were indeed to prove to be efficient asymmetric catalysts, their absolute configurations might be determined with

Scheme IV


Me
OH
Me
X
4
O
O
O
Me
Me
X
11
CO2R
OH
X
13
O
O
O
X
12
NEt2
OH
X
1
NEt2
OH
X
2
O
N
Et
O
OH
X
14
N
Et
OH
X
3

reasonable certainty simply by examining the known absolute configuration of the products.[16]

In summary, the examination of a series of compounds as asymmetric heterogeneous catalysts has been proposed. They might both prove to be excellent catalysts in their own right and provide information about many of the factors controlling this type of catalysis.

References and Notes

(1) Vineyard, B. P.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. J. Am. Chem. Soc. 1977, 99, 5946-5952.

(2) (a) Helder, R.; Arends, R.; Bolt, W.; Hiemstra, H.; Wynberg, H. Tetrahedron Lett. 1977, 2181-2184; (b) Pluim, H.; Wynberg, H. Ibid. 1979, 1212-1218; (c) Pracejus, H.; Wilcke, F.-W.; Hanemann, K. J. Prakt. Chem. 1977, 319, 219-229.

(3) (a) Trost, B. M.; Shuey, C. D.; DiNinno, F. J. Am. Chem. Soc. 1979, 101, 1284-1285; (b) Hermann, K.; Wynberg, H. J. Org. Chem. 1979, 44, 2238-2244.

(4) (a) Hajos, Z. G.; Parrish, D. R. J. Org. Chem. 1974, 39, 1615-1621; (b) Cohen, N. Accts. Chem. Res. 1976, 9, 412-417.

(5) Hiemstra, H.; Wynberg, H. J. Am. Chem. Soc. 1981 103, 417-430.

(6) In support of this, Wynberg has cited the 80-fold rate acceleration for amine quaternization observed with benzene versus hexane as solvent: Wiberg, K. B. "Physical Organic Chemistry"; Wiley: New York, 1964; p. 379.

(7) A solvent such as toluene was found to be best for

these processes due to its inability to coordinate either catalyst or reactants.

(8) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure"; McGraw-Hill: New York, 1968; p. 628.

(9) Ciganek, E. J. Org. Chem. 1980, 45, 1497-1505.

(10) This compound may be purchased from Aldrich Chemical Co.

(11) Kuhn, S. J.; Olah, G. A. J. Am. Chem. Soc. 1961, 83, 4564-4571.

(12) Dann, O.; Zeller, H.-G. Chem. Ber. 1960, 93, 2829-2833, and references therein.

(13) Ramirez, F.; Desai, N. B. J. Am. Chem. Soc. 1963, 85, 3252-3258.

(14) For a very mild method of carrying out this reaction on carboxylic acid substrates, see Yamada, S.; Shioiri, T.; Ninomiya, K. Tetrahedron 1974, 30, 2151-2157.

(15) In cases where normal reducing methods ($LiAlH_4$) might be too harsh, due to presence of a group such as nitro, a procedure involving O-alkylation of the amide followed by borohydride reduction might be used.

(16) These have been determined by Wynberg, using the

octant rule (Ref. 5): Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. J. Am. Chem. Soc. 1961, 83, 4013-4018.

PROPOSITION III

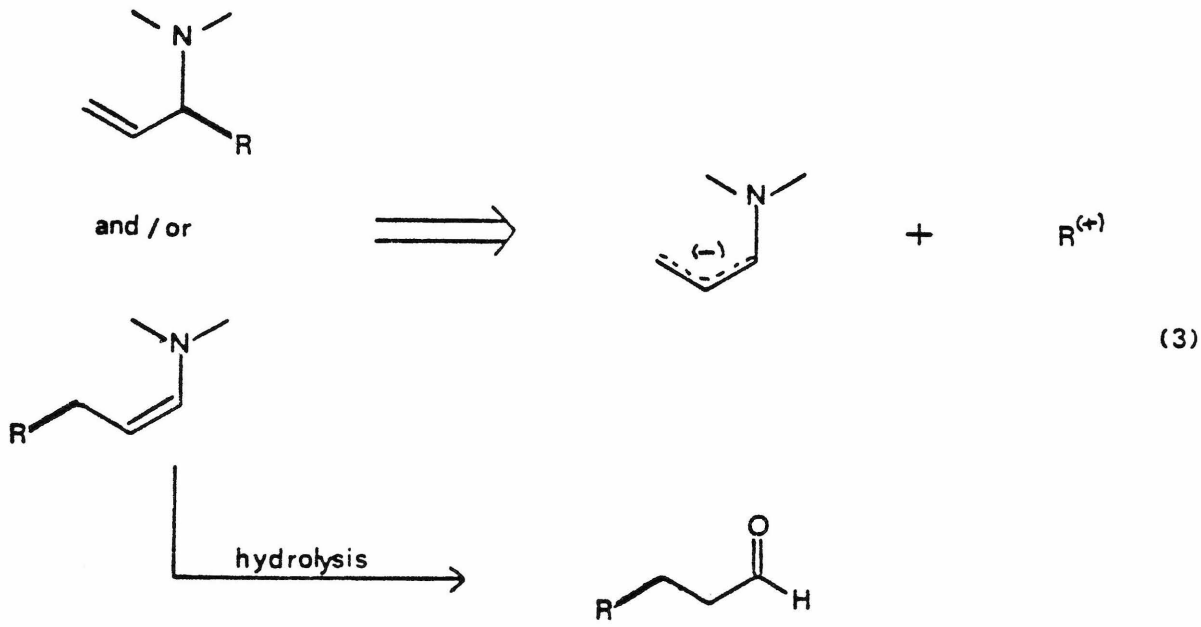
The enantioselective alkylation of chiral nitrosamine anions is proposed as a method of generating asymmetry alpha to an amine.

* * * * * * * *

A classical and often-used scheme for carbon-carbon bond formation alpha to nitrogen involves nucleophilic substitution (eq. 1). More recently, considerable work has been devoted to the inversion or "umpolung" of this reactivity pattern, whereby such a bond is formed <u>via</u> electrophilic substitution (eq. 2).[1] Such a procedure is quite useful both as a method of synthesis of complex amines and as a solution to the homoenolate anion problem (eq. 3).[3] The electrophilic substitution of an

(1)

(2)

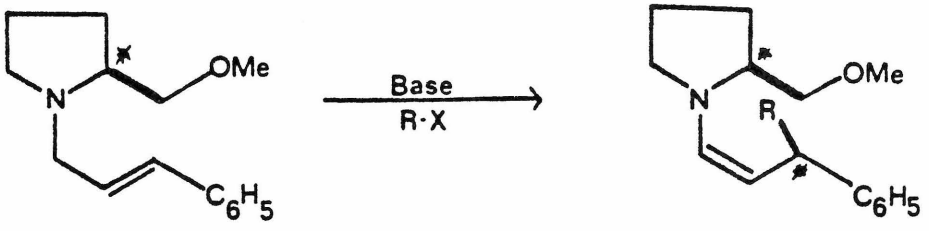


(3)

allylic amine might be induced to proceed either alpha or gamma to the nitrogen. The enamine resulting from gamma substitution may then be hydrolyzed to the resulting carbonyl derivative, affording a net homoenolate alkylation.

Although a number of procedures have been developed for the generation of highly nucleophilic alkyl, allyl,

and benzyl anions alpha to nitrogen, very little effort has been directed towards their asymmetric generation and alkylation in acyclic, unconstrained systems. A recent report by Enders[3] of the alkylation of chiral allyl amine anion 1 in fair to good optical yield suggests that other schemes for such asymmetric induction may be promising. Besides being of potential synthetic

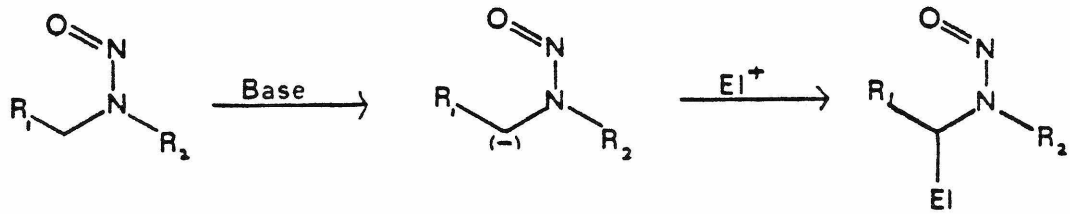


(S)-1

utility, the development of such asymmetric methodology should afford considerable mechanistic insight into these processes. The discussion of one prospective method for the generation and reaction of a chiral carbanion alpha to nitrogen will be the subject of this proposal.

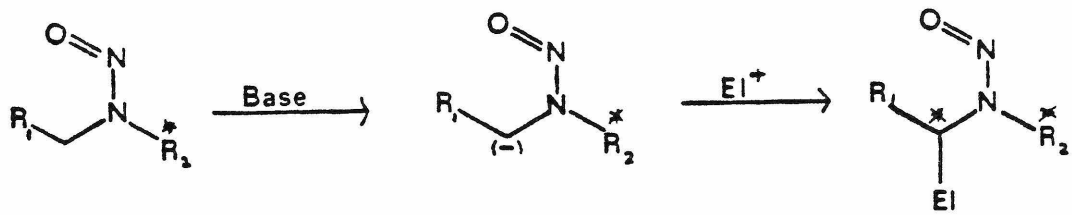
One commonly used and very effective activating group for amine alpha-alkylation is the N-nitrosamine.[4] Deprotonation with a strong, non-nucleophilic base

[usually lithium diisopropylamide (LDA)] provides a strongly nucleophilic anion, which reacts with a wide range of electrophiles at very low temperature (eq. 4). A variety of methods are available for removal of the



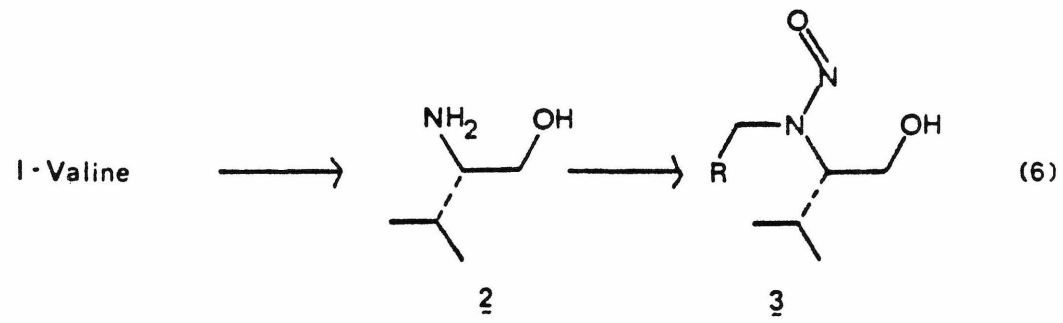
(4)

nitroso group to provide the corresponding amine.[5] Given such a process, it would be most interesting to determine whether the electrophile could be introduced asymmetrically alpha to nitrogen if a substrate with an appropriate chiral R_2 substituent were designed (eq. 5).



(5)

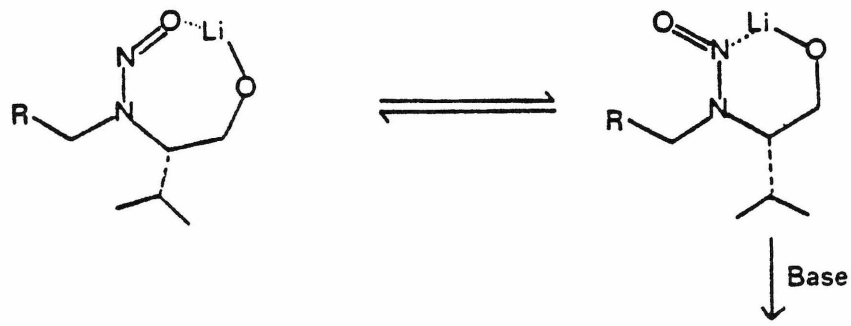
A potentially effective chiral nitrosamine for such a study would be the β-N-nitroso alcohol 3. A series of these substrates could easily be prepared from the amino-alcohol 2 by sequential N-alkylation and N-nitrosation. Aminoalcohol 2 has been prepared from the natural amino acid valine in excellent optical purity by reduction



2 3 (6)

(B_2H_6, BF_3).[6] Virtually any alkyl or aryl group may serve as the "R" substituent.

The treatment of alcohol-nitrosamine 3 with two equivalents of LDA should provide a lithium alkoxide-α-lithio nitrosamine dianion. Analysis of the probable structure of this dianion should allow for prediction of a significant degree of asymmetric induction in subsequent reaction with electrophiles. One might postulate that the lithium alkoxide 4 formed by reaction of 3 with the first equivalent of base would be deprotonated by the second equivalent as 6-membered chelate 4b. This

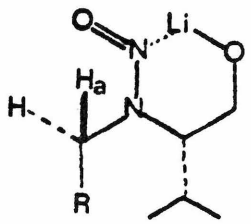


(7)

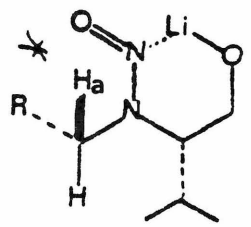
preference can be attributed both to the observed requirement for deprotonation of a dialkylnitrosamine syn to the -N=O bond[7] at the less substituted alkyl carbon[8] and to the greater favorability of a 6-membered rather than a 7-membered chelate. Four possible transition states can be drawn for the deprotonation of 4b, rotating the darkened C-N bond (Scheme I).

Studies of nitrosamine alpha deprotonation in cyclic, conformationally locked systems have shown a very strong kinetic preference for removal of a proton whose bond to carbon lies orthogonal to the plane of the N-N=O moiety.[9] This presumably affords greater conjugative negative charge stabilization. Thus, in each of the four conformations a-d shown in Scheme I, proton H_A, lying orthogonal to the N-N bond, should be removed by strong base. Further analysis of the relative stability and

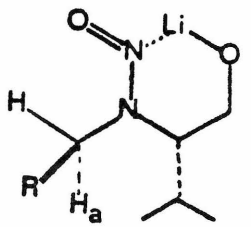
Scheme I



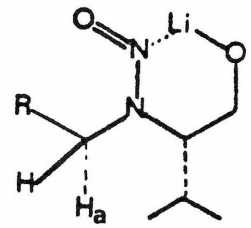
a



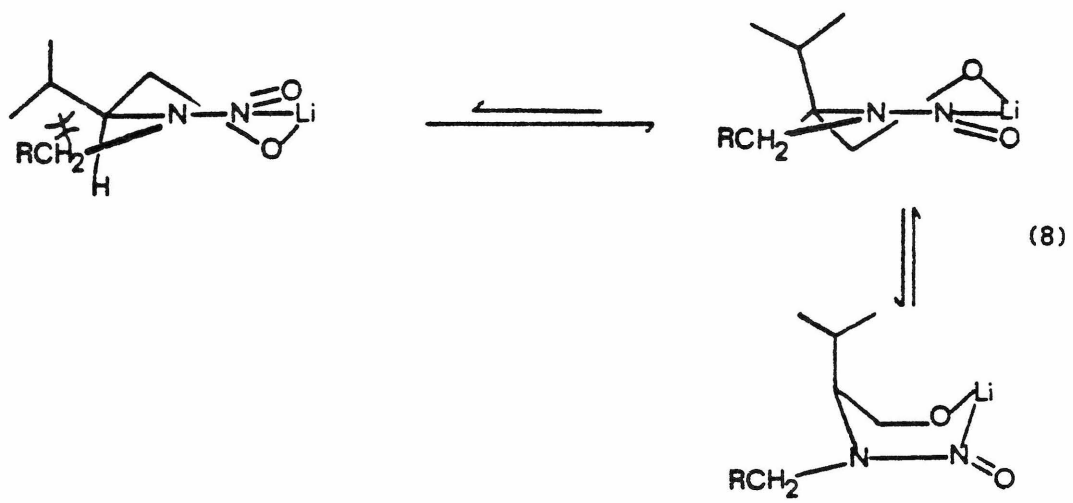
b



c



d



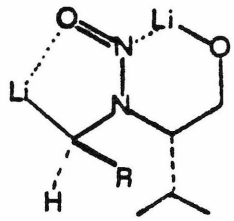
(8)

reactivity of these four conformers requires some discussion of the location of the isopropyl substituent. As can be seen in equation 8, the 6-membered chelate 4b should exist in half-chair form due to the planar nature of the N-N bond,[10] although a boat conformation is also possible. The structure on the right, with the isopropyl group occupying a pseudo-axial orientation, should be more stable. A pseudo-equatorial isopropyl group would suffer a more significant steric interaction with the acyclic N-alkyl substituent.

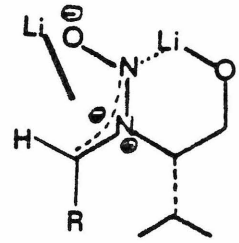
Thus, in conformations c and d in Scheme I, removal of H_A by a hindered base such as LDA should be disfavored relative to removal of H_A in conformations a and b due to the presence of this bulky pseudoaxial isopropyl group. Of these two conformers, one might predict that a is of lower energy. In conformation b, there should exist an $A_{1,3}$ interaction[11] between the R substituent and the nitroso oxygen which should be substantially greater than the interaction between R and the pseudoaxial isopropyl group in a. Therefore, it may be expected that proton H_A in conformation a will be preferentially removed.

The structure of this carbanion cannot be drawn with absolute certainty, although we may postulate two extremes:[12] one, 5a, in which the anionic carbon is tetrahedral and

the lithium counterion is coordinated to the nitroso oxygen; the other, 5b, in which the anionic carbon is trigonal and the negative charge is stabilized by direct conjugation with the nitroso group.[13] Fraser et al[14] have suggested, based on experimental evidence, that the



5a

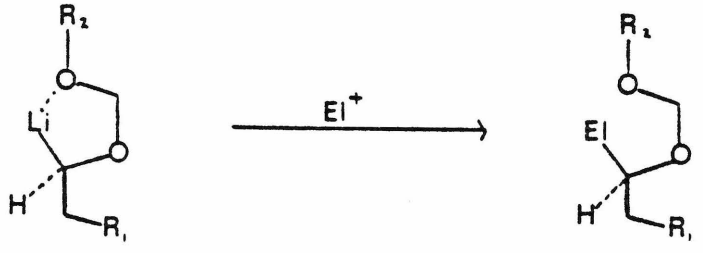


5b

actual structure may be more of the type shown in structure 5b. It should be noted at this juncture that the stereochemistry shown about the carbanionic center in both structures 5a and 5b is thermodynamically more stable than the opposite carbanionic stereochemistry which would be derived from deprotonation of H_A in the alternative rotomer b (Scheme I). Thus, the stereochemistry established by the initial deprotonation should be stable even in the unlikely event that it can equilibrate under the low temperature (-78°C) which would be employed for the entire metallation-electrophilic attact sequence.

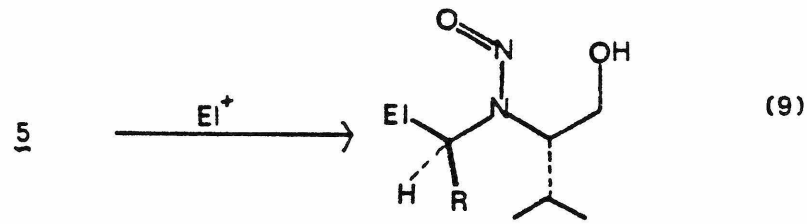
The attack of an electrophile on carbanion 5 should

proceed with the same high stereoselectivity regardless of its trigonal or tetrahedral structure. In structure 5a, one should expect substitution of the electrophile



6

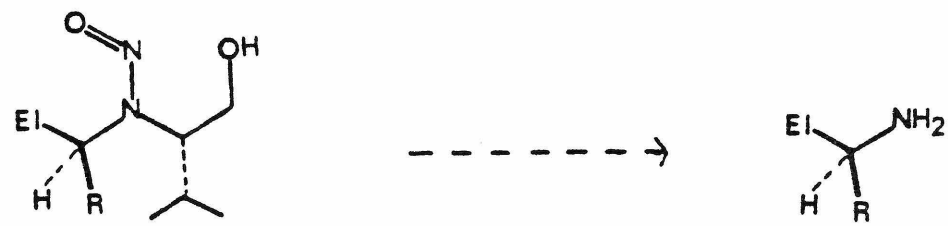
for lithium with retention of stereochemistry about carbon. Still and Sreekumar[15] have recently investigated the reaction of the chiral, internally chelated carbanion 6 with a variety of electrophiles and found substitution to occur exclusively with retention. Examination of structure 5a, containing the trigonal carbanion extreme, reveals that electrophilic attack should occur from the top side of the anion, anti to the bulky isopropyl group.[16] Thus, carbanion 5 should react with electrophiles to afford products having the stereochemistry shown in equation 9.



(9)

7

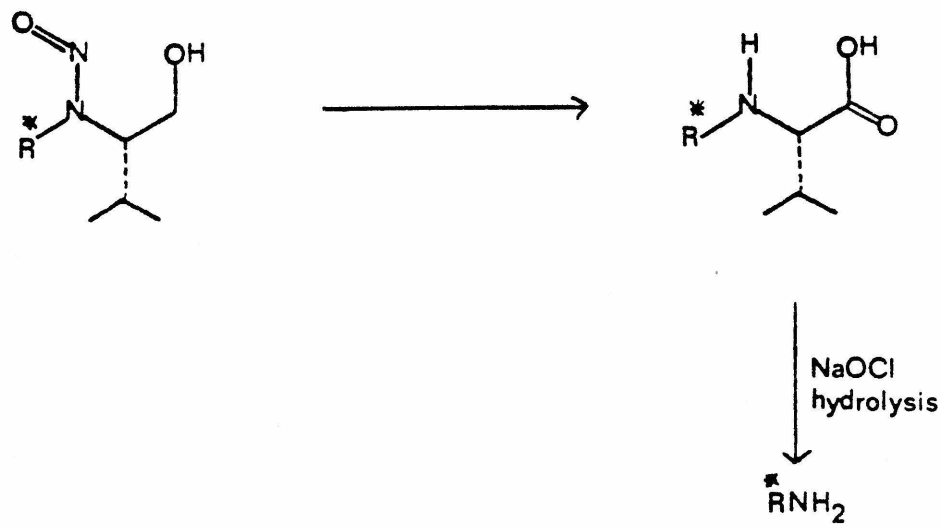
Although the above analysis might suggest that formation of amine derivatives such as 7 with good asymmetric induction is quite possible, the synthetic utility of such a scheme would not be great in the absence of a viable procedure for the conversion of 7 to the corresponding primary amine. Procedures for this



7

are outlined in Scheme II. The first sequence is directly analogous to a known procedure for the degradation of amino-acids;[17] the second involves conversion of the

Scheme II



primary alcohol to a bromide followed by exposure to an appropriate set of reductive conditions [e.g. Zn/HOAc, Zn(Hg), Li-napthalenide, Mg, etc.][18] to afford a primary nitrosamine, or, in case of over-reduction, the corresponding hydrazine. Either of these compounds could be cleaved to the primary amine under well-established conditions.

In summary, a promising method for the enantioselective alkylation of nitrosamine anions has been proposed. The results of such a study might be of synthetic utility and would provide an early example of asymmetric induction at a carbon alpha to a heteroatom in an unconstrained system.

References and Notes

(1) For an excellent compilation of observed and potential structures containing negative charge on the carbon adjacent to nitrogen, as well as early references to all of these, see: (a) Seebach, D.; Enders, D. Angew. Chem. Intl. Ed. 1975, 14, 15-32; (b) Beak, P.; Reitz, D. B. Chem. Rev. 1978, 78, 275-316.

(2) For some representative methods using metallated allyl amine derivatives, see: (a) Albrecht, H. Chimia 1977, 31, 391-403; (b) Martin, S. F.; DuPriest, M. T. Tetrahedron Lett. 1977, 3925-3928; (c) Coutrot, P.; Savignac, P. J. Chem. Res. 1977, 3401-3416; (d) Tischler, A. N.; Tischler, M. H. Tetrahedron Lett. 1978, 3407-3410; (e) Hassel, T.; Seebach, D. Angew. Chem. Intl. Ed. 1979, 18, 399-400.

(3) Albrecht, H.; Bonnet, G.; Enders, D.; Zimmerman, G. Tetrahedron Lett. 1980, 3175-3178.

(4) For a review, see Ref. 1a.

(5) A series of methods and references to these are listed in Ref. 1a.

(6) (a) Lane, C. F. U.S. Patent 3,935,280, Chem. Abstr. 1976, 84, 135101p; (b) For a discussion of several

methods of amino acid reduction, see Poindexter, G. S.; Meyers, A. I. Tetrahedron Lett. 1977, 3527-3528.

(7) Fraser, R. R.; Ng. L. K. J. Am. Chem. Soc. 1976, 98, 5895-5899.

(8) For an example involving the sequential 2,5-dialkylation of N-nitroso pyrollidine, see Fraser, R. R.; Passannanti, S. Synthesis 1976, 540-541.

(9) For a study of relative rates of deuteration, see Fraser, R. R.; Grindley, T. B.; Passannanti, S. Can. J. Chem. 1975, 53, 2473-2480.

(10) This can be concluded from the fact that the rotational barrier about this bond has been estimated to be about 23 kcal/mol: (a) Karabatsos, G. J.; Taller, R. A. J. Am. Chem. Soc. 1964, 86, 4373-4378; (b) D'Agostino, J. T.; Jaffe, H. H. Ibid. 1970, 92, 5160-5166.

(11) Fraser et al have estimated the $A_{1,3}$ strain between an equatorial methyl and the nitroso group in 2-methyl-nitrosopiperidine to be >4.1 kcal/mol: see Ref. 9.

(12) Given the similar behavior predicted for both extreme structures, we might expect any "mixed" structure to behave in a similar fashion.

(13) Such a structure would be isoelectronic with an oxime dianion.

(14) See Ref. 7.

(15) Still, W. C.; Sreekumar, C. J. Am. Chem. Soc. 1980, 102, 1201-1202.

(16) For examples of hindrance of electrophilic attack by a remote, bulky substituent on one side of a flat nucleophilic system, see: (a) Meyers, A. I. Accts. Chem. Res. 1978, 11, 375-381; (b) Hanson, J. F.; Cooper, C. S. J. Am. Chem. Soc. 1976, 41, 3219-3220; (c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. Pure & Appl. Chem. in press.

(17) For a recent example of such a procedure, see Vederas, J. C.; Schleicher, E.; Tsai, M.-D; Floss, H. G. J. Biol. Chem. 1978, 253, 5350.

(18) Such reagents have been used in the corresponding reductive fragmentation of β-halo alcohol derivatives.

PROPOSITION IV

A series of experiments involving measurement of the kinetic parameter "volume of activation" is suggested to resolve questions about the mechanism of an induced free radical decomposition.

* * * * * * * *

During the past fifteen years, considerable effort has been directed towards understanding the effects of pressure on chemical reactions.[1] An interesting outgrowth of this work has been the development of "volume of activation" ($\Delta V^{\ddagger}$) as a useful parameter for the description of transition states.[2] Such a parameter represents the change of volume which occurs when reactants go to the transition state in a rate-determing step, and can be calculated from the results of variable-pressure kinetic studies by the following equation. A very recent report has outlined a technique for measuring

$$\left(\frac{\delta \ln k}{\delta P}\right)_T = \frac{-\Delta V^{\ddagger}}{RT} \qquad (1)$$

$\Delta V^{\ddagger}$ in reactions having free-radical intermediates.[3] This involved the development of apparatus suitable for performing electron paramagnetic resonance (EPR)[4] kinetic studies at low temperature and concentrations and at pressures of greater than 300 atm.

As an illustration of this method, the authors studied the first-order decompositions of the di-tert-butyliminyl and tert-butoxytriethoxyphosphoranyl radicals (eq. 2 and 3). As can be seen in these reactions,

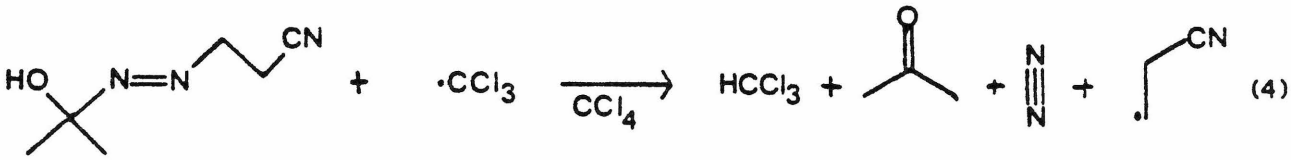
$$(\underline{t}\text{-Bu})_2C{=}N\cdot \longrightarrow \underline{t}\text{-Bu}\cdot + (\underline{t}\text{BuC}{\equiv}N) \qquad (2)$$
$$\Delta V^{\ddagger} \sim 3.0 \text{ cm}^3 \text{ mol}^{-1}$$

$$\underline{t}\text{-BuOP}\cdot(OEt)_3 \longrightarrow \underline{t}\text{-Bu}\cdot + OP(OEt)_3 \qquad (3)$$
$$\Delta V^{\ddagger} \sim 0.2 \text{ cm}^3 \text{ mol}^{-1}$$

the volume of activation for the phosphoranyl decomposition is much less positive than for the imidoyl decomposition, suggesting that the C-C bond in the imidoyl system is more stretched and therefore more broken in the transition state than is the case for the C-O bond in the phosphoranyl system. It was previously known that the phosphoranyl decomposition is the more exothermic of the two; application of the Hammond postulate to this fact would lead one

to conclude that this system should have an earlier transition state. This is clearly reflected in the differences in $\Delta V^{\ddagger}$, resulting in an excellent example of the utility of this parameter in predicting transition state characteristics.

Past efforts directed at the understanding of radical reactions have resulted in the measurement of $\Delta V^{\ddagger}$ for a number of different radical decompositions, giving rise to a number of good generalizations which could be used to interpret the results of future studies.[5] An interesting extension of this methodology would involve its use in the study of a very recently reported induced decomposition reaction, as shown in equation 4.[6] The authors found that this reaction is indeed a radical chain process which proceeds according to a first-order rate law and is severely



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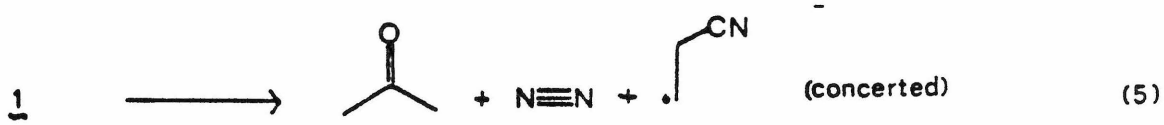

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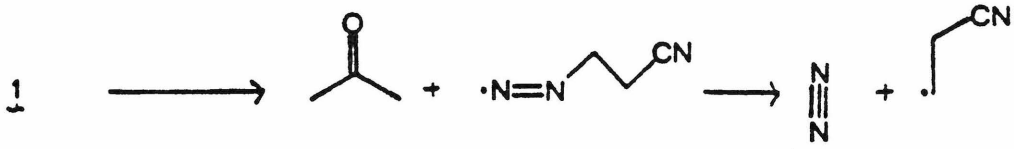

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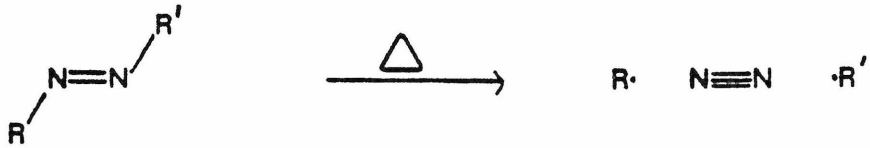


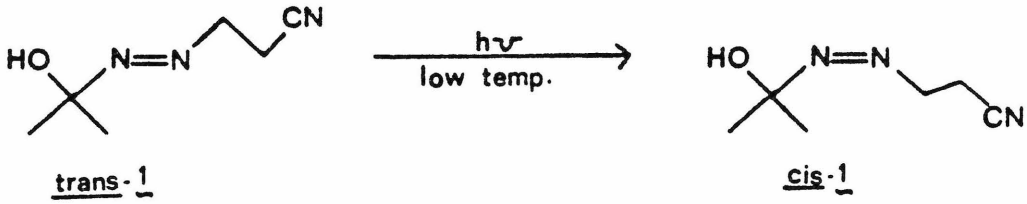
(7)

inhibited by addition of small amounts of radical scavengers. They propose that this process, which goes at a measurable rate even at RT, proceeds either through the concerted induced decomposition scheme shown in equation 5 or the stepwise scheme shown in equation 6, involving decomposition to an intermediate diazenyl radical which would rapidly lose dinitrogen to lead to observed products. The initial formation of an oxygen-centered radical was considered energetically unfavorable,[7] and the mildness of the conditions under which the reaction proceeds suggests that it is not directly analogous to the well-known thermolysis of unsymmetrical diazenes depicted in equation 7, which is thought to go through a stepwise mechanism. Some simple experiments involving $\Delta V^{\ddagger}$ determination which might lead to identification of a concerted or stepwise mechanism for the decomposition

of 1 will be discussed; experimentally, they will require the measurement of rate constants for this decomposition at different pressures at a number of temperatures, followed by analysis of this data *via* equation 1. In order to confirm the eventual conclusions drawn, another more-established method could then be used to distinguish the possible pathways. For example, the elegant ^{15}N CIDNP experiments used to detect an intermediate diazenyl radical in unsymmetrical diazene pyrolysis (eq. 7) by Porter *et al*[8] could be applied here.

The volumes of activation for the decomposition of several diazenes have in fact been determined,[2,5] and they have been used in conjunction with variation of solvent viscosity to support the hypothesis of existence of a diazenyl radical intermediate.[9] However, this procedure probably could not be applied to the study of the induced decomposition of 1, since cage-recombination of the postulated intermediate in the stepwise pathway (eq. 6) is not possible. Other new types of experiments are therefore suggested.

The first possibility would involve comparison of the $\Delta V^{\ddagger}$ for *trans*-1, which the authors studied, with the $\Delta V^{\ddagger}$ for *cis*-1. In accordance with established procedure, *cis*-1 could be produced by low-temperature photolysis of

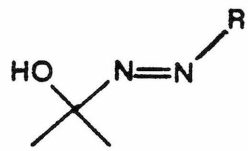


trans-1 cis-1

trans-1; progress of the isomerization could be monitored by UV spectroscopy. Since cis-diazenes are generally significantly more labile than the corresponding trans-isomers, isomerization and decomposition would probably be carried out in situ.[10] The difference in $\Delta V^{\ddagger}$ observed for decomposition of the two isomers may be indicative of the mechanism of decomposition of trans-1. If trans-1 decomposes via the stepwise mechanism, the similarly stepwise decomposition of cis-1 should be more exothermic to the extent that the greater lability of cis-1 is caused by the lower stability of its ground state. Therefore, based on the Hammond postulate and the precedent discussed earlier, one should expect the $\Delta V^{\ddagger}$ for cis-1 to be less possitive than the $\Delta V^{\ddagger}$ for trans-1.

However, if trans-1 decomposes via a concerted pathway, different results should be obtained. Such a concerted induced decomposition would not be available to cis-1 due to stereoelectronic factors. The effect of stereoelectronics on radical reactions has been appreciated for some time,[11] and free-radical additions to the π-bond of olefins has been suggested to be under stereoelectronic control.[12] A concerted induced decomposition of a diazene is analogous to a microscopic reverse of this process. Thus, cis-1 must decompose via some type of stepwise mechanism. In general, the $\Delta V^{\ddagger}$ for a process where more bonds are broken (i.e. concerted) is much less positive than for a corresponding process where fewer bonds are broken (i.e. stepwise).[2] This has been observed both in radical (perester pyrolysis)[13] and ionic (E^2 vs E^1cb)[14] fragmentations. Therefore, if trans-1 is decomposing through the concerted mechanism, the necessarily stepwise decomposition of cis-1 should have a much more positive $\Delta V^{\ddagger}$; this is the opposite of what would be observed if the fragmentation of trans-1 is stepwise.

Another potential probe for the decomposition mechanism of trans-1 would involve the synthesis of a variety of analogues 2 where R could be a variety of carbon residues with differing radical stability.[15] In a con-



2

certed mechanism, the R-N bond should be somewhat broken in the transition state; due to factors already discussed, $\Delta V^{\ddagger}$ should thus be sensitive to the stability of R•, becoming less positive for substrates with more stable R•.[16] In a corresponding stepwise decomposition, the R-N bond should not be breaking in the transition state, and $\Delta V^{\ddagger}$ should be much less affected by changes in the radical character of R. If trans-1 is actually decomposing via a stepwise process, an interesting effect which might be seen here is a change to a concerted mechanism as the leaving radical is made more stable in 2; this would be observed experimentally by a sudden drop in the value of $\Delta V^{\ddagger}$.

In summary, schemes have been discussed which could lead to the resolution of a fundamental mechanistic question by determining the nature of a transition state by $\Delta V^{\ddagger}$ measurements. Other tools are of course available

for such mechanistic work;[17] one (^{15}N CIDNP) has already been mentioned. However, given advances in experimental techniques such as the recently reported EPR kinetic method discussed above, along with the possibly successful investigation proposed, the utility of measurement of the quantity $\Delta V^{\ddagger}$ in physical organic chemistry should be on the increase.

References and Notes

(1) Kelm, H. Ed. "High Pressure Chemistry"; D. Reidel Publishing Co.: Dordrecht, Holland, 1978.

(2) For an exhaustive review including many tables of data, see Asano, T.; LeNoble, W. J. Chem. Rev. 1978, 78, 407-489.

(3) Marriott, P. R.; Griller, D. J. Am. Chem. Soc. 1981, 103, 1521-1524.

(4) For a recent review on the use of EPR in physical organic chemistry, see Griller, D.; Ingold, K. U. Accts. Chem. Res. 1980, 13, 193-200.

(5) For an earlier review on pressure effects on free radical chemistry, see Newman, R. C. Accts. Chem. Res. 1972, 5, 381-387.

(6) Nazran, A. S.; Warkentin, J. J. Am. Chem. Soc. 1981, 103, 236-237.

(7) This was suggested as the result of the authors earlier studies: (a) Yeung, D. W. K.; Warkentin, J. Can. J. Chem. 1976, 54, 1349-1354; (b) Ibid. 1976, 54, 1345-1348.

(8) Porter, N. A.; Dubay, G. R.; Green, J. G. J. Am. Chem. Soc. 1978, 100, 920-925.

(9) Neuman, R. C.; Lockyer, G. D.; Amrich, M. J.

Tetrahedron Lett. 1972, 1221-1224.

(10) This general procedure has been used to study a variety of cis-diazenes; for some examples, see Ref. 8.

(11) (a) For an early discussion of the effects of stereoelectronics on free radical olefin additions, see Beckwith, A. L. J. Chem. Soc. Special Publ. 1970, no. 24, p. 239.; (b) For a recent discussion of stereoelectronic effects in radical fragmentation reactions, see Ayral-Kaloustian, S.; Agosta, W. C. J. Am. Chem. Soc. 1980, 102, 314-323, and references therein.

(12) For what may be a particularly striking example of such an addition (100:0 stereospecificity), see Bougeois, J.-L.; Stella, L.; Surzur, J.-M. Tetrahedron Lett. 1981, 61-64.

(13) (a) Neuman, R. C.; Behar, J. V. J. Am. Chem. Soc. 1967, 89, 4549-4550; (b) Neuman, R. C.; Behar, J. V. Tetrahedron Lett. 1968, 3281-3284.

(14) Brower, K. R.; Muhsin, M.; Brower, H. E. J. Am. Chem. Soc. 1976, 98, 779-782.

(15) This synthesis would be quite simple; hydrazines RNH NH_2 would be prepared and converted to substrates 2 via the procedure outlined in Ref. 6.

(16) Polar effects may accentuate this trend for substrates where R is also ion-stabilizing; for discussion of these effects, see Refs. 2 and 13b.

(17) A variety of other methods used towards the solution of the diazene decomposition problem are listed in Ref. 8.

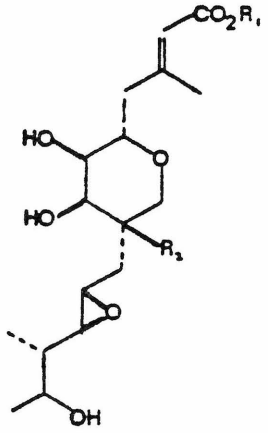
PROPOSITION V

A new application of π-allyl palladium chemistry is proposed, and its utility is demonstrated both as a method of resolving a conformational mechanistic question and as the key step in a chiral total synthesis of pseudomonic acid C.

* * * * * * *

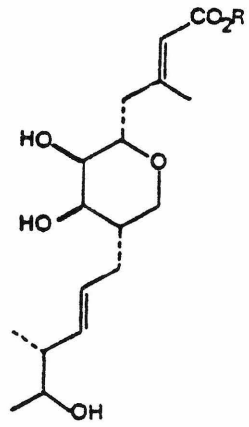
The pseudomonic acids A (1a) and B (1b) are C-glycoside antibiotics which are produced by a strain of Pseudomonas flourescens, and have been known for several years. Considerable antimicrobial activity has been observed in vitro for these compounds.[1] The structures, including absolute stereochemistry, have been proven by spectral, degradative, and X-ray studies.[2] Recently, Rogers et al[3] have isolated and characterized pseudomonic acid C (2), which is identical to pseudomonic acid A except for the absence of the epoxide oxygen. However, this minor structural change renders 2 much more stable to mildly basic and acidic conditions and therefore a more promising candidate for in vivo antibiotic activity. Within the past few months, Kozikowski et al[4] have reported a

synthesis of racemic 2. Although this synthesis proceeds through an excellent bond formation scheme, it suffers from the necessity of separating several diastereomeric mixtures, including one upon formation of the C_{10}-C_{11} double bond and two at the anomeric C_5. An alternative chiral synthesis of 2 will be proposed here, including the use of a novel palladium-catalyzed process for stereospecific bond formation at the anomeric carbon.



1a $R_1 = (CH_2)_8CO_2H$; $R_2 = H$

b $R_1 = (CH_2)_8CO_2H$; $R_2 = OH$

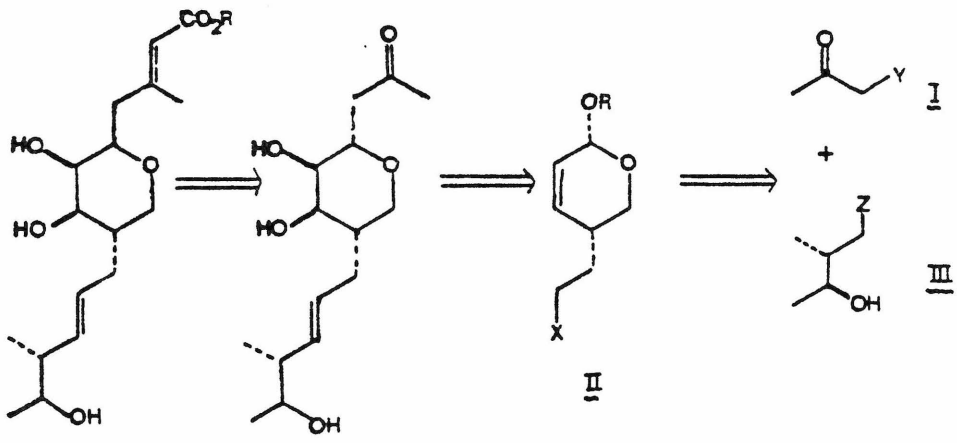


2 $R = (CH_2)_8CO_2H$

Examination of the structure of pseudomonic acid C reveals that the most rational scheme for bond disconnection

is the one shown in Scheme I; this is, in fact, the one employed by Kozikowski. It also becomes clear that, in order to carry out an efficient chiral synthesis of 2, the following conditions must be met: (1) chiral preparation of central subunit II; (2) chiral preparation of lower subunit III; (3) stereospecific introduction of subunit I with complete retention of stereochemistry at the anomeric C_5. None of these conditions, including stereospecific bond formation at C_5, were met in Kozikowski's synthesis.

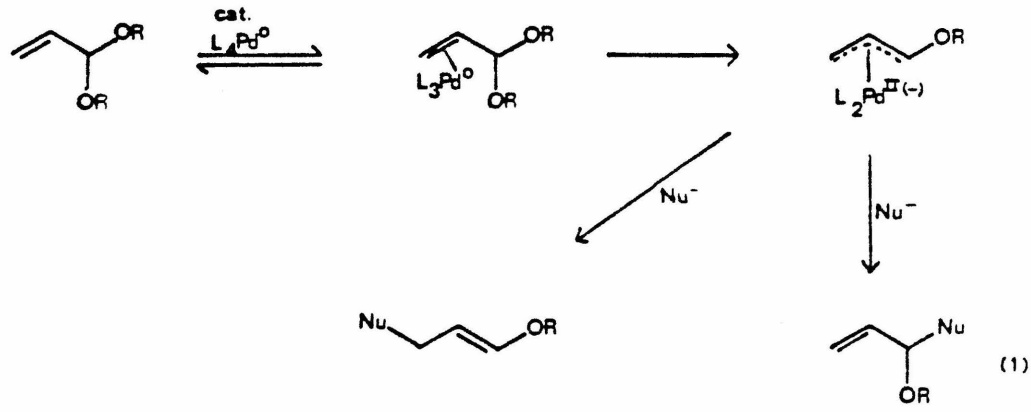
Scheme I



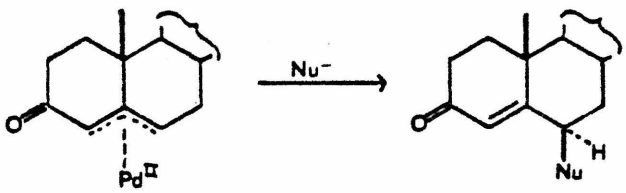
2

Before outlining the set of reactions through which this plan is proposed to be carried out, it is appropriate to discuss the π-allyl palladium-mediated coupling of subunits I and II, the key carbon-carbon bond forming step in the synthesis. Within the past decade, the understanding and application of π-allyl palladium intermediates have mushroomed.[5] A large number of these intermediates have been prepared,[6] and their reactions with a variety of "soft" nucleophiles have been studied. One intriguing application of this chemistry which has not yet been explored would involve the use of π-allyl complexes which are substituted with oxygen at a terminal position (Scheme II). Several questions regarding this are immediately apparent. Formation of the initial complex between Pd° and the electron-poor olefin (eq. 1) might seem unfavorable, but this has precedent in the fact that allylic sulfones[7] have recently been employed as π-allyl palladium precursors. Second, the regiochemistry of attack on the allylic complex needs to be determined. One might expect that nucleophilic attack would occur next to the oxygen substituent due to the greater stabilization of positive charge on that side of the allyl moiety. An example of the opposite electronic effect can be seen in equation 3, where a keto group

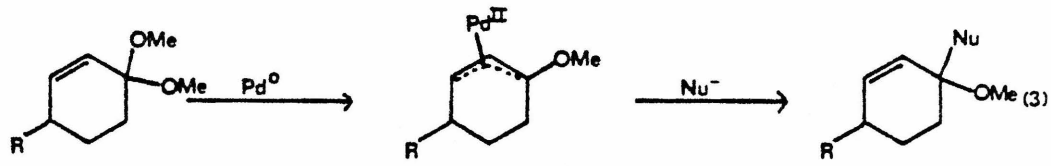
Scheme II



(1)



(2)



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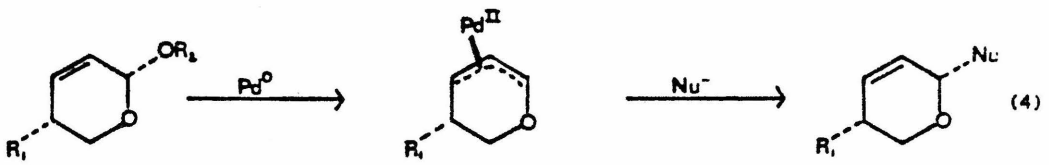


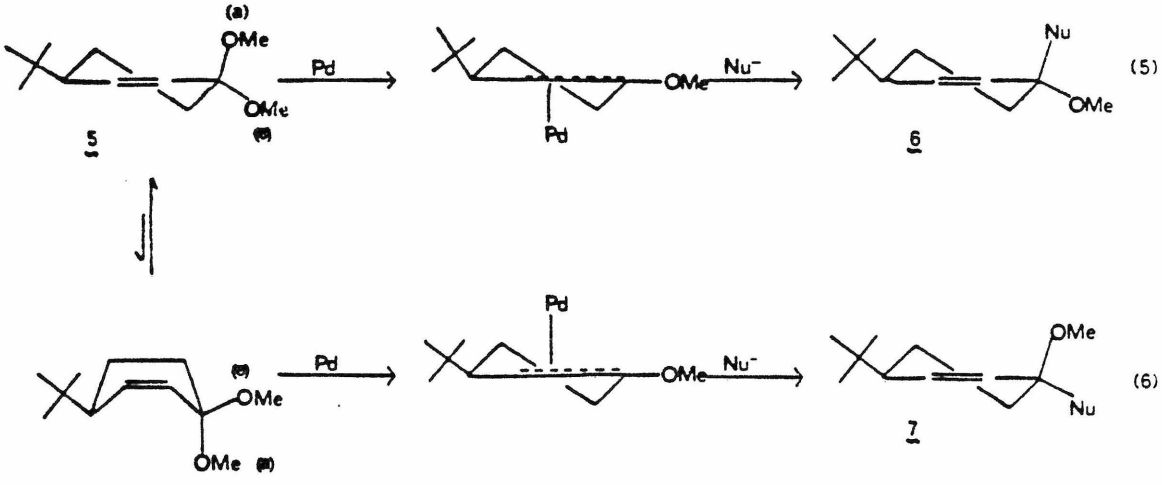
(4)

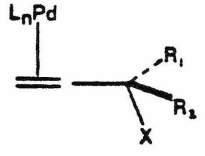
directs nucleophilic attack to the opposite side of the allyl system.[8] In addition, the Pd°-vinyl ether complex resulting from attack gamma to the oxygen should be of higher energy than the Pd°-alkyl olefin complex resulting from alpha attack due to the destabilization of p-π^* back-bonding by the electron-donating alkoxy group.[9]

Were nucleophilic attack indeed to occur alpha to the alkoxy substituent, it would appear that the resulting Pd°-olefin complex might itself go on to form a second π-allyl Pd species. However, judicious choice of reaction conditions might allow one to circumvent this problem. Since the ionization of the allylic leaving group from the Pd°-olefin complex seems to be the rate-determining step in formation and subsequent reaction of the π-allyl,[10] one should expect the formation of a π-allyl complex from the starting olefinic ketal 3 to be significantly faster than from the intermediate allylic ether 4.

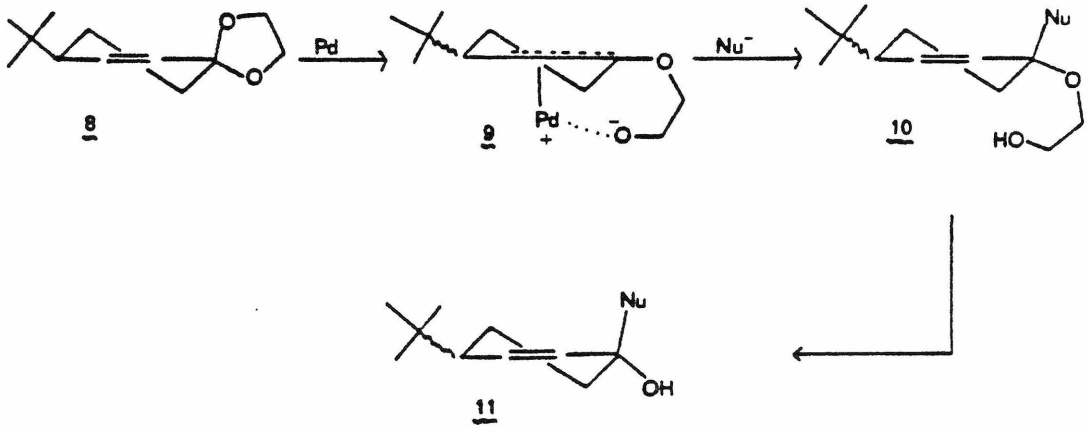
An interesting preliminary study would involve cyclic ketals 5 and 8, which are conformationally restricted in that the bulky t-butyl substituent will demand a pseudoequatorial or equatorial disposition. An excellent procedure for the preparation of the ketals of α,β-unsaturated ketones has recently been provided by

Scheme III


(a)
OMe
OMe
Pd
Nu⁻
Nu
OMe
Pd
5
6
(5)
(a)
OMe
OMe
Pd
OMe
Nu⁻
OMe
Nu
7
(6)


LnPd
R1
R2
X

A


Pd
Nu⁻
O
O
Pd
O
Nu
O
HO
OH
8
9
10
11

Noyori,[11] circumventing the oft-encountered problem of double-bond migration. As can be seen in Scheme III, some interesting stereochemical and mechanistic questions are posed in the Pd°-mediated displacement reaction on ketal 5. In equation 5, a process involving ionization of a pseudo-axial methoxyl group followed by anti nucleophilic attack to give product 6 is shown. Such anti attack is well-precedented.[12] However, an interesting question arises with regard to the stereoelectronic requirement for leaving-group ionization from the initially formed Pd°-olefin complex. One would expect that, in order to gain maximal orbital overlap in the transition state for formation of the π-allyl system during this ionization, a conformation as depicted in structure A should be most favorable, where the leaving group X will be oriented antiperiplanar to the axis of the Pd-olefin bond. However, in the Pd-olefin complex derived from the half-chair conformation of 5, the pseudoaxial methoxyl leaving group would be oriented at as small as a 67° angle from the plane of the olefin,[13] a far cry from the 90° angle required for antiperiplanarity. If such antiperiplanarity is indeed a necessity for formation of the π-allyl, a mechanism such as that shown in equation 6 might be operative, where the π-allyl is

formed from a cyclohexene boat conformation containing a truly axial leaving group. The energy difference between the half-chair and boat conformations of cyclohexenes has been suggested to be as low as 2.7 kcal/mol.[14] Since the final product 7 obtained via such a mechanism would be different from the product 6 obtained through the half-chair process, the results of this experiments should provide the answer to these interesting questions.

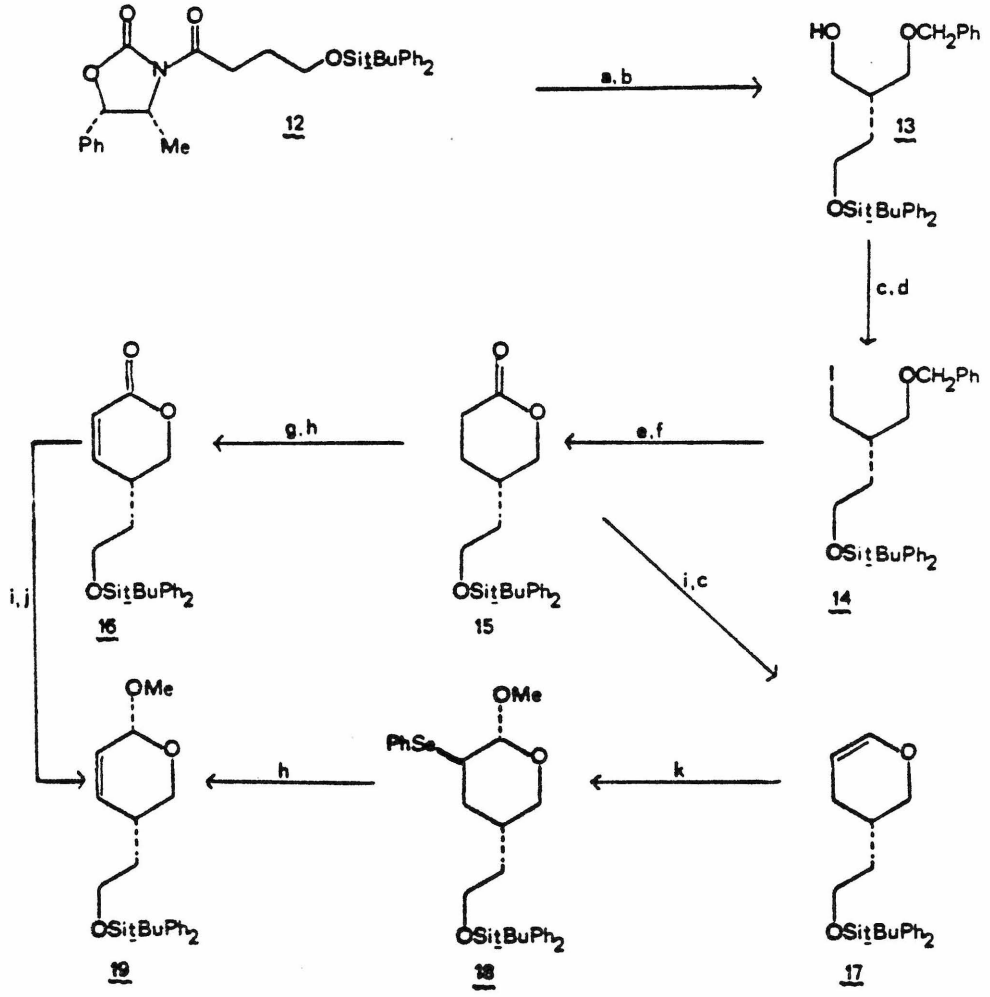
Comparison of these results with those obtained from performing a similar sequence on ethylene ketal 8 should be instructive. A derived π-allyl complex such as 9 would probably exist with the Pd^{II} intramolecularly chelated by the displaced ketal oxygen. This factor might influence the regiochemistry and stereochemistry of nucleophilic addition. If an adduct such as 10 were in fact formed specifically, the overall procedure would be quite valuable due to the ease of converting 10 to the corresponding tertiary alcohol 11. This could be accomplished by conversion of the primary hydroxyl group to a halide followed by a standard reductive fragmentation. Overall, such a scheme would be equivalent to the 1,2-addition of a "soft", stabilized nucleophile to an enone; in practice, 1,4-addition is usually observed upon exposure of an enone to such a nucleophile.

A related investigation would focus on dihydropyranoid ketals of the type shown in Scheme II, equation 4. Due to the well-known anomeric effect,[15] the allylic ether substituent in such systems has a built-in axial bias. Based on the stereochemical considerations mentioned above, application of the Pd°-catalyzed nucleophilic addition process to these systems should proceed as shown in equation 4 to provide a method for stereospecific introduction of a nucleophile at the anomeric carbon.

The synthetic utility of such a process could be illustrated within the context of a chiral synthesis of pseudomonic acid C. The combination of subunits I and II (Scheme I) would be accomplished by such procedure. A preparation of the dihydropyran intermediate is shown below in Scheme IV.

Alkylation of norephedrine-derived acyl oxazolidinone 12 [$LiN(i\text{-}Pr)_2$, $BrCH_2OCH_2Ph$], followed by reductive scission of the recyclable chiral auxiliary with $LiBH_4$ should furnish the alcohol 13 in excellent chemical yield.[16] After straightforward conversion to iodide 14, its displacement with the enolate of ethyl acetate followed by hydrogenolysis of the benzyl ether should lead to the δ-lactone 15. The required unsaturation could then be introduced by the methods of Sharpless[18] and Reich[19]

Scheme IV

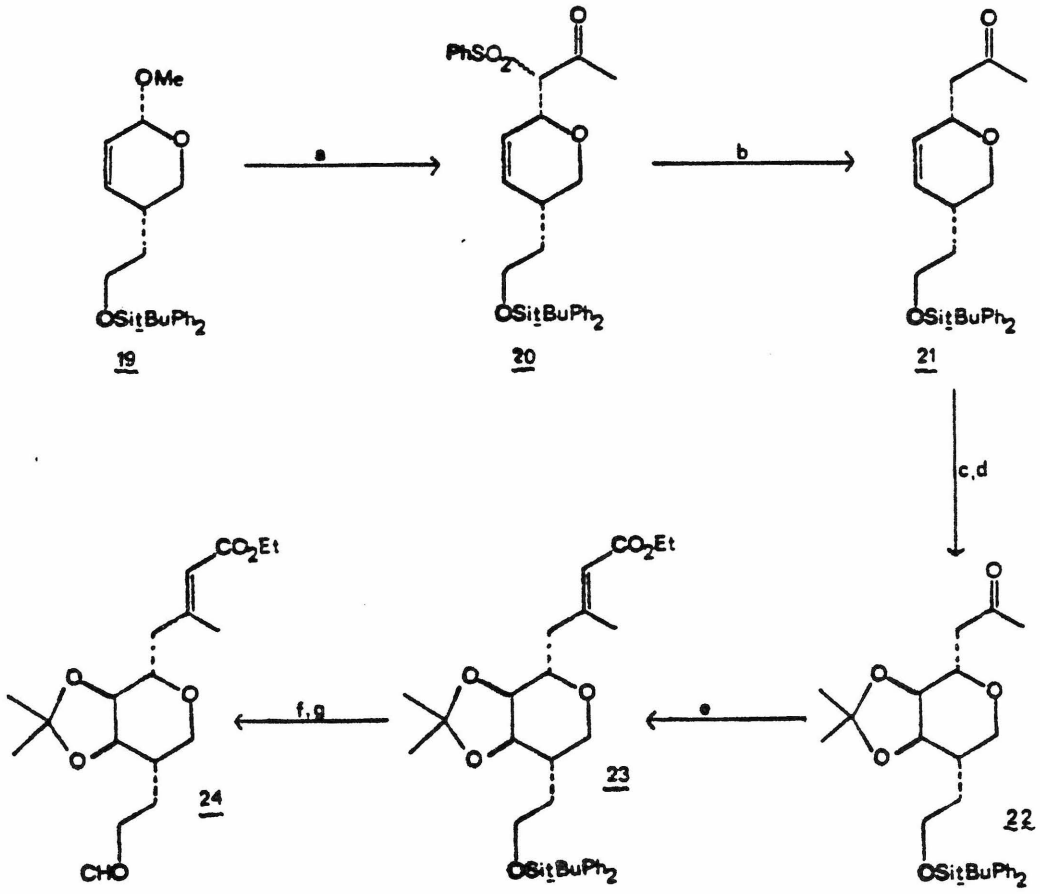


a) $LiN(\underline{i}\text{-}Pr)_2$, $BrCH_2OCH_2Ph$. b) $LiBH_4$. c) Et_3N, $MeSO_2Cl$. d) NaI. e) $LiCH_2CO_2Et$. f) H_2, Pd-C. g) $LiN(\underline{i}\text{-}Pr)_2$, PhSeBr. h) [0]. i) DIBAL-H. j) MeOH, $HC(OMe)_3$, H^+. k) PhSeBr, CH_3OH.

giving 16. Reduction (DIBAL-H) to a moderately unstable acidic methanol, should then give the key intermediate 19; the cis stereochemistry shown should predominate due to the preferred axial orientation of the alkoxy substituent at the anomeric center. A potential problem here is the epimerization of the chiral center during the acid-catalyzed hemiacetal to acetal conversion; if conditions mild enough to avoid this cannot be found, a sequence adapted from Kozikowski's racemic synthesis could be used. After elaboration of saturated lactone 15 to dihydropyran 17, alkoxyselenation was found to give isomer 18 preferentially. Subsequent oxidative elimination of selenium would then furnish the desired intermediate 19 without any epimerization.

Further elaboration of this intermediate is shown in Scheme V. Reaction of 19 with the anion of α-phenylsulfonylacetone in the presence of $Pd(PPh_3)_4$ and PPh_3, as discussed earlier, might afford 20, the product of substitution at the anomeric carbon with retention of stereochemistry. Removal of the phenylsulfonyl group with buffered aluminum amalgam,[19] a very mild procedure, followed by vic-hydroxylation[20] and protection of the two secondary alcohols, should then give ketone 22. Carboethoxy olefination of this ketone, as carried out by

Scheme V

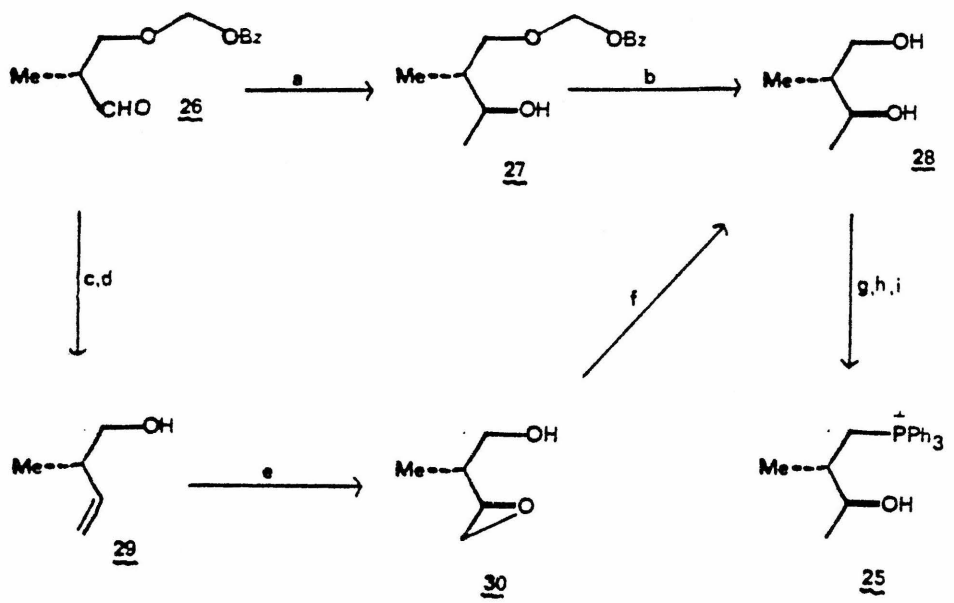


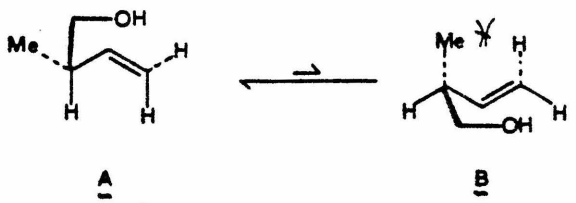
a) $PhSO_2CH_2COCH_3$, NaH, $Pd(PPh)_4$, PPh_3. b) Al(Hg). c) OsO_4. d) 2-methoxypropene, pyridinium tosylate. e) $(Et_2O)_2POCHLiCO_2Et$. f) n-Bu_4NF. g) PCC, CH_2Cl_2.

Kozikowski, yields predominantly the trisubstituted olefin shown. Subsequent deprotection of the primary alcohol and oxidation [pyridinium chlorochromate (PCC)] gives the aldehyde 24.

From a corresponding racemic aldehyde having only a slight difference in the dihydroxyprotecting group, Kozikowski completed the synthesis of pseudomonic acid C by Wittig condensation with the β-oxido ylid derived from phosphonium salt 25 (racemic), followed by separation of the resulting mixture of diastereomers. Since chiral aldehyde 24 is available *via* our route, it is necessary to prepare 25 of correct chirality for an olefination which would lead to the natural product. Two potential routes to the chiral phosphonium salt are presented in Scheme VI. The first involves chelation controlled addition of a methyl Grignard reagent to chiral aldehyde 26.[21] Still *et al*[22] have observed 5:1 diastereoselectivity in the addition of a magnesium ketone enolate to this aldehyde resulting from apparent chelation control. Deprotection of the correct diastereomer 27 would then give rise to chiral diol 28. Alternatively, the diastereoselective epoxidation of homoallylic alcohol 29, also derived from chiral aldehyde 26, could be explored. One would expect preferential formation of epoxide 30.

Scheme VI

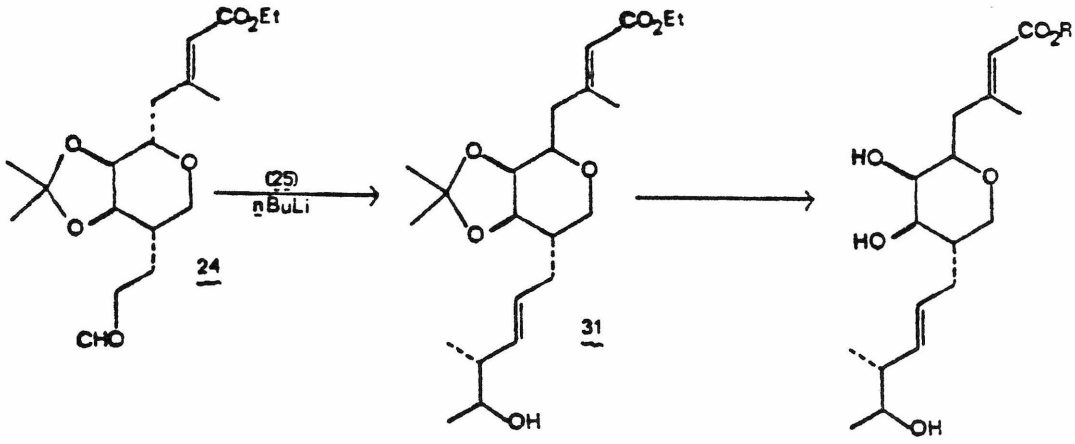




a) CH_3MgBr. b) H_2, Pd-C. c) Ph_3PCH_2. d) H_3O^+. e) MCPBA or $VO(AcAc)_2$. f) $LiAlH_4$. g) CH_3SO_2Cl, Et_3N. h) NaI. i) PPh_3.

This might be explained by preference of conformer A over conformer B due to relief of methyl $A_{1,3}$ strain. Direction of epoxidation by the hydroxy group oriented as in conformer A would lead to the desired product 30. Some precedent exists for this in the work of Kishi,[23] who observed complete diastereoselection upon MCPBA oxidation of a more highly substituted allylic alcohol. Although the crucial transition state interactions are somewhat less severe in our case, high selectivity might be insured by use of one of the transition metal-catalyzed epoxidations developed by Sharpless.[24]

Ring opening of epoxide 30 by hydride attack would afford chiral diol 28. The primary hydroxyl group of this diol could then be elaborated to the phosphonium



2 R = $(CH_2)_8CO_2H$

salt 25 via the straightforward procedure used by Kozikowski. This phosphonium salt would then be deprotonated to give a β-oxido ylid, which would then be combined with chiral aldehyde 24 to give E-olefin[25] 31. This compound would then be transformed to chiral pseudomonic acid C by transesterification and removal of the acetonide protecting group.

In summary, a new application of π-allyl palladium chemistry has been discussed, and its utility both as a mechanistic probe and as a synthetic tool has been illustrated.

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