TOTAL SYNTHESIS OF NEOLIGNANS

by

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of the Requirement for the
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May, 1978

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Department of Chemistry, May, 1978

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Thesis Supervisor

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ABSTRACT

The total synthesis of (±)-guianin (1), (±)-burchellin (2), (±)-2-epi-3a-epiburchellin (3), and (±)-futoenone (4) are described. Condensation of isosafrole (E- and Z-, 5) with 2-allyl-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (20a) or 2-allyl-4,4,5-trimethoxycyclohexa-2,5-dienone (100a) under different acidic conditions gave products with either the bicyclo[3.2.1] octane, dihydrobenzofuranone, and spiro-[5.5]undecane skeletons. They were converted into the titled compounds. Various substituted cyclohexa-2,5-dienones (quinone ketals) were conveniently prepared by oxidation of the corresponding phenols with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ferric chloride.

Appendix A. Acid catalyzed condensation reactions of various quinone ketals with simple olefins and alkynes are

Abstract cont'd

described. Attempts to convert the condensation products into cyclopentanones are also discussed.

Appendix B. The synthesis of 2-methoxy-5-methyl-4-(3,4-methylenedioxyphenyl)-6-propyltropone (25) is reported. 2,4,6-Trinitrobenzenesulfonic acid catalyzed condensation of isosafrole (5) and 2-propyl-4,4,5-trimethoxycyclohexa-2,5-dienone (6) afforded 3-methoxy-6-exo-methyl-7-endo-(3,4-methylenedioxyphenyl)-5-propylbicyclo[3.2.1]oct-3-ene-2,8-dione (4), which was converted to tropone 25 in five steps.

Thesis Supervisor: George H. Büchi

Title: Camille Dreyfus Professor of Chemistry

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Without the love, understanding, and encouragement from my wife Kwan, who also typed the manuscript, this thesis might not have been possible. For all this, this thesis is dedicated to her.

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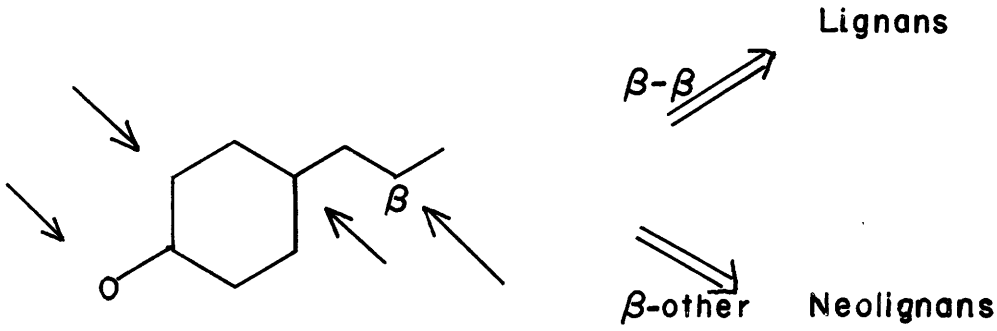
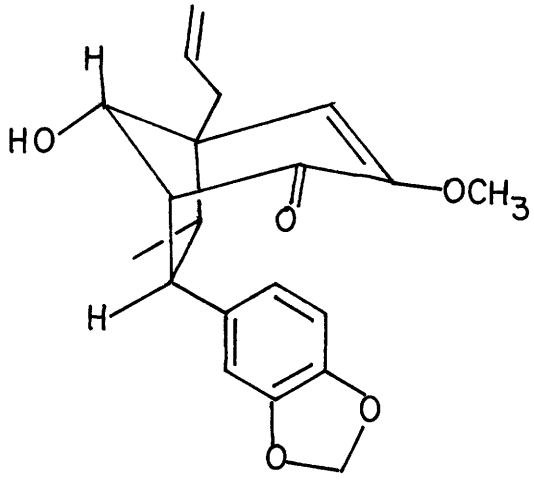
Introduction[66]

Neolignans are a group of secondary plant metabolites characterized by the presence of two arylpropanoid units.[1] In contradistinction to the related lignans, the β-position of one arylpropane moiety is linked to one of the three additional positions of the other. (Scheme I)

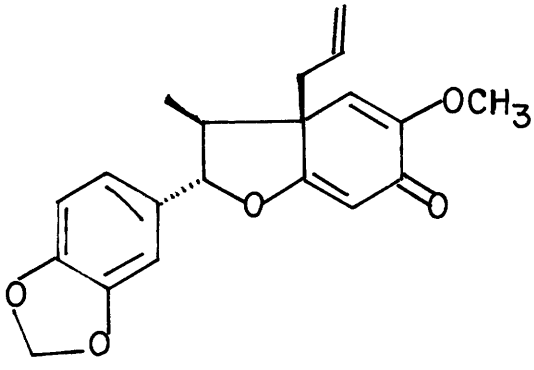


Scheme I

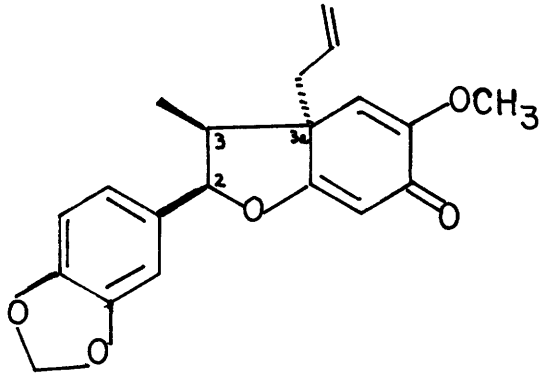
As an continuing effort in studying the chemistry and chemosystematics of the Brazilian Lauraceae, a predominantly arboreous family, Gottlieb and co-workers[1,2] have isolated a vast variety of neolignans from the trunk wood of these plants. Within this class of compounds, substances with bicyclo[3.2.1]octane and hydrobenzofuran skeletons are encountered. Guianin (1)[3] and burchellin (2)[2,4] (from Aniba burchellii Kosterm.) and 2-epi-3a-epiburchellin (3)[5] (from Aniba terminalis) are representative. Their occurrence in Nature has been attributed to oxidative coupling of propenyl and allyl phenols either by combination of radicals or ionic intermediates.[1] (Scheme IIa, IIb, IIc, IId)



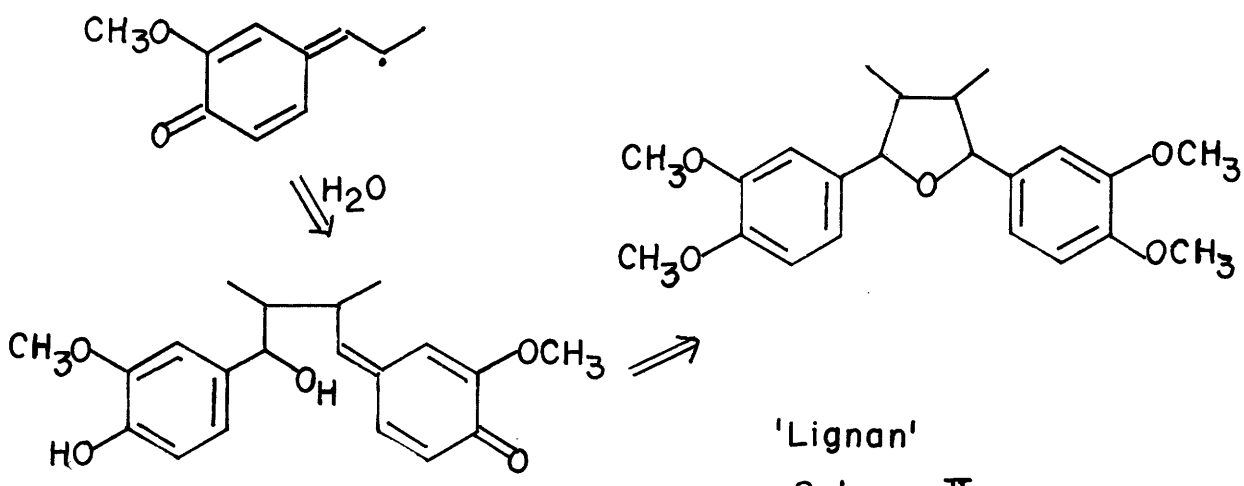
guianin (1)



burchellin (2)

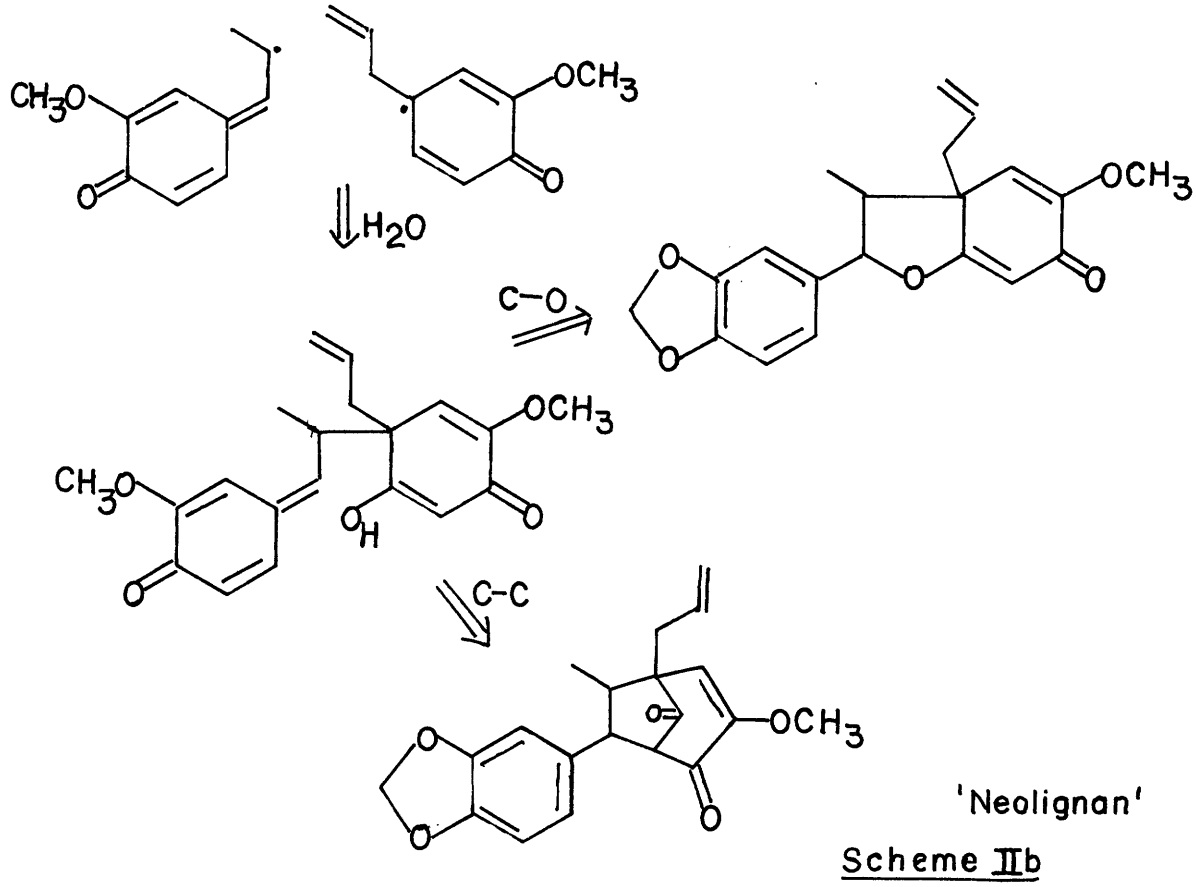


2-epi-3a-epiburchellin (3)



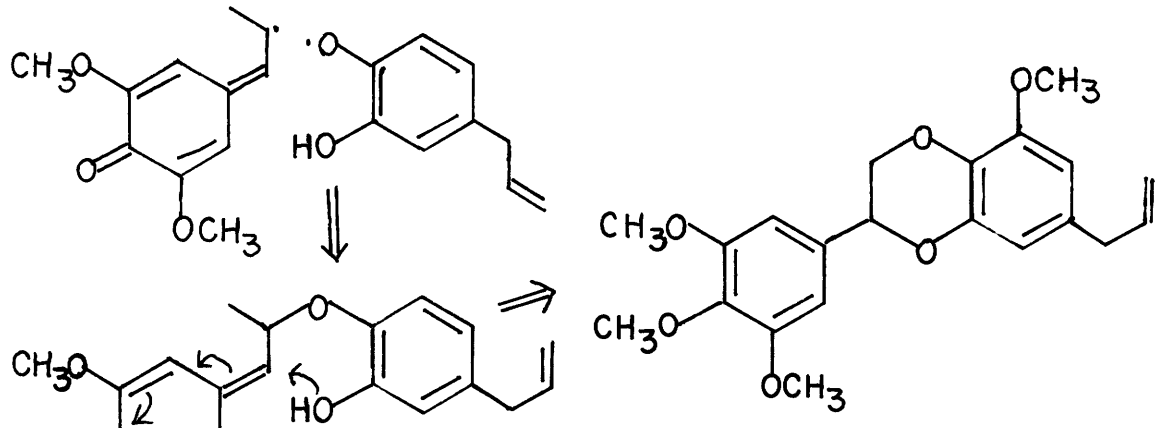
'Lignan'

Scheme IIa

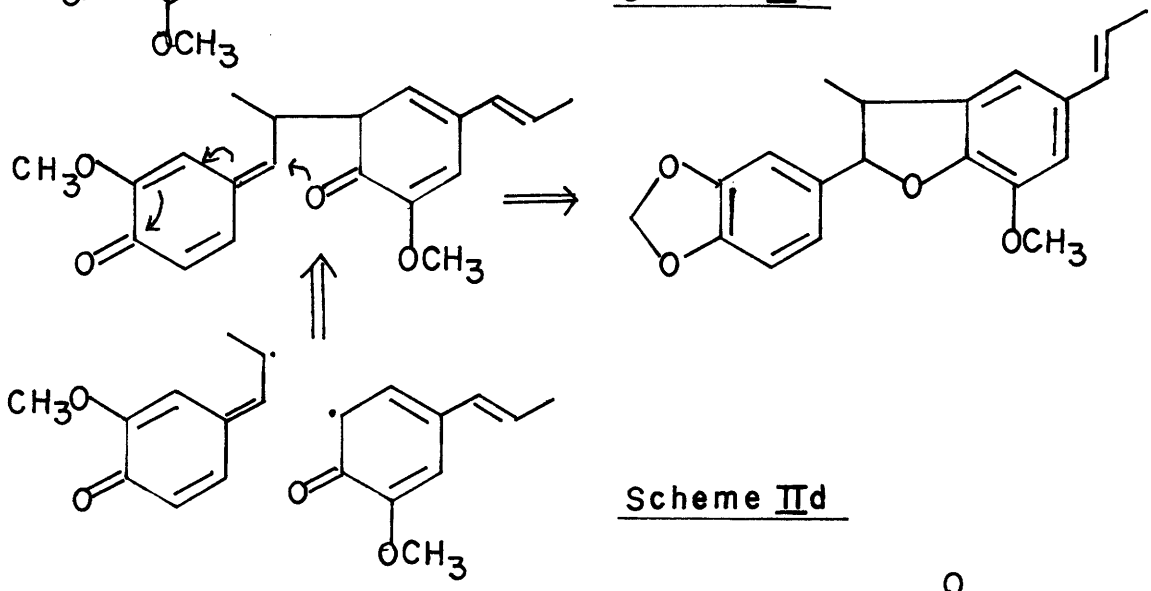


'Neolignan'

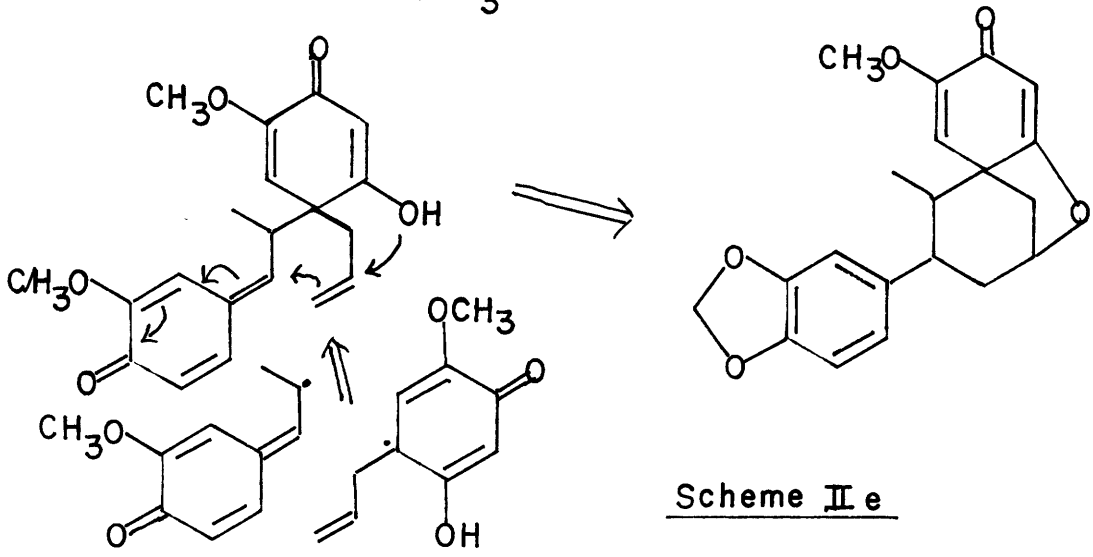
Scheme IIb



Scheme IIc

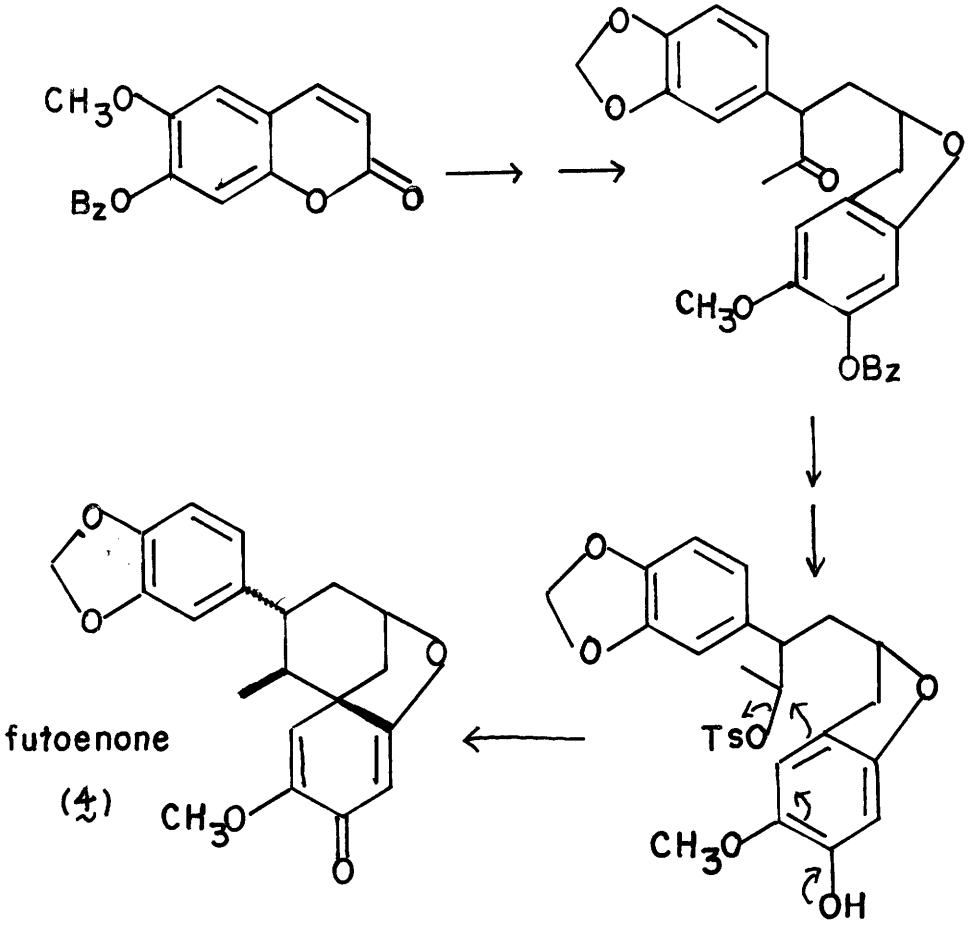


Scheme IId



Scheme IIe

Futoenone (4)[6] was isolated by Ogiso and co-workers in 1970 from the leaves and stem of Piper futokadzura Sieb et Zucc. (Piperaceae). It possesses an unique spiro[5.5]-undecane skeleton and its existence can also be rationalized by similar biosynthetic pathway. (Scheme IIe) The synthesis was first reported by the Japanese workers and includes an intramolecular phenol alkylation to form the cyclohexadienone. (Scheme III)

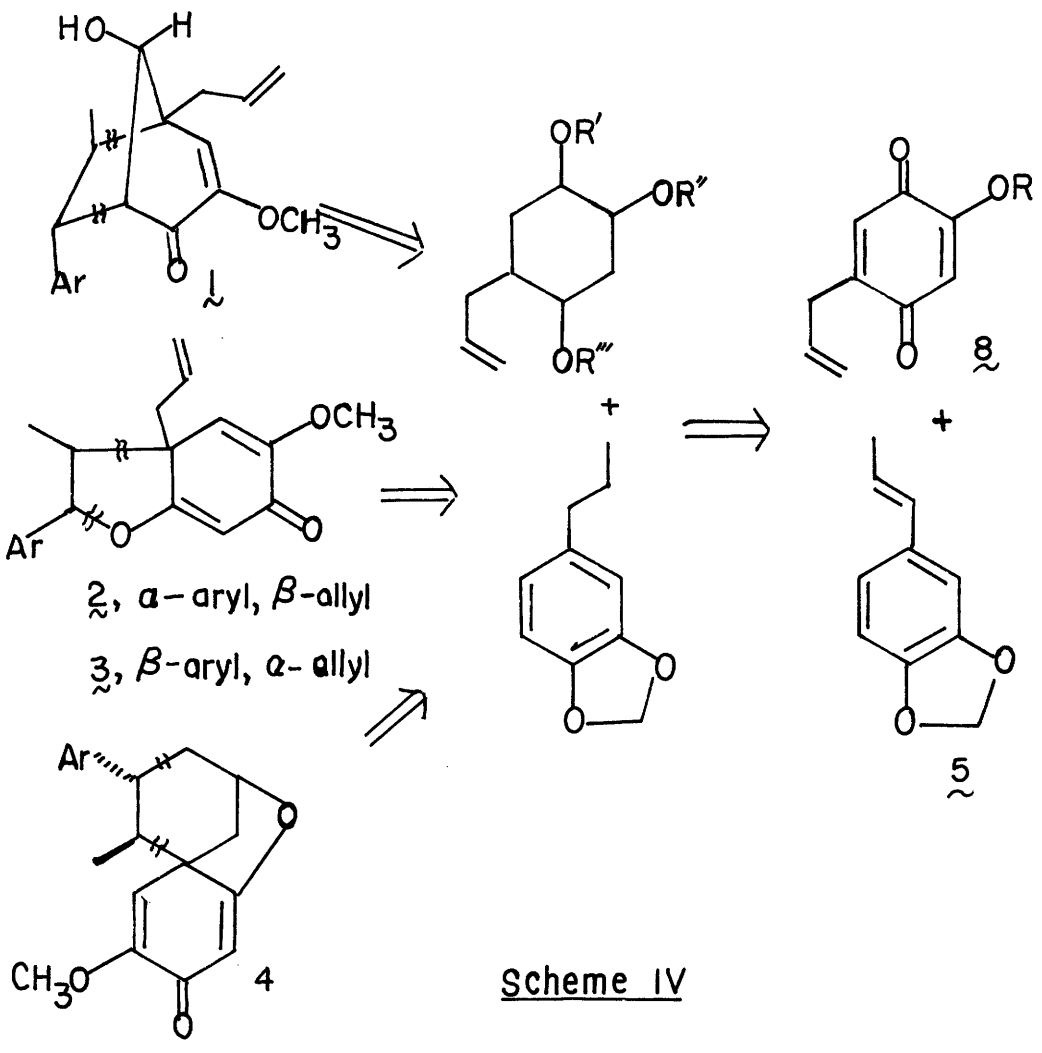


Scheme III

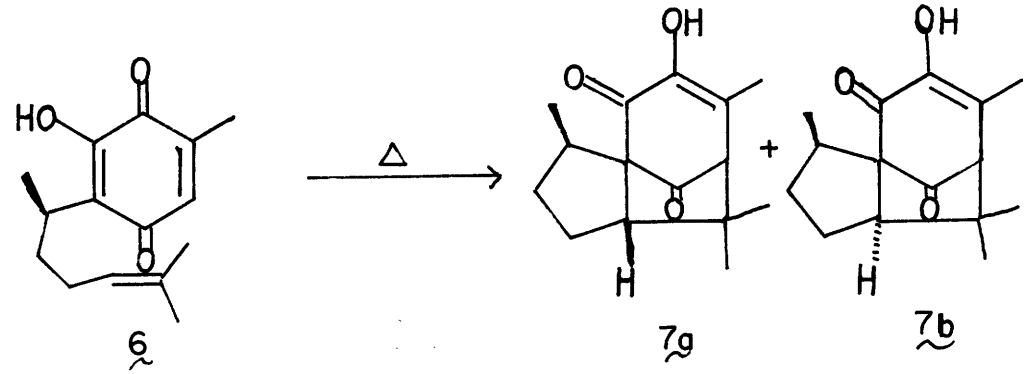
Although the above-mentioned compounds have not yet been shown to possess any useful pharmacological activities,[45] they are important compounds in view of the fact that they provide valuable information about the occurrences of "related" compounds within a taxonomical group.[1,7] Therefore, a successful total synthesis of these compounds would not only verify the proposed structures,[8] but might also provide tools for studying their biosynthetic relationships.

Retrosynthetic inspection of the structures would lead to the two moieties A and B, which can be derived from isosafrole (5) and some substituted 1,4-benzoquinone. (Scheme IV)

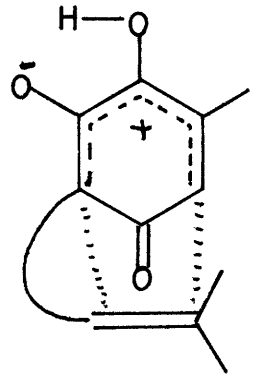
Our synthetic plan was based on the remarkable thermal transformation of perezone (6) to pipitzols (7).[9] (Scheme V) This was first postulated[10] and later shown[11] to be a [2 + 4] concerted cycloaddition reaction. It probably involves the reactive species C, which undergoes an intramolecular cyclization to give the observed products. Therefore, a successful condensation of isosafrole with the quinone (Scheme VI) would not only demonstrate the applicability of such process in an intermolecular fashion but would also provide an entry to the guianin skeleton. The advantages of this synthetic plan lie on he fact that the two moieties can be linked together in one step and the stereochemical requirements may be met in the reaction is indeed concerted.[10]



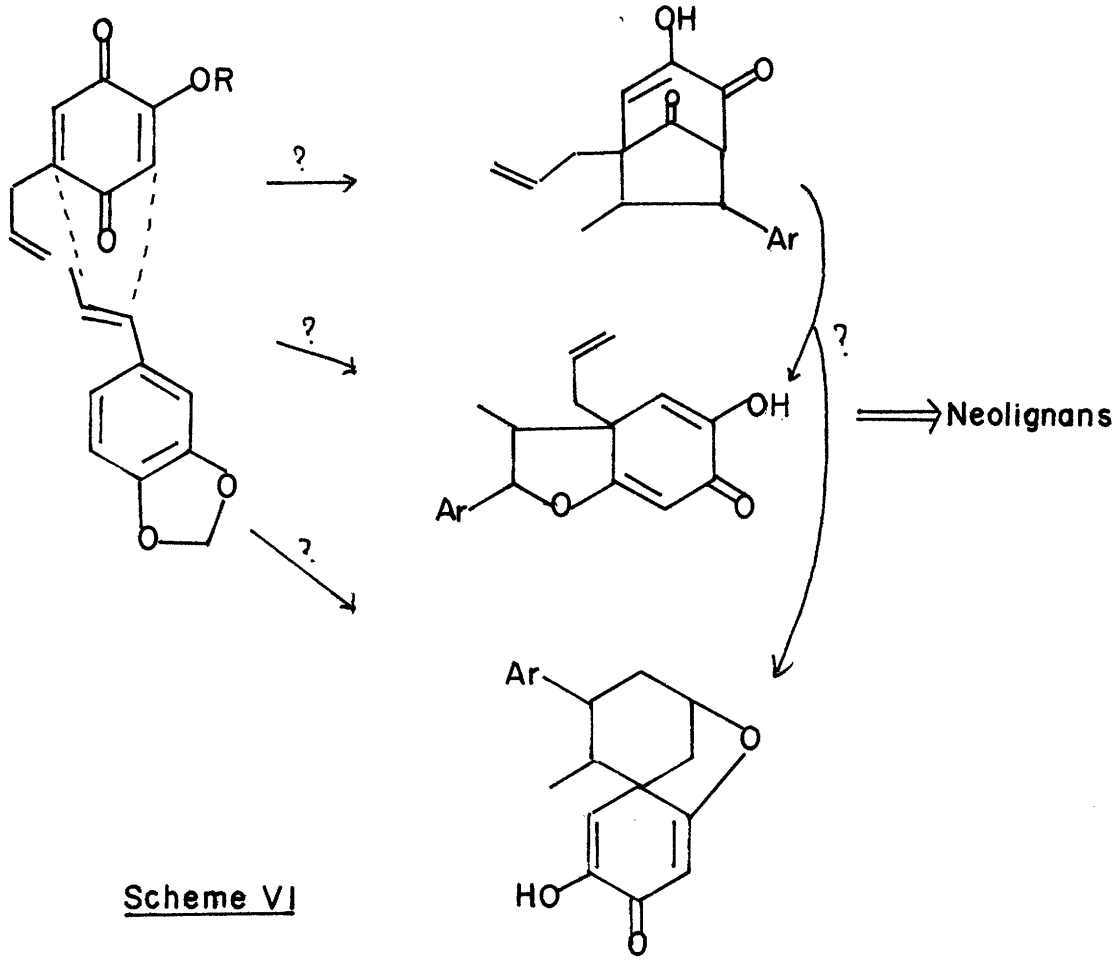
Scheme IV



Scheme V



C

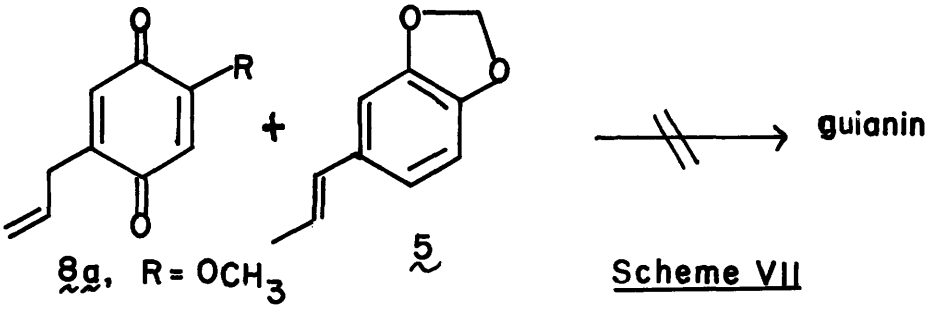


Scheme VI

Results and Discussion

Part I:

The obvious approach to our synthetic problem was to prepare various substituted quinones 8 and react them with isosafrole (5). Earlier, Williams[12] in this laboratory attempted the condensation of methoxyquinone 8a (R = OCH_3) with 5 under various conditions. However, only complex mixtures of products were obtained, and no carbonyl containing compounds were detected. (Scheme VII)

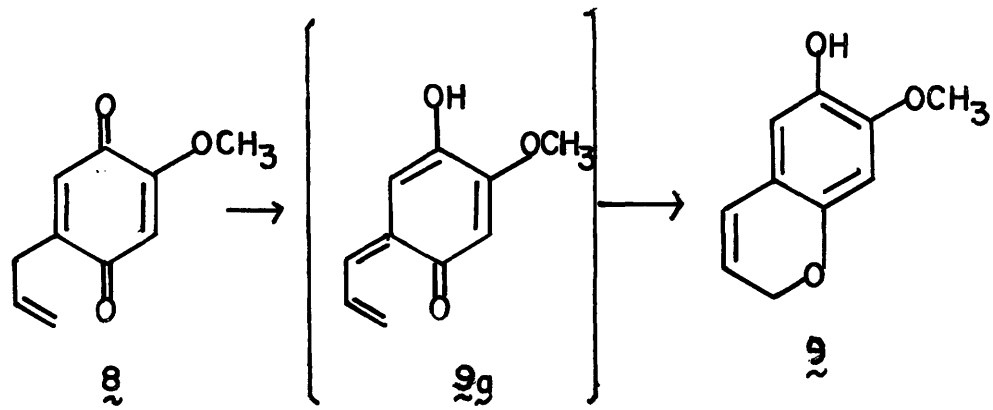


8g, R = OCH_3 5

Scheme VII

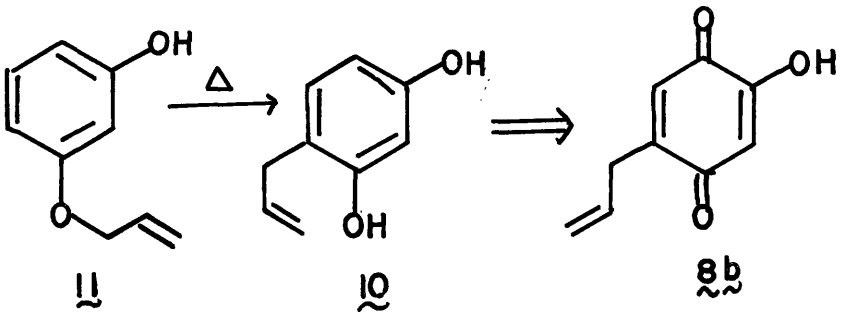
Re-examination of the reactions indicated that the major products were derived from polymerization of isosafrole under the reaction conditions. The methoxy-substituted quinone was not "active" enough to react with 5. Therefore our immediate objective was to prepare more nucleophilic quinones, such as hydroxy or amino substituted ones (8, R = OH, NR_2 etc.). Direct replacement of methoxy groups with hydroxy and amino functions in quinone systems in not without precedence.[13-15] Unforturnately, in most cases, we isolated either unreacted starting mat-

terials or decomposed products. When 8a was treated with diethylamine in boiling tert-butyl alcohol, no diethylamino substituted quinone was observed. Instead, chromene 9 was isolated in 40% yield. This was not surprising, because such facile electrocyclic reactions are well documented in the literature.[16] Base catalyzed prototropic shifts would give rise to the quinone methide 9a, which would subsequently be converted to the observed product 9. (Scheme VIII)



Fremy's salt[17,18] [$\cdot ON(SO_3K)_2$] is known to oxidize various substituted phenols and anilines to the corresponding benzoquinones. A probable intermidate to the hydroxyquinone 8b (R = OH) would be resorcinol 10, which could be obtained via Claisen rearrangement from the mono-allyl ether 11. (Scheme IX) This route was quickly abandoned due to difficulties encountered in every step. Preparation of the mono-allyl ether from resorcinol was accompanied by various C-alkylated and dialkylated products.[19] Claisen rearrangement of the allyl ether resulted in an equal amount

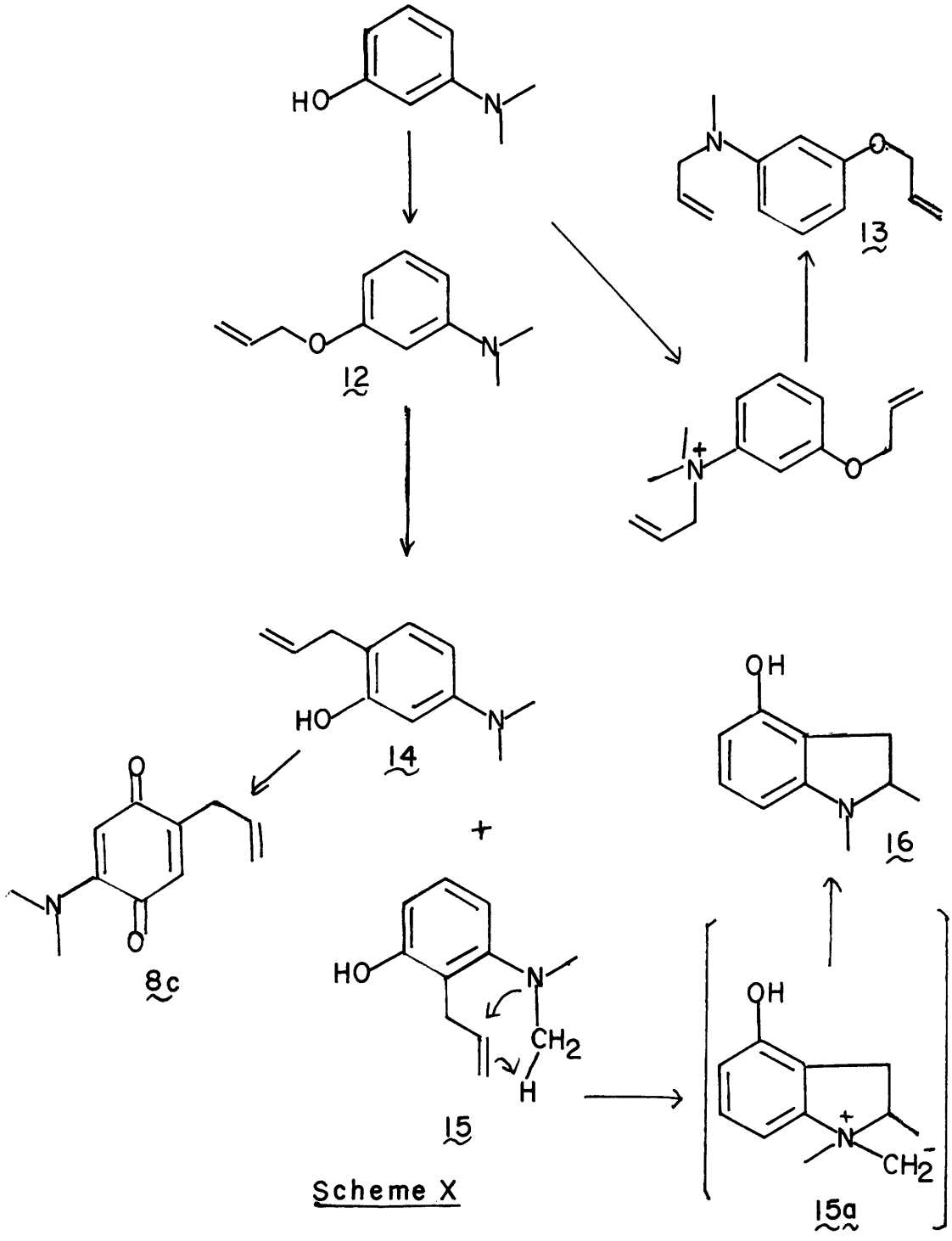
Scheme IX



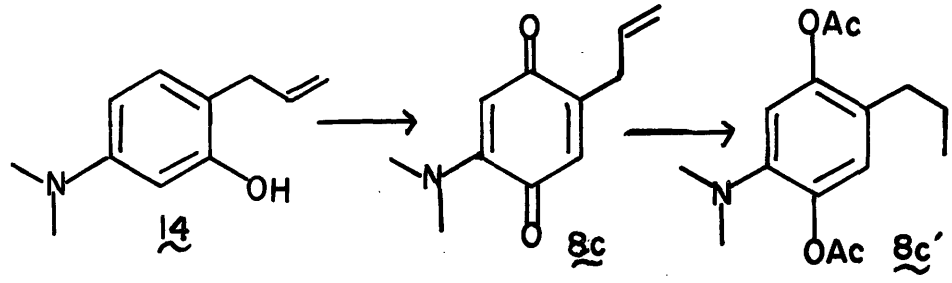
11 10 8b

of the two isomeric allyl resorcinols, which could only be separated by tedious chromatography or cumbersome fractional distillation.[20] Above all, oxidation with Fremy's salt failed to give any desirable product.

Nevertheless, an amino-substituted quinone was readily prepared via this procedure. 3-Dimethylaminophenyl allyl ether 12 was prepared in excellent yield by a standard procedure, accompanied by a small amount of compound 13. Claisen rearrangement gave phenol 14 as the major product, which can be isolated quite efficiently by column chromatography. Besides the isomeric phenol 15, another interesting product, characterized as indoline 16, was also isolated in low yield. It is probably derived from 15, via an intermediate such as 15a. (Scheme X) A similar transformation has been recently reported for the synthesis of indoles.[35] It involed palladium assisted intramolecular amination of an olefin.


HO
N
12
O
13
14
8c
15
16
15a
OH
CH2
H
+
Scheme X

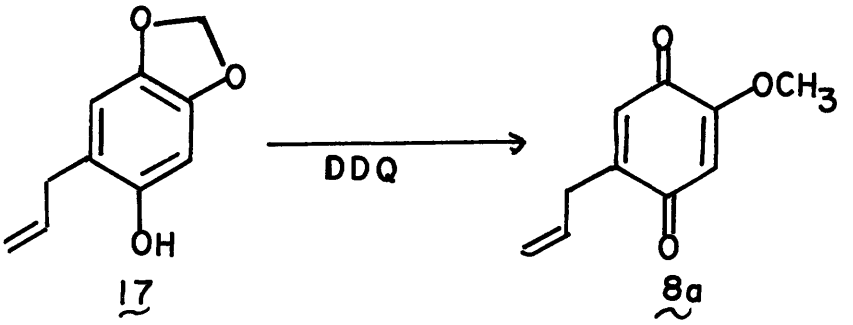
Treatment of aminophenol 14 with Fremy's salt in methanol gave the desired aminoquinone 8c (R = $N(CH_3)_2$) as an unstable red oil in moderate yield. Attempts to crystallize it failed; it decomposed slowly on silica gel and in concentrated solution. The structure was confirmed by the charateristic spectroscopic data of the compound.[28] Moreover, hydrogenation of 8c over 10% Pd/C in ethanol gave the corresponding n-propyl hydroquinone which was isolated as the diacetate 8c'. (Scheme XI)



With the aminoquinone in hand, various conditions were tried to realize the condensation reaction with isosafrole (5). It appeared that 8c was too unstable under the reaction conditions, since we only obtained decomposition products.

Since the hydroxyquinone 8b was still beyond our reach by conventional methods, a new approach was undertaken. The methoxyquinone 8a was prepared in this laboratory by Williams[12] using a rather unconventional route. Treatment of 2-allyl-4,5-methylenedioxyphenol (17)[21] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 18) in methanol in the

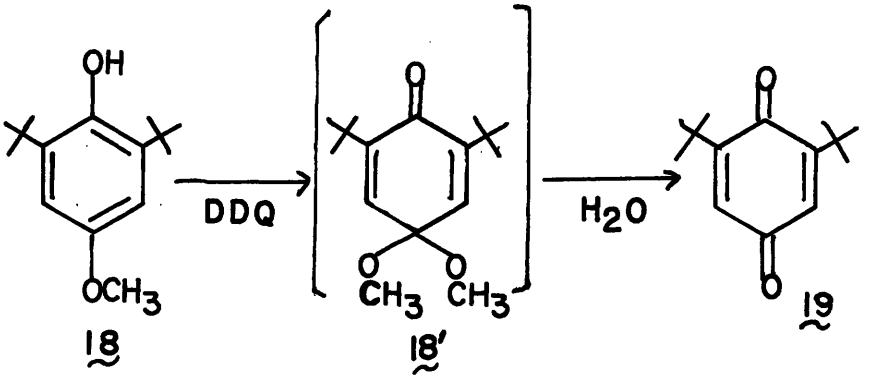
presence of a catalytic amount of concentrated sulfuric acid gave 8a in 74% yield.



17 8a

Usually, the chief product in DDQ oxidation of monohydric phenols is a dimeric substance formed by either C-C or C-O coupling.[22] However, Becker[23] reported that oxidation of 2,6-di-tert-butyl-4-methoxyphenol (18') with DDQ in methanol did give an 81% yield of 2,6-di-tert-butyl-1,4-benzoquinone (19). An intermediate dimethyl ketal 18" was suggested, although no experimental details were given. (Scheme XII)

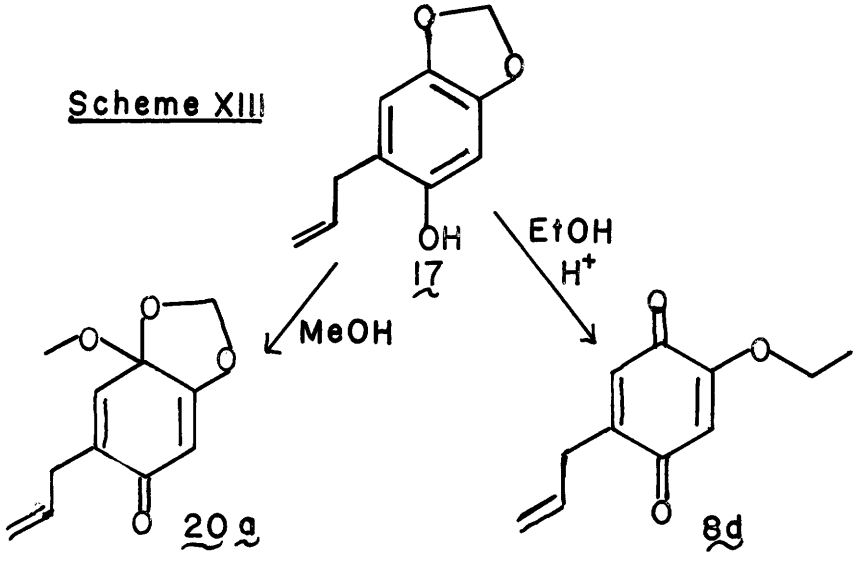
Scheme XII



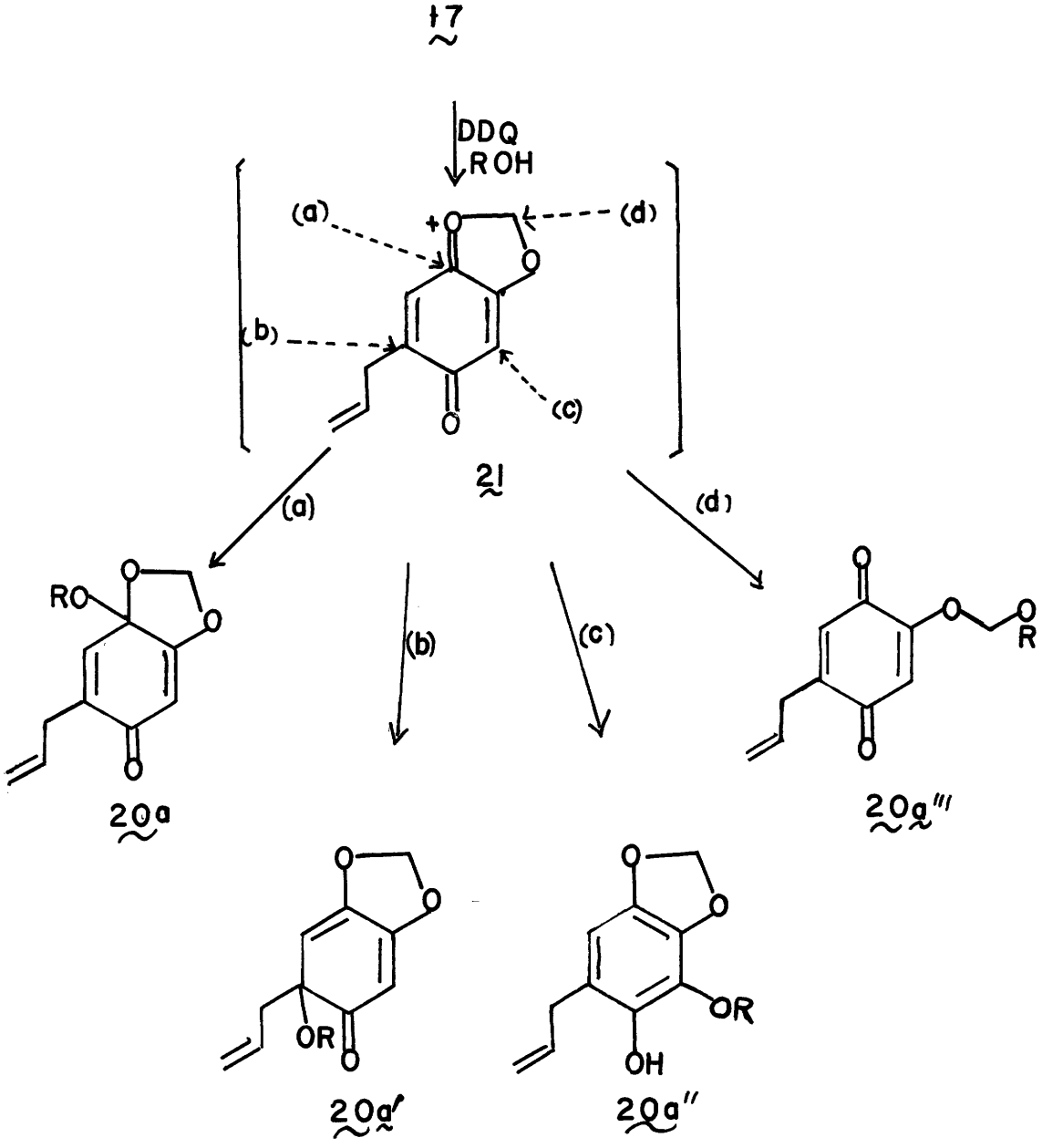
18 18' 19

It was thus possible that, in the oxidation of 17 to 8a, a quinone ketal was involved and was subsequently transformed into the observed product; indeed, when the reaction was carried out in ethanol, ethoxyquinone 8d (R = OCH_2CH_3) was isolated in low yield. More importantly, when phenol 17 was treated with DDQ in methanol in the presence of a catalytic amount of p-nitrophenol, an 88% yield of a white crystalline compound was obtained after chromatography and crystallization from ether-pentane. (Scheme XIII) Its ultraviolet and infrared spectra were distinctly different from those of 1,4-benzoquinones. However, the ^1H NMR spectrum of the compound in $CDCl_3$ did not conclusively confirm the structure to be the quinone ketal 20a. If one looks at the possible mechanism of this oxidation (Scheme XIX), structures 20a', 20a'', and 20a''' should also be considered.

Scheme XIII

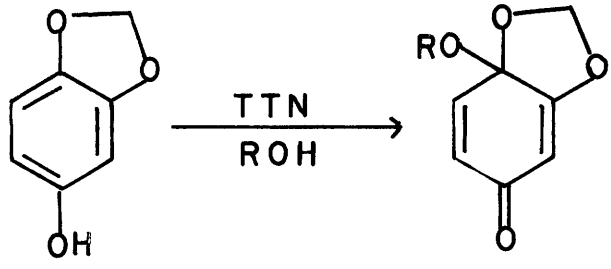


Initial oxidation of phenol 17 by DDQ probably gave rise to the oxonium ion 21. At this stage, one molecule



Scheme XIV

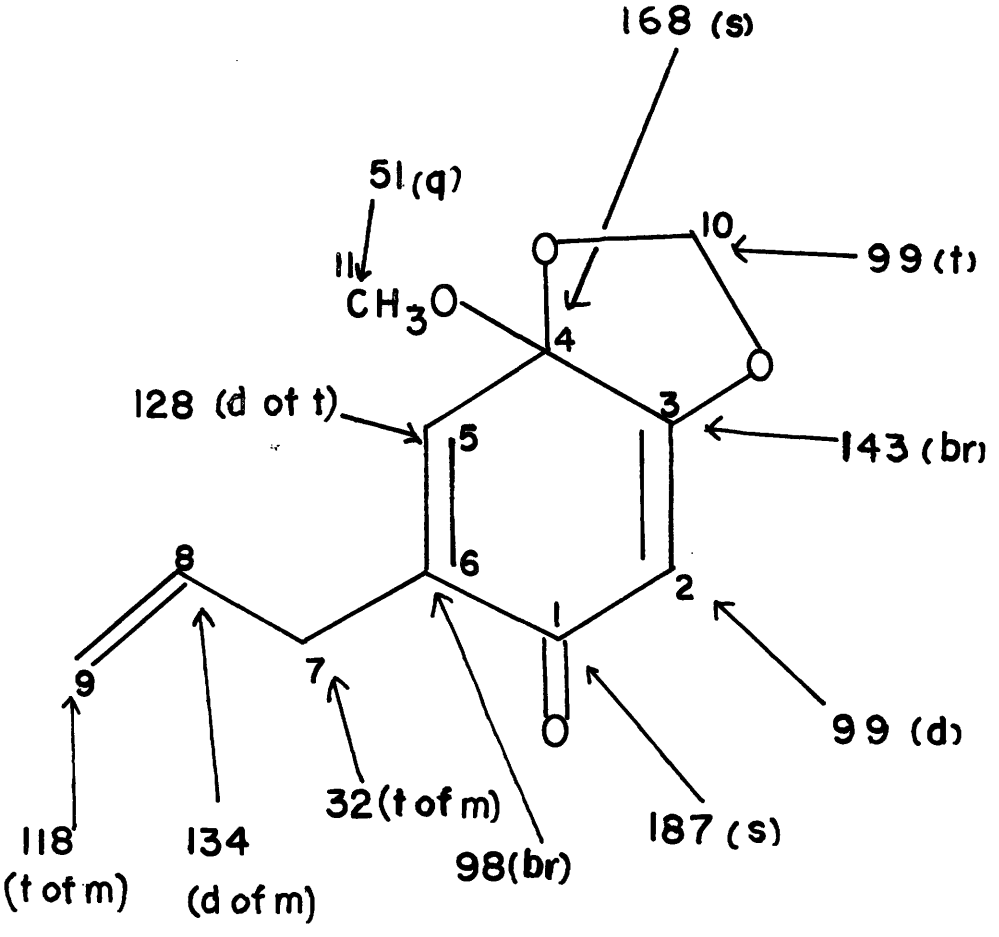
of solvent could attack at any one of the four sites as indicated. Path (C) could be ruled out immediately because the compound was not a phenol. Structure 20a' was disregarded because both UV and IR spectra were not indicative of a linearly-conjugated cyclohexadienone. Also, ^{1}H NMR showed a vinyl proton at δ6.67 (t) with a coupling constant of 1 Hz. If structure 20a' were correct, both vinyl protons should be singlets. Structures 20a and 20a''' are consistent with the above observation. However, in $CDCl_3$, a two proton singlet was observed at δ5.63. Since we would expect the methylene protons in the methylenedioxy bridge of structure 20a to be significantly different, the proposed structre for this product seemed improbable.[24] A noted exception to this was recently reported by McKillop and co-workers.[25] They obtained quinone ketals 22a and 22b by oxidation of sesamol with thallium(III) nitrate in an alcohol solvent. (Scheme XV) The ^{1}H NMR signals for the methylene protons coincidentally appeared as a two-proton singlet in $CDCl_3$. As for 20a''' the methylene protons should appear as a singlet.



22 a, R = CH_3
b, R = C_2H_5

Scheme XV

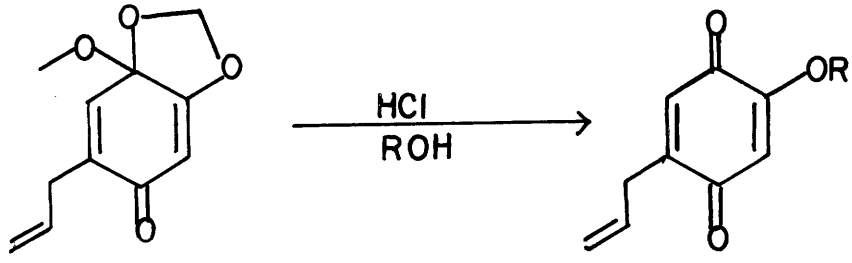
This dilemma was quickly solved when the ^{1}H NMR was recorded in carbon tetrachloride as the solvent. The two methylene protons appear as two distinct singlets; this was indicative of the structure 20a. More convincingly, ^{13}C NMR of the compound was obtained in $CDCl_3$ and the structure was assigned as 20a beyond any doubt. (Scheme XVI)



Scheme XVI

C-10 and C-11 appear as clean triplet and quartet respectively in the spectrum as predicted. The signals for the corresponding carbons in a compound with structure 20a''' would show additional couplings from the protons due to proximity of the two atoms.[26] (For example, CH_3OCH_3 shows J_{COCH} = 5.4 Hz)[27]

The structure of 20a was further proven when it was quantitatively converted to the alkoxy substituted 1,4-benzoquinone in the corresponding alcohol with traces of concentrated hydrochloric acid. (Scheme XVII) This was consistent with the findings in the DDQ oxidation with a catalytic amount of concentrated sulfuric acid. An even more encouraging result was obtained when the quinone ketal was treated with acid in ether or tetrahydrofuran (aqueous), hydroxyquinone 8b was produced in good yield. This was best achieved (80-90%) by stirring 20a in a mixture of water, and ether (or tetrahydrofuran) in the presence of

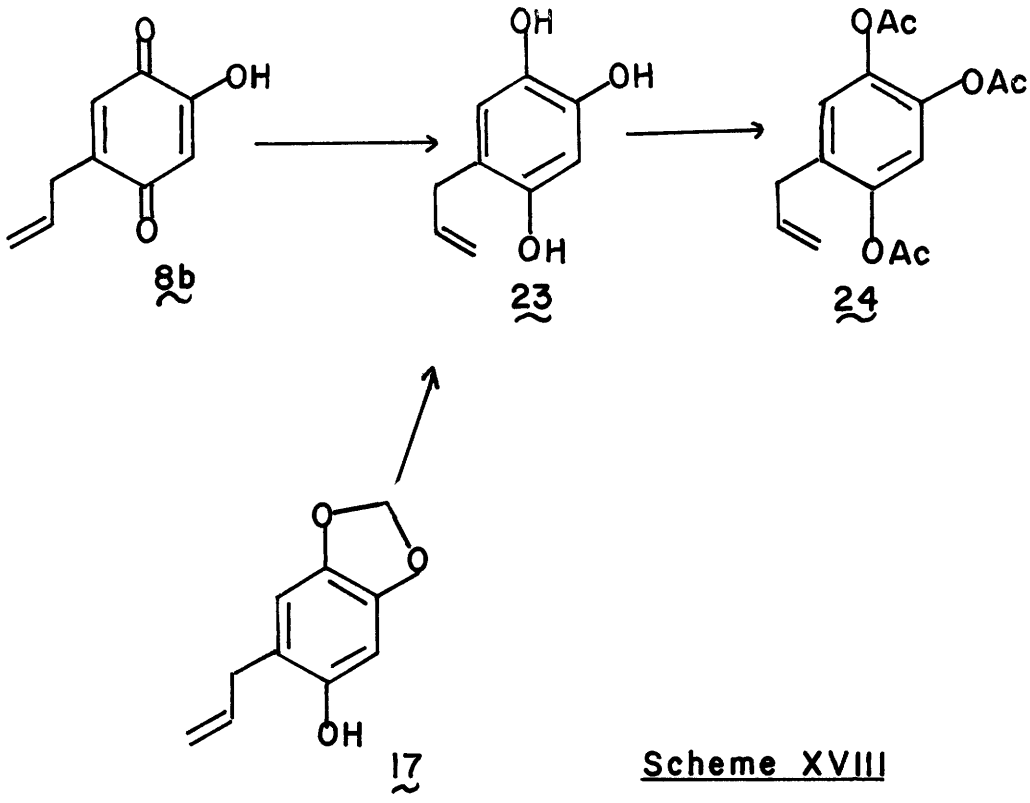


20a 8

Scheme XVII

cation exchange resin. The yellow oily quinone was obtained pure by means of an acid-base extraction procedure during the isolation. It is stable in cold ether solution but decomposed quickly in crystalline form, even at low temperature. Crystalline 8b was obtained by sublimation of the crude oil, although with much decomposition. It developed a characteristic deep red color[28] in mild alkaline solution (5% $NaHCO_3$). However, in the presence of a stronger base (1N NaOH), the compound underwent an irreversible rearrangement that could be followed by measuring its ultraviolet spectrum in 95% EtOH. The structure of hydroxyquinone 8b was confirmed by reduction with sodium dithionite to the hydroquinone 23 which was characterized as the triacetate. Its spectroscopic properties were in accord with structure 24. 24 was prepared independently by treatment of phenol 17 with boron tribromide in CH_2Cl_2 at -78°C to give 23, followed by acetylation. (Scheme XVIII)

With the acquisition of this hydroxyquinone, we hoped that isosafrole (5) would react to give a bicyclic adduct, which could be transformed into guianin (1). Numerous attempts were made, under a variety of conditions. In most of the cases, there was rapid decomposition of the hydroxyquinone, especially at elevated temperatures. Addition of radical inhibitors, such as hydroquinone and 2,6-di-*tert*-butyl-4-methylphenol[29], to the reaction mixture did not alter the outcome of the reaction. Since the quinone ketal



Scheme XVIII

9a was a precursor of the hydroxyquinone, it was also used under a variety of conditions, in the hope that the "reactive" intermediate could be generated in situ and would react with the olefin substrate before it was destroyed. Uses of protic acid produced mainly the hydroxyquinone which failed to react further with isosafrole under mild conditions. Lewis acids gave either no reaction or created an intractable mixture of products.

Our faith in the hydroxyquinones to fulfill our synthetic goal prompted us to prepare yet another version of the protected quinone. The perezone-pipitzol rearrangement

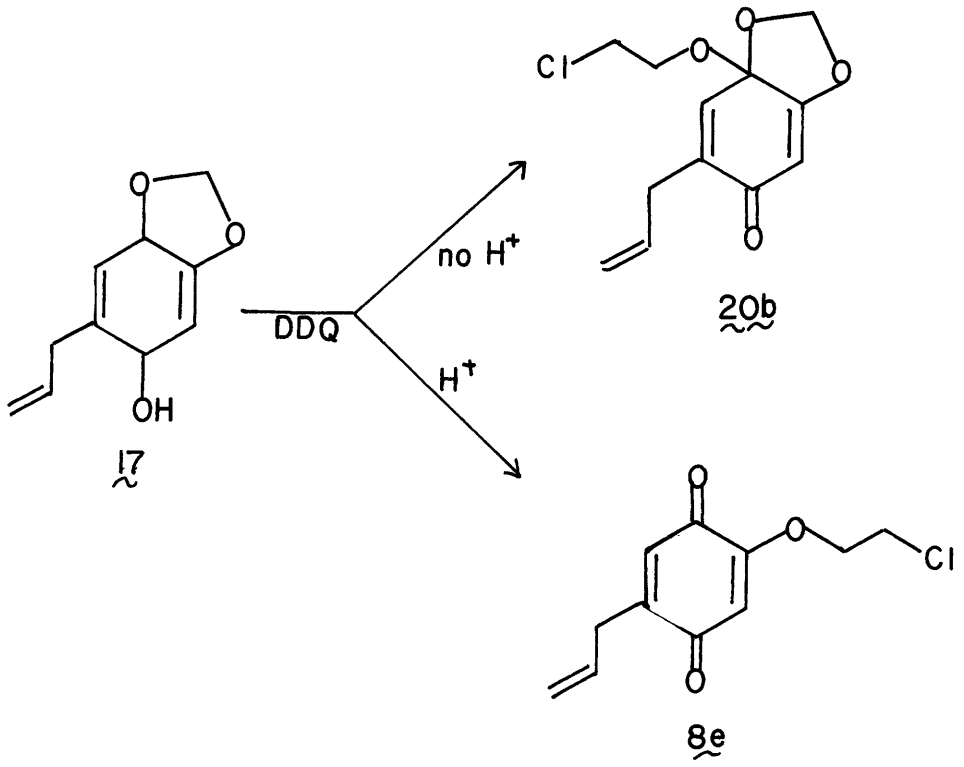
is a thermal process and it is conceivable that, if an intermolecular analog of this process were to occur, similar conditions would be necessary. We therefore required a compound which could liberate the hydroxyquinone or its equivalent in this manner.

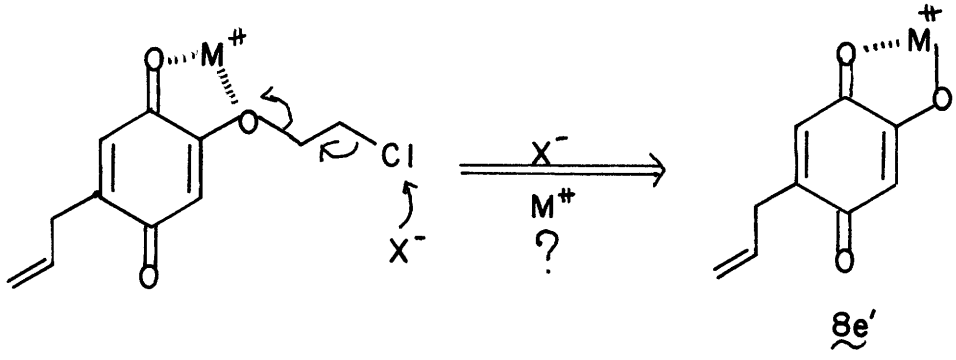
Treatment of phenol 17 with DDQ in 2-chloroethanol under different conditions (Table 1) gave varying amounts of quinone 8e and quinone ketal 20b, depending on the acidity of the reaction medium. In the absence of any external proton source, 2-chloroethanol is acidic enough to facilitate the oxidation of 17 to provide mainly the quinone ketal, whereas the presence of an acid or the use of more dilute conditions, gave predominantly the quinone 8e. (Scheme XIX)

Table 1

Oxidation of phenol 17 with DDQ in 2-chloroethanol

Amount of Phenol used	Amount of solvent used	acid catalyst	yield of 8e	Yeild of 20b
1 mmol	25 mL	p-nitrophenol	60%	---
2 mmol	7.5 mL	p-nitrophenol	11%	62%
3.88 mmol	30 mL	---	39%	20%
10 mmol	15 mL	---	2%	63%
5 mmol	40 mL	conc. H_2SO_4	62%	---





8e'

"hydroxyquínone equivalent"

Scheme XIX

Vicinal dibromides are known to react with iodide ion to give bromide ion and the corresponding olefin.[30] We hoped that upon treatment of the quinone 8e with iodide ion in the presence of a Lewis acid, coordination of the metal with the carbonyl oxygen and ether oxygen would facilitate nucleophilic attack by iodide ion on the molecule to produce one equivalent of ethylene and the "hydroxyquinone equivalent" 8e'. Unforturnately, all endeavours proved to be in vain. A summary of unsucessful reaction conditions applied to the attempted condensation of isosafrole (5) with different quinones and quinone ketals appears in Table 2.

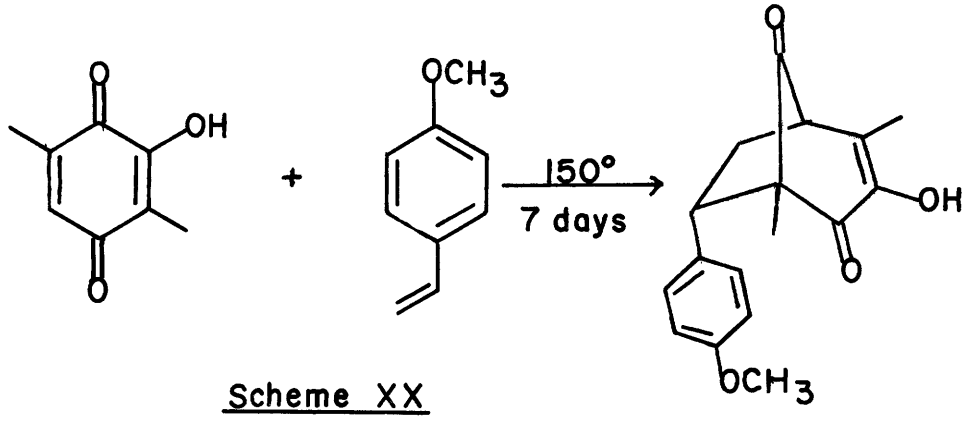
Table 2

Quinones/ Quinone Ketals	Conditions
8b	$HClO_4$/HOAc/CH_2Cl_2/r.t.
8b	EtOH/sealed tube/120°
8b	$AlCl_3$/o-dichlorobenzene/r.t.
8b	TsOH/acetone/r.t.
8b	TsOH/benzene/r.t.
8b	EtOH/1,6-di-tert-butyl-4-methyl phenol/r.t.
8b	o-dichlorobenzene/1,6-di-tert-butyl-4-methylphenol/160°
8b	ZnI_2/CH_2Cl_2/r.t.
8b	o-dichlorobenzene/r.t.

Table 2 cont'd

Quinones/ Quinon Ketals	Conditions
8c	ϱ-dichlorobenzene/r.t., 70°
20a	$AlCl_3/CH_2Cl_2$/r.t.
20a	$HClO_4$/HOAc/CH_2Cl_2/r.t.
20a	$ZnBr_2/CH_2Cl_2$/reflux; r.t.
20a	$ZnBr_2$/toluene/reflux
20a	MgI_2/ether/reflux
20a	EtOH/sealed tube/120°
20a	$ZnBr_2$/dioxane/reflux
20a	ethylene glycol/sealed tube/ 180°
20a	$TsOH.H_2O$/acetone/r.t.
20a	$TsOH.H_2O$/benzene/r.t.
20a	aqueous dioxane/ion exchange resin/reflux
20a	$BF_3.Et_2O/CH_2Cl_2$
8e	$LiI/ZnI_2/CH_3CN$/reflux
8e	LiI/ϱ-dichlorobenzene/110°
phenol 17	DDQ/benzene/r.t.
phenol 17	Chlorinal/dioxane/r.t.
phenol 17	DDQ/tert-butanol/r.t.
phenol 17	DDQ/CH_2Cl_2/r.t.

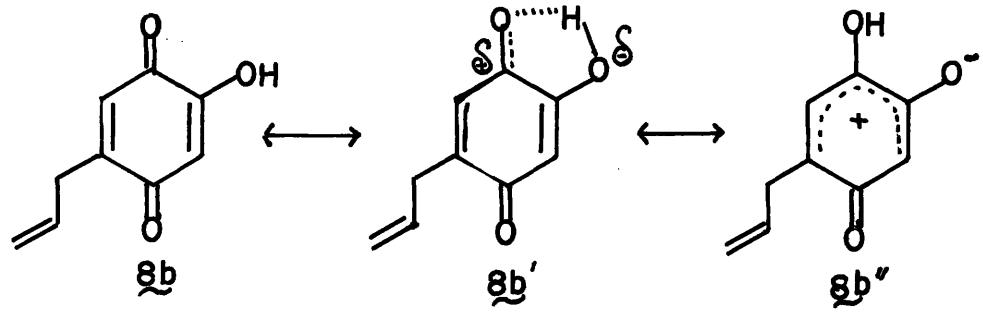
The decisive blow to this approach was finally delivered by work performed in Professor R. B. Woodward's Laboratory at Harvard University.[31] McGregor[32] previously investigated the scope of similar intermolecular cycloaddition reaction. Of the many hydroxyquinone/olefin combinations studied, only 2,5-dimethyl-3-hydroxy-1,4-benzoquinone (25) combined with p-methoxystyrene (26) to give the anticipated adduct 27 in 36% yield. (Scheme XX) The conditions employed were by no means gentle and it was obviously not applicable to our hydroxyquinone 8b, which decomposed rapidly above ambient temperature. An encouraging aspect of this result was that it indicated to us the feasibility of such an intermolecular process. An alternative approach to the problem was sought.



Scheme XX

Part II:

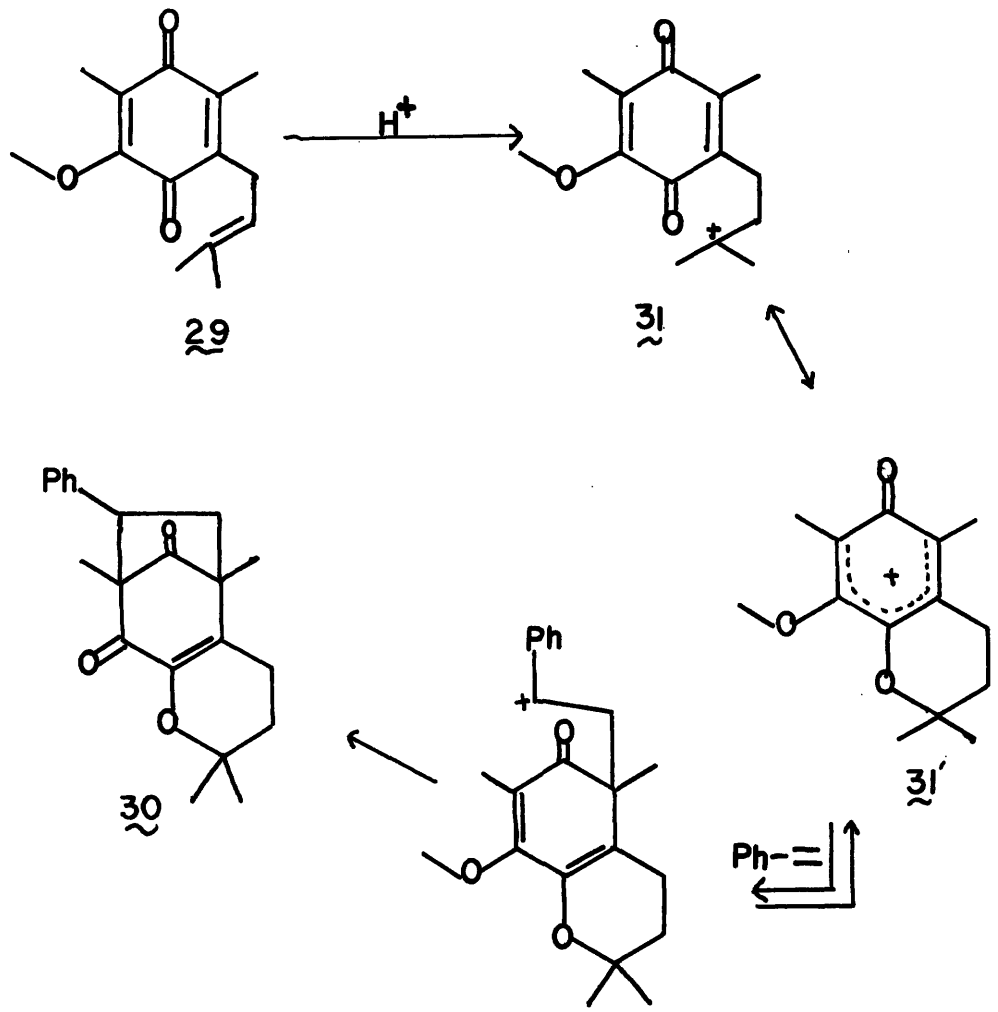
In our previous approach using the hydroxyquinone, we have attempted to generate the reactive soecies 8b' which could react with the olefin. Apparently, 8b was too unstable so that 8b' was not the major contributing structure. (Scheme XXI) We now decided to examine the possibility of generating a cationic species similar to 8b" (and C, in the perezone-pipitzols rearrangement) via a different route.



Scheme XXI

In acid-catalyzed cyclization studies with styrene (28) and various quinones such as 29, Mamont[33] has observed the formation of a tricyclic adduct 30. He suggested that a cationic intermediate such as 31 might be important and would make it highly electrophilic. (Scheme XXII)

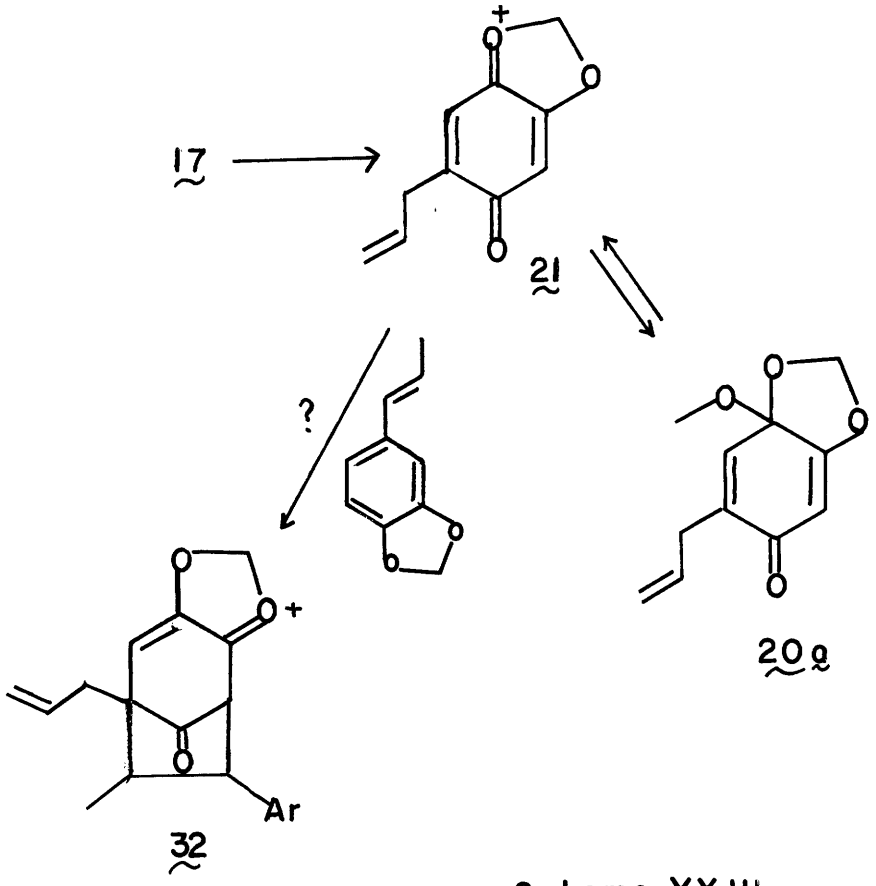
In the oxidation of phenol 17 with DDQ, we proposed oxonium ion 21 to be the oxidized product which was then captured by the solvent to give the observed product 20a. It was then our hope that if the olefin were used in an unreactive solvent, the cation could be captured to form the



Scheme XXII

bicyclic adduct 32. (Scheme XXIII) Phenol 17 was treated with DDQ in benzene in the presence of isosafrole (5) under various conditions. Complex mixtures were produced and it was not possible to isolate and identify any pure products. This may be due to polymerization of both the phenol and the olefin under the reaction conditions.

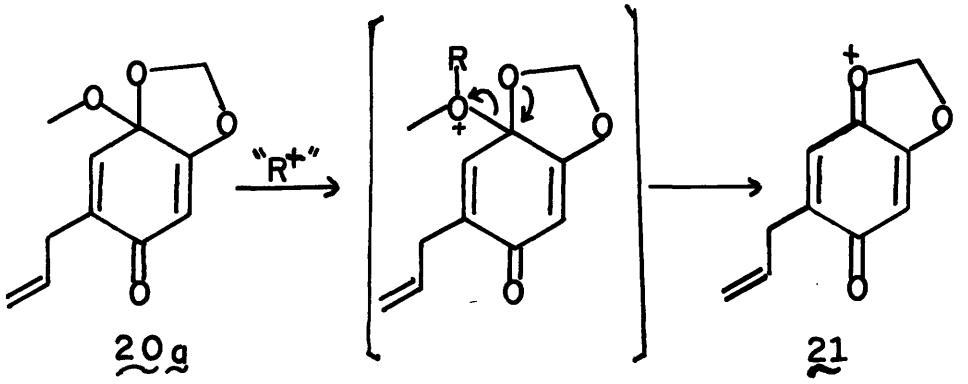
In order to circumvent this problem, we decided to



Scheme XXIII

prepare the cation 21 by a non-oxidizing route. Quinone ketal 20a appeared to be the obvious choice because displacement of an alcohol under appropiate acidic condition should lead to 21, although there was also the danger of converting it to the corresponding quinone! Since the latter was observed with the use of strong mineral acid in a protic solvent, a Lewis acid was first chosen to generate the required intermediate 21. Triethyloxonium fluoroborate

(Meerwein's salt) has been used in alkylation of alcohol phenols and ethers.[34] Ethylation of 20a at the oxygen bearing the methyl group should produce ethylmethyl ether and the oxonium ion 21. (Scheme XXIV)

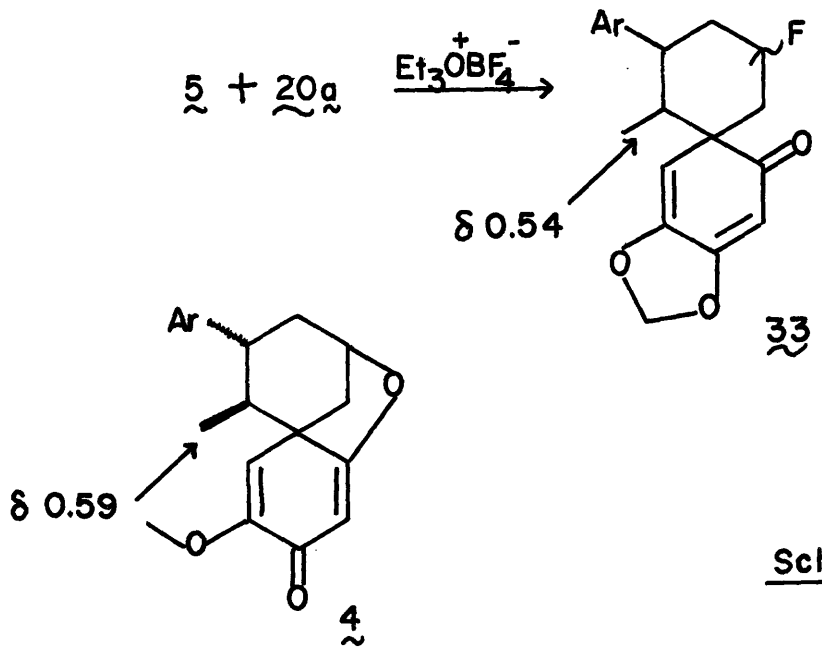


20g 21

Scheme XXIV

When quinone ketal 20a and isosafrole (5) was treated with excess triethyloxonium fluoroborate in CH_2Cl_2, and followed by basic work-up, a white crystalline product was obtained after chromatography in 60-70% Yield. Both melting-point and ^1H NMR indicated that it consisted of a mixture of products, which were not separable by chromatography. High resolution mass spectrometry gave a molecular ion of 358.12575 with a rapid loss of twenty mass-units. This was indicative of a monofluorinated compound and suggested a molecular composition of $C_{20}H_{19}O_5F$. ^1H NMR showed two distinct features: firstly, the allyl group from the quinone ketal had disappeared and there were additional aliphatic protons; secondly, a set of methyl doublets appeared at

exceedingly high field (δ0.54). Based on comparison with the spectrum of futoenone (4), which has a spiro[5.5]undecane skeleton,[6] we proposed the tentative structure 33 for this compound. (Scheme XXV)

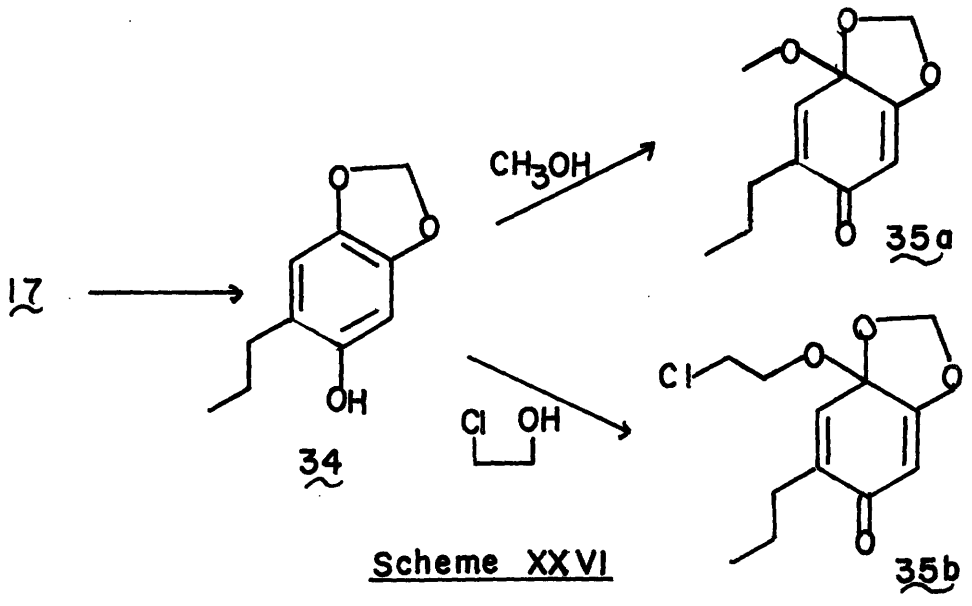


Scheme XXV

The secondary methyl signal of futoenone also appeared at rather high field (δ0.59) because of its orientation with respect to the dienone ring. The carbonyl absorption of 33 in the infrared region appeared at 1625 cm^{-1}, and this would be consistent with the proposed structure. Obviously, the allyl group was involved in the condensation of the two moieties; fluorine, which could come from BF_4^-, was incorporated into the molecule. In order to provide insight into the mechanism for the formation of 33, it was decided to study the condensation of isosafrole (5) with a quinone

ketal that lacks an allyl group.

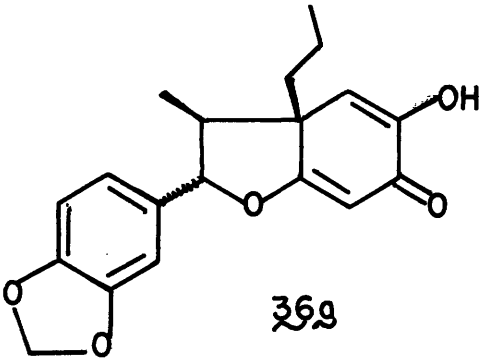
Hydrogenation of phenol 17 over Pd/C gave a quantitative yield of the n-propyl phenol 34, which on treatment with DDQ in methanol gave the corresponding methoxy quinone ketal 35a in 86% yield as a low melting white crystalline solid. The two protons from the methylenedioxy group appeared as clean singlets as expected. (Scheme XXVI)



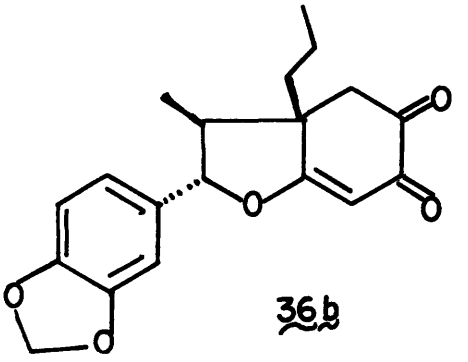
Scheme XXVI

Condensation of 35a with isosafrole at room temperature in the presence of Meerwein's salt or the reaction of the chloroethoxyquinone ketal 35b with isosafrole catalyzed by silver fluoroborate produced, after chromatography on silica gel, a major fraction, which crystallized eventually. Both NMR and IR supported the presence two compounds; however, the mixture gave a homogenous spot on TLC in various solvent systems. The two compounds were finally separated

by fractional recrystallization. Based upon spectroscopic and chemical properties, the two compounds were shown to be 36a and 36b, which are a pair of enol-keto tautomers of the burchellin skeleton.[2]



36a



36b

The more soluble enol-form 36a (positive $FeCl_3$ test) exhibited prominent absorptions at 3400 (hydroxyl) and 1630 cm^{-1} (C = C and C = O)[36] in the infrared region, which were consistent with a cross-conjugated cyclohexadienone structure. The 60 MHz NMR spectrum of this compound displayed a doublet (J = 10 Hz) at δ5.18 and this was assigned to the proton at C-2 (the corresponding signal appeared at δ5.17, J = 9.5 Hz in natural burchellin). Two vinyl protons appeared as singlets, one at δ5.71 and the other at δ5.84, suggested the presence of the dienone ring. In contrast to the enol, the keto-form 36b showed absorptions at 1730 cm^{-1} (α-diketone), 1665 cm^{-1} (C = O of vinylogous

ester) and 1620 cm^{-1} (C = C of vinylogous ester) in the carbonyl region of its infrared spectrum. The two methylene protons at C-4 appeared as an AB quartet (δ2.66 and 3.02, J = 16 Hz). Only one vinyl proton at δ6.10 was present in the molecule.

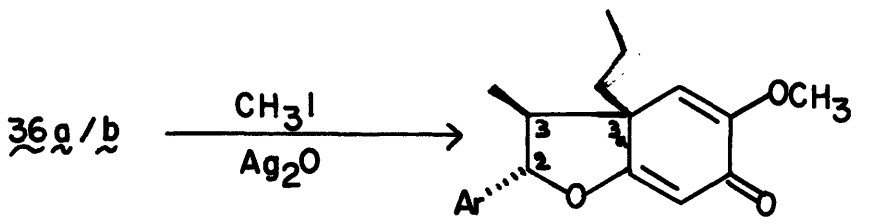
When 36b was treated with methanolic potassium hydroxide for 6 h, acidified, and then extracted with CH_2Cl_2, ^1H NMR of the crude extract showed a complete conversion to the tautomeric enol 36a. However, on purification by silica gel chromatography, a 3:1 (36a:36b) mixture was again obtained (NMR measurement). The interconversion of 36a and 36b could also be followed by their ultraviolet spectra. (Table 3)

Table 3

	95% EtOH nm(ε)	1N HCl	1N NaOH nm(ε)	Reacidification/nm(ε)
Enol 36a	261(15,500)	no	234(24,500)	original
	287(10,700)	change	272(22,400)	spectrum
Keto 36b	240(6950)	no	235(20,200)	261(16,100)
	292(14,500)	change	272(18,900)	287(10,000)

Under basic conditions, both 36a and 36b were converted to an identical intermediate which on reacidification gave the enol form. Their relationship was finally confirmed when they were converted to the corresponding methyl ether 37. Initial attempts using dimethyl sulfate, methyl iodide or trimethyloxonium fluoroborate[37] under various conditions

gave only recovered starting material. However, treatment of the tautomeric mixture with methyl iodide and silver(I) oxide in dimethylformamide provided dihydroburchellin (37) in 63% yield. (Scheme XXVI) Except for the absence of signal associated with the allyl group in the ^{1}H NMR, all other pertinent spectroscopic properties were almost identical with those of burchellin (2).



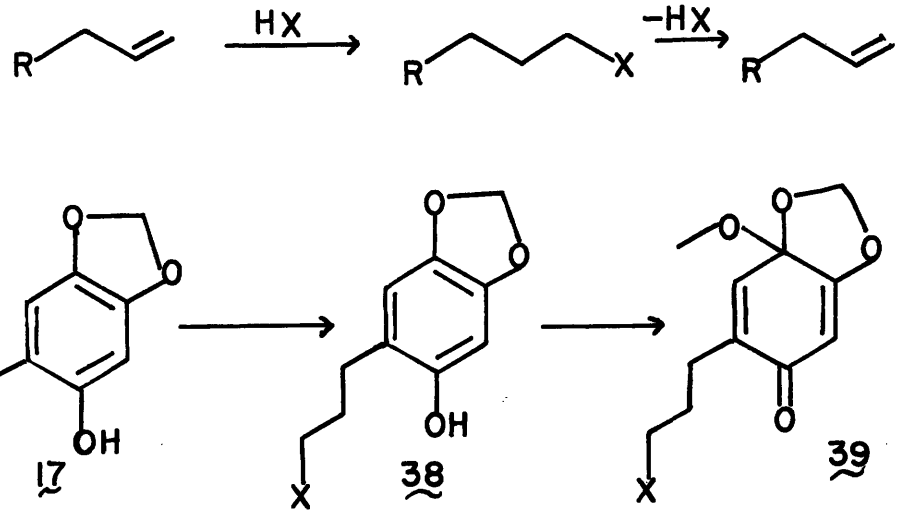
37

Scheme XXVI

The stereochemistry at C-2 and C-3 was assigned as shown (α-aryl, β-methyl) by virtue of the resemblances of the ^{1}H NMR spectra (almost identical chemical shifts and coupling constants with those of the natural product). Stereochemistry at C-3a was only tentatively assigned at this point because of the lack of the allyl group. The chemical shift of the methylene protons in the allyl function is characteristic of the relative stereochemical environment.[3]

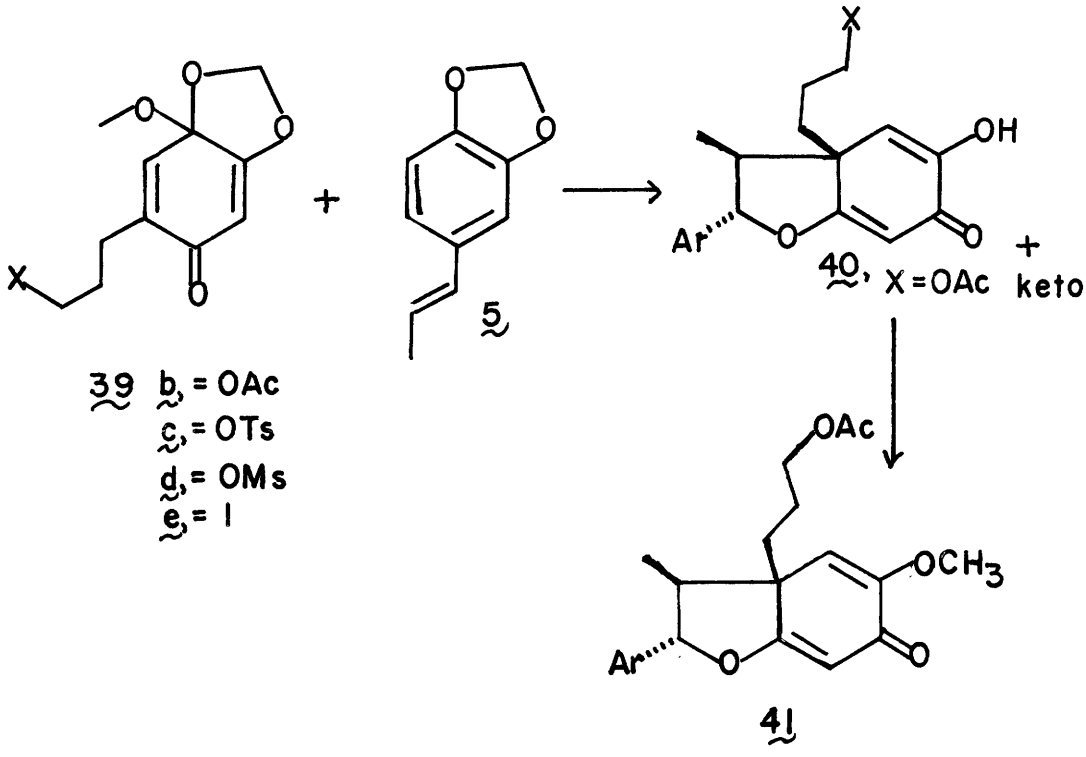
Clearly, the methodology involved in this approach to burchellin was feasible if the double bond in the allyl function were protected during the condensation reaction and then regenerated at a later stage. Numerous methods

exist in the literature for such purposes, but we chose to transform the double bond into an alkyl group bearing a leaving group such that the double bond can be regenarated via ∝-elimination. (Scheme XXVII)



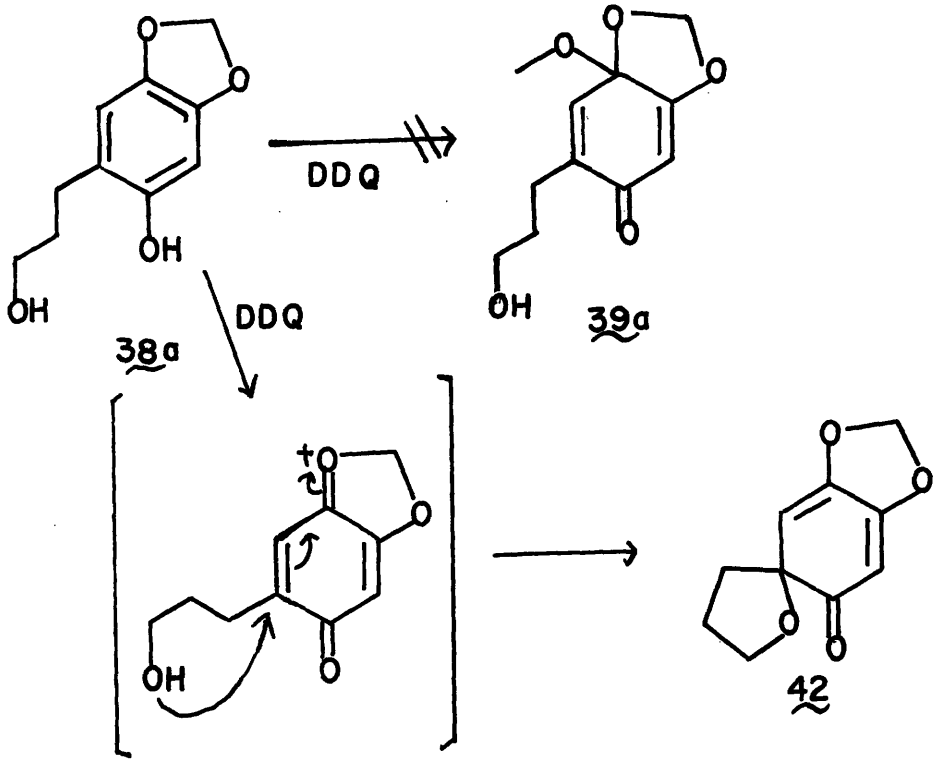
Phenol 38 was chosen for obvious reasons in this sequence. Hydroboration of phenol 17 with diborane-tetrahydrofuran complex followed by oxidative work-up[38] gave a 9:1 mixture of primary alcohol and secondary alcohol in quantitative yield. The desired primary alcohol 38a (X = OH) could be separated easily as the major component by crystallization and chromatography. Attempts to prepare the primary mesylate and tosylate proved to be difficult because we encountered formation of di-ester and in some cases ether formation due to cyclization of the initially formed monoester. Acetylation of 38a with excess pyridine and acetic anhydride gave the diacetate in 90% yield and it was possible to selectively hydrolyse the phenol acetate in

aqueous methanol with $KHCO_3$, to form the monoacetate 38b (X = OAc). Oxidation with DDQ under the usual conditions gave the corresponding quinone ketal 39b (X = OAc) and on treatment with isosafrole in the presence of Meerwein's salt, acetate 40 (enol-keto mixture) was isolated in 61% yield after chromatography. The methyl ether 41 was prepared as usual with methyl iodide and silver oxide. (Scheme XXVIII)



No attempts were made to convert the acetate to burchellin (2) because pyrolysis at high temperature is usually necessary to convert a primary acetate to an olefin.[39] However, this sequence of experiments had certainly demonstrated

the compatibility of a protected double bond in the quinone ketal under the acidic conditions. Also, it was necessary to have a protected alcohol during the oxidation because treatment of diol 38a with DDQ under the usual conditions, gave spiro-ether 42 in low yield, along with numerous unidentified products. The initially formed carbonium ion was captured intramolecularly instead of by methanol.[40] (Scheme XXIX)

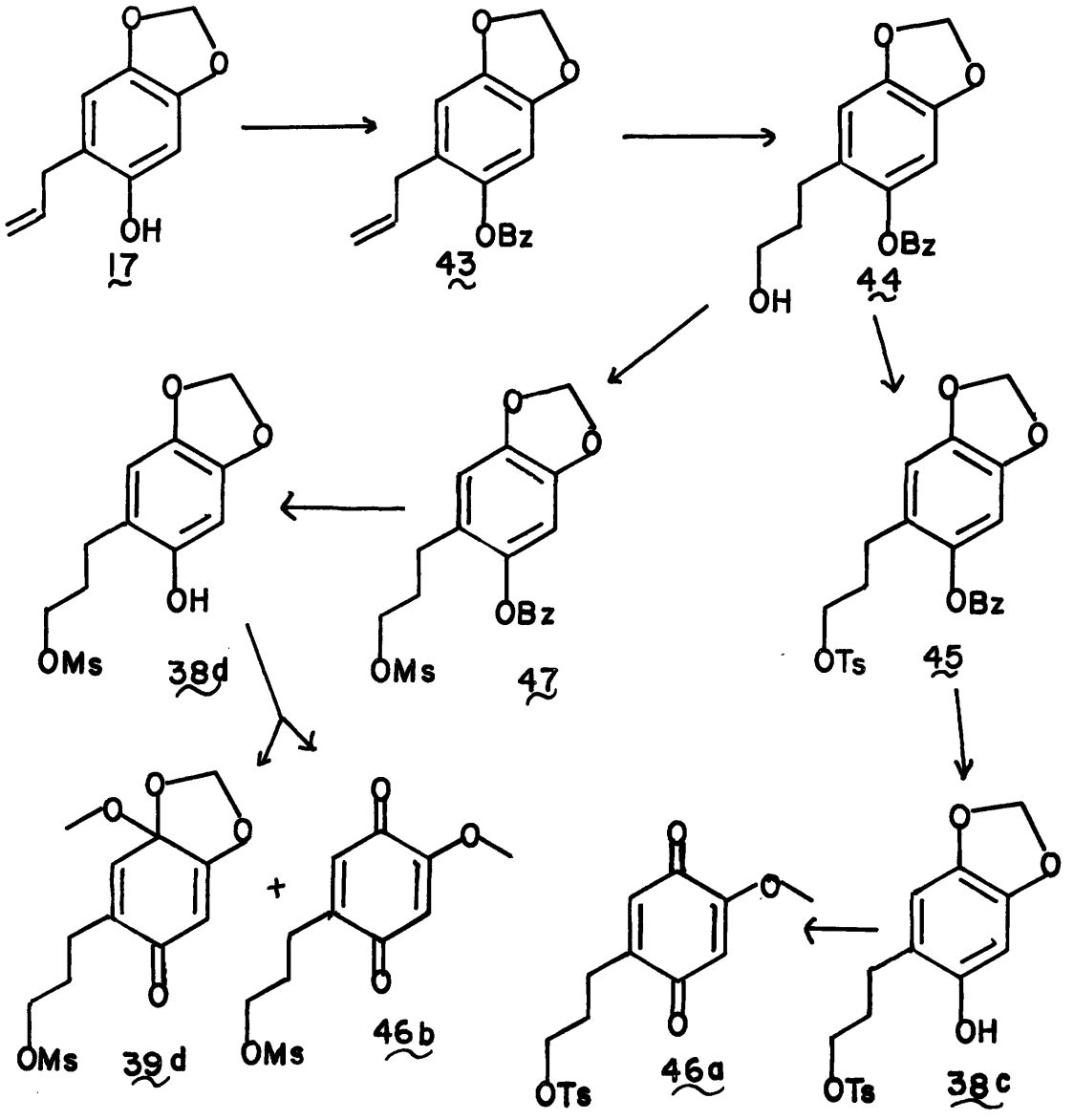


In order to obtain the desired tosylate 38c and mesylate 38d more efficiently, it became apparent that the phenol had to be protected before the hydroboration. Thus, reaction of

phenol 17 with benzyl bromide under standard conditions gave the benzyl ether 43 in 88% yield, which on application of the hydroboration procedure[39] gave a 98% yield of two alcohols (93:7,1°:2°). The desired primary alcohol 44 was obtained in excellent yield by recrystallization. Tosylation was achieved with p-toluenesulfonyl chloride in pyridine and the oily tosylate 45 was hydrogenated over Pd/C to provide the unstable phenol 38c. Unforturnately, no desired quinone ketal 39c was isolated when 38c was treated with DDQ in methanol. Decomposition occurred on silica gel when attempts were made to separate the quinone ketal from the methoxyquinone 46a, which was isolated in 31% yield. The methoxyquinone also decomposed quite rapidly, even when stored in a refrigerator.

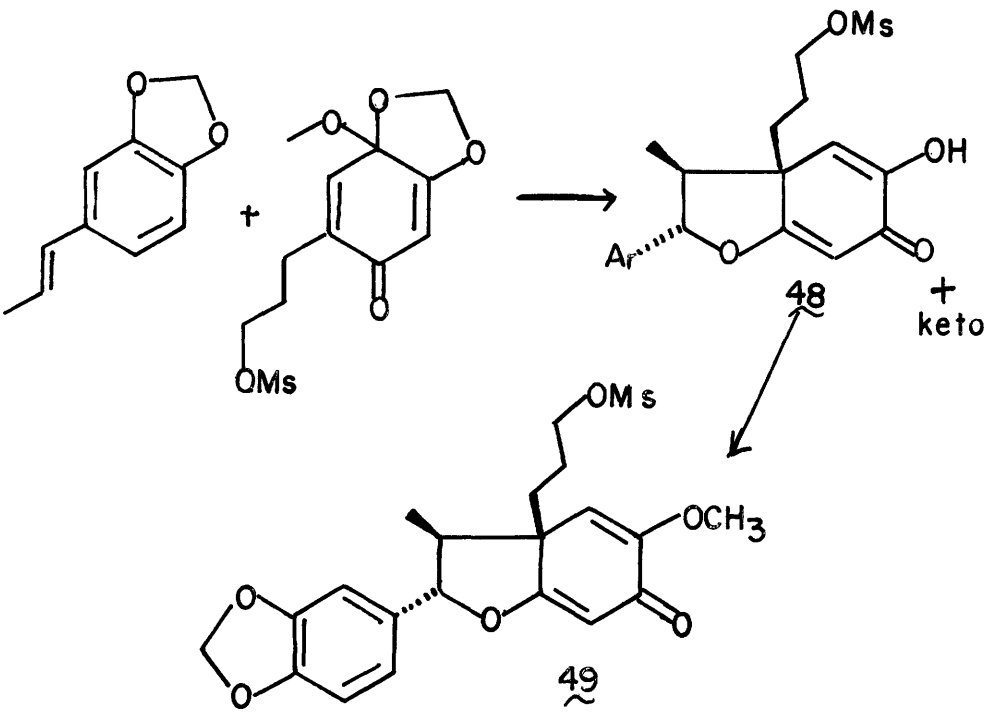
Next, we turned our attention to the mesylate. The alcohol 44 was converted to the crystalline mesylate 47 in 90% with pyridine and methanesulfonyl chloride at 0°C. Removal of the benzyl group gave the phenol 38d in quantitative yield. It was more stable than the corresponding tosylate and highly crystalline. Conversion to the quinone ketal 39d took place under the usual conditions and it was isolated in 78% yield after purification by chromatography. Although it was apparently more stable than the corresponding tosylate, the compound slowly darkens on storage and was usually used immediately without further purification. The more polar methoxyquinone 46b was obtained in 10% yield

as bright yellow crystals. (Scheme XXX)



Reaction of isosafrole (5) with the quinone ketal 39d under the same condition afforded the expected dihydrobenzofuranone 48 in 62% yield as a mixture of enol-keto tautomers. When the reaction was done in more than 10 mmol

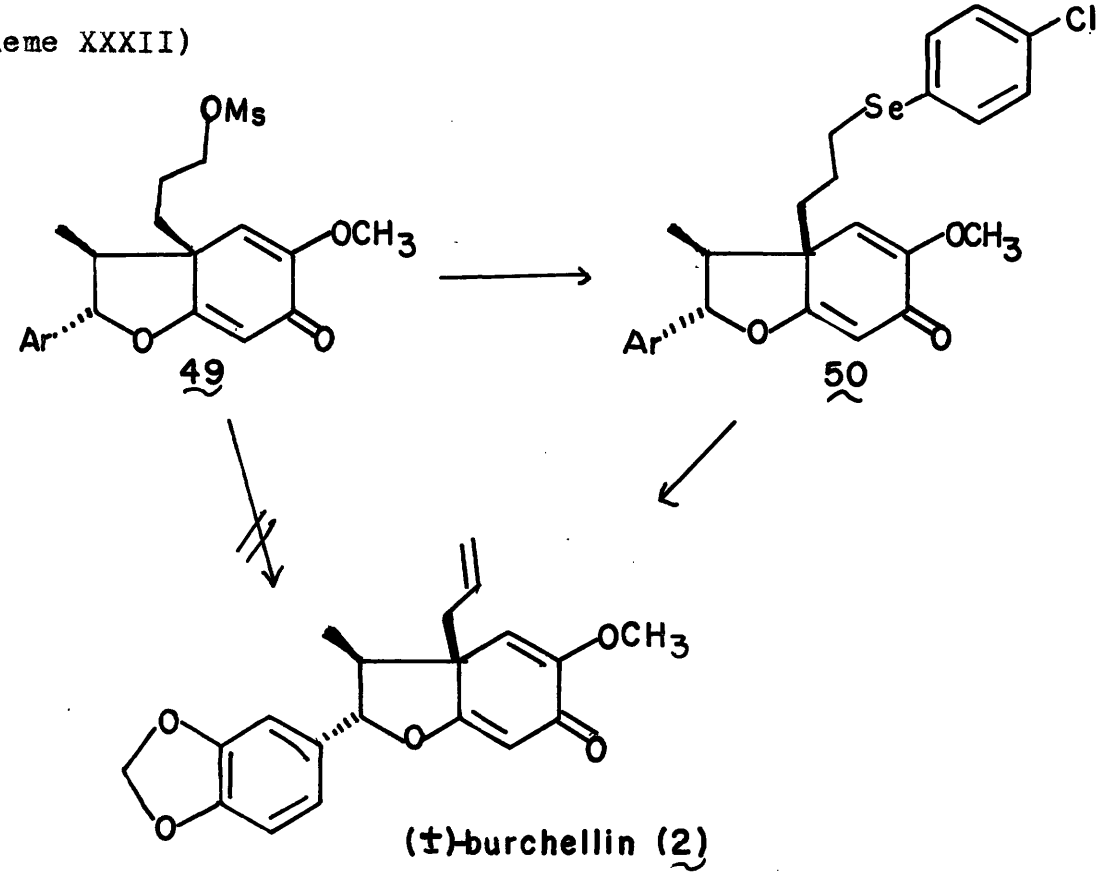
scale, a compound which corresponded to the 2,3-cis isomer was observed in less than 2% yield, noticeable by the appearance of the upfield secondary methyl peaks in the ^{1}H NMR spectrum.[3] However, owing to insufficient quantities available at the time, no further experiments were performed on this compound.[41]



Scheme XXXI

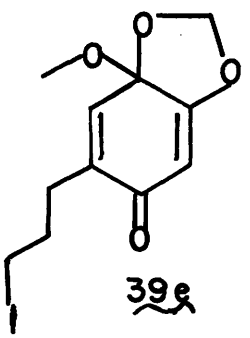
The enol-keto mixture was methylated to give methyl ether 49. At this point, it was only necessary to eliminate the mesylate to regenerate the allyl double bond. Various attempts at base-catalysed elimination resulted in decomposition of 49. Finally we decided to displace the mesylate with selenide and elimination via the selenoxide.[42] In view

of the known difficulties encountered in the elimination of primary selenoxides,[43] p-chlorophenyl selenide 50 was prepared according to the procedure of Sharpless.[42] Treatment of 50 with sodium metaperiodate in aqueous methanol at 70°C gave racemic burchellin (2) in an overall yield of 85% from the mesylate. Ultraviolet, infrared, and NMR spectra of racemic burchellin (2) were identical with those of natural material and identity was confirmed by chromatographic comparision and high resolution mass spectroscopy. (Scheme XXXII)

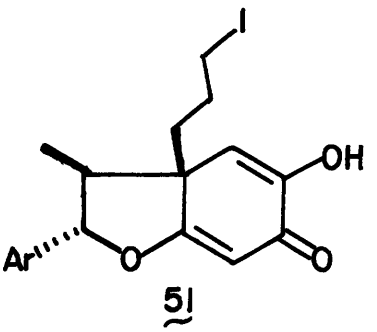


Scheme XXXII

During our investigation into the methods for the regeneration of the allyl group, iodide 51 was prepared from tosylate 38c via the quinone ketal 39e in 39% overall yield. When 51 was treated with the usual methylation conditions, only a low yield of the expected methyl ether 52 was obtained, together with the isolation of faintly yellow-colored tricyclic diketone 53 in trace quantities. However, when 51 was treated with 1,5-diazabicyclo[4.3.0]non-5-ene(DBN) in THF, a nearly quantitative amount of 53 was obtained. This undoubtedly arose from the facile base-catalyzed intramolecular cyclization of 51. This approach towards burchellin (2) was therefore quickly abandoned.



39e



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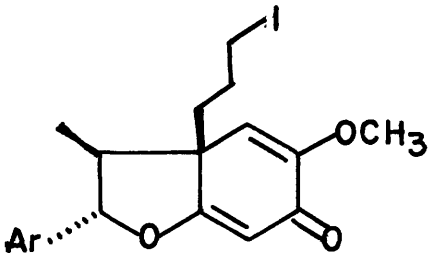

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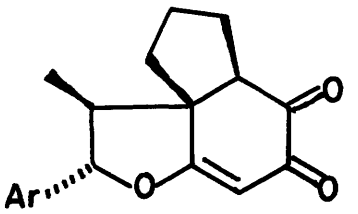
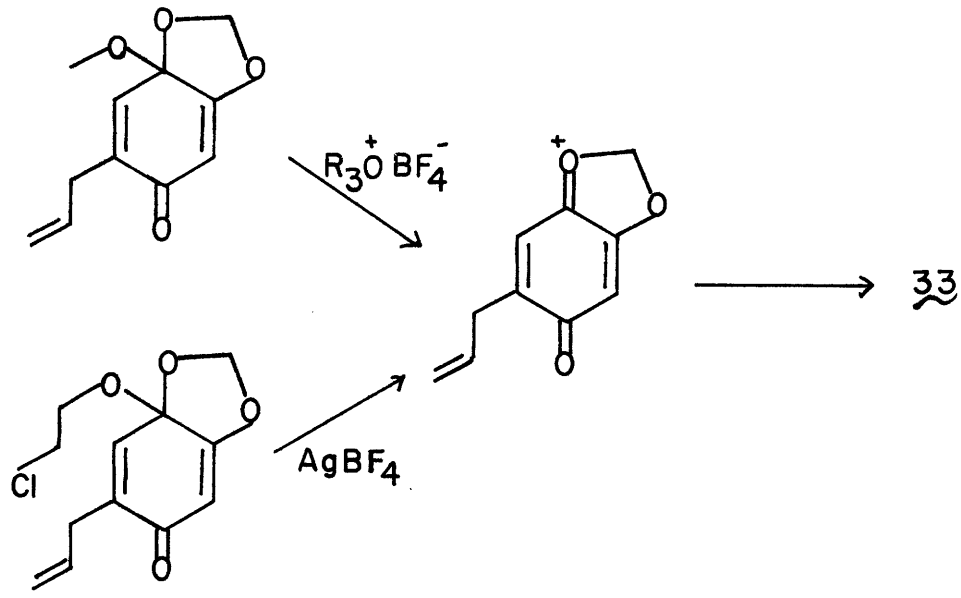


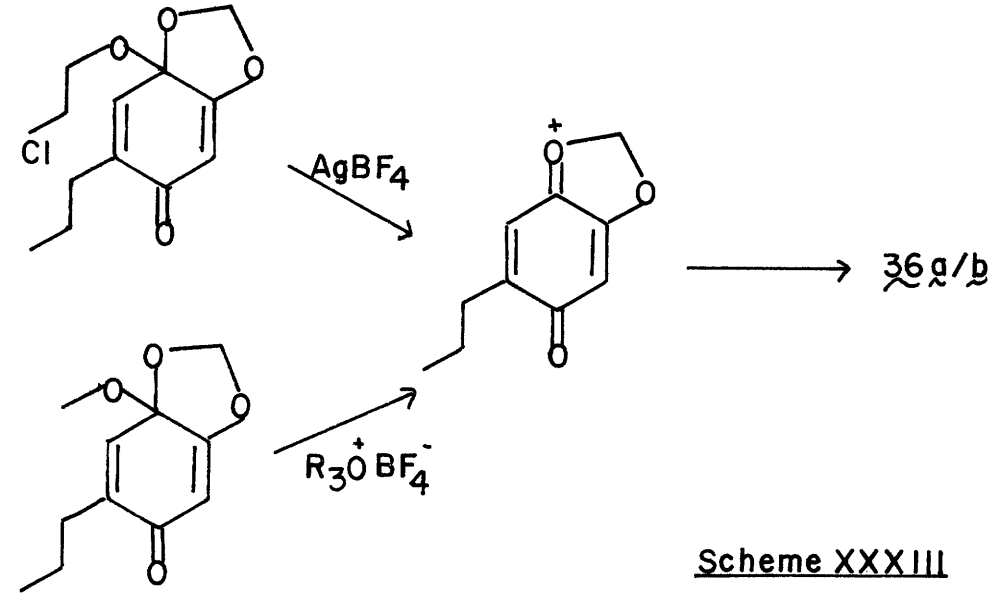
53

To account for the formation fo the two different condensation products, namely, the fluorinated spiro-cyclohexadienone 33, and the dihydrobenzofuranone 36a/b, rather than products drived directly from the hydrolysis of the bicyclo adduct 32, we assumed that all reactions were initiated by a concerted cycloaddition of ion 21 to olefin 5, leading to the adduct 32 first, with endo-oriented aryl groups. (Scheme XXXV)

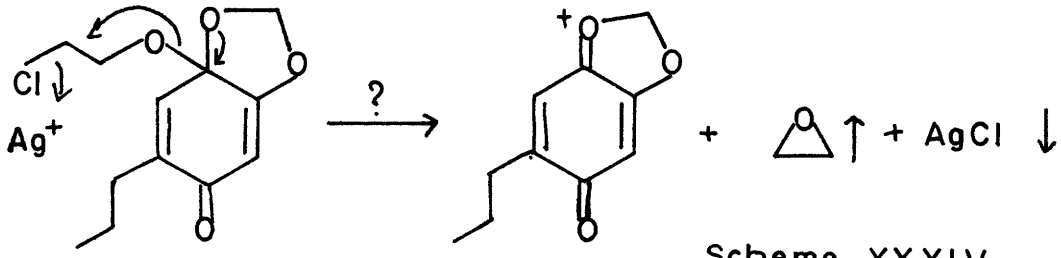
The intermediacy of ion 21, first proposed in the oxidation of the phenol to the corresponding quinone ketal, was apparent in the condensations using Meerwein's salt. Its presence was further indicated when similar condensation products were obtained using quinone ketal 20b or 35b and silver fluoroborate instead. (Scheme XXXIII)

In the latter case, reaction with silver fluoroborate probably gave silver choride first, followed by extrusion of ethylene oxide to produce the same oxonium ion 21 as generated by Meerwein's reagent.[44] (Scheme XXXIV) The oxonium ion thus formed reacted with the olefin to give the bicycloadduct 32, which rearranged to the more extensively delocalized isomer 55 (R = alkyl) which on hydrolysis would lead to the observed product 36a/b or 48/49. Cation 54, probably an intermediate between 32 and 55, might also cyclize further to 56 (participation of the allyl function) to provide the spiro-fluoride 33. The origin of fluorine probably derives from the decomposition of the fluoroborate

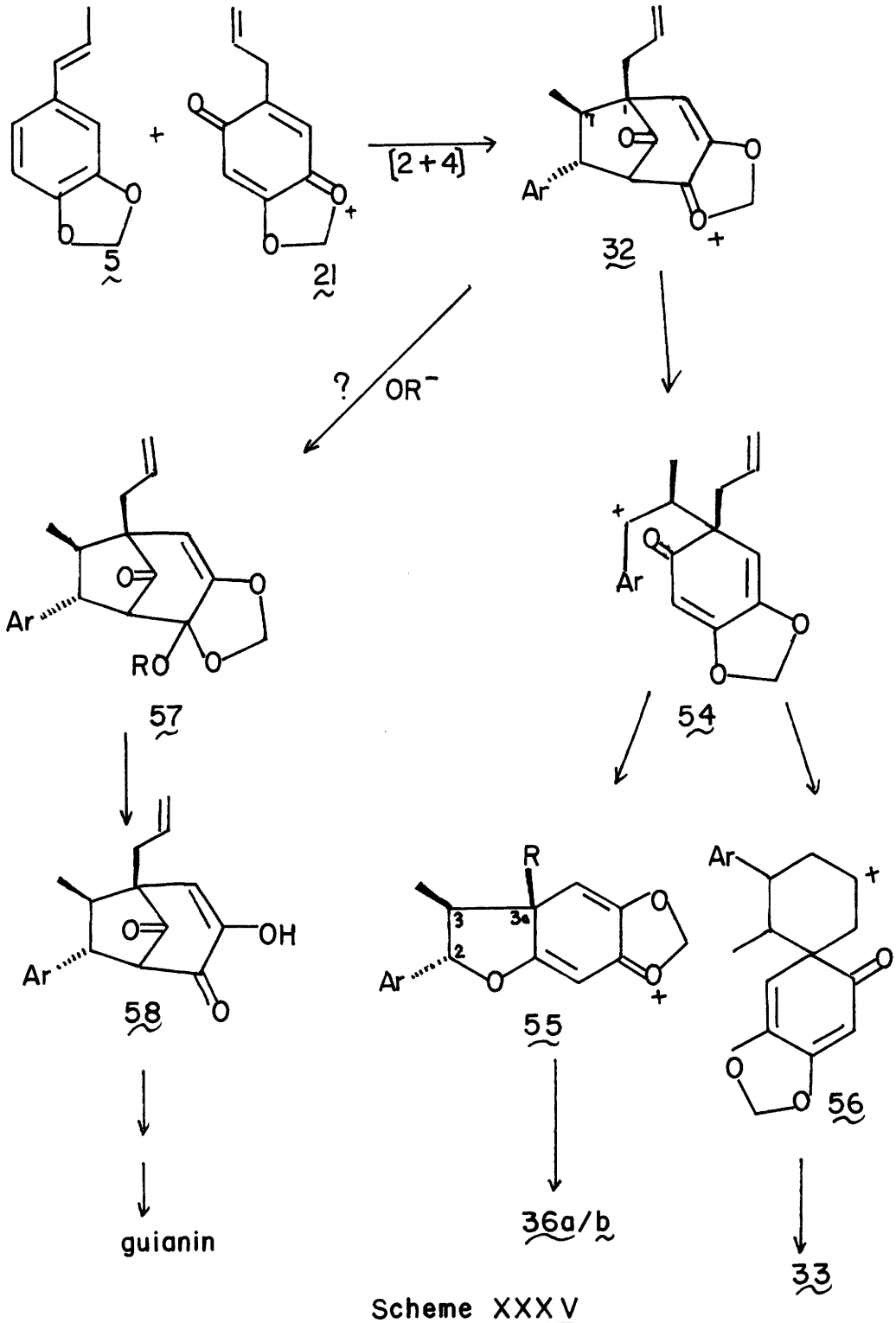




Scheme XXXIII



Scheme XXXIV



Scheme XXXV

anion. Therefore in the presence of the allyl function, fluoride 33 was the only observed product, whereas when the allyl group was blocked, the dihydrobenzofuranone was observed.

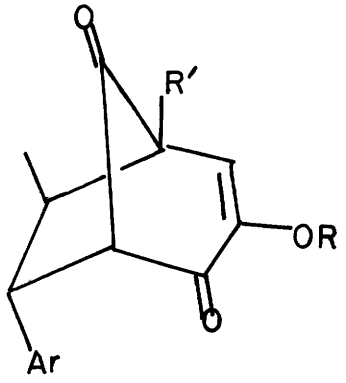
The relative stereochemistry at C-3 and C-3a of 36a/b was found to be cis. A concerted endo-attack of the trans-olefin should give the relative stereochemistry in 32 as indicated. However, the subsequent isomerization of 32 to 55 or 56 will not affect the outcome of the relative configuration of the two chiral centers at C-1 and C-7 of 32. During this rearrangement, the aryl substituent remained trans to the methyl group because an axial oriented alkyl substituent at C-3a (36a/b) would interact unfavorably with the aryl group if it were cis and axial.

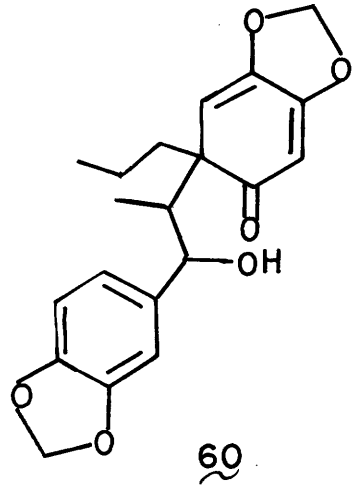
If, on the other hand, oxonium ion 32 can be trapped by some nucleophile such as an alcohol or water, a mixed ketal 57 may be formed and rearrangement to 54 might be blocked. Upon hydrolysis, the desired bicyclooctanone 58 would be formed. Under the reaction conditions using Meerwein's salts or silver fluoroborate, no good nucleophile was formed (presumably, dimethyl or ethylmethyl ether or ethylene oxide were formed). The use of a protic acid would thus seem to be appropiate for this purpose. In addition to the generation of the reactive intermediate 21, one

equivalent of methanol would be formed from quinone ketal 20a, which would serve to trap oxonium ion 32.

p-Toluenesulfonic acid was chosen as the catalyst. Unforturnately, when quinone ketal 20a and isosafrole (5) were treated with one equivalent of TsOH in CH_2Cl_2 or CH_3CN, no reaction occurred even after one day at room temperature, except for slight decomposition of the quinone ketal. However, when propyl quinone ketal 35a was treated under similar conditions, a mixture of three crystalline products were isolated. As expected, bicyclooctanone 59 was produced in 28% yield. This was characterized by the presence of a carbonyl absorption at 1760 cm^{-1}, resulting from the strained cyclopentanone. In contrast to the isomeric dihydrobenzofuranone 36, it exists exclusively in the diosphenol form; (no α-diketone features were seen in IR or NMR spectra) on methylation under the usual conditions it gave the enol ether 61 in 76% yield. The familar dihydrobenzofuranones 36a/b were also isolated as the enol-keto mixture in 25% yield, together with a new product bearing a secondary alcohol function. Structure 60 was assigned based on spectroscopic evidence. This compound would then correspond to the capture of carbonium ion 54 by water, thereby supporting the existence of such a species in the rearrangement from 32 to 55. (Scheme XXXV)

Its identity and intermediacy was further proven when it was converted quantitatively to 36a/b in the presence of





60

58, R = H; R' = allyl

59, R = H; R' = propyl

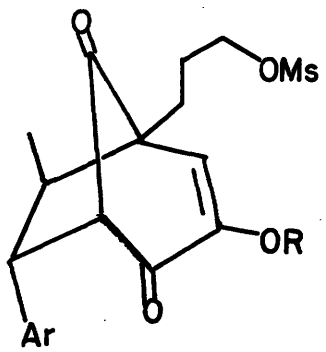
61, R = CH_3; R' = propyl

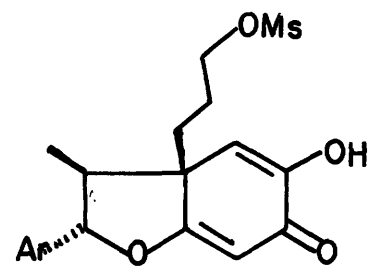
70, R = CH_3; R' = allyl

TsOH. The bicyclooctanone 59 was stable under the conditions used for its generation but on treatment with trifluoromethanesulfonic acid in acetonitrile resulted in quantitative conversion to the enol-keto mixture of 36a/b. The latter mixture decomposed gradually on prolonged exposure to the strong acidic medium. These results demonstrated that the dihydrobenzofuranones are more stable than the bicyclooctanones.

Having established conditions to prepare the bicyclooctane skeleton, the synthesis of guianin proceeded smoothly using the mesylate-quinone ketal 39d. Condensation of 39d with isosafrole (5) promoted by TsOH gave two major products after column chromatography. The less polar material proved to be mesylate 62 while the other compound was identical with

the previously prepared enol-keto mixture 48. Methylation of 62 with Ag_2O/DMF/MeI gave the methyl ether 63 in moderate yield. Both mesylates 62 and 63 were found to be sensitive





48

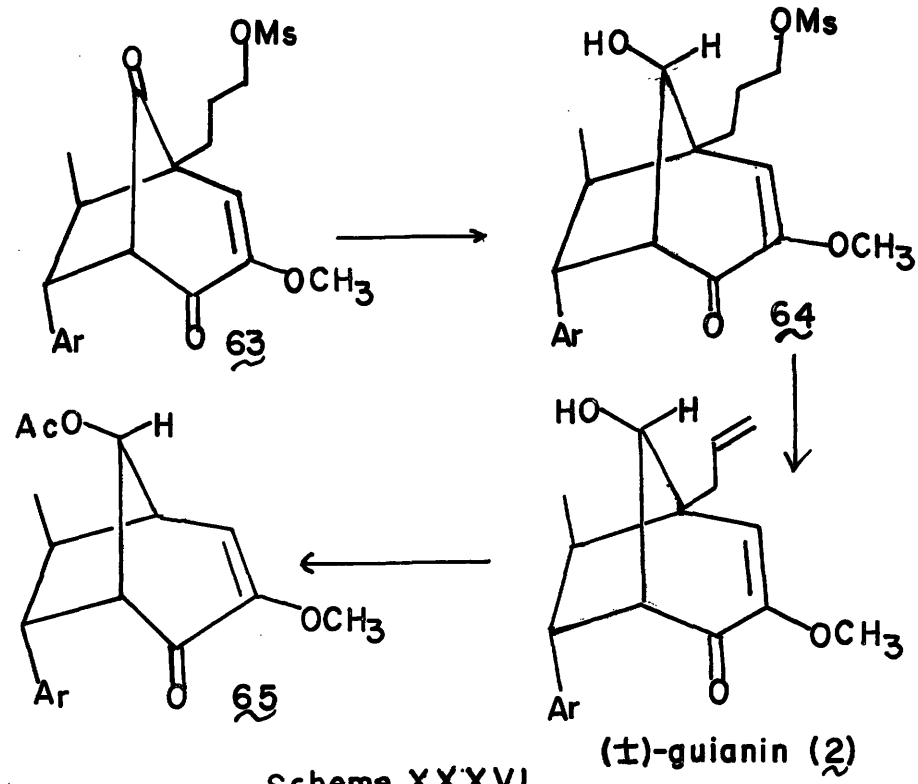
62, R = H

63, R = CH_3

to silica gel. In order to avoid much decomposition, the crude mixture from the condensation was filtered through a short column of silica gel to remove unreacted isosafrole and base-line materials. This crude filtrate was methylated without further purification, under the usual conditions and the two methyl ethers were then separated by chromatography. Using this procedure, 63 could be obtained in an overall yield of 16%, while dihydrobenzofuranone 49 was obtained in 21% yield.

Sodium borohydride reduction of the adduct 63 gave an alcohol 64 and again without purification (chromatography also led to extensive loss of material) was subjected to the procedures developed for the synthesis of (±)- burchellin. After chromatography and crystallization, racemic guianin (1)

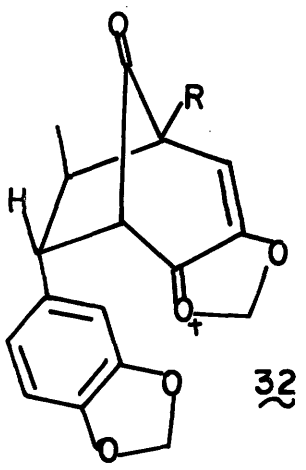
was obtained in an overall yield of 30% from methyl ether 63. (Scheme XXXVI) Ultraviolet, infrared, high-resolution mass spectrum and 270 MHz ^{1}H NMR spectra were indistinguishable from those of the natural material.



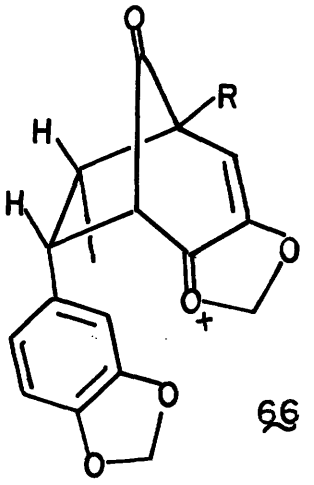
Scheme XXXVI

Acetate 65 was prepared by reacting synthetic guianin with excess acetic anhydride in pyridine. The benzylic proton experiences a diamagnetic shift from δ3.54 to δ3.42 (Δ0.12 ppm) in the ^{1}H NMR upon acetylation. This is only possible if the hydroxyl group is <u>syn</u> to the two-membered bridge as it is in the natural product.[3] Reduction of the ketone in 63 had proceeded stereoselectively as expected to give only the alcohol 64, probably due to steric hindrance from the other side.

Apart from the successful synthesis of guianin, an important observation was made during this sequence of reactions. Isasofrole (5) recovered from condensation was found to be enriched in the Z-isomer. Commercial isosafrole contains a 9:1 (E:Z) mixture and this was always used without prior separation. The recovered material was found to be a 1:1 mixture (glc). It was concluded that the E-isomer was more reactive. The concerted cycloaddition reaction leading to 66 with two endo-substituents is slower and less favorable than that resulting in 32 (E-isomer) with only one such destabilizing substituent.



32

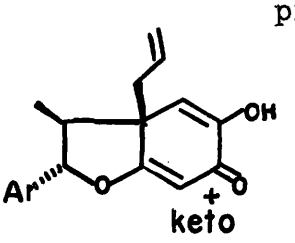
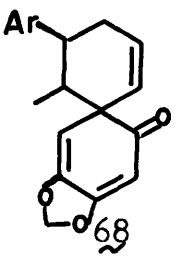


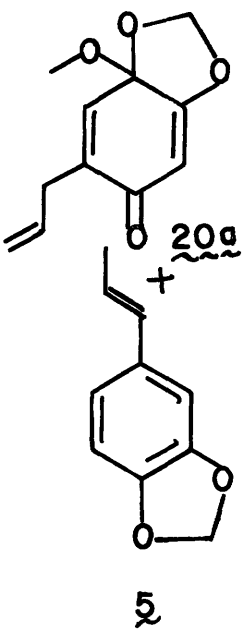
66

Although the syntheses of (±)-burchellin and (±)-guianin via the mesylate-quinone ketal 39d were instructive in the understanding of the mechanistic consideration involved in the construction of the ring systems, they suffered from the presence of many protection and deprotection react-

ions. The ideal solution would be the utilization of the allyl quinone ketal (20a or 20b) directly without interference from the allyl function. As noted earlier, 20a did not react with isosafrole to give any desired product. However, the conversion of 59 to 36a/b with a strong acid (CF_3SO_3H, see pg 60) prompted us to investigate its use as the condensation catalyst. The results are summarized in Table 4.

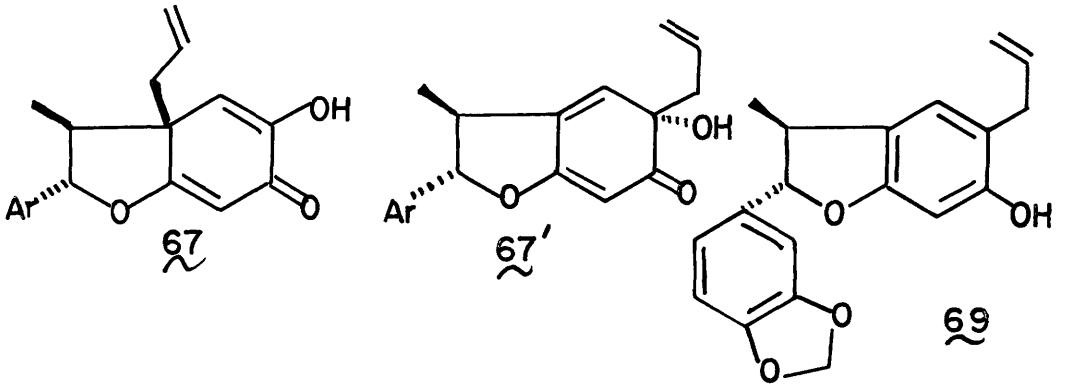
Table 4

Conditions	yield of products:  67	 68	others
TsOH; CH_3CN 25°C	--	--	starting material only
CF_3SO_3H; -70°C; CH_2Cl_2	31%	18%	20a (14%)
CF_3SO_3H; CH_3CN; -40°C	33%	3%	--
CF_3SO_3H; 0°C; CH_3CN	27%	2%	--
CF_3SO_3H; CH_3CN; 25°C	12%	8%	69 (10%)



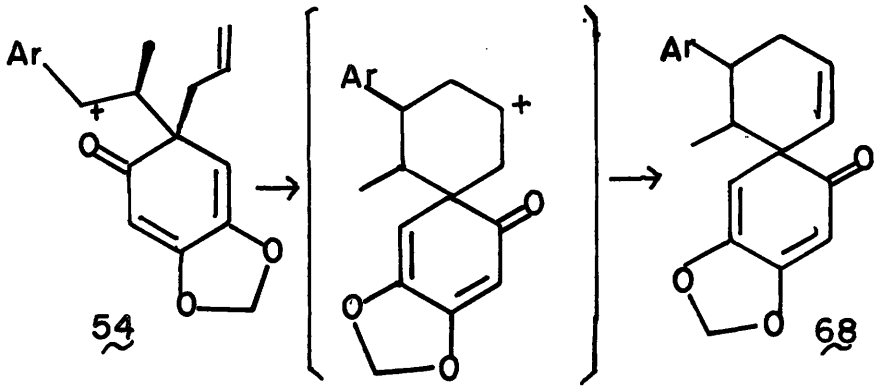
5

The desired dihydrobenzofuranone 67 was obtained in varying amounts with the best yields of products realized at lower temperatures. However, the reactivity of the quinone ketal also seems to be lowered. At higher temperatures, both starting materials and products tended to decompose more rapidly. This was manifested by the isolation of a small amount of the dihydrobenzofuran 69 when the reaction was carried out at room temperature. This compound evidently derived from the dihydrobenzofuranone 67, via perhaps, the Cope Rearrangement[46] product, followed by reduction.



The presence of the spiro-dienone 68 was not altogether surprising. Results from experiments using Meerwein's reagent indicated that the formation of the spiro [5.5] undecane skeleton to be quite facile. The structure of the fluorinated dienone 33 (mixture of diastereomers) was now confirmed, since the dienone 68 was isolated as a single product, and their relationship was easily seen on compari-

sion of their spectroscopic properties. The formation of 68 derived from the capture of benzyl cation 54 by the



Scheme XXXVII

allyl group to afford the secondary carbonium ion 56, followed by elimination of a proton to give the observed olefin. (Scheme XXXVII)

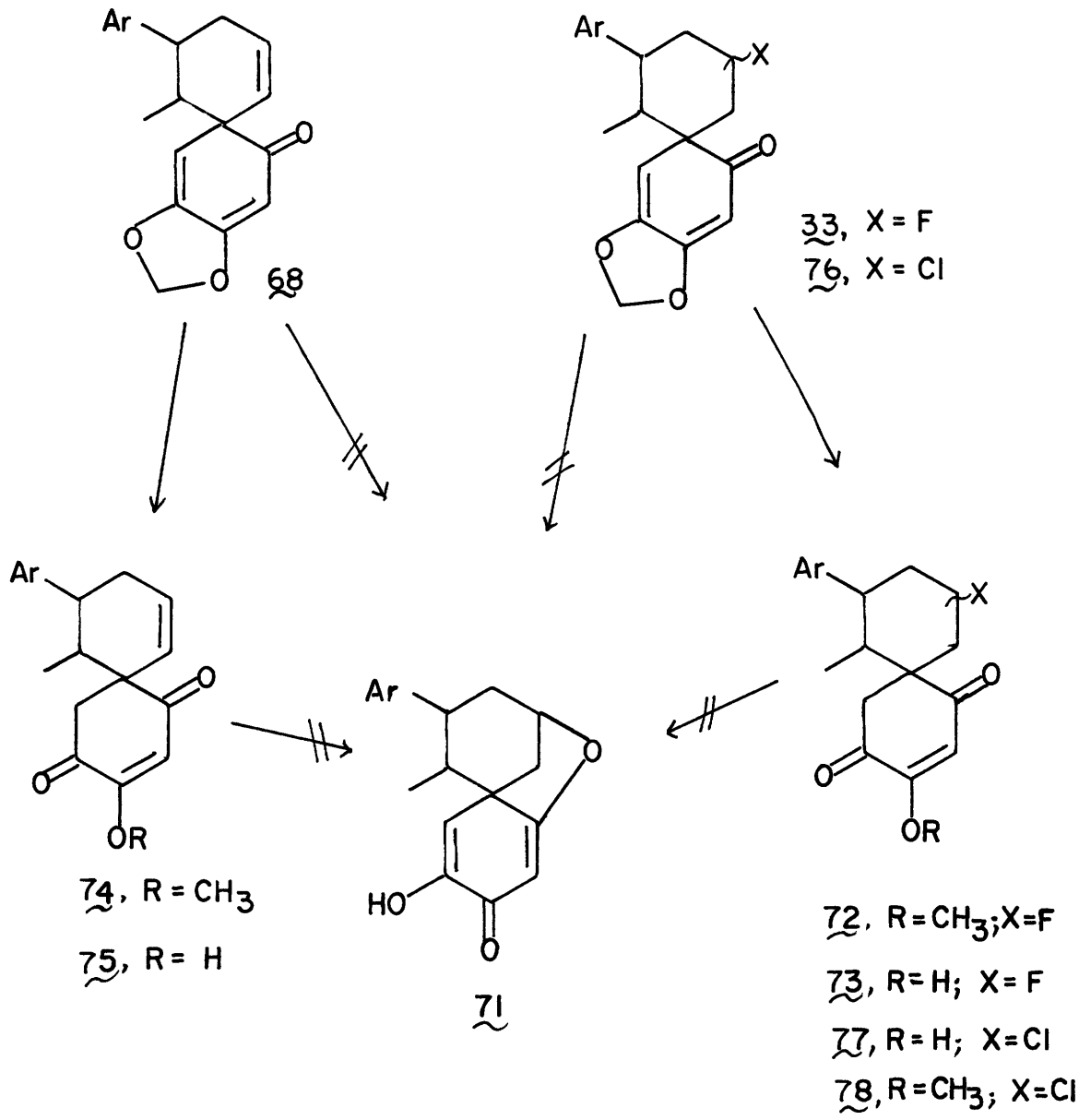
In this way, (±)-burchellin (2) was available from the quinone ketal in two steps, after silver(I) oxide promoted methylation of 67. Although the condensation products were obtained in relatively low yield (30-50%), it is a greatly improved synthesis because of the reduction of the number of steps involved. Moreover, it might provide another entry to the futoenone skeleton. We also felt that if a weaker acid were used (but strong enough to form the reactive species 21), the bicyclic adduct 58 should be stable for isolation.

When a mixture of quinone ketal 20a and isosafrole was treated with a catalytic amount of 2,4,6-trinitrobenzenesulfonic acid[47,48] in acetonitrile at 0°C, the bi-

cyclooctanone 58 was isolated in 20% yield after chromatography. In addition, dihydrobenzofuranone 67 (27%) and spiro-dienone 68 (trace) were also obtained. Accordingly, 58 was converted to its methyl ether 70[49] with trimethyloxonium fluoroborate and diisopropyl ethylamine in 90% yield and this on reduction with sodium borohydride gave 83% yield of racemic guianin (1), identical in all respects with previously prepared material.

Our attention was then focused upon the synthesis of futoenone (4). The availability of the two spiro derivatives, 33 and 68, gave us an opportunity to investigate the possible cyclization reaction to the tetrahydrofuran structure 71.(Scheme XXXVIII) Significantly, neither 33 nor 68, nor their respective derivatives, 72, 73, 74, and 75, prepared by basic treatment, could be cyclized to 71 under a variety of conditions. Even chlorides 76, obtained by condensation of quinone ketal 20a and isosafrole (5) with diethyloxonium hexachloroantimonate[50] in 47% yield, and the corresponding vinylogous acid 77 and ester 78, failed to provide the desired product.

A closer look into the mechanism of formation and inspection of molecular models immediately showed that all these spiro compounds prepared by the condensation with trans-isosafrole had the incorrect configurations at the spiro-carbon atom. Initial formation of the bicycloadduct 32 should leave the methyl and allyl group "cis". Rearran-



Scheme XXXVJII

gement to the intermediate benzyl cation 54 was then followed by capture of the carbonium ion to form the new C-C bond. (Scheme XXXIX) The approach of the allyl group could conceivably be directed via path A (back-side) or path B (front-side). Since the newly-formed six-membered ring was required to assume the more stable chair-configuration, then four different cationic species could be formed. Pertinent stereochemical features of each one are summarised in Table 5.

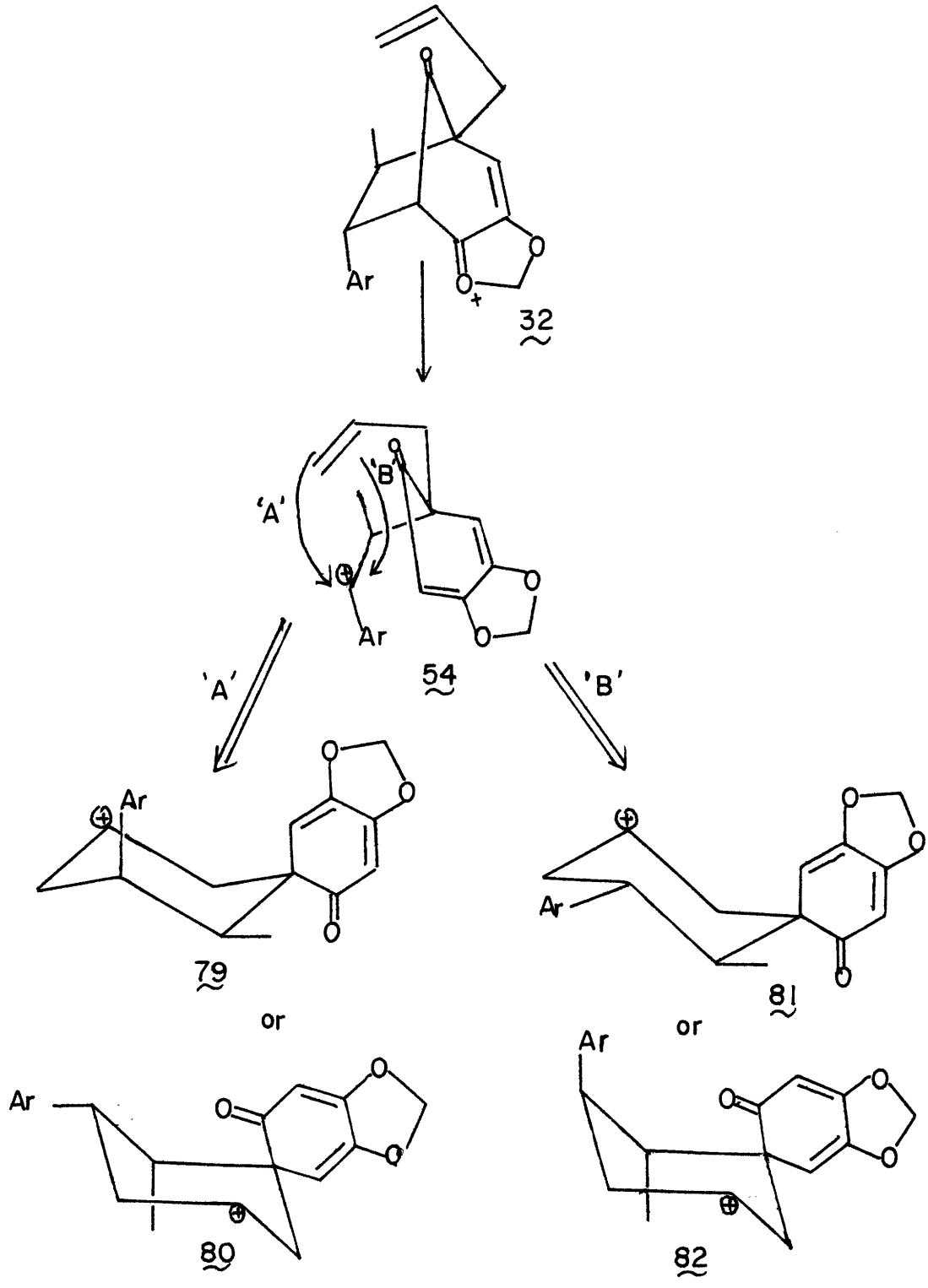
Table 5

	back side (A)		front side (B)	
	79	80	81	82
methyl group	equatorial	axial	equatorial	axial
aryl group	axial	equatorial	equatorial	axial
relative stereo-chemistry	cis	cis	trans	trans
methyl group shielded by dienone	yes	no	yes	no
tetrahydrofuran possible	no	yes	no	yes

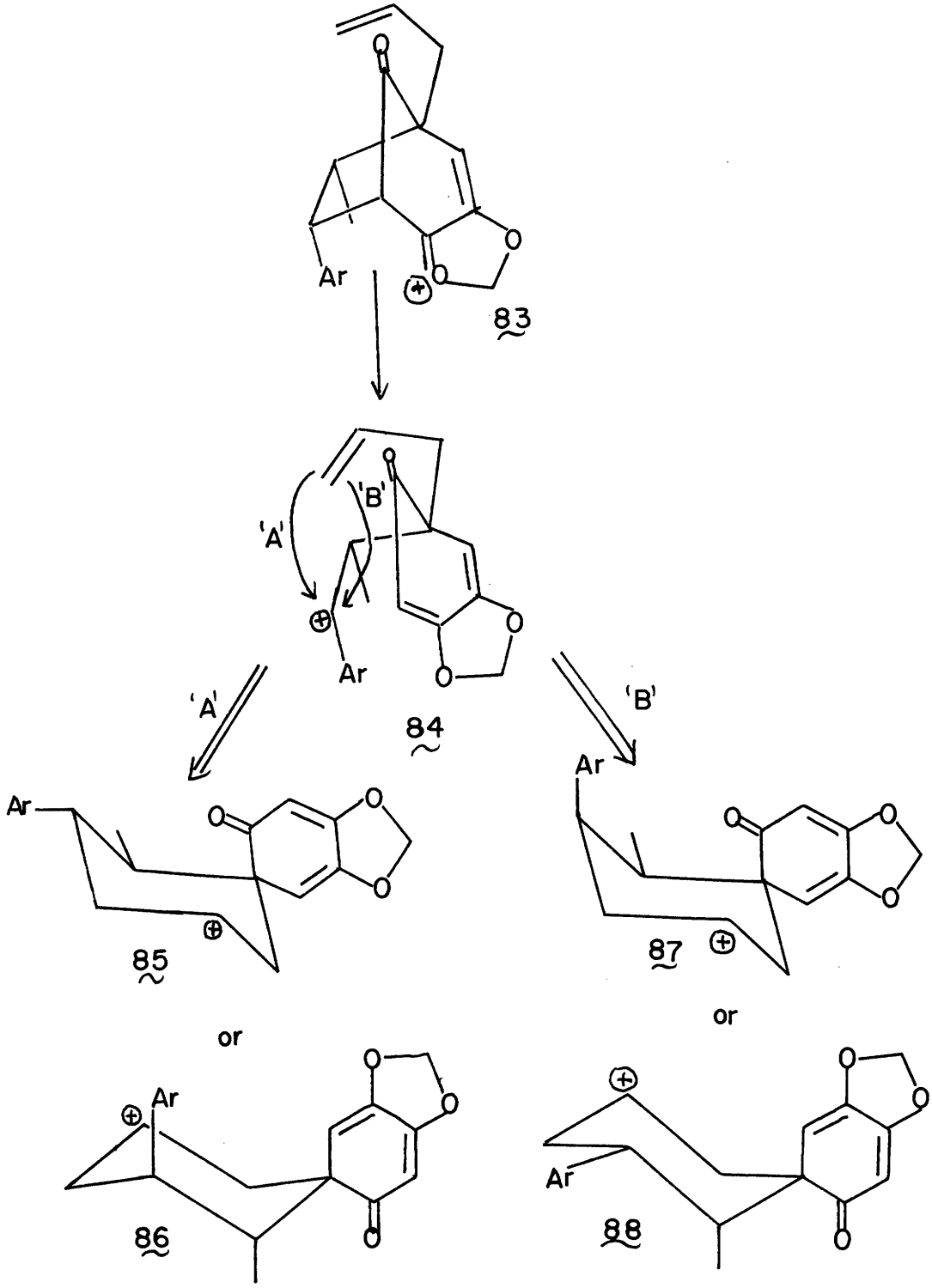
Both structures 80 and 82 are capable of cyclizing to give the required tetrahydrofuran ring since the C-C bond which bears the carbonyl group is axial and overlap of

orbitals with the carbonium ion is possible; however, this pathway would be thermodynamically unfavorable because it would result in cis-substitution in structure 80 or trans-diaxial substituents in structure 82, leading to diastereomers of futoenone (4). Cyclization is impossible from structure 79 which has the C-C bond bearing the carbonyl function equatorial; in addition, the other two substituents are cis (aryl is axial!). It is therefore not surprising to find that all the previous obtained spiro derivatives were derived from structure 81. Indeed, ^{1}H NMR data indicated that the methyl group was shielded by the dienone ring and appeared upfield at δ0.5 ppm.[6] Also, the aryl and methyl groups were indicated to be diequatorial by the coupling constant of 11 Hz between the two adjacent protons.[6,24] The C-C cond bearing the carbonyl group is equatorial and trans to the methyl group whereas in futoenone (4), a cis arrangement exists. As noted earlier, all attempts to cyclize those spiro derivatives to the futoenone skeleton had failed; this is consistent with the fact that the required conformational change for cyclization from 81 to 82 would give a thermodynamically less favorable product.

On the other hand, if the methyl group is "trans" to the allyl group as in 83, a different stereochemical outcome would be expected. Analysis of models gave also four possible products (Scheme XXXX) and pertient features are summarised in Table 6.



Scheme XXXIX



Scheme XXXX

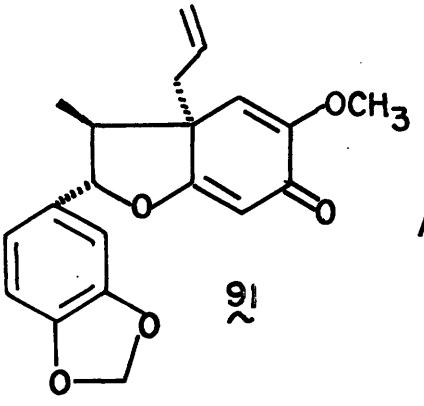
Table 6

	Path A (back-side attack)		Path B (front-side attack)	
	85	86	87	88
methyl group	equatorial	axial	equatorial	axial
aryl group	equatorial	axial	axial	equatorial
relative stereo-chemistry	trans	trans	cis	cis
tetrahydrofuran possible	yes	no	yes	no

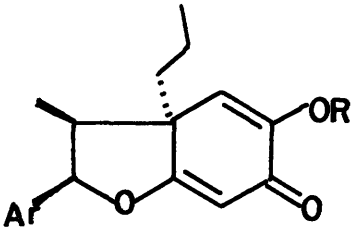
It is quite obvious that structure 85 should lead to the futoenone skeleton because it is the most thermodynamically stable product. Presumably, if we were to start out with cis-isosafrole in the condensation, a concerted [2+4] cycloaddition should give the intermediate 83, which would quickly rearrange to 84 and then to 85, capable of elaboration into futoenone (4). Also, one might expect to find a product derived by the capture of the cation 84 by the carbonyl-oxygen with carbon framework similar to that of burcellin (2). Condensation of quinone ketal 20a with pure cis-isosafrole (5) gave two major products after chromatography in low yield. (Scheme XXXXI) The minor and more polar component (13%) was found to be a mixture of enol-keto tautomers of a dihydrobenzofuranone 89, the structure of which was assigned on the basis of spectroscopic evidence.

Most significantly, the secondary methyl protons appeared as two sets of doublets (J = 7 Hz) at δ 0.5 (enol) and δ 0.65 (keto) in the ^{1}H NMR. This is in agreement with the reported value[3] for a 2,3-cis substitution pattern owing to shielding of the methyl group by the aryl function. The allyl group was assigned as trans to the methyl on the basis of mechanistic arguements proposed earlier. (see Scheme XXXX)

The fact that the aryl and methyl group exist in a cis fashion is probably due to thermodynamic reasons. Although the corresponding trans product is also known (3a-epiburchellin (91)[5]), this would create very severe 1,3-diaxial interactions when both the bulky aryl and allyl group are cis/diaxially oriented. Therefore, the prefered and observed product was the one with the aryl substituent trans to

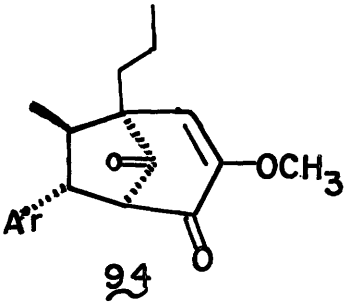


91



92, R = H

93, R = CH_3

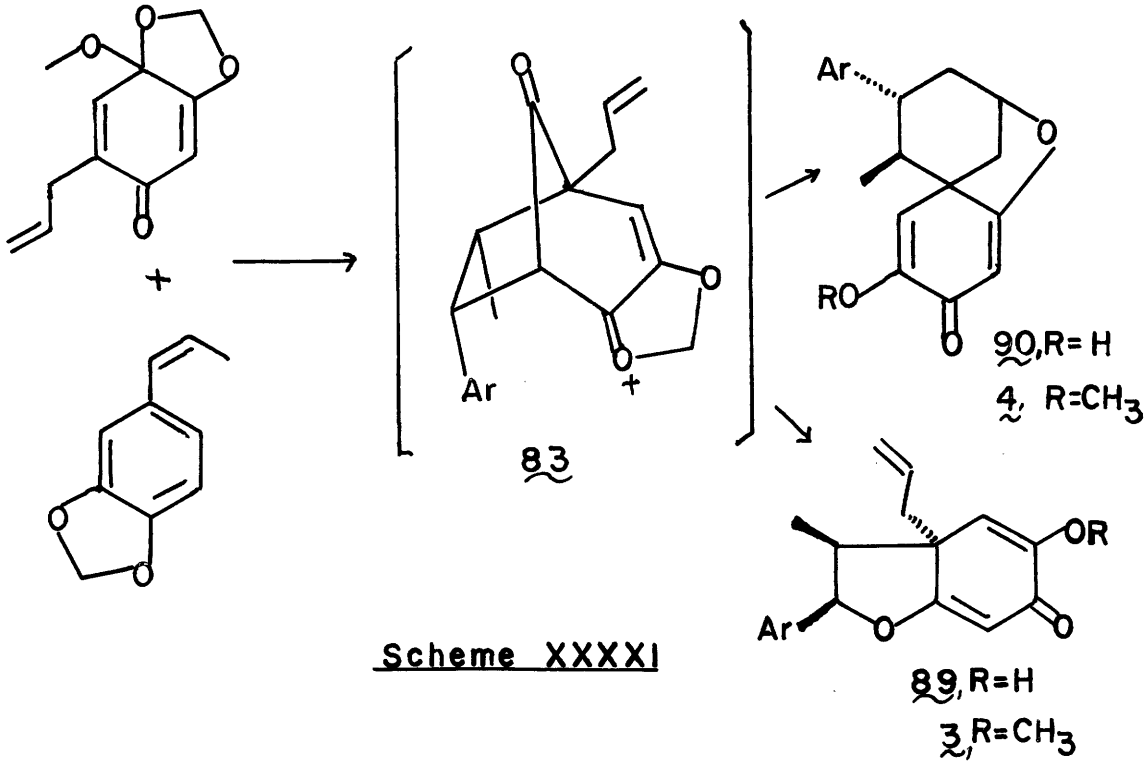


94

the allyl group but cis to the methyl. The stability of the stereochemical arrangements is emphasised when 2-epi-3a-epidihydroburchellin (93), obtained in 61% yield by condensation of quinone ketal 35a with Z-isosafrole followed by methylation, was treated with excess p-toluenesulfonic acid

in methanol for 4 days. Over 60% of starting material was recovered, together with 30% of a new bicyclooctane derivative 94.[52,53]

The other product, obtained in 30% yield, also existed as an enol-keto mixture. Spectroscopic data indicated that it was identical to desmethylfutoenone (90), a degradation product obtained when futoenone (4) was treated with acid.[6] Undoubtedly, formation of the final tetrahydrofuran ring was a favorable process if proper stereochemical requirements at all the chiral centers were met. It is also possible that the proposed intermediates 84 and 85 might not be important for the transformation. Rearrangement from the initially formed bicycloadduct 83 to the observed product should



83

90, R=H

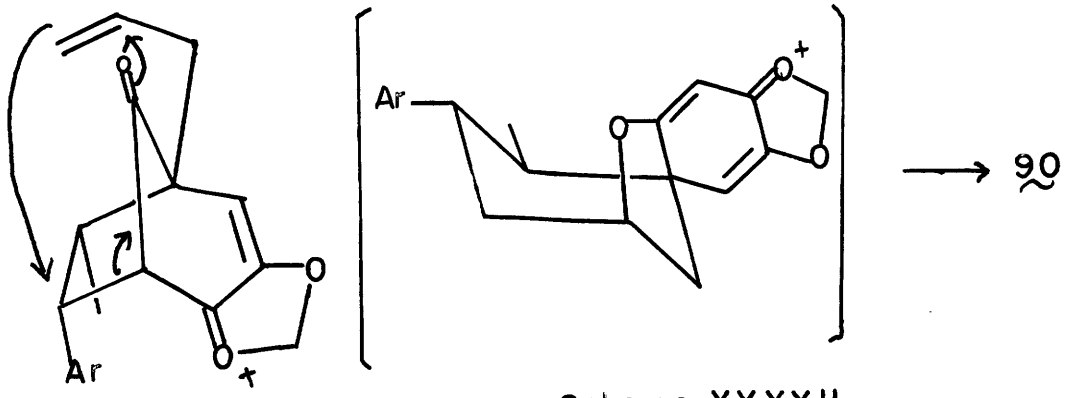
4, R=CH_3

89, R=H

3, R=CH_3

Scheme XXXXI

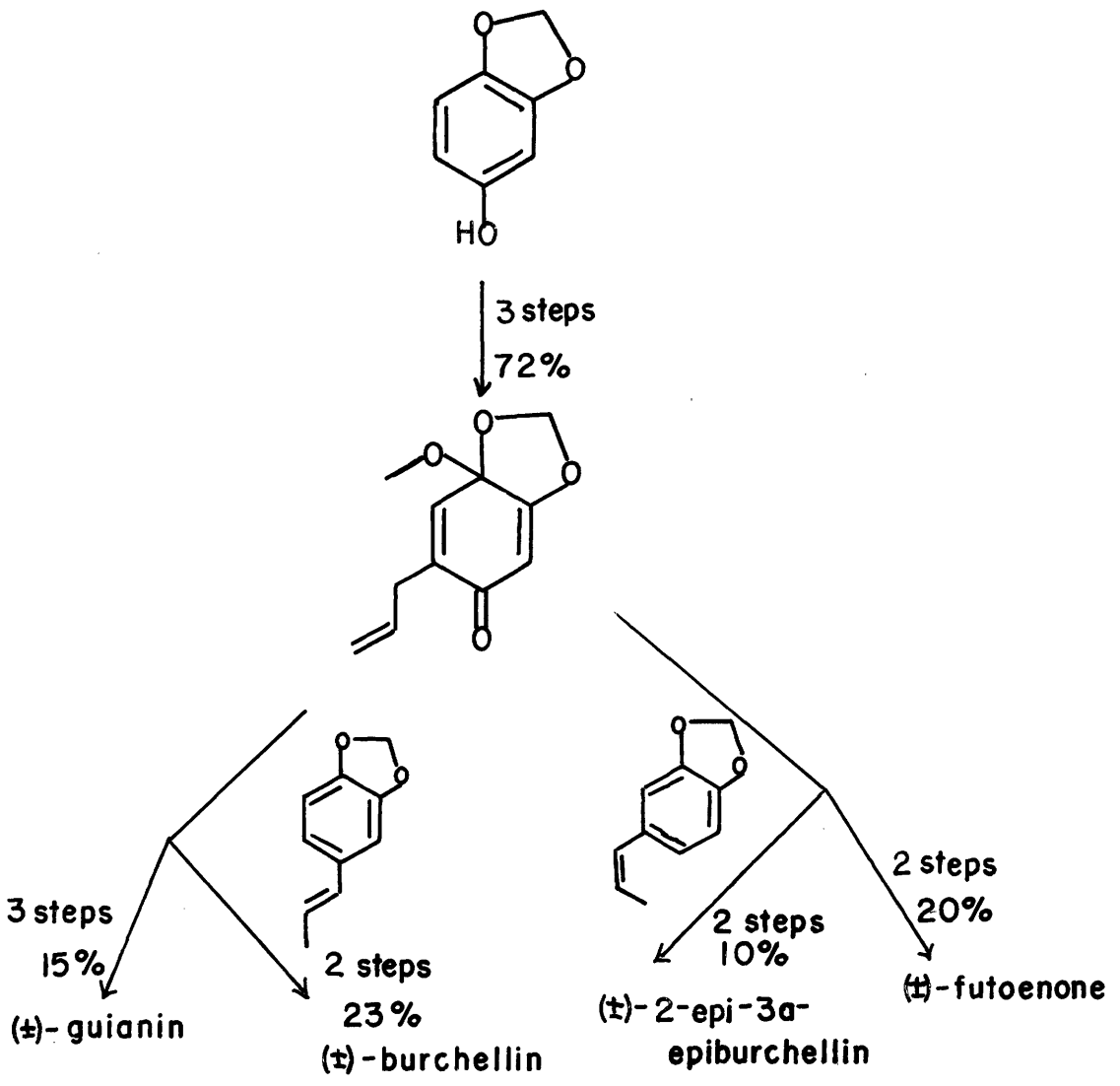
be a facile process in which formation of the cyclohexane moiety could be encouraged by the participation of the carbonyl group, with concomitant cyclization. (Scheme XXXXII)



Scheme XXXXII

Finally, methylation fo both 89 and 90 with silver oxide and methyl iodide gave (±)-2-epi-3a-epiburchellin (3) and (±)-futoenone (4) in 10% and 20% overall yield respectively. The racemic compounds were found to be indistinguishable in all respects from that of natural materials.[3,6] The most efficient synthesis of the two compound involved direct methylation of the crude mixture (after filtration through a short column of silica gel to remove unreacted isosafrole) without purification of the desmethyl derivatives.

With the use of quinone ketal 20a and either E- or Z-isosafrole (5), four different compounds with different ring structures were prepared in a straight forward manner by controlling the reaction conditions. A summary of the syntheses is listed as follows:



To this end, we have achieved biomimetic syntheses of (±)-guianin (1), (±)-burchellin (2), (±)-2-epi-3a-epiburchellin (3), and (±)-futoenone (4).

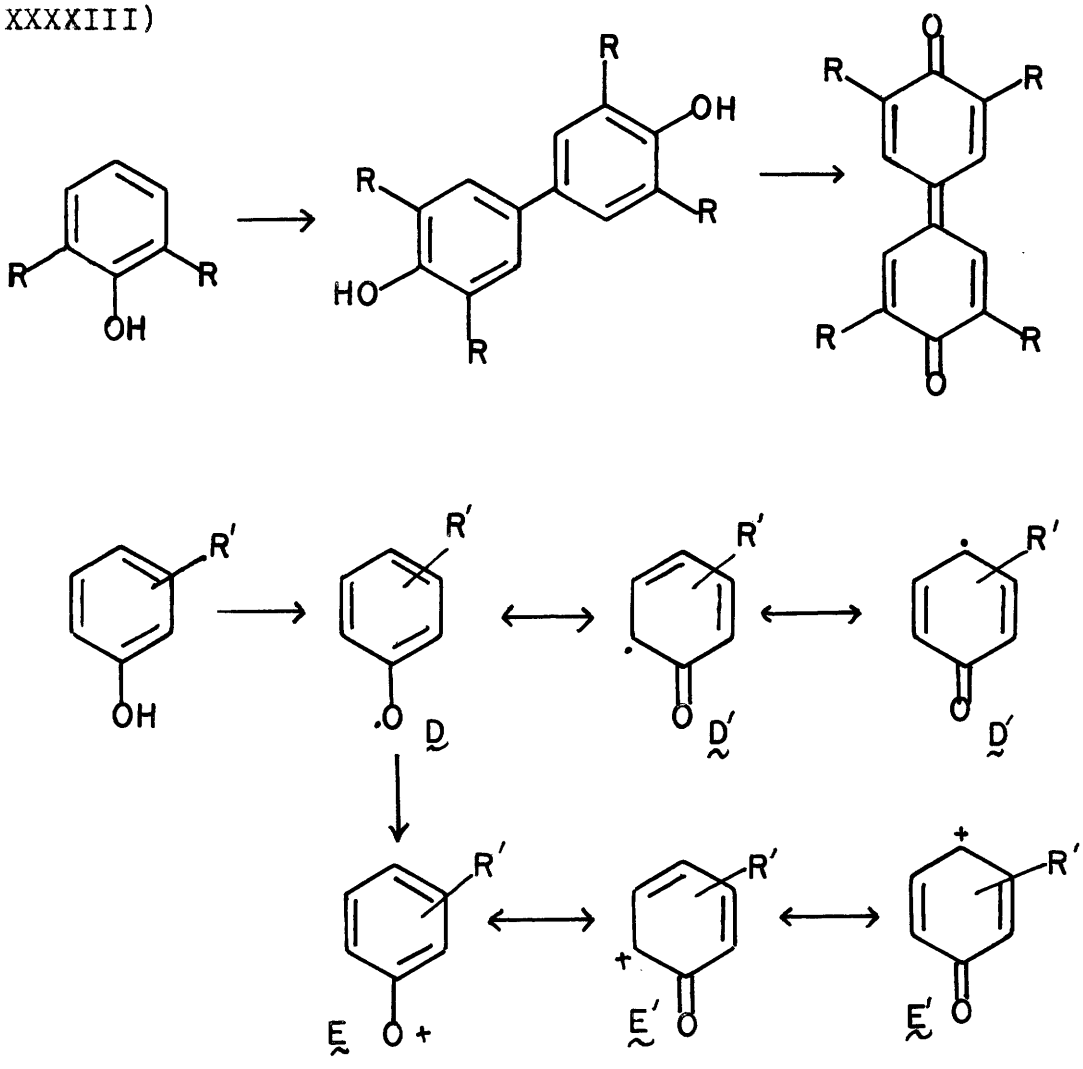
Part III:

Owing to the increasing importance in the use of quinone ketals in natural product synthesis,[54] there is a need for a more efficient and inexpensive way of preparing this class of compounds. A survey of literature[55-7] indicated that the variety of existing methods are not general and rather complicated. McKillop and co-workers[25] have reported the use of thallium(III) nitrate in the preparation of a large number of quinone ketals. We were able to repeat the procedure only after modification of the experimental conditions.[58] Quinone ketals are acid-labile compounds. We have found that in order to obtain good and reproducible yields of products, either $NaHCO_3$ or K_2CO_3 had to be added to the reaction mixture. These served to neutralize the nitric acid which is formed in the reaction medium. In addition, the major drawback in the use of thallium reagents is their high toxicity and therefore difficulties encountered in the handling of large quantities of the reagents.

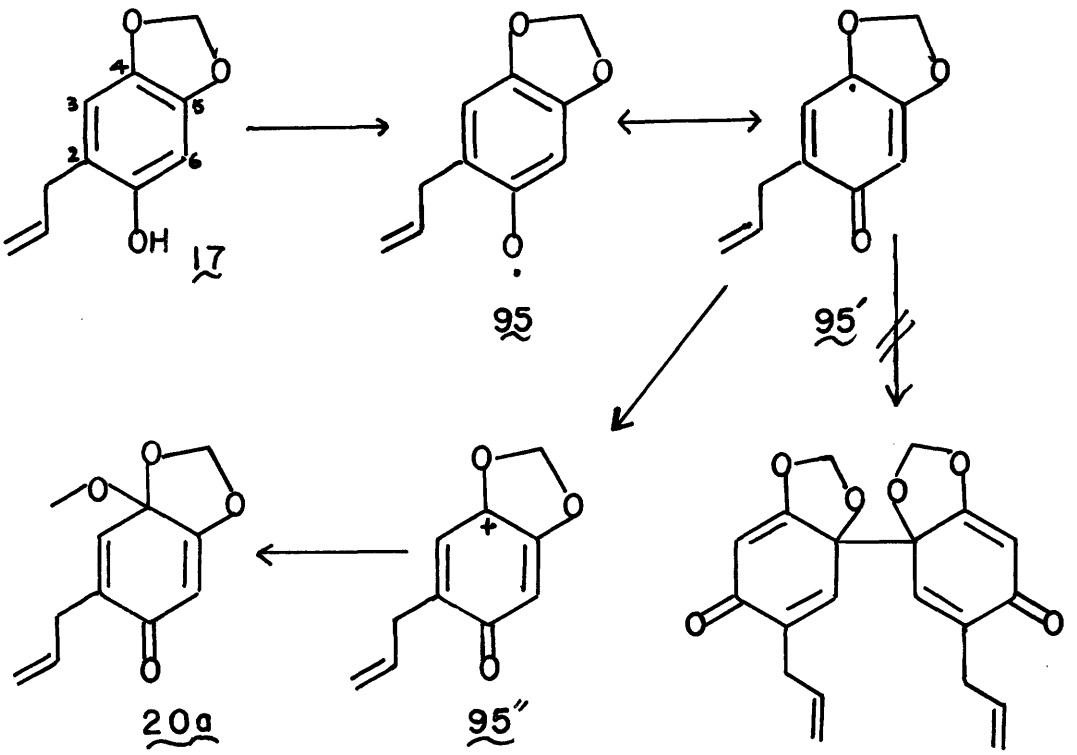
We have demonstrated the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the oxidation of phenol substrates to quinone ketals. However, a major disadvantage in the use of this reagent is of course its high cost. So, an alternative reagent was sought.

In general, most monohydric phenols are oxidized to form dimeric and polymeric products.[59] Common reagents used

included ferric chloride, silver oxide and potassium ferricyanide. With strong oxidizing agents, diphenoquinones are the final products resulting from further oxidation of the dimer. The formation of coupling products involved probably a free phenoxy radical D which is resonance stablized. When two radicals combine, dimers result. They are formed rapidly and irreversibly under kinetic control. However, the phenoxy radical can also be oxidized further to give cation E, which can now be coupled to an anionic species.(Scheme XXXXIII)



Oxidation of phenol 17 should give a radical 95 and resonance stabilization predicts the highest spin density to be on C-4. Coupling at this site would be sterically hindered.[59] Further oxidation to the highly stabilized cation 21 would then be favored. If the oxidation were done in methanol, nucleophilic attack on 21 would give the same quinone ketal as obtained by DDQ oxidation. (Scheme XXXXIV)



Ferric chloride was chosen first because of its availability and solubility in methanol. Oxidation of phenol 17 with an excess of ferric chloride at room temperature gave after

aqueous work-up mostly the methoxyquinone 8a. However, when the reaction was carried out in the presence of a suspension of finely-ground potassium carbonate with vigorous mixing, quinone ketal 20a was obtained in 84% yield after crystallization. Apparently, the quinone ketal formed initially was converted to the methoxyquinone by the HCl liberated in the reaction medium. The suspended base served to remove any acid formed. Other phenol substrates were studied and ferric chloride oxidation was not compatible with some of the quinone ketals. The result of these investigations employing the three main methods in this laboratory are listed in Table 7.

Table 7

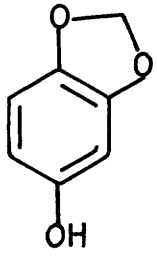
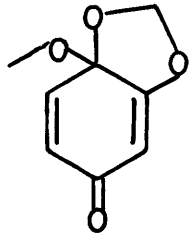
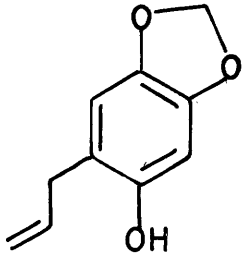
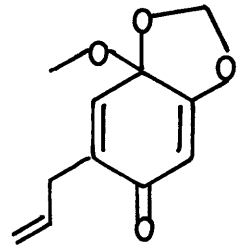
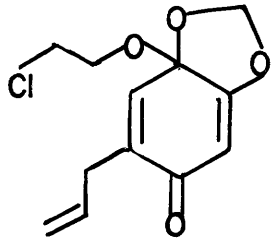
Phenol	Quinone[b] Ketal	Oxidant (% yield)[a] $FeCl_3$	DDQ	$Tl(NO_3)_3$
		poor	poor	83
		84	88	---
		---	63[c]	---

Table 7 cont'd

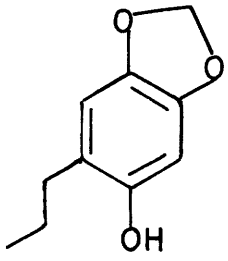
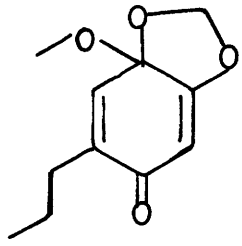
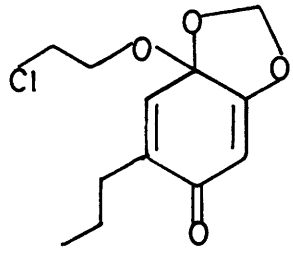
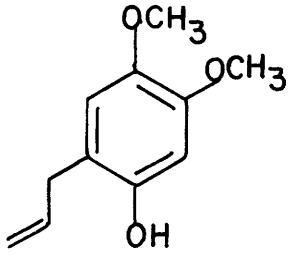
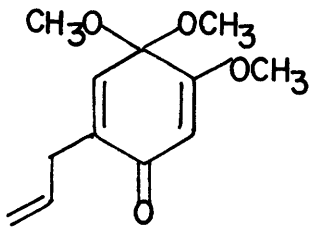
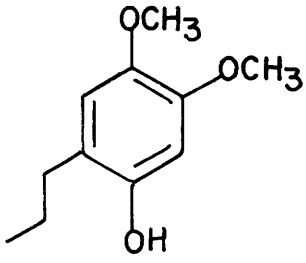
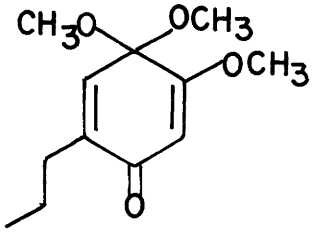
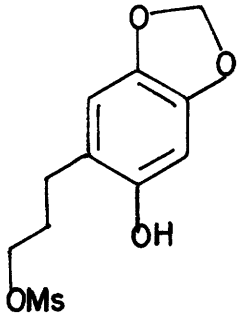
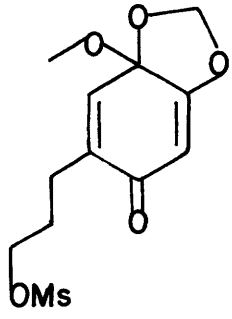
Phenol	Quinone[b] Ketal	$FeCl_3$	DDQ	$Tl(NO_3)_3$[a]
		85	85	--
		---	41[c]	---
		90	---	---
		90	---	---
		---	78	---

Table 7 cont'd

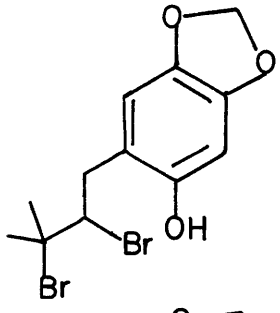
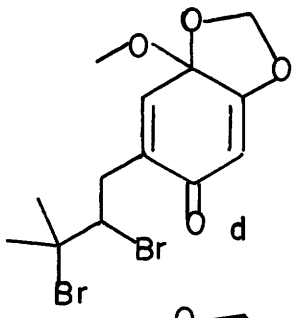
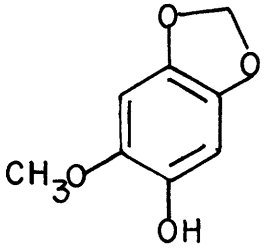
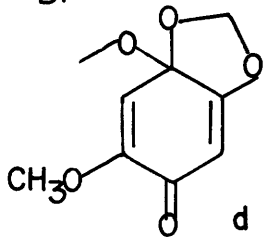
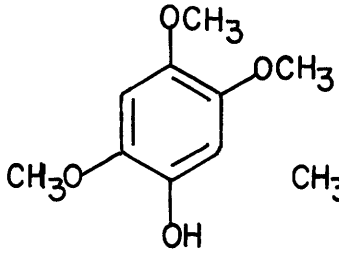
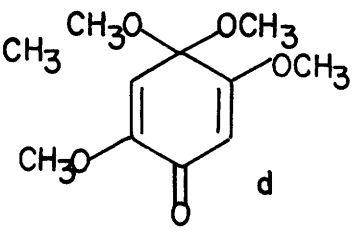
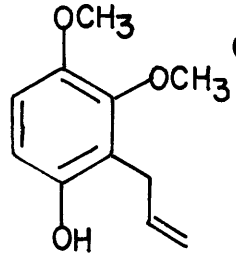
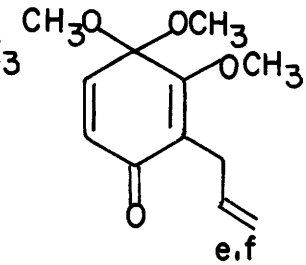
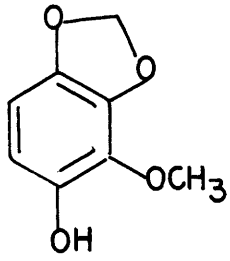
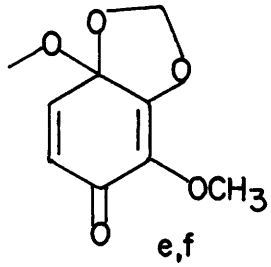
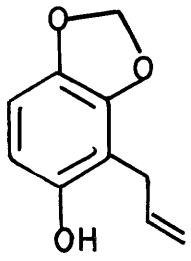
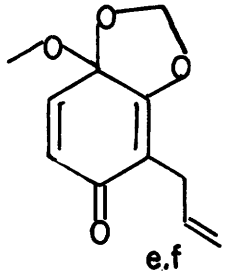
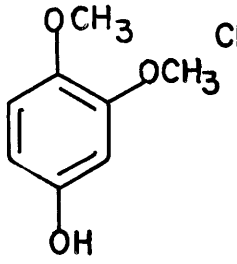
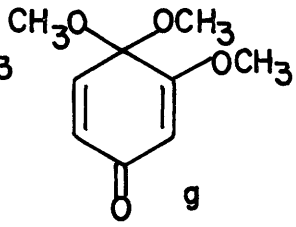
Phenol	Quinone[b] Ketal	$FeCl_3$	DDQ	$Tl(NO_3)_3$[a]
	 d	---	97	---
	 d	50	50	70
	 d	78	poor	poor
	 e,f	poor	75	poor
	 e,f	poor	57	68

Table 7 cont'd

Phenol	Quinone[b] Ketal	$FeCl_3$	DDQ	$Tl(NO_3)_3$[a]
	 e,f	---	31	21
	 g	poor	poor	66

Notes:

a. Modification of A. McKillop's procedure[25]

b. Usually accompanied by a small amount of the corresponding methoxyquinone.

c. Reaction was carried out in 2-chloroethanol; all others were carried out in methanol.

d. Data were kindly provided by Dr. Andy Pearce.

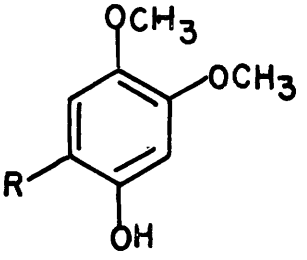
e. Data were kindly provided by Mr. Ping-Sun Chu.

f. Small amounts of dimeric products were isolated.

g. Data were kindly provided by Dr. Angela Hoppmann.

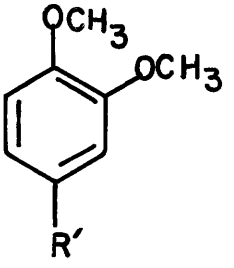
This list of quinone ketals by no means represents a complete scope of the preparative methods. At this time, it seems that at least two electron-donating substitents are necessary for reaction. More phenol substrates should be tried, especially with halogens and some functional groups on the benzene ring. This will be pursued by other co-workers in this laboratory.

Quinone ketals 100a and 100b were prepared by oxidation of the corresponding phenols 96 and 97, which were obtained from commercially available veratraldehyde (98) via 3,4-dimethoxyphenol (99).[60] The availability of quinone ketals 100a and 100b enabled us to investigate the synthesis of



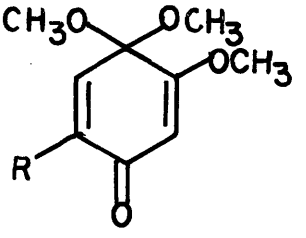
96, R = allyl

97, R = propyl



98, R' = CHO

99, R' = OH

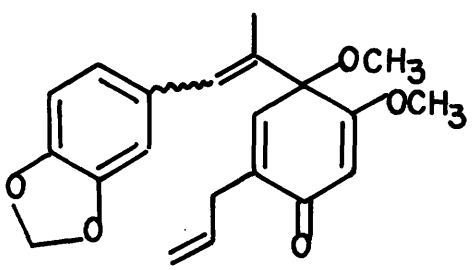


100a, R = allyl

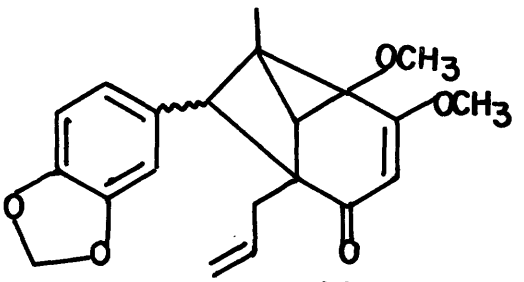
100b, R = propyl

another class of neolignans. Futoquinol (101) was isolated from Piper futokazura, together with its photocyclized product isofutoquinol A (102).[61] This would represent a direct electrophilic attack of the cation 103 on isosafrole (5). When the methylenedioxy quinone ketals (20a, 35a etc) were used, only products derived from [2+4] cycloaddition

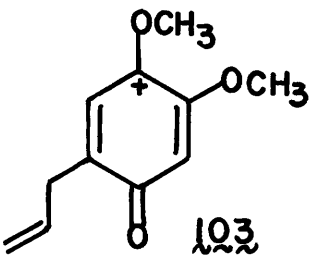
were isolated. It was then our hope that reactivity might change with a less rigid system (103).



101



102

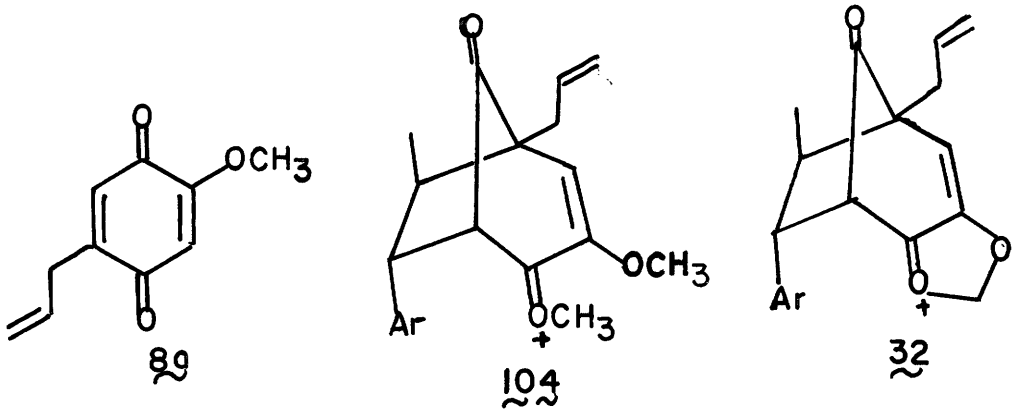


103

When quinone ketal 100a and isosafrole (E-, 5) was treated with a catalytic amount of trinitrobenzenesulfonic acid in CH_3CN at 0°, the major product (45%) obtained after work-up and chromatography was methyl ether 70. Racemic burchellin (3) was also isolated in 3% yield. No product related to 101 could be observed. It was thus concluded that the only mode of reaction for this type of ionic species is cycloaddition reaction.

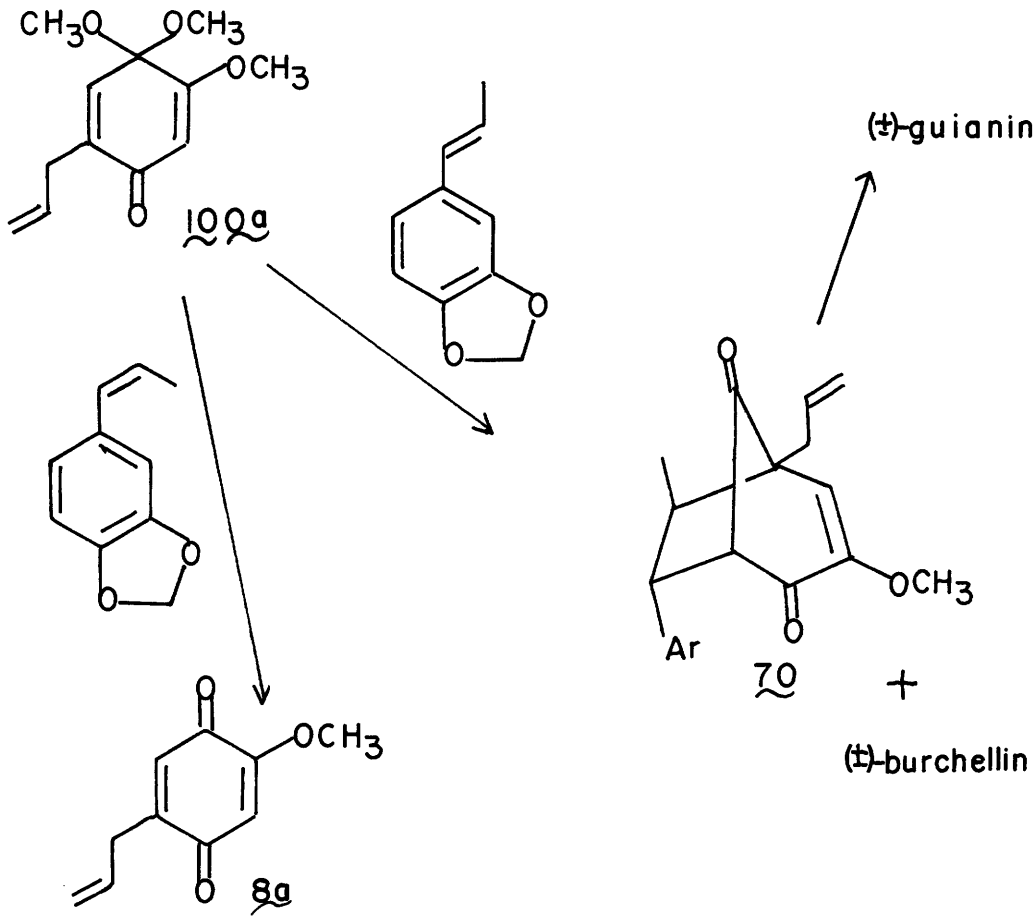
Although no new compound was obtained, this constituted the most efficient synthesis of (±)-guianin, for methyl ether 70 could be obtained directly and specifically via a condensation. The corresponding dihydrobenzofuranone (burchellin) was only obtained in trace quantities. This may have been

due to the ease of decomposition of the initially formed bicycloadduct 104, as opposed to 32, obtained when quinone ketal 20a was used.



89 104 32

When Z-isosafrole was used, only traces of (±)-futoenone (4) and (±)-2-epi-3a-epiburchellin (3) could be detected. The major product was found to be methoxyquinone 8a. Apparently, quinone ketal 100a decomposed more rapidly to 8a; this effectively competed with the cis-olefin. Amounts of 8a was also found during the condensation with E-isosafrole but they could be easily removed by washing the crude product mixture with a saturated solution of sodium dithionite. Similarly, methyl ether 61 was prepared in 61% yield from quinone ketal 100b. (Scheme XXXXV)



Scheme XXXXV

Conclusion

The quinone ketals represent a new class of synthetic intermediates capable of dipolar reactions under very mild condition. The ease of preparation and versatility have warranted their uses in other transformations and applications in the synthesis of other complex natural products.[54] Attempts should be made to study the reactions of quinone ketals with other systems, such as less reactive olefins, enol ethers, enol acetates, enamines, alkynes and dienophiles commonly used in Diels-Alder reaction.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are corrected. Proton magnetic resonance (NMR) spectra were measured on a Varian T-60 (60 MHz) or a Perkin-Elmer R-22 (90 MHz) instrument and are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. ^{13}C NMR spectrum was recorded on a Bruker HFX-90 (22.63 NHz) instrument and chemical shifts are give in parts per million (δ) downfield from tetramethylsilane. Ultraviolet (UV) spectra were obtained on a Cary 14 or a Perkin-Elmer 202 spectro-photometers and 95% ethanol was used as solvent (unless otherwise indicated). Infrared (IR) spectra were recorded on a Perkin Elmer 247 or 237B grating spectrophotometers. Low resolution mass spectra (MS) were obtained at an ionizing voltage of 70 eV (EI) on a Varian Mat 44 or a Hitachi Perkin-Elmer RMU-6E instruments and are reported as m/e (rel intensity). High resolution mass spectra (HRMS) were recorded on a Dupont CEC-110B instrument. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

Progress of most reaction was followed by thin layer chromatography (TLC) using Merck pre-coated silica gel 60F-204 plates. Preparative layer chromatography (PLC) was performed on E. Merck silica gel plate. Visualization of the bands (spots) on these plates was done with the aid of

a UV lamp in conjunction with iodine or spraying with an ethanolic soltion of 2,4-dinitrophenylhydrazine, or other reagents where appropiate. Merck silica gel (.063-.02 mm) was used for column chromatography. The 2,3-dichlore-5,6-dicyano-1,4-benzoquinone (DDQ) used was purchased from Aldrich Chemical Company and no further purification was necessary. Isosafrole was purchased from Eastman Kodak Company and was distilled before use. It contains an approximately 9:1 (E:Z, glc) mixture of isomers. Condensation reactions were performed using this mixture, unless otherwise indicated. Ferric chloride (hexahydrate) used was purchased from J.T. Baker Chemical Company and no purification was necessary.

General Procedure for the Oxidation of Phenols to 4,4-Disubstituted cyclohexa-2,5-dienones. Method A: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). To a stirred solution of the phenol (10 mmol) in methanol (100 mL) was added DDQ (11 mmol) followed by p-nitrophenol (100 mg). The mixture was stirred at room temperature for about 60 min, and then solvent was removed in vacuo. After the residue was taken up in ether, it was washed twice with sat. sodium bicarbonate, once with brine, and then dried ($MgSO_4$). Solvent was again evaporated in vacuo to give the crude product, which was quickly filtered through a short column of silica gel. Pure dienone was collected first as a fast moving fraction

and usually crystallized on standing. One recrystallization usually gave analytically pure sample.

The corresponding 1,4-benzoquinone usually could be obtained in small amounts by eluting a fast running yellow band coming right after the dienone.

Method B: Ferric Chloride (hexahydrate). To a vigorously stirred solution of the phenol (10 mmol) in methanol (50 mL) containing finely powdered potassium carbonate (50 mmol) was added ferric chloride (50 mmol) all in one portion. The resulting mixture was kept at room temperature with continuous vigorous stirring for 30 min, and then poured into a sat. sodium bicarbonate solution. The aqueous mixture was extracted thoroughly with ether; combined organic extracts were washed once with brine and dried ($MgSO_4$). Evaporation of solvent in vacuo gave the crude product which was usually the spectroscopically pure dienone. Further recrystallization provide analytical samples. Only trace amounts of the corresponding 1,4-benzoquinone were produced.

General Procedure for the Work-up of Condensation Reaction between Isosafrole (5) and Methylenedioxy-substituted Quinone ketals. After the complete consumption of the quinone ketal, (as followed by TLC) the mixture was poured immediately into a sat. solution of sodium bicarbonate. The aqueous mixture was then extracted thoroughly with methylene

chloride. Combine organic extracts were washed once with brine and dried (Na_2SO_4). After solvent was removed in vacuo, the oil obtained was chromatographed on silica gel and pure products were obtained.

In cases where the initial enol-keto mixtures were unstable, the crude products were first filtered through a short column of silica gel to remove unreacted isosafrole and base-line materials, and then immediately subjected to methylation conditions. The methyl ethers were then separated by column chromatography.

General Procedure for the Work-up of Condensation Reaction between Isosafrole (5) and Trimethoxy-substituted Quinone Ketals. Reaction mixture was poured into a sat. solution of sodium bicarbonate; this was then extracted thoroughly with methylene chloride. The combined organic extracts were washed twice with sat. sodium dithionite, (to reduce the benzoquinone formed to hydroquinone) followed by sat. sodium bicarbonate (to remove the hydroquinone) and brine. It was then dried (Na_2SO_4) and concentrated in vacuo to give an oil which was chromatographed to give the bicyclo-octane derivative as the major product.

6-Hydroxy-7-methoxychromene (9). A mixture of quinone 8a (120 mg, 0.625 mmol) and diethylamine (49 mg, 0.625 mmol) in tert-butanol (10 mL) was heated at reflux for 5 h.

After the dark mixture was cooled, it was acidified with dilute acetic acid and then extracted with chloroform. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give an oil. Purification by PLC (20 cm × 20 cm × 0.1 cm; 50% ethyl acetate in hexane) gave 47 mg (40%) of chromene 9 as an oil which crystallized from ether-hexane to give white crystals: mp 90-1°C; IR ($CHCl_3$) 3550, 3200 (br), 1500, 1280, 1160 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (s, 3), 4.70 (d of d, 2, J = 4 Hz, 1 Hz), 5,30 (s, 1, D_2O exchangable), 5.67 (d of t, 1, J = 10 Hz, 4 Hz), 6.23-6.50 (m, 2), 6.57 (s, 1); UV 221 nm (ε 21, 300), 228 (21, 200), 276 (3100), 325 (6400); MS 178 (M^+, 94), 177 (100).

Claisen Rearrangement of 3-(N,N-dimethyamino)phenol Allyl Ether (12). The reaction was carried out either by heating the neat liquid at 220°C or in boiling tetralin, under a nitrogen atmosphere for 30 min. After solvent was removed by vacumn distillation, the crude oil was chromatographed on silica gel.

2-Allyl-3-(N,N-dimethylamino) phenol (15) was isolated as an oil (20-30%): IR ($CHCl_3$) 3500, 3300 (br), 1610, 1580, 1480, 1460 cm^{-1}; NMR ($CDCl_3$) δ 2.63 (s, 6), 3.57 (d, 2, J = 6 Hz), 4.90-5.33 (m, 2), 5.70 (br. s, 1), 5.80-6.40 (m, 1), 6.53 (d, 1, J = 7.5 Hz), 6.66 (d, 1, J = 7.5 Hz), 7.05 (t, 1, J = 7.5 Hz).

1,2-Dimethyl-4-hydroxyindoline (16) was obtained in

less than 5% yield as white crystals (ether-hexane) : mp 148-50°C; IR ($CHCl_3$) 3200, 2900, 1620, 1280 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 2, $\underline{J}$ = 6 Hz), 2.40-3.60 (m, 3), 2.67 (s, 3), 4.73 (br. s, 1), 6.10 (d of d, 2, $\underline{J}$ = 3 Hz, 8 Hz), 6.97 (t, 1, $\underline{J}$ = 8 Hz); UV 230, 257, 295 nm; MS 163 (M^+, 32), 148 (100).

2-Allyl-5-(N,N-dimethylamino)phenol (14) was produced in 45-55% yield as crystalline solid. It was eluted as the most polar component that moves away from the origin. Recrystallization from hot hexane gave white plates: mp 88-90°C; IR ($CHCl_3$) 3550, 3300 (br), 2850, 1620, 1520, 1360, 1100 cm^{-1}; NMR ($CDCl_3$) δ 2.90 (s, 1), 3.34 (d, 2, $\underline{J}$ = 6 Hz), 4.93-5.37 (m, 3, 1H exchangable with D_2O), 5.70-6.20 (m, 1), 6.23 (d, 1, $\underline{J}$ = 2 Hz), 6.30 (d of d, 1, $\underline{J}$ = 9 Hz, 2 Hz), 6.97 (d, 1, $\underline{J}$ = 9 Hz).

Unreacted starting allyl ether 12 was usually recovered in about 10% yield.

2-Allyl-5-(N,N-dimethylamino)-1,4-benzoquinone (8c). A solution of Fremy's salt (1.0 g of the salt in 24 mL of water and 3 mL of 1N sodium acetate) was added to methanol (3 mL) containing the aminophenol 14 (177 mg, 1.0 mmol). The mixture was stirred at room temperature for 30 min and then extracted thoroughly with chloroform. The combined organic layers were washed once with brine and dried (Na_2SO_4). Removal of solvent in vacuo gave 118 mg (63%) of the pure

quinone 8c as a red unstable oil: IR ($CHCl_3$) 1670, 1645, 1600, 1575, 1125 cm^{-1}; NMR ($CDCl_3$) δ 3.17 (s, 6), 3.10-3.33 (m, 2), 5.00-5.40 (m, 2), 5.60 (s, 1)., 5.63-6.20 (m, 1), 6.33 (m, 1); UV 235, 272 (sh), 510 nm.

Atempts to crystallize or purify 8c by chromatography resulted mainly in decomposition of the compound. However, the crude oil obtained was spectroscopically pure and it was carried directly to subsequent reaction. Hydrogenation of the crude quinone over 10% Pd/C in ethanol followed by the usual acetylation procedure gave the corresponding n-propyl hydroquinone diacetate 16 as a pure oil: IR ($CHCl_3$) 1760, 1510, 1375, 1155 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (br. t, 3, J = 7 Hz), 1.30-1.80 (m, 2), 2.30 (s, 6), 2.40 (br. t, 2, J = 7 Hz), 2.73 (s, 6), 6.63 (s, 1), 6.83 (s, 1).

2-Allyl-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (20a): Method A (DDQ). Reaction was carried out according to the general procedure. Oxidation of phenol 17 (1.78 g, 10 mmol) gave 1.84 g (88%) of the pure quinone ketal 20a. Recrystallization from ether-pentane gave white crystals: mp 49-50°C; IR ($CDCl_3$) 1690, 1655, 1630, 1180 cm^{-1}; NMR (CCl_4) δ 3.09 (br. d, 2, J = 7 Hz), 3.26 (s, 3), 4.98-5.26 (m, 2), 5.49 (s, 1), 5.55 (s, 1), 5.60 (s, 1), 5.70-6.10 (m, 1), 6.53 (t, 1, J = 1 Hz); ^{13}C NMR ($CDCl_3$) δ 32.6 (t of m), 51.2 (q), 97.6 (br), 98.9 (d), 98.9 (t), 117.9(t of m), 127.8 (d of t), 134.4 (d of m), 142.8 (br), 168.3 (s),

186.8 (s); UV 237 nm (ε 9350), 295 (3200); MS 208 (M^+, 13), 69 (100). Exact mass. Calcd for $C_{11}H_{12}O_4$: 208.07356. Found 208.07275.

Method B (Ferric Chloride). Oxidation of phenol 17 (1.78 g, 10 mmol) using the general procedure gave 84% (1.75 g) of the desired 20a with properties identical to that prepared by method A.

2-Allyl-5-ethoxy-1,4-benzoquinone (8d). To a solution of the quinone ketal 20a (208 mg, 1 mmol) in 10 mL of ethanol was added a few drops of concentrated hydrochloric acid and the resulting mixture was stirred in room temperature for two h. After removal of the solvent in vacuo, the residue was taken up in ether and washed once with brine and then dried ($MgSO_4$). The oil obtained after concentration of the solvent was passed through a short column of silica gel with methylene chloride as solvent. This afforded 148 mg (77%) of yellow plates: mp 63-4°C; IR ($CHCl_3$) 1675, 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, 3, J = 7 Hz), 3.20 (d, 2, J = 7 Hz), 4.00 (q, 2, J = & Hz), 4.90-5.30 (m, 2), 5.50-6.20 (m, 1), 5.88 (s, 1), 6.47 (m, 1); UV 267 nm.

The same quinone 8d could be prepared in low yield from phenol 17 using DDQ in ethanol according to the procedure of Williams.[21] Also, it decomposes slowly at room temperature but is quite stable when stored in refrigerator.

2-Allyl-5-hydroxy-1,4-benzoquinone (8b). A mixture of quinone ketal 20a (208 mg, 1 mmol) and 0.5-1.0 g of cation exchange resin (Bio-Rad AG-50WX8, 50-100 mesh, H^+ form) in 12 mL of 40% aqueous ether was stirred vigorously under argon for 18 h at room temperature. After removal of the resin by filtration and separation of layers, the aqueous layer was extracted repeatedly with ether until the golden-yellow color had disappeared. The combined ethereal solution was then extracted with 5% sodium bicarbonate solution and the ethereal layer was discarded. The deep-red aqueous solution was now acidified carefully with cold dilute hydrochloric acid, followed by extraction with ether. After the combined ether solution was dried ($MgSO_4$), solvent was evaporated in vacuo to yield 139 mg (85%) of spectroscopically pure 8b as an unstable oil. Analytical sample was obtained by sublimation (0.1 mm Hg, $<60^\circ C$) of the crude oil (with much decomposition) to produce yellow crystals which also decomposed rapidly even at low temperature: mp 50-54°C; IR ($CHCl_3$) 3400, 1655, 1615, 1400, 1310, cm^{-1}; NMR ($CDCl_3$) δ 3.20 (d, 2, J = 7 Hz), 4.95-5.40 (m, 2), 5.60-6.20 (m, 1), 6.13 (s, 1), 6.57 (m, 1), 6.93 (br., 1, D_2O exchangable); UV 263 nm (ε 14,800), 378 (860); upon treatment with 5% $NaHCO_3$: 268 nm (ε 11,500), 510 (3600) with white precipitate; reacidification gave original spectrum; upon treatment with 1 M NaOH: 235 nm (sh, ε 17,000), 243 (sh, 15,200), 280 (sh, 9400), 361 (28,000), 379 (sh, 20,400), 495 (2250); upon

reacidification: 277 nm (sh, ε14,000), 262 (11,000), 315 (7500); MS 164 (M^+, 80), 136 (24), 108 (20), 69 (100).

1-Allyl-2,4,5-triacetoxybenzene (24). In an oven-dried flask chilled at -78°C, was placed 178 mg (1 mmol) of phenol 17 in 10 mL of dry methylene chloride under nitrogen atmosphere. To this sitrred mixture was added dropwise, a solution of boron tribromide (99.99%, 0.285 mL, 3.0 mmol) in 5 mL of dry methylene chloride. Upon completion, the cold bath was removed and the reaction flask was allowed to warm up to ambient temperature and kept for 3 h. The flask was again cooled to -50°C and 10 mL of methanol was slowly added to the reaction. The cold bath was then removed and more methanol was added. The solvent was evaporated in vacuo; methanol was again added and evaporated, and the process was repeated five times. The unstable oil obtained was immediately treated with excess pyridine and acetic anhydride and after the usual work-up and PLC (20 cm × 20 cm × 0.1 cm; ether) gave 145 mg (50%) of crystalline 24: mp 68-70°C; IR ($CHCl_3$) 1765, 1500, 1370, 1155 cm^{-1}; NMR ($CDCl_3$) δ 2.27 (s, 9), 3.27 (d, 2, J = 7 Hz), 4.83-5.30 (m, 2), 5.60-6.20 (m, 1), 7.00 (s, 1), 7.07 (s, 1).

Triacetate 24 was independently prepared by reduction of the hydroxyquinone 8b with excess sodium dithionite to give the triol 23, followed by immediate acetylation. The triacetate prepared from both routes were identical.

2-Allyl-4-(2-chloroethoxy)-4,5-methylenedioxycyclohexa-2,5-dienone (20b). Oxidation of phenol 17 (1.78 g, 10 mmol) with DDQ (2.5 g, 11 mmol) in 2-chloroethanol (15 mL) under the general procedure, except without any p-nitrophenol, produced 1.62 g (63%) of the desired quinone ketal 20b as white crystals. Recrystallization from ether-pentane gave analytical sample: mp 105-6°C; IR ($CHCl_3$) 1690, 1655, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (d, 2, J = 7 HZ), 3.40-3.90 (m, 4), 4.90-5.30 (m, 2), 5.63 (s, 2), 5.77 (s, 1), 5.60-6.20 (m, 1), 6.67 (t, 1, J = 1 Hz); UV 239 nm (ε 9400), 296 (3000); MS 256 (M^+, 3), 191 (100), 177 (64), 69 (82). Anal. ($C_{12}H_{13}ClO_4$) C, H.

2-Allyl-5-(2-chloroethoxy)-1,4-benzoquinone (8e). Reaction of phenol 17 (890 mg, 5 mmol) in 40 mL of 2-chloroethanol with DDQ (1.25 g, 5.5 mmol) using the procedure of Williams[21] gave 710 mg (62%) of quinone 8e. Analytical sample was obtained after recrystallization from ether-pentane to give yellow needles: mp 66-9°C; IR ($CHCl_3$) 1675, 1650, 1610, 1175 cm^{-1}; NMR ($CDCl_3$) δ 3.20 (d, 2, J = 7 Hz), 3.80-4.40 (m, 4), 5.00-5.40 (m, 2), 5.60-6.10 (m, 1), 5.82 (s, 1), 6.53 (t, 1, J = 1 Hz); UV 262 nm (ε 15,900), 360 (855); MS 226 (M^+, 23), 191 (53), 163 (26), 69 (100).

2-Allyl-4,5-methylenedioxyphenol Benzyl Ether (43). A mixture of phenol 17 (1.78 g, 10 mmol), benzyl bromide

(2.5 mL), and potassium carbonate (1.7 g, 12 mmol) was heated in boiling dimethoxyethane (100 mL) for 24 h. Solvent was then removed in vacuo and the residue was taken up in ether. The ethereal solution was washed with 10% NaOH, brine, and dried ($MgSO_4$). After concentration of solvent, the crude oil was purified by Kugelrohr distillation to yield 2.35 g (88%) of pure oil, which solidifies on standing: bp 165°C/0.05 mm Hg (lit.[62] mp 45-6°C); IR (neat) 1640, 1505, 1480, 1440, 1220, 1040 cm^{-1}; NMR ($CDCl_3$) δ 3.37 (d of m, 2, $\underline{J}$ = 7 Hz), 4.87-5.33 (m, 2), 5.02 (s, 2), 5.70-6.40 (m, 1), 5.93 (s, 2) 6.60 (s, 1), 7.43 (s, 5); MS 268 (M^+, 30), 91 (100).

2-(3-Hydroxypropyl)-4,5-methylenedioxyphenol Benzyl Ether (44). In an oven-dried flask was placed 1.05 g (3.92 mmol) of benzyl ether 43 in 3.0 mL of anhydrous tetrahydrofuran. This was cooled in an ice bath and 2.0 mL of a molar solution of BH_3/THF in 4 mL tetrahydrofuran was added dropwise to the stirred solution under a nitrogen blanket. After the addition was completed, the mixture was stirred for 60 min at room temperature. The flask was again chilled and 1.0 mL of water was carefully added to the solution, (gas evolution!) followed by quick addition of 2.0 mL of 10% NaOH and then 1.5 mL of 30% H_2O_2. The resulting mixture was then heated at 50°C for 60 min, cooled, and then diluted with ether. Ether solution was washed with brine

and dried ($MgSO_4$). Removal of solvent gave 1.06 g (98%) of white crystalline solid, containing about 93% of 44 and 7% of the corresponding secondary alcohol (by NMR integration). Recrystallization of the crude solid gave pure 44 in 90% yield. Further recrystallization from hot ether-hexane gave needles: mp 118-119°C; IR ($CHCl_3$) 3500 (br), 1505, 1485, 1180, 1060 cm^{-1}; NMR ($CDCl_3$): δ 1.53-2.03 (m, 3, 1 H exchangable with D_2O), 2.63 (t, 2, J = 7 Hz), 3.50 (t, 2, J = 7 Hz), 4.93 (s, 2), 5.93 (s, 2), 6.44 (s, 1), 6.55 (s, 1), 7.28 (s, 5); MS 286 (M^+, 30), 91 (100).

2-(3-Methanesulfonyloxypropyl)-4,5-methylenedioxyphenol Benzyl Ether (47). Alcohol 44 (3.6 g, 12.6 mmol) was dissolved in 80 mL of dry pyridine and cooled in an ice-bath. Methanesulfonyl chloride (1.07 mL) was added to the stirring solution and the flask was maintained at between -5° to 0°C for three h. The mixture was poured into cold 1 N HCl and let stir for 15 min, during which the mesylate precipitated out. This was extracted with a mixture of ethyl acetate and ether (1:1, v/v). The combined organic layers were washed with sat. sodium bicarbonate, 1 N HCl, brine and dried ($MgSO_4$). Concentration of solvent gave an oil which crystallized from ether to give 4.28 g (94%) of white crystals. Recrystallization from ether-hexane gave small white needles: mp 110°; IR ($CHCl_3$) 1505, 1490, 1370, 1170, 1040, 975, 935 cm^{-1}; NMR ($CDCl_3$) δ 1.99-2.15 (m, 2), 2.55-2.90 (m, 2), 2.92

(s, 3), 4.22 (t, 2, J = 7 Hz), 5.02 (s, 2), 5.94 (s, 2), 6.62 (s, 1), 6.68 (s, 1), 7.40 (s, 5); MS 364 (M^+, 50), 91 (100).

Conversion of Mesylate 47 to 2-(3-Methanesulfonyloxypropyl)-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (39d) and (46b). Mesylate 47 (673 mg, 1.85 mmol) was taken up in methanol (45 mL) and ethyl acetate (10 mL) and hydrogenated over 10% Pd/C (200 mg) at room temperature and atmospheric pressure. After the theorectical uptake of hydrogen, the catalyst was filtered and solvent removed in vacuo to yield phenol 38d as off-white crystals in quantitative yield: IR (neat) 3500 (br) 3350 (br), 1350, 1170, 1035, 930 cm^{-1}; NMR ($CDCl_3$/acetone-d_6) δ1.75-2.30 (m, 2), 2.68 (t, 2, J = 7 Hz), 3.07 (s, 3), 4.23 (t, 2, J = 7 Hz), 5.85 (s, 2), 6.50 (s, 1), 6.63 (s, 1); MS 274 (M^+, 25), 178 (100), 151 (40), 150 (45).

Phenol 38d was again dissolved in 15 mL of methanol and to this was added DDQ (460 mg, 2 mmol) and a catalytic amount of *p*-nitrophenol. After 30 min at room temperature, solvent was evaporated under reduced pressure at below 30°C bath temperature. The residue was taken up in ether and any insoluble material was removed by filtration. The filtrate was concentrated and purified by column chromatography (30 g silica gel, hexane-ethyl acetate, 1/1, v/v). Two fractions were collected. The faster running fraction gave 440 mg (78%) of 39d as an unstable oil: IR ($CHCl_3$) 1690, 1660,

1645, 1365, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.78-2.16 (m, 2), 2.55 (br. t, 2, J = 7 Hz), 3.10 (s, 3), 338 (s, 3), 4.21 (t, 2, H = 7 Hz), 5.64 (d, 1, H = 1 Hz), 5.66 (s, 1), 5.71 (d, 1, J = 1 Hz), 6.72 (t, 1, J = 1 Hz).

The slower running fraction gave 50 mg (10%) of quinone 46b as yellow crystals. Recrystallization from $CHCl_3$-ether gave yellow needles: mp 143-145°C; IR ($CHCl_3$) 1680, 1665, 1615, 1365, 1180 cm^{-1}; NMR ($CDCl_3$): δ 1.85-2.20 (m, 2), 2.62 (br. t, 2, J = 7 Hz), 3.04 (s, 3), 3.85 (s, 3), 4.28 (t, 2, J = 7 Hz), 5.98 (s, 1), 6.58 (t, 1, J = 1 Hz); MS 274 (M^+, 2), 178 (62), 69 (100).

2-(3-Hydroxypropyl)-4,5-methylenedioxyphenol (38a). This was done according to the method used in the conversion of benzyl ether 43 to alcohol 44. A mixture of diols (38 a/b) were produced in 90% yield from 1.78 g (10 mmol) of phenol 17. On standing, 38a crystallized out partially. The two diols were separated more efficiently by column chromatography. A total of 1.4 g (72%) of diol 38a was isolated as an oil, which crystallized on standing. Recrystallization from ether-hexane, gave white crystals: mp 87-88°C; IR ($CHCl_3$) 3300 (br), 1500, 1490, 1180, 1040, 935 cm^{-1}; NMR ($CDCl_3$) δ 1.56-1.96 (m, 2), 2.63 (t, 2, J = 7 Hz), 3.17 (br, 1), 3.57 (t, 2, J = 7 Hz), 5.76 (s, 2), 6.33 (s, 1), 6.44 (s, 1), 7.30 (br, 1); MS 196 (M^+, 48), 178 (23), 151 (100).

Dienone 42. Oxidation of diol 38a (156 mg, 0.79 mmol) with DDQ (200 mg) in methanol (10 mL) using the general procedure for 90 min gave a complex mixture of products. The least polar crystalline component (20 mg, 13%) was isolated after chromatography on a 20 cm × 20 cm × 0.1 cm silica gel plate with 50% ethyl acetate in hexane as the solvent; it was identified to be the spiro-dienone 42. Recrystallization from ether-hexane gave off white plates: mp 104-109 °C; IR ($CHCl_3$) 1640, 1415, 1390, 1230, 1050 cm^{-1}; NMR ($CDCl_3$) δ 1.80-2.30 (m, 4), 4.0-4.3 (m, 2), 5.52 (s, 1), 5.60 (s, 1), 5.84 (s, 2); UV 310 nm (ε 3500), 253 (10,400); MS 194 (M^+, 100), 151 (34), 138 (43), 69 (72). Exact mass. Calcd for $C_{10}H_{10}O_4$: 194.05791. Found: 194.05647.

3,4-Methylenedioxy-6-(3-tosyloxypropyl)phenol Benzyl Ether (45). Treatment of alcohol 44 (533 mg, 1.86 mmol) with p-toluenesulfonul chloride (531 mg) in pyridine (10 mL) at 0°-5°C for 24 h, gave, after aqueous work up, 630 mg (77%) of tosylate 45 as an oil: IR (neat) 1505, 1485, 1360, 1180 cm^{-1}; NMR ($CDCl_3$) δ ca 1.60-2.05 (m, 2), 2.40 (s, 3), 2.57 (br. t, 2, J = 7 Hz), 3.95 (t, 2, J = 7 Hz), 4.78 (s, 2), 5.80 (s, 2), 6.40 (s, 1), 6.45 (s, 1), 7.27 (s, 5), 7.17 (d, 2, J = 8 Hz), 7.67 (d, 2, J = 8 Hz).

Conversion of Tosylate 45 to 2-(3-Iodopropyl)-4,5-methylenedioxy -4-methoxycyclohexa-2,5-dienone (39e). Crude tosylate

45 (450 mg, 1.02 mmol) was hydrogenated over 10% Pd/C (200 mg) to give the oily phenol 38c: NMR ($CDCl_3$) δ 2.40 (s, 3, Ar-CH_3), 5.60 (br, 1, D_2O exchangable).

This crude oil was treated immediately with sodium iodide (1.5 g) in boiling acetone for 3 h. After removal of the solvent in vacuo, the residue was taken up in CH_2Cl_2 and washed with H_2O and dried (Na_2SO_4). After concentration of the solution, an unstable browish yellow oil identified to be the iodophenol was obtained: NMR ($CDCl_3$) δ 1.77-2.23 (m, 2), 2.40-2.80 (m, 2), 3.00-3.63 (m, 2), 5.20 (br, 1), 5.83 (s, 2), 6.33 (s, 1), 6.57 (s, 1).

This was oxidized at once with DDQ (175 mg), according to the procedure as in the preparation of 39d. After purification by PLC (20 cm x 20 cm x 0.2 cm; hexane:EtoAc, 1:1, v/v), 180 mg (53%, overall from 45) of 39e was isolated as an unstable oil: IR ($CHCl_3$) 1690, 1655, 1635, 1410, 1280, 1200, 980, 905 cm^{-1}; NMR ($CDCl_3$) δ 1.70-2.23 (m, 2), 2.30-2.66 (m, 2), 3.06-3.70 (m, 2), 3.33 (s, 3), 5.59 (s, 1), 5.61 (s, 1), 5.64 (s, 1), 6.70 (br, s, 1).

2-Methoxy-5-(3-tosyloxypropyl)-1,4-benzoquinone (46b). Oxidation of phenol 38c (350 mg, 1 mmol) with DDQ (250 mg) according to the method for the preparation of 39d gave, after chromatography, 60 mg (17%) of the yellow crystalline quinone 46a. Recrystallization from CH_2Cl_2-heptane gave yellow needles: mp 126-128°C; IR ($CHCl_3$) 1680, 1660, 1615,

1365, 1190, 1180 cm^{-1}; NMR ($CDCl_3$) δ1.70-2.07 (m, 2), 2.30-2.60 (m, 5), 3.77 (s, 3), 4.00 (t, 2, $\underline{J}$ = 7 Hz), 5.82 (s, 1), 6.27 (t, 1, $\underline{J}$ = 1 Hz), 7.23 (d, 2, $\underline{J}$ = 8 Hz). 7.67 (d, 2, $\underline{J}$ = 8 Hz).

2-(3-Acetoxypropyl)-4,5-methylenedioxyphenol (38b). Diol 38a (210 mg, 1.07 mmol) was treated with excess acetic anhydride in pyridine to give, after the usual aqueous work-up, 270 mg (90%) of the oily diacetate: IR (neat) 1760, 1735, 1505, 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.70-2.05 (m, 2), 2.08 (s, 3), 2.28 (s, 3), 2.53 (t, 2, $\underline{J}$ = 7 Hz), 4.09 (t, 2, $\underline{J}$ = 7 Hz), 5.98 (s, 2), 6.61 (s, 1), 6.70 (s, 1).

A solution of the crude diacetate (81 mg, 0.29 mmol) and potassium bicarbonate (50 mg) in methanol (2 mL) was stirred at room temperature for 60 min. It was acidified with dilute acid and methanol was removed in vacuo. The residue was taken up in water-methylene chloride and layers were partitioned. Organic phase was washed once with brine and dried (Na_2SO_4). Solvent was removed and acetate 38b was obtained (55 mg, 80%) as a solid. Recrystallization from ether-hexane gave white crystals: mp 110°C; IR ($CHCl_3$) 3600, 3350 (br), 1725, 1505, 1490, 1175 cm^{-1}; NMR ($CDCl_3$) δ1.80-2.10 (m, 2), 2.10 (s, 3), 2.62 (t, 2, $\underline{J}$ = 7 Hz), 4.11 (t, 2, $\underline{J}$ = 7 Hz), 5.44 (s, 1, D_2O exchangable), 5.91 (s, 2), 6.43 (s, 1), 6.62 (s, 1); MS 238 (M^+, 31), 178 (100), 151 (63).

2-(3-Acetoxypropyl)-4-methoxy-4,5-methylenedioxycyclohexa-2,5-dienone (39a). Oxidation of acetate 38b (24.7 mg, 0.11 mmol) with DDQ (25 mg) in methanol (10 mL) under the general procedure gave, after PLC (20 cm × 20 cm × .05 cm; 30% ethyl acetate in hexane), 25 mg (85%) of 39a as an oil: IR ($CHCl_3$) 1740, 1695, 1660, 1640, 1415, 1250, 1200 cm^{-1}; NMR ($CDCl_3$) δ1.85-2.06 (m, 2), 2.06 (s, 3), 2.48 (br. t, 2, J = 7 Hz), 3.34 (s, 3), 4.13 (t, 2, J = 7 Hz), 5.64 (s, 2), 5.68 (s, 1), 6.71 (t, 1, J = 1 Hz).

3,4-methylenedioxy-6-propylphenol (34). Phenol 17 (534 mg, 3 mmol) was hydrogenated over 10% Pd/C (50 mg) at room temperature and atmospheric pressure in ethanol (50 mL). After the theorectical uptake of hydrogen, catalysts and solvent were removed to give 540 mg (100%) of 34. Further purification by sublimation (80°C/0.35 mm Hg) followed by recrystallization from hexane gave long white needles: mp 76-8°C; IR ($CHCl_3$) 3300 (br), 1520, 1180, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (br. t, 3, J = 7 Hz), 1.40-2.00 (m, 2), 2.50 (br. t, 2, J = 7 Hz), 4.80 (s, 1, D_2O exchangable), 5.90 (s, 2), 6.40 (s, 1), 6.60 (s, 1); MS 180 (M^+, 30), 151 (100).

Oxidation of Phenol 34 in 2-Chloroethanol. Reaction of phenol 34 (464 mg, 2.18 mmol) in 2-chloroethanol (5 mL) with DDQ (645 mg) using the general procedure (except no p-nitrophenol!) gave two crystalline products, quinone ketal 35b

(275 mg, 41%) and chloroethoxyquinone 35b' (92 mg, 16%), after column chromatography (50 g silica gel, hexane-ethyl acetate, 4:1, v/v).

The less polar compound, 4-(2-chloroethoxy)-4,5-methylenedioxy-2-propylcyclohexa-2,5-dienone (35b), was isolated as an oil; it was further purified by recrystallization from ether-pentane: mp 70-71°C; IR ($CHCl_3$) 1685, 1640, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (t, 3, J = 7 Hz), 1.36-1.74 (m, 2), 2.32 (t, 2, J = 7 Hz), 3.48-3.84 (m, 4), 5.56 (s, 1), 5.60 (s, 1), 5.74 (s, 1), 6.60 (t, 1, J = 1 Hz); UV 240, 297 nm; MS 260 (M^+ + 2, 1.5), 258 (M^+, 5), 230 (11), 228 (33), 193 (100), 69 (78).

2-(2-Chloroethoxy)-5-propyl-1,4-benzoquinone (35b') was recrystallized from ether-pentane to give yellow crystals: mp 98°C; IR ($CHCl_3$) 1680, 1655, 1605, 1190 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (t, 3, J = 7 Hz), 1.33-1.70 (m, 2), 2.43 (t, 2, J = 7 Hz), 3.70-4.30 (m, 4), 5.90 (s, 1), 6.30 (t, 1, J = 1 Hz); MS 228 (M^+, 2), 193 (65), 165 (49), 149 (27), 69 (100); UV 266 nm.

Oxidation of Phenol 34 in Methanol: Method A. 3,4-Methylenedioxy-4-methoxy-6-propylcyclohexa-2,5-dienone (35a) (897 mg, 86%) was isolated as a pale oil after phenol 34 (900 mg, 5 mmol) was treated with DDQ (1.20 g) in methanol (15 mL) in the usual manner. The oil obtained crystallized at -15°C. Recrystallization from pentane at -15°C gave large white

crystals: mp $<30^{\circ}$C; IR ($CHCl_3$) 1700, 1660, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (br. t, 3, $\underline{J}$ = 7 Hz), 1.20-1.80 (m, 2), 2.37 (br. t, 2, $\underline{J}$ = 7 Hz), 3.32 (s, 3), 5.50 (s, 1), 5.53 (s, 1), 5.57 (s, 1), 6.60 (t, 1, $\underline{J}$ = 1 Hz); MS 210 (M^+, 19), 180 (83), 179 (64), 165 (76), 69 (100); UV 241, 298 nm.

2-Methoxy-5-propyl-1,4-benzoquinone (35a') was produced in 4% yield as yellow crystals. Recrystallization from ether-pentane gave yellow plates: mp 120-123°C; IR ($CHCl_3$) 1680. 1655, 1615, 1180, 910 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (br. t, 3, $\underline{J}$ = 7 Hz), 1.30-1.70 (m, 2), 2.41 (br. t, 2, $\underline{J}$ = 7 Hz), 3.80 (s, 3), 5.90 (s, 1), 6.47 (t, 1, $\underline{J}$ = 1 Hz); MS 180 (M^+, 2), 151 (17), 137 (11), 123 (30), 69 (100): UV 265 nm (ε 18,200), 363 (630).

Method B. The desired product was prepared via the general procedure by treatment of 1.8 g (10 mmol) of phenol 34 with ferric chloride and potassium carbonate in methanol. Pure quinone ketal 35a (1.75 g, 84%) was obtained after filtration of the crude oily solid through a short column of silica gel and recrystallization.

Desmethyldihydroburchellin (36a/b): Method A. To a stirred mixture of quinone ketal 35a (246 mg, 0.95 mmol) and isosafrole (5, 243 mg) in anhydrous methylene chloride (20 mL) was added silver fluoroborate (388 mg) in one portion. The resulting solution was kept under argon for 24 h, during

which greyish precipitates appeared on the side of flask. After the usual work-up and column chromatography (60 g; 25% ethyl acetate in hexane), 208 mg (64%) of a pale yellow solid (which was shown to be a 3:1 mixture of 36a and 36b by NMR) was isolated. Fractional Recrystallization from ethyl acetate gave firstly the enol 36a as white crystals: mp 150-54°C; IR ($CHCl_3$) 3400, 1630, 1455, 1380, 1260, 1175, 1045, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.70-1.95 (m, 10), 2.00-2.45 (m, 1), 5.18 (d, 1, J = 10 Hz), 5.71 (s, 1), 5.84 (s, 1), 6.00 (s, 2), 6.63-6.83 (m, 3); MS 328 (M^+, 6), 162 (100). Exact mass. Calcd for $C_{19}H_{20}O_5$: 328.13107. Found 328.13039.

The keto-tautomer 36b was obtained as pale yellow crystals: mp 169-72°C; IR ($CHCl_3$) 1730, 1665, 1620, 1455, 1375, 1260, 1175, 1040, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.80-1.95 (m, 10), 2.00-2.40 (m, 1), 2.66 (d, 1, J = 16 Hz), 3.02 (d, 1, J = 16 Hz), 5.18 (d, 1, J = 10 Hz), 6.00 (s, 2), 6.10 (s, 1), 6.63-6.83 (m, 3); MS 328 (M^+, 5), 162 (100). Exact mass. Calcd for $C_{19}H_{20}O_5$: 328.13107. Found 328.13108.

Method B. To a stirred mixture of quinone ketal 35a (129 mg, 0.6 mmol) and isosafrole (5, 160 mg) in anhydrous methylene chloride (10 mL) was added, under argon atmosphere, trimethyloxonium fluoroborate (0.3 g) in one batch. The mixture was stirred for 5.5 h and then worked up as usual. Purification by column chromatography as in method A gave 152 mg (74%) of 36a and 36b indistinguishable by all spectroscopic

methods to those prepared previously.

Method C. To a stirred mixture of quinone ketal 35a (70 mg, 0.33 mmol) and isosafrole (5, 54 mg, 0.34 mmol) in anhydrous acetonitrile (4 mL) was added dropwise a solution of methanesulfonic acid (distilled over P_2O_5; 100 μL in 1.5 mL of acetonitrile). After 15 min at room temperature, the mixture was worked up as usual and purification by chromatography gave 99 mg (92%) of 36a/b identical to previously prepared material.

Dihydroburchellin (37). A mixture of silver (I) oxide (300 mg), methyl iodide (300 μL), and 110 mg (0.34 mmol) of 36a/b in dimethylformamide (10 mL) was stirred at room temperature for 15 h. It was then filtered to remove any insoluble silver salts; the filtrate was diluted with water and extracted twice with ethyl acetate. The combined organic fractions were washed three times with water and then dried ($MgSO_4$). Solvent was removed in vacuo to afford an oil; trituration with ether gave pale crystals (90 mg, 80%). Further recrystallization from CH_2Cl_2-heptane gave white crystals: mp 196-9°C; IR ($CHCl_3$) 1655, 1615, 1505, 1495, 1455, 1390, 1370, 1260, 1160, 1040, 940 cm^{-1}; NMR ($CDCl_3$) δ 0.76-1.40 (m, 8), 1.50-1.90 (m, 2), 2.00-2.42 (m, 1), 3.69 (s, 3), 5.18 (d, 1, J = 10 Hz), 5.45 (s, 1), 5.80 (s, 1), 6.00 (s, 2), 6.69-6.87 (m, 3); UV 288 nm (ϵ 13,500), 260 (21,600).

Exact mass. Calcd for $C_{20}H_{22}O_5$: 342.14672. Found 342.14859.

Spiro-fluorodienone 33. Reaction of quinone ketal 20b (513 mg, 2 mmol) with isosafrole (5, 0.5 g) in anhydrous methylene chloride (35 mL) in the presence of silver fluoroborate (440 mg) under the condition as described for the preparation of 36a/b gave, after the usual work-up and chromatography (80 g; methylene chloride), 610 mg (86%) of white solid; recrystallization from hexane-ethyl acetate gave crystal: mp 177-200°C; IR ($CHCl_3$) 1625, 1420, 1390 cm^{-1}; NMR ($CDCl_3$) δ 0.42, 0.46 (two sets of d, 3, J = 7 Hz), 1.71-3.0 (m, 6), 5.13 (d of m, 1, J = 48 Hz), 5.66-6.27 (m, 6), 6.62-6.90 (m, 3); UV 244 nm (ϵ 10,700), 256 (sh, 9600), 268 (sh, 6050), 290 (7200), 315 (sh, 4100); MS 358 (M^+, 100), 338 (35), 187 (59), 162 (26), 151 (90). Exact mass. Calcd for $C_{20}H_{19}FO_5$: 358.12165. Found 358.12575. Spectroscopic data indicate that it contains a mixture of diastereomers.

The same dienone was obtained in lesser amounts (63%) when quinone ketal 20a and triethyloxonium fluoroborate were used instead.

3aβ-(3-Acetoxypropyl)-3,3a-dihydro-5-methoxy-3β-methyl-2α-(3,4-methylenedioxyphenyl)-6(2H)-benzofuranone (41). Treatment of quinone ketal 39a (25 mg, 0.09 mmol) and isosafrole (5, 0.1 g) with trimethyloxium fluoroborate (0.5 g) in anhydrous methylene chloride (5 mL) for 3.5 h gave, after the

usual work-up and PLC (20 cm × 20 cm × 0.05 cm; 30% ethyl acetate in hexane), 22 mg (61%) of the enol-keto tautomers of acetoxy-dihydrobenzofuranone 40 (2:1, enol:keto by intergration) as crystalline solid: mp 134-9°C; IR ($CHCl_3$) 3420, 1740, 1675, 1630 cm^{-1}; NMR ($CDCl_3$)δ 2.07 (s, 3), 4.04 (br. t, 2, J = 6 Hz); MS 386 (M^+, 3), 162 (100).

The acetoxy adduct 40 (16 mg, 0.0415 mmol) was then methylated using the procedure described for the preparation of 37. Methylether 41 was obtained in 74% yield (12 mg) as white crystals (ether-methanol): mp 100-2°C; IR ($CHCl_3$) 1740, 1660, 1620, 1260, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (d, 3, J = 7 Hz), 1.40-2.00 (m, 4), 2.06 (s, 3), 2.14-2.46 (m, 1), 3.73 (s, 3), 3.95-4.13 (m, 2), 5.18 (d, 1, J = 10 Hz), 5.45 (s, 1), 5.89 (s, 1), 6.02 (s, 2), 6.75-6.80 (m, 3); MS 400 (M^+, 100), 162 (40). Exact Mass. Calcd for $C_{22}H_{24}O_7$: 400.15220. Found: 400.15743.

3,3a-Dihydro-3aβ-(3-iodopropyl)-5-methoxy-3β-methyl-2α-(3,4-methylenedioxyphenyl)-6(2H)-benzofuranone (52). Reaction of quinone ketal 39c (180 mg, 0.535 mmol) with isosafrole (0.15 g) in anhydrous methylene chloride (15 mL), in the presence of triethyloxonium fluoroborate (0.35 g) gave after the usual work-up and column chromatography (10 g; 50% ethyl acetate in hexane), 185 mg (74%) of the crystalline iodo-dihydrobenzofuranone 51. Recrystallization from ether-chloroform gave yellow rods: mp 180-2°C; IR ($CHCl_3$) 3400, 1720

(weak), 1620, 1505, 1495, 1450 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (d, 3, $\underline{J}$ = 7 Hz), 1.58-2.00 (m, 4), 2.10-2.40 (m, 1), 3.00-3.65 (m, 2), 5.25 (d, 1, $\underline{J}$ = 10 Hz), 5.78 (s, 1), 5.91 (s, 1), 6.03 (s, 2), 6.74-6.93 (m, 3); MS 454 (M^+, 8), 326 (8), 162 (100). Spectroscopic data indicates that the crude and pure product existed predominantly as the enol-form.

A mixture of the iodo adduct 51 (88 mg, 0.188 mmol), silver (I) oxide (270 mg), and methyl iodide (0.25 mL) in 10 mL of dimethylformamide was stirred at room temperature for 16 h. After the usual work-up and PLC (20 cm × 20 cm × 0.2 cm; 50% ethyl acetate in hexane), methyl ether 52 was obtained in 54% yield (31 mg). Recrystallization from ether-methanol gave white crystals: mp 180-1°C; IR ($CHCl_3$) 1655, 1615, 1255, 1165 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (d, 3, $\underline{J}$ = 7 Hz), 1.28-1.90 (m, 4), 2.07-2.20 (m, 1), 3.48 (br. t, 2, $\underline{J}$ = 6 Hz), 3.68 (s, 3), 5.16 (d, 1, $\underline{J}$ = 10 Hz), 5.39 (s, 1), 5.81 (s, 1), 5.97 (s, 2), 6.80 (br. s, 3); MS 468 (M^+, 20), 162 (100).

Trace amount of the α-diketone 53 was also isolated after the methylation procedure.

α-Diketone 53. To a solution of the iodo-dihydrobenzofuranone 51 (40 mg, 0.086 mmol) in anhydrous tetrahydrofuran (2 mL) was added 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 30 μL). Precipitation started at once and after 15 min, the mixture was poured into dilute hydrochloric acid and then extracted with methylene chloride. The combined organic extracts were washed once with brine and dried (Na_2SO_4). The oil obtained after removal of solvent in vacuo was purified by PLC (20 cm × 20 cm × .05 cm; 50% ethyl acetate in hexane). Pure diketone 53 was obtained (26 mg, 90%) as pale yellow crystals. Further recrystallization from ether-methanol gave an analytical sample: mp 188-91°C; IR ($CHCl_3$) 1720, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (t, 3, J = 7 Hz), 1.58-3.10 (m, 8), 5.05 (d, 1, J = 10 Hz), 6.04 (s, 1), 6.09 (s, 2), 6.93 (br. s, 3); MS 326 (M^+, 22), 175 (23), 162 (100). Exact mass. Calcd for $C_{19}H_{18}O_5$: 326.11542. Found: 326.11589.

3,3a-Dihydro-3aβ-(3-methanesulfonyloxypropyl)-5-methoxy-3β-methyl-2α-(3,4-methylenedioxyphenyl)-6(2H)-benzofuranone (49). A solution of the quinone ketal 39d (2.3 g, 7.57 mmol) and isosafrole (5, 1.6 g) in anhydrous methylene

chloride (60 mL) was treated with triethyloxonium fluoroborate (2.5 g) at room temperature. After 3.5 h, the mixture was worked up in the usual manner to yield a foam; this was chromatographed (220 g; 30% ethyl acetate in methylene chloride) and 1.97 g (62%) of mesylate 48 was obtained. NMR indicates it to be a 3:1 (enol:keto) mixture: IR ($CHCl_3$) 1720, 1625, 1370, 1130 cm^{-1}; NMR ($CDCl_3$) δ 2.97 (s, 3), 4.17 (br. t, 2, J = 6 Hz), 5.17 (d, 1, J = 10 Hz); MS 422 (M^+, 1%), 326 (25), 162 (100).

Conversion to the methyl ether was done according to the procedure as described for the preparation of 37. Mesylate 48 (310 mg, 0.735 mmol) afforded 277 mg (85%) of the methyl ether 49 as a foam when it was treated with 0.75 g of silver oxide and 0.9 mL of methyl iodide in 10 mL of dimethylformamide for 16 h: IR ($CHCl_3$) 1650, 1615, 1355, 1250, 1155, 930 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3, J = 7 Hz), 1.53-2.00 (m, 4), 2.13-2.50 (m, 1), 3.04 (s, 3), 3.73 (s, 3), 4.24 (br. t, 2, J = 7 Hz), 5.23(d, 1, J = 10 Hz), 5.46 (s, 1), 5.87 (s, 1), 6.02 (s, 2), 6.74-6.88 (m, 3); MS 436 (M^+, 12), 340 (60), 162 (100). Exact mass. Calcd for $C_{21}H_{24}O_8S$: 436.11919. Found: 436.12063.

(±)-Burchellin (2). To a stirred suspension (yellow) of p-chlorodiphenyl diselenide (118 mg, 0.314 mmol) in absolute ethanol (2 mL) was added slowly, under a heavy nitrogen atmosphere, small quantities of solid sodium borohydride,

until a persistent colorless solution was obtained. The flask was then cooled to 0°C, and methyl ether 49 (259 mg, 0.595 mmol) in 3.5 mL of anhydrous tetrahydroforan was added quickly using a pipette. The resulting solution was stirred at room temperature for 2.5 h, then cooled to 0°C, and sodium metaperiodate (1.0 g) in 20 mL of 50% aqueous methanol was added. Cooling bath was removed and the resulting mixture was heated at 70°C for 2.5 h, and then diluted with water, and extracted thoroughly with ethyl acetate. The combined organic extracts were washed with 5% sodium bicarbonate, brine, and dried ($MgSO_4$). The oil obtained after evaporation of solvent in vacuo was chromatographed (30 g; 25% ethyl acetate in methylene chloride). (±)-Burchellin (2) was isolated as a white solid (170 mg, 85%). Recrystallization from ether-hexane gave white plates: mp 135°C; IR ($CHCl_3$) 1650, 1620, 1495, 1450, 1360, 1260, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (d, 3, J = 7 Hz), 2.14-2.58 (m, 3), 3.68 (s, 3), 4.87-5.18 (m, 2), 5.19 (d, 1, J = 10 Hz), 5.42 (s, 1), 5.35-5.73 (m, 1), 5.80 (s, 1), 5.98 (s, 2), 6.73-6.80 (m, 3); UV 260 nm (ϵ 17,400), 288 (10,350). Exact mass. Calcd for $C_{20}H_{20}O_5$: 340.13107. Found: 340.13111.

About 5% of selenide 50 was recovered as a foam after chromatography: IR ($CHCl_3$) 1650, 1615, 1500, 1495, 1475, 1450, 1160 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (d, 3, J = 7 HZ), 1.34-2.00 (m, 4), 2.00-2.40 (m, 1), 2.85 (t, 2, J = 6 Hz), 3.65 (s, 3), 5.14 (d, 1, J = 10 Hz), 5.37 (s, 1), 5.80 (s, 1),

6.01 (s, 2), 6.70-6.90 (m, 3), 7.17-7.50 (m, 4). Exact mass. Calcd for $C_{26}H_{25}{}^{35}ClO_5{}^{80}Se$: 532.05558. Found: 532.05587.

p-Toluenesulfonic Acid Catalyzed Condensation of Quinone Ketal 35a with Isosafrole (5). A mixture of quinone ketal 35a (96 mg, 0.455 mmol), isosafrole (5, 120 mg), and p-toluenesulfonic acid (160 mg) in acetonitrile (5 mL) was stirred at room temperature for 60 min. The reaction mixture was worked up according to the general procedure and then purified by PLC (20 cm × 20 cm × 0.2 cm; 25% ethyl acetate in hexane). Three products were isolated.

The least polar compound, obtained in 28% yield (42 mg), was identified to be bicyclooctanone 59: mp 140-3°C (ether-hexane); IR ($CHCl_3$) 3470, 1760, 1680, 1510, 1495 cm^{-1}; NMR ($CDCl_3$) δ 0.83-1.25 (m, 3), 1.10 (d, 3, J = 7 Hz), 1.33-1.96 (m, 4), 2.48 (m, 1, J = 7 Hz), 3.10 (t, 1, J = 7 Hz), 3.66 (d, 1, J = 7 Hz), 5.83 (s, 1), 5.96 (s, 2), 6.40-6.80 (m, 3); UV 240, 280 nm. Exact mass. Calcd for $C_{19}H_{20}O_5$: 328.13107. Found: 328.13118. Spectroscopic data indicate that it exists entirely as the diosphenol form.

The next product isolated (37 mg, 25%) was identical to previously prepared dihydrobenzofuranone 36a/b.

The most polar component was characterized to be dienone 60. It was produced in about 7% yield (12 mg) as white crystals (CH_2Cl_2-heptane): mp 151-2°C; IR ($CHCl_3$) 3600, 3400 (br), 1630, 1505, 1490 cm^{-1}; NMR ($CDCl_3$) δ 0.55

(d, 3, J = 7 Hz), 0.80-1.33 (m, 5), 1.77-2.60 (m, 4, 1H exchangable with D_2O), 4.56 (br. d, 1, J = 8 Hz), 5.67 (s, 1), 5.71 (s, 1), 5.90 (s, 2), 6.03 (s, 2), 6.85 (m, 2), 6.97 (s, 1); UV 243 nm (ε11,200), 255 (8000), 266 (sh, 6700), 290 (7000), 310 (4700); MS 358 (M^+, 1), 193 (58), 180 (61), 93 (83), 65 (100). Anal. ($C_{20}H_{22}O_6$) C, H.

3-Methoxy-6-exo-methyl-7-endo-(3,4-methylenedioxyphenol)-5-propylbicyclo[3.2.1]oct-3-ene-2,8-dione (61). Bicyclooctanone 59 (22 mg, 0.0675 mmol) was methylated with silver oxide (40 mg) and methyl iodide (70 μL) in dimethylformamide (5 mL) using the procedure for the preparation of 37. After work-up and PLC (20 cm × 20 cm × .05 cm; 30% ethyl acetate in hexane), 17 mg (75%) of the methyl ether was obtained as an oily solid. Recrystallization from ether-hexane gave white crystals: mp 125°C; IR ($CHCl_3$) 1760, 1690, 1615, 1505, 1495 cm^{-1}; NMR ($CDCl_3$) δ1,15 (d, 3, J = 7 Hz), 1.10-1.30 (m, 3), 1.45-2.18 (m, 4), 2.51 (m, 1, J = 7 Hz), 3.10 (t, 1, J = 7 Hz), 3.74 (s, 3), 3.75 (d, 1, J = 7 Hz), 5.96 (s, 2), 6.27 (s, 1), 6.56 (d, 1, J = 1 Hz), 6.58 (d of d, 1, J = 1 Hz, 8 Hz), 6.76 (d, 1, J = 8 Hz); UV 235 nm (ε7450), 275 (8400). Exact mass. Calcd for $C_{20}H_{22}O_5$: 342.14672. Found: 342.14727.

Conversion of Dienone 60 to Desmethyldihydroburchellin 36a/b. To a stirred solution of the dienone 60 (5 mg) in acetonit-

rile (2 mL) was added one crystal of anhydrous p-toluenesulfonic acid. After stirring at room temperature for 10 min, the mixture was neutralized and after the usual work-up gave 36a/b in quantitative yield, identical in all respect to an authentic sample.

Conversion of Bicyclooctanone 59 to Desmethyldihydroburchellin 36a/b. Bicyclooctanone 59 was treated with trifluoromethanesulfonic acid in acetonitrile for 10 min and then worked up as usual to give a quantitative yield of 36a/b, identical in all respect to an authentic sample.

5-(3-Methanesulfonyloxypropyl)-3-methoxy-6-exo-methyl-7-endo-(3,4-methylenedioxyphenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (63). Treatment of quinone ketal 39d (340 mg, 1.1 mmol) with isosafrole (5, 190 mg) in anhydrous acetonitrile (10 mL), in the presence of p-toluenesulfonic acid (anhydrous, 190 mg) for 30 min at room temperature gave 500 mg of oil after the usual work-up. This was quickly filtered through a short column of silica gel to remove unreacted isosafrole and base-line materials. The filtrate obtained was shown to be a mixture of 62 and 48 by NMR. Methylation with excess silver (I) oxide and methyl iodide, followed by work-up according to the procedure described for the preparation of 37, gave 370 mg of product. This was chromatographed (25 g; 30% ethyl acetate in hexane) and the desired

bicyclooctanone 63 was obtained as a foam (77 mg, 16%): IR ($CHCl_3$) 1760, 1695, 1615, 1499, 1360, 1180, 940 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3, J = 7 Hz), 1.63-2.20 (m, 4), 2.50 (m, 1), 3.05 (s, 3), 3.00-3.20 (m, 1), 3.68 (s, 3), 3.70 (d, 1, J = 7 Hz), 4.19-4.28 (m, 2), 5.90 (s, 2), 6.17 (s, 1), 6.50-6.70 (m, 3); MS 436 (M^+, 23), 340 (11), 162 (100). Exact mass. Calcd for $C_{21}H_{28}O_8S$: 436.11919. Found: 436.11688.

Mesylate-methyl ether 49 was also obtained in 20% yield and was identical to previously prepared material.

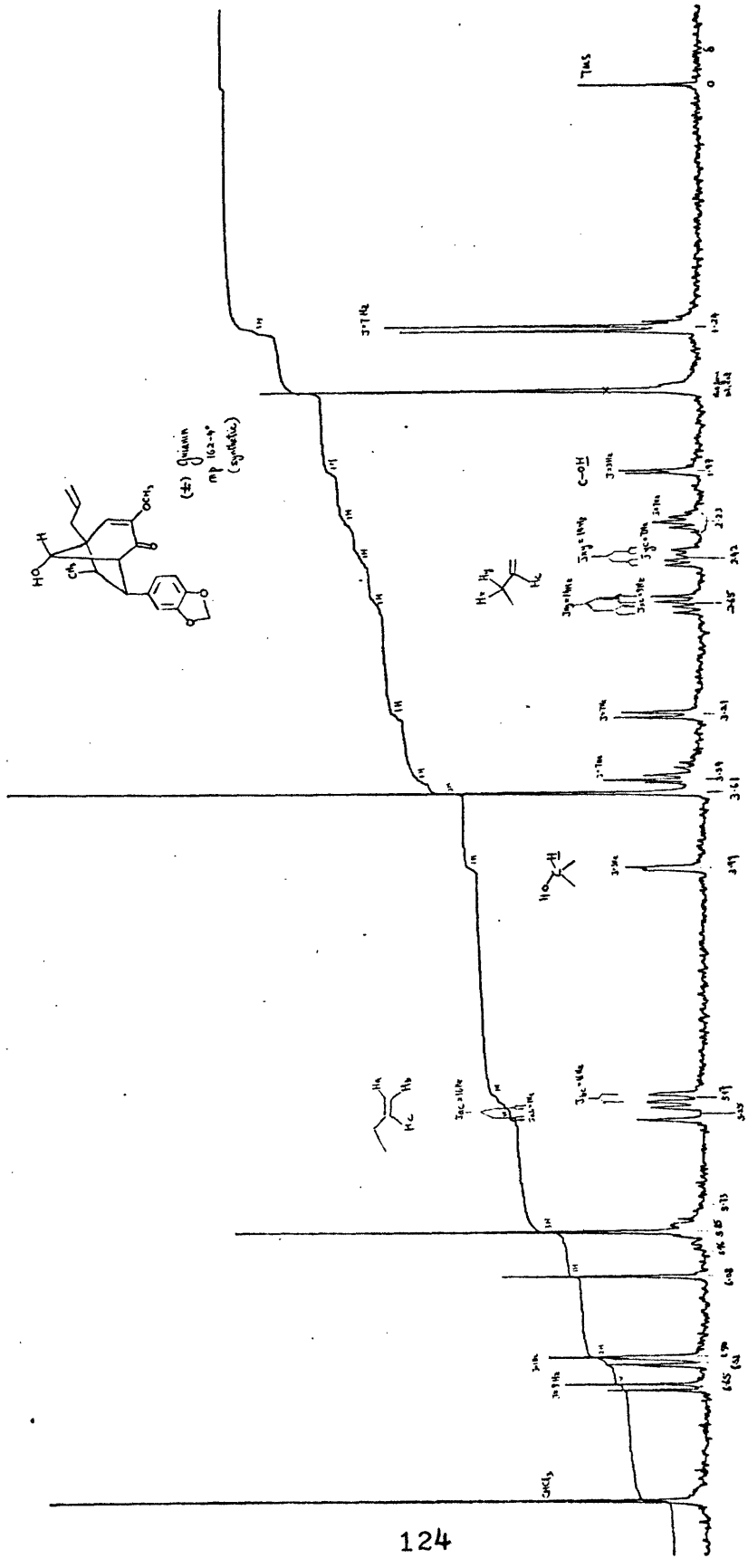
8-Hydroxy-1-(3-methanesulfonyloxypropyl)-3-methoxy-7-exo-methyl-6-endo-(3,4-methylenedioxyphenyl)-4-oxobicyclo[3.2.1]-oct-2-ene (64). A solution of the bicyclooctanone 63 (42 mg, 0.096 mmol) in methanal: tetrahydrofuran (1 mL:0.5 mL) was cooled to 0°C and sodium borohydride (1.2 mg) was added all at once. After 25 min, aqueous methanal was added, followed by small amount of solid sodium chloride (to break up emulsion!). Aqueous mixture was extracted with methylene chloride and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 41 mg of foam. Purification by PLC (20 cm × 20 cm × 0.1 cm; 40% ethyl acetate in hexane) gave 64 (22 mg, 50%) as a foam which seems to decompose on silica gel: IR ($CHCl_3$) 3500 (br), 1695, 1620, 1500, 1450, 1360, 1180 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, 3, J = 7 Hz), 1.50-2.40 (m, 5), 2.70 (br. s, 1), 3.06 (s, 3), 3.20 (d, 1, J = 7 Hz), 3.56 (t, 1, J = 7 Hz), 3.65 (s, 3), 4.01(br. s,

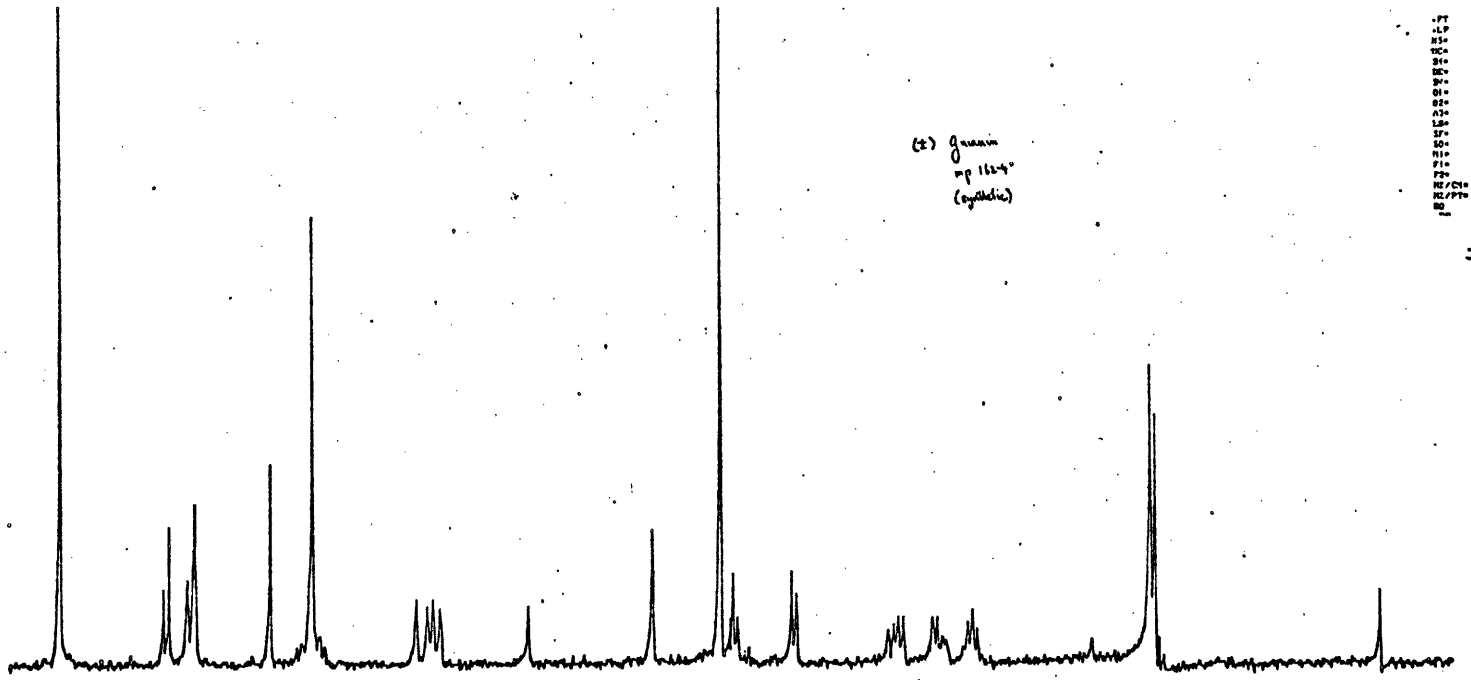
1), 4.35 (br. t, 2, $\underline{J}$ = 6 Hz), 5.91 (s, 2), 6.03 (s, 1), 6.46-6.62 (m, 2), 6.72 (d, 1, $\underline{J}$ = 8 Hz); MS 438 (M^+, 13), 342 (100), 180 (48), 162 (71). Exact mass. Calcd. for $C_{21}H_{26}O_8S$: 438.13484. Found: 438.13836.

(±)-Guianin (1). Bicyclooctanone 63 (30 mg, 0.0675) was reduced with sodium borohydride (0.8 mg) under the same condition as described for its conversion to 64. The crude foam obtained, without any purification, was again dissolved in anhydrous tetrahydrofuran and treated with the same procedure for the conversion of mesylate-methyl ether 49 to (±)-burchellin (via the elimination of selenoxide). After the usual work-up and PLC (20 cm × 20 cm × .05 cm; 50% ethyl acetate in hexane), racemic guianin was obtained (7 mg, 30%) as an oil, which on trituration with ether gave white crystals. Recrystallization from ether-hexane gave an analytical sample: mp 162-4°C; IR ($CHCl_3$) 3575, 3450, 1680, 1615, 1500, 1490, 1035 cm^{-1}; NMR ($CDCl_3$) see attached 270 MHz spectra;[63] UV 234 nm (ε 7900), 265 (8700); MS 342 (M^+, 100), 180 (26), 162 (87). Exact mass. Calcd for $C_{20}H_{22}O_5$: 342.14672. Found 342.14628.

The acetate 65 was obtained as a foam when (±)-guianin was treated with excess acetic anhydride in pyridine followed by aqueous work-up: IR ($CHCl_3$) 1740, 1690, 1620, 1500, 1445, 1385, 1220, 1150 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (d, 3, $\underline{J}$ = 7 Hz), 2.18 (s, 3), 2.30-2.54 (m, 3), 3.27 (d, 1, $\underline{J}$ = 7 Hz),

270 MHz NMR Spectrum of
(±)-Guianin




(±) guaiazulene
mp 114-4°
(synthetic)
4/1/77
30 treated

3.42 (t, 1, $\underline{J}$ = 7 Hz), 3.65 (s, 3), 5.08-5.40 (m, 3), 5.78-6.40 (m, 1), 5.93 (s, 2), 6.15 (s, 1), 6.51-6.65 (m, 2), 6.73 (d, 1, $\underline{J}$ = 8 Hz); MS 384 (M^+, 19), 324 (13), 283 (67), 162 (36), 43 (100).

Trifluoromethanesulfonic Acid Catalyzed Condensation of Quinone Ketal 20a and Isosafrole (5). Three products were isolated in varying amounts under different condensation conditions.[64] (catalytic amount of trifluoromethanesulfonic acid was used in each run)

Desmethylburchellin (67) was obtained as a foam and was shown to be a mixture of the enol-keto tautomers (1:1, NMR intergration): IR ($CHCl_3$) 3400 (enol), 1735 (keto), 1660 (keto), 1630 (enol), 1455, 1370, 1260 cm^{-1}; NMR ($CDCl_3$) δ1.09, 1.16 (two sets of doublets, 3, $\underline{J}$ = 7 Hz, methyl protons), 2.18-2.75 (m, 3), 2.71, 3.09 (keto, AB quartet, $\underline{J}$ = 16 Hz), 4.90-5.40 (m, 3), 5.60-6.10 (m, 1), 5.78 (s, enol, vinyl proton), 5.89 (s, enol, vinyl proton), 6.02, 6.04 (two singlets, 2, methylene protons), 6.15 (s, keto, vinyl proton), 6.50-6.93 (m, 3); MS 326 (M^+, 14), 285 (81), 162 (100).

Methylation of 67 with excess silver(I) oxide and methyl iodide in dimethylformamide under the condition described for the conversion of 36a/b to 37 gave (±)-burchellin in 70% yield. The product obtained was indistinguishable form that of previously prepared material.

Dienone 68 was obtained as a white crystalline solid (ether-hexane): mp 168-70°C; IR ($CHCl_3$) 1630, 1495, 1420, 1400, 1045 cm^{-1}; NMR ($CDCl_3$) δ 0.61 (d, 3, J = 7 Hz), 1.80-2.44 (m, 2), 2.67-3.10 (m, 2), 5.58-5.84 (m, 3), 5.86 (s, 1), 5.89 (s, 1), 5.90 (s, 1), 5.98 (s, 2), 6.62-6.85 (m, 3); UV 243 nm (ε 12,100), 255 (sh, 10,300), 267 (sh, 7000), 290 (8000), 310 (sh, 5000); MS 338 (M^+, 100), 337 (53), 323 (11), 187 (25), 174 (39), 162 (17). Exact mass. Calcd for $C_{20}H_{18}O_5$: 338.11542. Found: 338.11609.

5-Allyl-2,3-dihydro-6-hydroxy-3β-methyl-2α-(3,4-methylenedioxyphenyl)benzofuran (69) was obtained as a crystalline solid (chloroform-ether-hexane): mp 137-8°C; IR ($CHCl_3$) 3600 (br), 1510, 1490, 1450, 1260 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 3, J = 7 Hz), 3.10-3.56 (m, 3), 4.71 (s, 1, D_2O exchangable), 5.05 (d, 1, J = 9 Hz), 5.09-5.25 (m, 2), 5.78-6.05 (m, 1), 5.98 (s, 2), 6.65 (s, 2), 6.73-6.98 (m, 3); MS 310 (M^+, 100), 254 (25). Exact mass. Calcd for $C_{19}H_{18}O_5$: 310.12051. Found: 310.12318.

2,4,6-Trinitrobenzenesulfonic Acid Catalyzed Condensation of Isosafrole (5) and Quinone Ketal 20a. A mixture of quinone ketal 20a (416 mg, 2.0 mmol), isosafrole (5, 350 mg), and 2,4,6-trinitrobenzenesulfonic acid (0.6 g) in anhydrous acetonitrile (7 mL) was stirred at 0°C for 1.5 h. It was worked up according to the general procedure and after chromatography, (40 g; 25% ethyl acetate in hexane) gave

two major products.

The less polar product was identified to be 5-allyl-3-hydroxy-6-exo-methyl-7-endo-(3,4-methylenedioxyphenyl)-bicyclo[3.2.1]oct-3-ene-2,8-dione (58), isolated in 20% yield (130 mg) as an oily solid. Recrystallization from ether-hexane gave white crystals: mp 147-9°C; IR ($CHCl_3$) 3490, 1765, 1680, 1500, 1450, 1240, 1040 cm^{-1}; NMR ($CDCl_3$) δ1.14 (d, 3, J = 7 Hz), 2.24-2.78 (m, 3), 3.16 (t, 1, J = 7 Hz), 3.80 (d, 1, J = 7 Hz), 5.15-5.42 (m, 2), 5.70-6.10 (m, 1), 5.87 (s, 1), 5.97 (s, 2), 6.50-6.80 (m, 3); MS 326 (M^+, 20), 285 (14), 162 (100); UV 232 nm (ϵ 9100), 280 (9900). Exact mass. Calcd for $C_{19}H_{18}O_5$: 326.11542. Found: 326.11839.

The more polar product, desmethylburchellin (67), was obtained in 20% yield (135 mg).

5-Allyl-3-methoxy-6-exo-methyl-7-endo-(3,4-methylenedioxyphenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (70). To a stirred solution of bicyclooctanone 58 (29 mg, 0.089 mmol) in anhydrous methylene chloride (2 mL) was added diisopropyl ethylamine (40μL), followed by trimethyloxonium fluoroborate (0.1 g). The resulting mixture was kept at room temperature for 16 h, diluted with methylene chloride, washed once with water, and then dried (Na_2SO_4). The oil obtained after removal of solvent in vacuo was purified by PLC (20 cm × 20 cm × 0.1 cm; 30% ethyl acetate in hexane). The desired methyl

ether 70 was isolated (27 mg, 90%) as a foam which crystallized on standing. Recrystallization from ether-hexane gave an analytical sample, which is spectroscopically indistinguishable from that of natural product[49]: mp 117-8°C; IR ($CHCl_3$) 1765, 1695, 1615, 1500, 1450, 1240, 1160 cm^{-1}; NMR ($CDCl_3$) δ1.16 (d, 3, J = 7 Hz), 2.30-2.84 (m, 3), 3.13 (d of d, 1, J = 7 Hz, 6 Hz), 3.69 (s, 3), 3.77 (d, 1, J = 7 Hz), 5.18-5.44 (m, 2), 5.83-6.15 (m, 1), 5.95 (s, 2), 6.30 (s, 1), 6.50- 6.65 (m, 2), 6.75 (d, 1, J = 8 Hz); UV 232 nm (ε 8100), 275 (8500); MS 340 (M^+, 58), 299 (11), 271 (40), 162 (100). Exact mass. Calcd for $C_{20}H_{20}O_5$: 340.13107. Found: 340.13285.

About 10% of starting bicyclooctanone 58 was recovered.

Conversion of Methyl Ether 70 to (±)-Guianin (1). Reduction of methyl ether 70 (34 mg, 0.1 mmol) with sodium borohydride (1 mg) in methanol (1.5 mL) at -20°C under the usual conditions and work-up gave, after PLC (20 cm × 20 cm × 0.1 cm; 20% ethyl acetate in hexane), 28 mg (83%) of racemic guianin, identical to previously prepared product.

Spiro-chlorodienone 76. A mixture of quinone ketal 20a (104 mg, 0.5 mmol) and isosafrole (5, 0.1 g) in anhydrous methylene chloride (5 mL) was treated with diethyloxonium hexachloroantimonate[50] (0,5 g) under an atmosphere of argon at 0°C. The mixture turned dark immediately upon mixing and

it was worked up at once using the general procedure. After chromatography (15 g; 25% ethyl acetate in hexane), 89 mg (47%) of 76 was obtained as a foam. Crystallization from ether-hexane gave pure 76 as a mixture of diastereomers: mp 170-210°C; IR ($CHCl_3$) 1630, 1490, 1420, 1395, 1230, 1040 cm^{-1}; NMR ($CDCl_3$) δ 0.36-0.53 (m, 3), 1.83-2,63 (m, 6), 3.96-4.79 (m, 1), 5.76-6.01 (m, 6), 6.61-6.85 (m, 3); UV 243 nm (ϵ 11,400), 256 (10,500), 267 (sh, 6800), 289 (7400), 310 (4600); MS 376 (M^++2, 25), 374 (M^+, 71), 338 (29), 187 (22), 162 (24), 151 (100), 135 (24). Exact mass. Calcd for $C_{20}H_{19}{}^{35}ClO_5$: 374.09210. Found: 374.09403.

Vinylogous Ester 74. A mixture of dienone 68 (28 mg, 0.082 mmol) in 5% methanolic potassium hydroxide (5 mL) was stirred at room temperature for 30 min. After removal of solvent in vacuo, the residue was taken up in methylene chloride and washed successively with 1N HCl and brine, and dried (Na_2SO_4). Evaporation of solvent gave 29 mg (100%) of 74 contaminated by small amounts of impurities (NMR). Recrystallization from ether-hexane gave off-white crystals: mp 217-8°C; IR ($CHCl_3$) 1695, 1640, 1620, 1495, 1220, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (d, 3, J = 7 Hz), 1.90-2.86 (m, 4), 2.89 (s, 2), 3.78 (s, 3), 5.60 (br, s, 2), 5.90 (s, 2), 5.92 (s, 1), 6.50-6.78 (m, 3); UV 240 nm (ϵ 7700), 277 (12,600); MS 340 (M^+, 8), 174 (30), 162 (6) 153 (10), 135 (18), 91 (100). Exact mass. Calcd for $C_{20}H_{20}O_5$: 340.13107. Found: 340.12994.

Condensation of Quinone Ketal 20a with Z-Isosafrole (5)[51]; Preparation of (+)-2-Epi-3a-epiburchellin (3) and (+)-Futoenone (4). A mixture of quinone ketal 20a (104 mg, 0.5 mmol) and Z-isosafrole (5, 80 mg) in anhydrous acetonitrile (5 mL) was treated with methanesulfonic acid (50 μL; distilled over P_2O_5) at 0°C for 60 min. The mixture was then worked up as usual to give 160 mg of oil, which was purified by PLC (20 cm × 20 cm × 0.2 cm; 30% ethyl acetate in hexane) to give two major products.

The less polar compound, (22 mg, 13%) desmethylepiburchellin 89, was obtained as an oil consisting of the enol-keto tautomeric mixture (3:1): IR ($CHCl_3$) 3450 (enol), 1730 (keto), 1625 (enol) cm^{-1}; NMR ($CDCl_3$) δ 0.50, 0.65 (two sets of doublets, 3, J = 7 Hz, methyl), 2.38-3.00 (m, 3), 4.87-5.40 (m, 3), 5.50-6.00 (m, 1), 5.78 (s, enol, vinyl proton), 5.87 (s, enol, vinyl proton), 5.91, 5.96 (two sets of singlets, 2), 6.09 (s, keto, vinyl proton), 6.37-6,93 (m, 3). Without more purification, 89 was methylated with excess silver oxide and methyl iodide under the usual conditions to give (±)-2-epi-3a-epiburchellin (3) in 50% yield as an oil. Trituration with ether gave crystals which on recrystallization from ether-hexane gave white needles: mp 140-2°C; IR ($CHCl_3$) 1650, 1615, 1495, 1450, 1230, 1165 cm^{-1}; NMR ($CDCl_3$) δ 0.53 (d, 3, J = 7 Hz), 2.55-2.85 (m, 3), 3.68 (s, 3), 5.02-5.32 (m, 2), 5.50 (s, 1). 5.80-6.10 (m, 1), 5.90 (s, 1), 5.96 (d, 1, J = 5 Hz), 6.02 (s, 2), 6.60-6.90

(m, 3); UV 258 nm (ε 16,400), 288 (8500); MS 340 (M^+, 100), 300 (27), 299 (96), 239 (49), 162 (58). Exact mass. Calcd for $C_{20}H_{20}O_5$: 340.13107. Found: 340.12959. Anal. ($C_{20}H_{20}O_5$) C, H.

The more polar compound (49 mg, 30%), obtained as a waxy solid, was shown to be desmethylfutoenone (90), which also exists as a 2:1 (enol:keto) mixture by NMR intergration: mp 220-3°C (ether-methanol); IR ($CHCl_3$) 3400 (enol), 1730 (keto), 1660 (keto), 1630 (enol) cm^{-1}; NMR ($CDCl_3$) δ 0.62, 0,69 (two sets of doublets, 3, J = 7 Hz), 1.70-2.65 (m, 6), 2.70, 3.20 (AB quartet, J = 17 Hz, keto), 4.95-5.27 (m, 1), 5.78 (s, enol, vinyl proton), 5.89 (s, enol, vinyl proton), 6.00 (s, 2), 6.22 (s, keto, vinyl proton), 6.50-6.89 (m, 3); Ms 326 (M^+, 50), 177 (40), 162 (100). Methylation under the usual conditions as described for the preparation of 37 gave (±)-futoenone in 53% yield. An analytical sample was obtained after recrystallization from ether: mp 242-6°C; IR ($CHCl_3$) 1655, 1615, 1250, 1145 cm^{-1}; NMR ($CDCl_3$) δ 0.64 (d, 3, J = 7 Hz), 1.70-2.78 (m, 6), 3.96 (s, 3), 5.07 (br. t, 1, J = 6 Hz), 5.50 (s, 1), 5.83 (s, 1), 5.98 (s, 2), 6.60-6.87 (m, 3); UV 258 nm (ε 17,200), 287 (8200); MS 340 (M^+, 39), 177 (42), 176 (29), 164 (32), 163 (100), 162 (77). Exact mass. Calcd for $C_{20}H_{20}O_5$: 340.13107. Found: 340.13666. Anal. ($C_{20}H_{20}O_5$) C, H.

2-Epi-3a-epidihydroburchellin (93). Condensation of quinone ketal 35a (60 mg, 0,286 mmol) with Z-isosafrole (5, 60 mg) in anhydrous acetonitrile (5 mL), in the presence of methanesulfonic acid (50 μL) at 0°C for 15 min gave an oil after the general work-up procedure. This was filtered through a short column of silica gel and 110 mg of the desmethyl derivative 92 was obtained as a foam, containing an enol/keto tautomeric mixture: NMR ($CDCl_3$) δ 0.52, 0.69 (two sets of doublets, 3, J = 7 Hz; enol:keto, 3:1).

Without further purification, the crude mixture was methylated with silver oxide and methyl iodide and 60 mg (61%) of the desired methyl ether 93 was obtained. An analytical sample was obtained after recrystallization from ether-hexane: mp 154-6°C; IR ($CHCl_3$) 1650, 1615, 1490, 1450, 1230, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.53 (d, 3, J = 7 Hz), 0.96 (t, 3, J = 7 Hz), 1.09-1.53 (m, 2), 1.73-2.04 (m, 2), 2.50-2.82 (m, 1), 3.69 (s, 3), 5.51 (s, 1), 5.89 (s, 1), 5.97 (d, 1, J = 5 Hz), 6.00 (s, 2), 6.67-6.90 (m, 3); UV 257 nm (ε 18,500), 288 (9600); MS 342 (M^+, 19), 313 (12), 299 (6), 162 (100), 149 (28). Exact mass. Calcd for $C_{20}H_{22}O_5$: 342.14672. Found: 342.14830.

Acid Rearrangement of 2-Epi-3a-epidihydroburchellin (93). A mixture of 2-epi-3a-epidihydroburchellin (93, 19.2 mg) and p-toluenesulfonic acid monohydrate (12 mg) in methanol (1 mL)[53] was stirred under an atmosphere of nitrogen for

96 h. After methanol was removed in vacuo, the residue was taken up in methylene chloride, washed with sat. sodium bicarbonate, and dried (Na_2SO_4). The oil obtained after concentration of solvent was chromatographed on a 20 cm × 20 cm × .05 cm silica gel plate with 40% ethyl acetate in hexane as solvent. Two products were obtained.

The more polar product (13 mg, 66%) was recovered starting material 93. The other compound was obtained as an oil in 31% yield (6 mg) and was shown to be bicyclooctanone 94[52]: IR ($CHCl_3$) 1765, 1685, 1485, 1440, 1240 cm^{-1}; NMR ($CDCl_3$) δ 0.96-1.20 (m, 6), 1.30-2.00 (m, 4), 2.22-2.55 (m, 1), 3.37 (d, 1, J = 7 Hz), 3.62 (s, 1), 3.69 (s, 3), 5.62 (s, 1), 5.91 (s, 2), 6.44-6.76 (m, 3); MS 342 (M^+, 100), 162 (100).

2-Allyl-4,4,5-trimethoxycyclohexa-2,5-dienone (100a). Oxidation of phenol 96 (1.25 g, 6.45 mmol) with ferric chloride using the general procedure as described gave 1.3 g (90%) of 100a as an oil which crystallized on cooling. Recrystallization from ether-pentane gave white needles: mp 50-1°C; IR ($CHCl_3$) 1680, 1660, 1640, 1470, 1240, 1180, 1100 cm^{-1}; NMR (CCl_4) δ 3.00 (br.d, 2, J = 7 Hz), 3.22 (s, 6), 3.75 (s, 3), 4.93-5.20 (m, 2), 5.44 (s, 1), 5.58-5.98 (m, 1), 6.18 (t, 1, J = 1 Hz); UV 233 nm (ϵ 11,300), 293 (3600); MS 224 (M^+, 6), 209 (13), 193 (78), 162 (40), 69 (100).

2-Propyl-4,4,5-trimethoxycyclohexa-2,5-dienone (100b). This was obtained in 88% yield (2.3g) when phenol 97 (2.28 g, 11.6 mmol) was oxidized with ferric chloride in the presence of potassium carbonate under the condition described. An analytical sample was obtained after recrystallization from ether-pentane: mp 57-8°C; IR ($CHCl_3$) 1675, 1645, 1625, 1225, 1170, 1075 cm^{-1}; NMR (CCl_4) δ 0.95 (t, 3, J = 7 Hz), 1.49 (m, 2), 2.23 (t, 2, J = 7 Hz), 3.24 (s, 6), 3.73 (s, 3), 5.58 (s, 1), 6.11 (br. s, 1); UV 235 nm (ϵ 12,300), 293 (3400); MS 226 (M^+, 6), 211 (32), 195 (73), 69 (100). Anal. ($C_{12}H_{18}O_4$) C, H.

Condensation of Quinone Ketal 100a with Isosafrole (5). To a stirred mixture of the quinone ketal 100a (0.5 g, 2.22 mmol) and isosafrole (5, 0.4 g) in anhydrous acetonitrile (10 mL) at 0°C, under an atmosphere of argon, was added 2,4,6-trinitrobenzenesulfonic acid (0.7 g). After 15 min, the reaction mixture was worked up according to the general procedure and after chromatography, (60 g; 25% ethyl acetate in hexane) bicyclooctanone 70 was isolated in 45% yield (340 mg), together with 24 mg (3%) of (±)-burchellin.

Condensation of Quinone Ketal 100b with Isosafrole (5). This was carried out according to the conditions described for the condensation of 100a with 5. Bicyclooctanone 61 (2.1 g, 61%) and dihydroburchellin (235 mg, 6%) were obtained

from 2.3 g (10 mmol) of quinone ketal 100b and 1.8 g of isosafrole.

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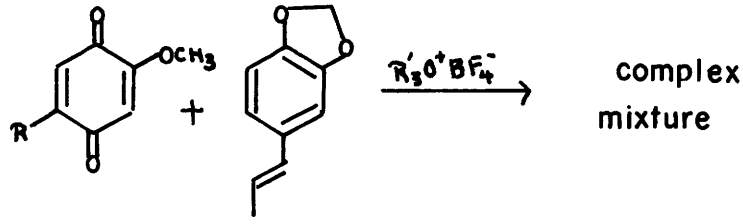

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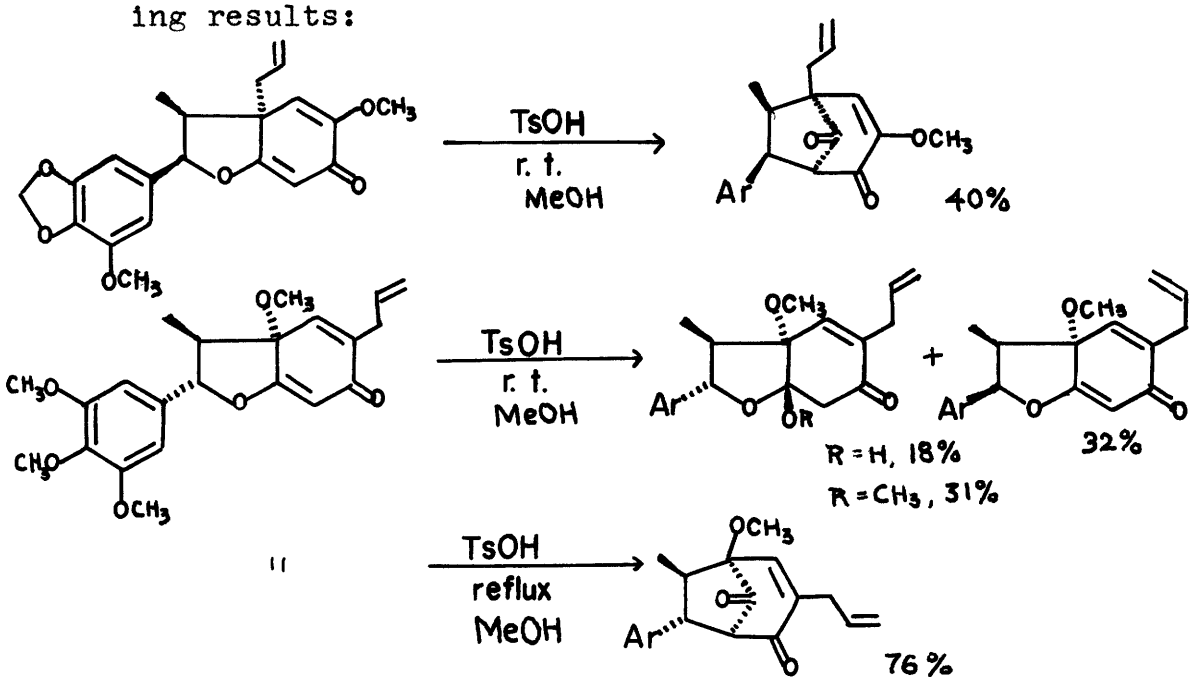

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currently using quinone ketals as intermediates in the total synthesis of miroestrol and other types of neolignans.

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63. Spectra were recorded on a Bruker-270 MHz FT-spectrometer operated by the Magnet Laboratory at M. I. T.

64. See p. 64 for experimental conditions and yields.

65. G. Büchi and Ping-Sun Chu, J. Org. Chem., submitted for publication.

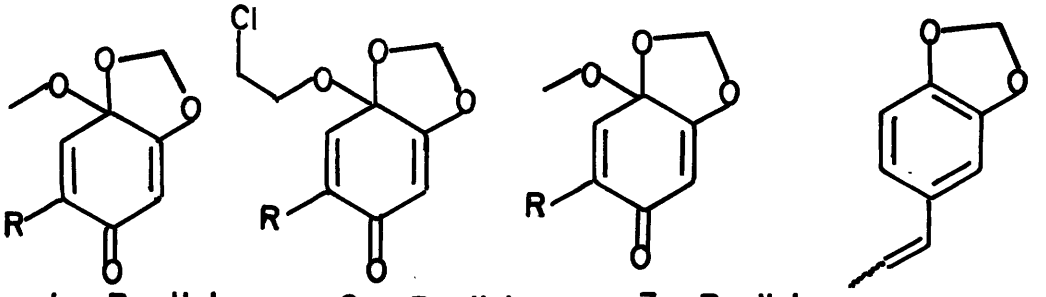
66. Part of this work has been published: G. Büchi and C.-P. Mak, J. Am. Chem. Soc., 99, 8073 (1977).

Appendix A

Studies on the Reaction of Quinone Ketals with Olefins: Approaches towards the Synthesis of Cyclopentanones from Olefins.

Introduction

The ability of quinone ketals 1-3 to react with isosafrole (A) under different conditions to give cycloaddition products has been demonstrated.[1] However, no investigation of the reaction of quinone ketals with other types of olefins, such as enol ethers, enamines, enol acetates, and alkynes has been made. Also, it would be interesting to investigate the reactivity of less electron-rich olefins towards quinone ketals. If successful, this procedure would lead to another method for the construction of cyclopentane rings, starting from an olefin.[2] Presumably, the bicyclooctanone obtained from the condensation of a quinone ketal with an olefin, could be elaborated into a cyclopentanone by cleavage of the C-2/C-3 or C-3/C-4 bond. (Scheme I)

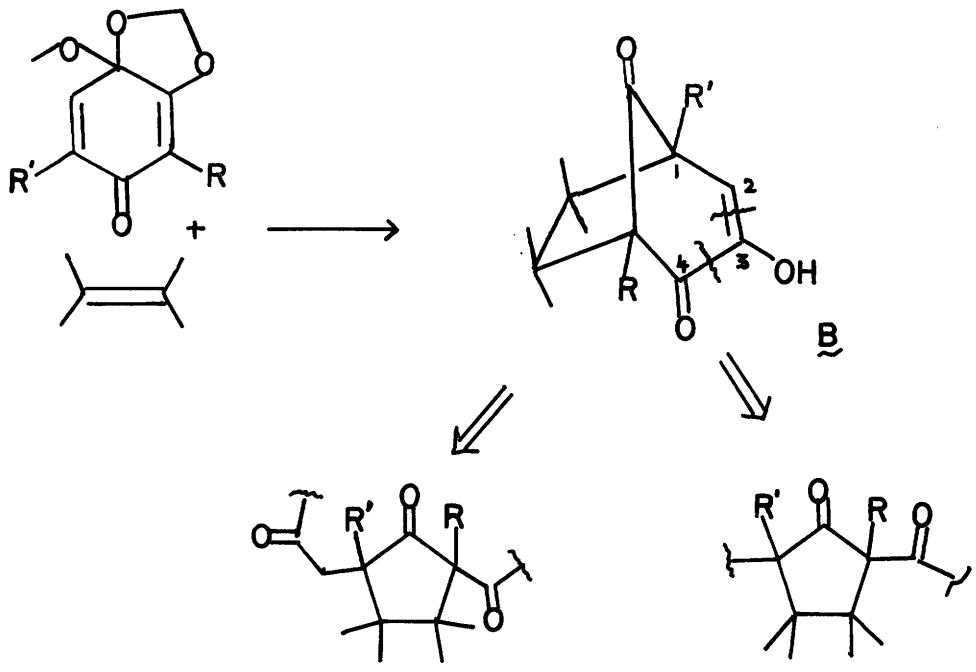


1a, R=allyl
b, R=propyl
c, R=OCH_3

2a, R=allyl
b, R=propyl

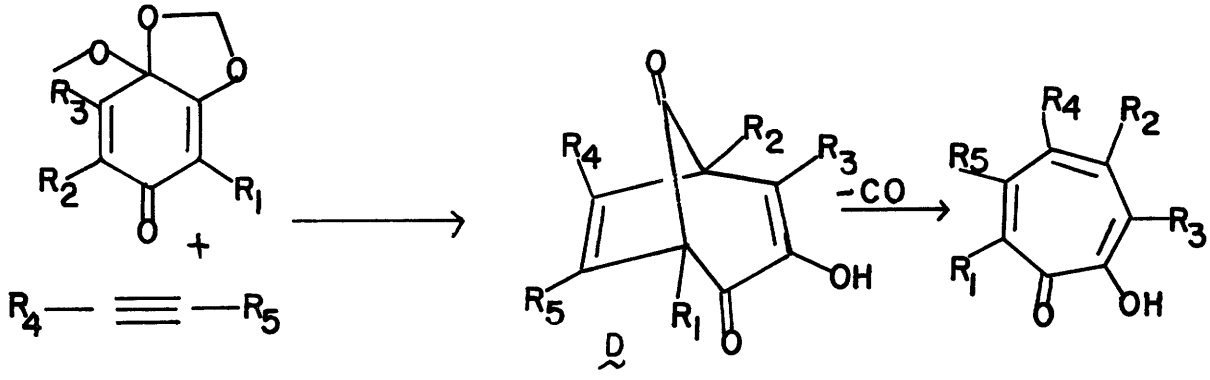
3a, R=allyl
b, R=propyl

A



Scheme I

Furthermore, the reaction of quinone ketals with acetylenes may lead to a tropolone synthesis, since the presence of the additional double bond in compounds such as D might facilitate the extrusion of carbon monoxide, which in turn would provide the tropolone ring system.[3] (Scheme II)



It was therefore our goal to examine the condensation reactions of some simple olefins and acetylenes with different readily available quinone ketals, and to study the possible transformation from these products.

Results and Discussion

A number of readily available olefins and acetylenes were condensed with different quinone ketals. A summary of the results is listed in Table 1.

Table 1

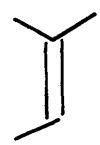
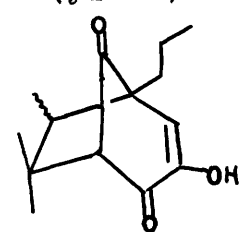
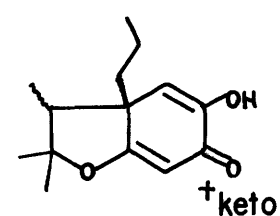
Quinone Ketal	Olefin/ Alkyne	Conditions	Products (yield)
1b	 12	A	 4 (32)
1b	12	B	 5 (27)[a]

Table 1 cont'd

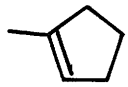
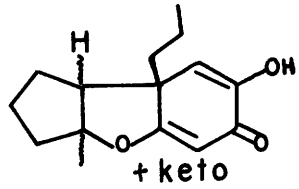
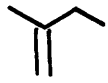
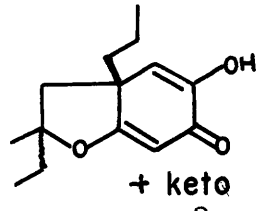
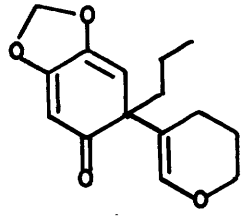
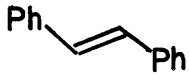
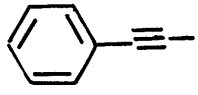
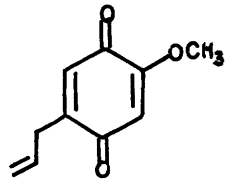
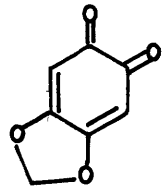
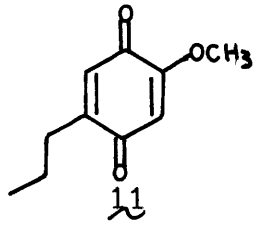
Quinone Ketal	Olefin/ Alkyne	Conditions	Products (yield)
1b	 13	A	 6 (40)[a]
1b	13	B	6 (trace)[a]
1b	 14	A	 7 (20)[a]
1b	 15	A	 8 (20)
1b	 16	A	complex mixture[b]
1b	 17	A	complex mixture[b]
1b	 18	C	complex mixture[b]

Table 1 cont'd

Quinone Ketal	Olefin/ Alkyne	Conditions	Products (yield)
3a	18	C	 9 (30)
1c	$MeO_2C-\equiv-CO_2Me$ (19)	B	 10 (30)[4]
1b	19	A	 11

Notes:

a. Since the product obtained contained an epimeric mixture of enol-keto tautomers, it was difficult to fully characterize them at this stage, but the corresponding methyl ethers were prepared and characterized.

b. The mixture contained some methoxyquinone derived from the quinone ketal.

c. Yields were not optimized.

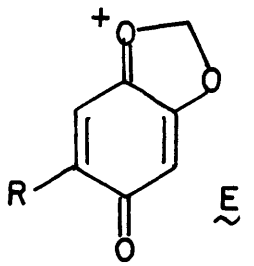
Conditions: A. methanesulfonic acid/methylene chloride;

0°C to 25°C.

B. triethyl or trimethyloxonium fluoroborate/ methylene chloride; 25°C.

C. 2,4,6-trinitrobenzenesulfonic acid/acetonitrile; 0°C.

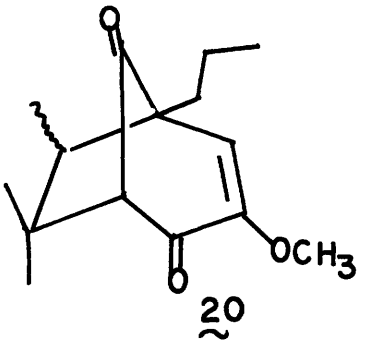
Clearly, the condensation reaction between isosafrole and quinone ketals is not unique. Both aliphatic di- and tri-substituted olefins (14 and 12) are capable of undergoing the cycloaddition reaction but the alicyclic di-substituted olefin (cyclohexene, 17) failed to afford any product. 1-Methylcyclopentene (13) gave only the dihydrobenzofuranone 6 in 40% yield. Dihydropyran (15) reacted with the quinone ketal 1b to form the dienone adduct 8; this compound probably did not derive from a cycloaddition reaction but was simply an electrophilic attack of the carbonium ion E on the vinyl ether.[4] The formation of the mixture of epimers is not surprising. Without the presence of the aryl group or any pi system, there should not be any preferred mode of attack. (In contrast to the case when isosafrole was used[1])



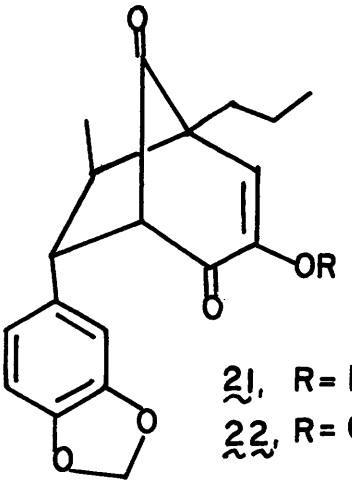
Results on the reaction with acetylenic compounds were not promising. In the cases tried, they appeared to be un-

reactive, and decomposition of the quinone ketals took place.

Our effort was then directed towards the elaboration of the bicyclooctanone system into cyclopentanones. Bicyclooctanones 4 and 21, and their respective methyl ethers 20 and 22,[5] were used in the attempts. Numerous conditions had been tried: Ozonolysis under a variety of conditions gave very complicated mixtures mainly. Peracids usually gave no oxidation product, except in some cases where products derived from Bayer-Villiger reaction were detected. Lead tetraacetate,[6] potassium permanganate/sodium metaperiodate,[7] and potassium iodate/iodine/potassium acetate/acetic acid,[8] all led to decomposition of the starting materials. Strong basic conditions resulted in the formation of cycloheptenones.[9] Various conditions employing osmium tetraoxide were investigated,[10] but unforturnately did not result in the isolation of the required product. However, when methyl ether 22 was subjected to the condition of VanRheenen[11] using N-methylmorpholine-N-oxide 23, a single product was isolated in about 20% yield after chromatography; it was tentatively given the structure 24, on the basis of spectroscopic data: IR ($CHCl_3$) 3590, 3450, 1780, 1725, 1700 cm^{-1}; NMR (acetone-d_6) δ 4.67 (s, 1, OCH-), 5.93 (s, 2, $-OCH_2O$) mass spectrum (70 eV) m/e (rel intensity) 362 (M^+, 10), 204 (12), 193 (12), 176 (36), 162 (23), 148 (100).

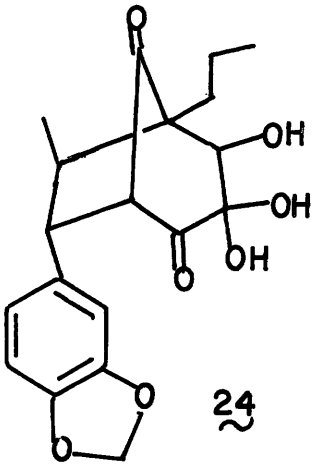


20

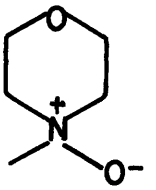


21, R = H

22, R = CH_3



24



23

Attempts are now being made to further oxidize 24 to a cyclopentanone derivative. Other alternative methods are being investigated to efficiently convert the bicyclo-octanone into cyclopentanone.

Experimental

Melting points were determined on a Richert hot-stage microscope and are corrected. Proton magnetic resonance (NMR) soectra were recorded in parts per millon (δ) downfield from tetramethylsilane as internal standard. Mass spectra were determined on a Varian Mat 44 instrument. Infrared (IR) spectra were taken on a Perkin-Elmer 247 Or 237B grating spectrometer.

Physical Properties of the Adducts:

3-Hydroxy-1-propyl-6,6,7-trimethylbicyclo[3.2.1] oct-2-ene-4,8-dione (4). Oil; mixture of epimers at C-7; IR ($CHCl_3$) 3495, 1770, 1680, 1420, 1230, 1170 cm^{-1}; NMR (CCl_4) δ 0.80-2.02 (m, 17), 3.10 (s, 1), 6.06 (br, 1), 6.09, 6.47 (two sets of singlets, 1).

3-Methoxy-1-propyl-6,6,7-trimethylbicyclo[3.2.1] oct-2-ene-4,8-dione (20). Oil; 1:1 mixture of epimers at C-7; IR ($CHCl_3$) 1765, 1685, 1615, 1160 cm^{-1}; NMR ($CDCl_3$) δ 0.80-2.00 (m, 17), 1.95, 1.97 (two sets of singlets, 1), 3.66, 3.68 (two sets of singlets, 3), 5.70, 6.13 (two sets of singlets, 1); mass spectrum (70 eV) m/e (rel intensity) 250 (M^+, 21), 207 (21), 182 (26), 179 (74), 153 (37), 152 (23), 151 (21), 137 (52), 124 (21), 83 (53), 69 (45), 55 (97), 41 (100).

3,3a-Dihydro-5-methoxy-3a-propyl-2,2,3-trimethyl-6(2H)-benzofuranone (25). Oil; 1:1 mixture of epimers at C-3; IR ($CHCl_3$) 2950, 1650, 1615, 1385, 1255, 1140, 1110, 1080, 845 cm^{-1}; NMR (CCl_4) δ0.72-2.33 (m, 17), 3.55, 3.56 (two sets of singlets, 3), 5.27, 5.35 (two sets of singlets, 1), 5.40, 5.43 (two sets of singlets, 1); mass spectrum (70eV) m/e (rel intensity) 250 (M^+, 12), 208 (69), 207 (82), 193 (18), 179 (20), 165 (20), 161 (12), 147 (12), 137 (10), 123 (12), 121 (12), 106 (15), 91 (22), 77 (22), 69 (100).

Dihydrobenzofuranone 26. Oil; 3:1 epimeric mixture at C-2 and C-3; IR ($CHCl_3$) 2990, 1650, 1620, 1460, 1390, 1200, 1160 cm^{-1}; NMR (CCl_4) δ0.76-2.33 (m, 17), 3.55, 3.58 (two sets of singlets, 3), 5.23, 5.27 (two sets of singlets, 1), 5.36, 5.47 (two sets of singlets, 1); mass spectrum (70eV) m/e (rel intensity) 262 (M^+, 10), 247 (5), 232 (13), 220 (60), 219 (96), 191 (20), 177 (11), 91 (26), 81 (100), 43 (76), 41 (96).

3,3a-Dihydro-2-ethyl-5-methoxy-2-methyl-3a-propyl-6(2H)-benzofuranone (27). Oil; mixture of epimers at C-2; IR ($CHCl_3$) 2960, 1645, 1615, 1390, 1250, 1175, 1130, 850 cm^{-1}; NMR (CCl_4) δ0.73-2.22 (m, 17), 3.53 (s, 3), 5.33-5.43 (m, 2); mass spectrum (70eV) m/e (rel intensity) 250 (M^+, 6), 208 (37), 107 (42), 179 (10), 137 (10), 91 (14), 69 (88), 43 (69), 41 (100).

Cyclohexadienone 8. Oil; IR ($CHCl_3$) 2950, 2920, 2860, 1630, 1410, 1380, 1150, 1045, 950 cm^{-1}; NMR (CCl_4) δ0.78-2.22 (m, 11), 3.82 (br. t, J = 4 Hz), 5.29 (s, 1), 5.40 (s, 1), 5.79 (s, 2), 6.30 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 262 (M^+, 37), 232 (12), 219 (52), 203 (27), 177 (51), 85 (69), 43 (100).

General Procedure for the Condensation of Quinone Ketals with Olefins and Acetylenes. Condensation reactions were done on 0.5-1.0 mmol scale. Quinone ketal and excess olefin (acetylene) were dissolved in 5 mL of solvent (see Table 1) and the appropiate acid was added all in one portion. After 30-60 min, the mixture was poured into sat. sodium bicarbonate and thoroughly with methylene chloride. The combined organic extracts were washed once with brine and dried (Na_2SO_4). Removal of solvent in vacuo gave an oil which was either purified by silica gel chromatography or methylated without purification with excess silver (I) oxide and methyl iodide in dimethylformamide.[1] After the usual aqueous work-up, the oil obtained was chromatographed to give the desired product.

References and Notes

1. See previous parts of this thesis.
2. R.Noyori, K. Yokoyama, S. Makino, and H. Hayakawa, J. Am. Chem. Soc., 94, 1772 (1972); J. M. Conia and M. L. Leriverend, Tetrahedron Lett., 2101 (1968); J. P. Marino and W. B. Mesbergen, J. Am. Chem. Soc., 96, 4050 (1974); B. M. Trost and S. Kurozumi, Tetrahedron Lett., 1929 (1974).
3. S. Yankelevich and B. Fuchs, Tetrahedron Lett., 4945 (1967).
4. This result is consistent with some work performed by Dr. Andy Pearce of this laboratory. Vinyl ethers and enol acetates seem to undergo electrophilic addition reactions with quinone ketals.
5. See p.120 for experimental details.
6. L. Canonica, B. Danieli, P. Manitto, G. Russo, S. Maroni and T. Salvatori, Gazz. Chim. Ital., 1370 (1967); ibid., 1026 (1970).
7. S. W. Pelletier, K. N. Iyer, and C. W. J. Chang, J. Org. Chem., 35, 3535 (1970).
8. L. Mangoni, M. Adinolgi, C. Barone, and K. Parrili, Tetrahedron Lett., 4485 (1973).
9. See Appendix B of this thesis.
10. K. A. Hofmann, Chem. Ber., 45, 3329 (1912); R. Pappo,

D. S. Allen Jr., R. U. Lemieux, and W. S. Johnson, J. Org. Chem., 25, 257 (1960); R. Daniels and J. L. Fischer, J. Org. Chem., 28, 320 (1963).

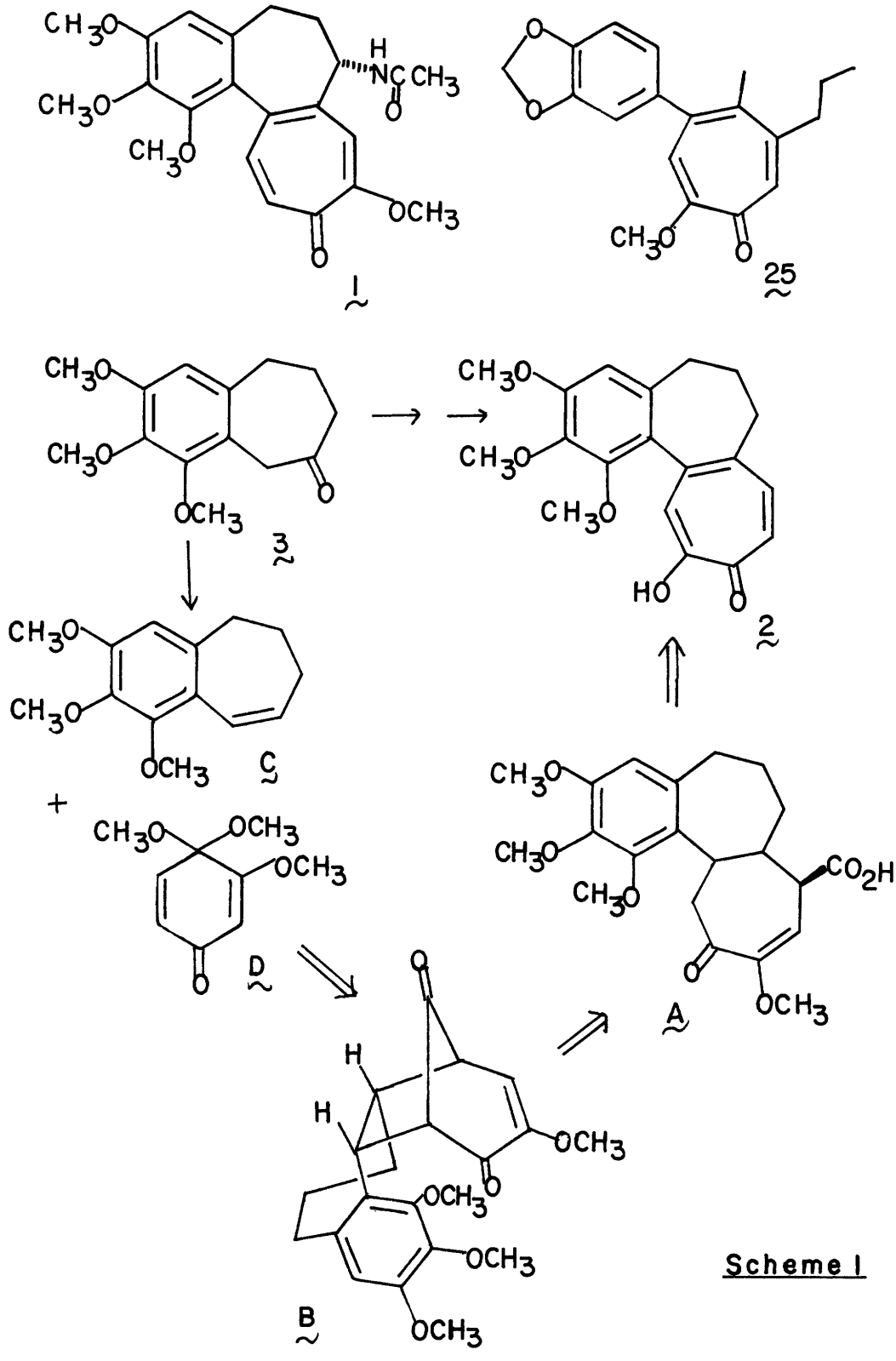
11. V. VanRheenen, R. C. Kelly, and D. Y. Cha, Tetrahedron Lett., 1973 (1976).

APPENDIX B

Preparation of 2-Methoxy-5-methyl-4-(3,4-methylenedioxyphenyl)-6-propyltropone: A Model for the Synthesis of Colchicine.

Introduction

The potent and specific antimitotic activity of colchicine (1) has been known for about forty years. To date, five total syntheses of this compound have been reported in the literature.[1-5] Tropolone 2, a critical intermediate in the Eschenmoser's synthesis, was available via a multistep sequence from ketone 3. Retrosynthetically, we envisioned that 2 could be obtained via keto-acid A, which could, in turn be prepared by hydroxide treatment of the β-diketone B. The cycloaddition reaction between olefin C and quinone ketal D should provide the diketone B under previously established conditions.(Scheme I) The availability of bicyclooctanone 4 enabled us to investigate the methodology for the conversion of such a diketone to a tropolone. The synthesis of the tropolone methyl ether 25 is herein reported.

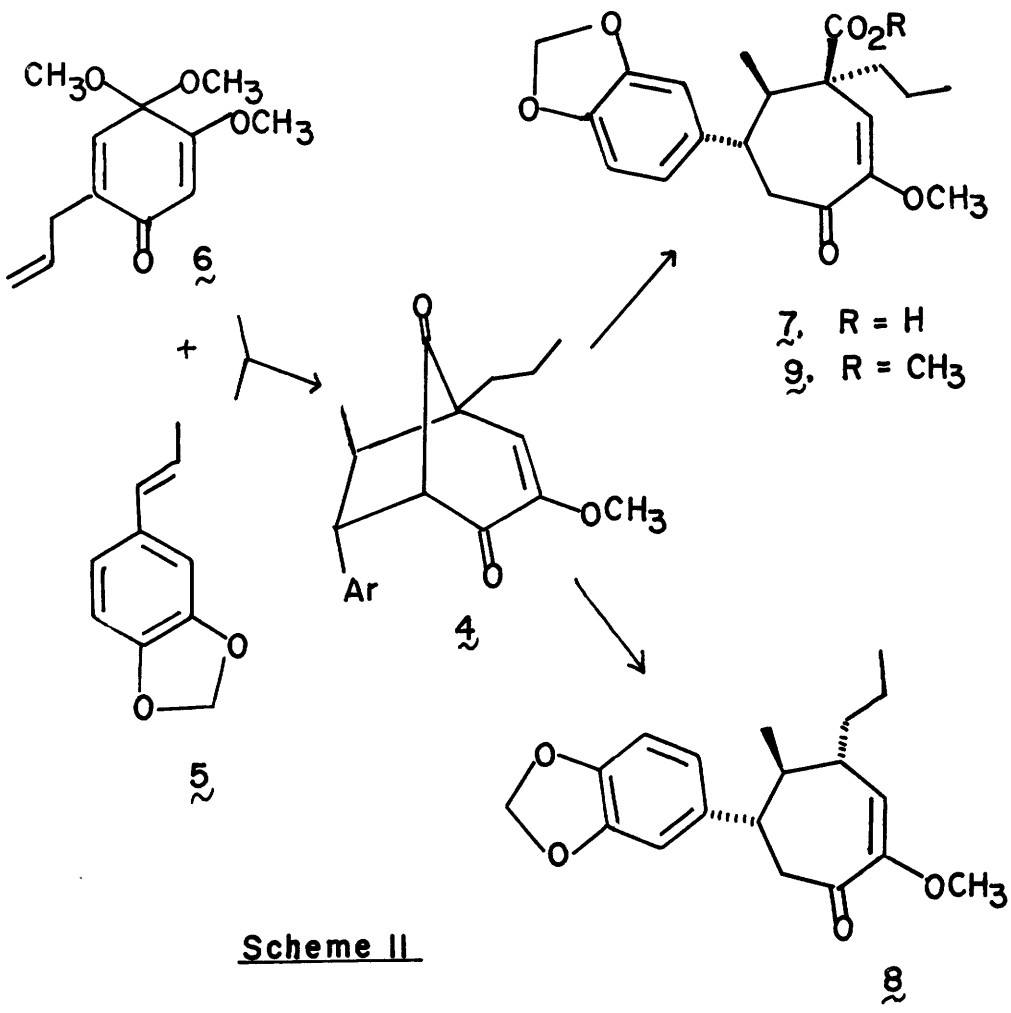

CH3O
CH3O
CH3O
H
NC
CH3
O
OCH3
O
1
O
O
CH3O
O
25
CH3O
CH3O
OCH3
3
CH3O
CH3O
CH3O
HO
O
2
CH3O
CH3O
OCH3
C
+
CH3O
OCH3
OCH3
O
D
CH3O
CH3O
CH3O
CO2H
O
OCH3
A
H
H
OCH3
O
OCH3
OCH3
OCH3
B

Scheme I

Discussion

Bicyclooctane 4 was obtained in 61% yield by the condensation[6] of isosafrole (5) and quinone ketal (6). Treatment of this diketone with methanolic potassium hydroxide at room temperature gave the keto-acid 7 in quantitative yield, while at reflux for a short period of time, the decarboxylated product 8 could be obtained as a single product in lower yield.(Scheme II) Compound 8 could not be crystallized; however, spectroscopic evidence suggested a single diasteromer, since the methoxy and methylenenedioxy protons appeared as sharp singlets at δ3.56 and 5.91 respectively, while the secondary methyl group appeared as a clean doublet at δ0.78. The fact that the vinyl proton in 7 and 9 (methyl ester of 7 prepared quantitatively by treatment with diazomethane) appeared as a singlet, indicated that the carboxyl group was γ to the ketone (rather than α, the alternative possibility from 4), since in the decarboxylated product, it became a doublet (J = 7Hz).

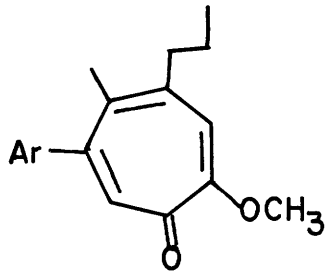
Oxidation of 7 or 8 directly to the tropolone 10 failed when attempts were made to use either excess 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or by catalytic dehydrogenation. The only isolated product which could be identified was the dienone 11 (<5%). However, dienone-methyl ester 12



Scheme II

was prepared in 90% yield as a pale yellow crystalline compound from methyl ester 9 by DDQ oxidation. Hydrolysis of the ester 12 could only be achieved with potassium hydroxide in boiling methanol to give a mixture of oily acids 13 and 14. They were not separated and purification was difficult. There were two sets of both methoxy and methylenedioxy protons. Unforturnately, all efforts to oxidatively decarboxylate the acids to the desired tropolone

failed.



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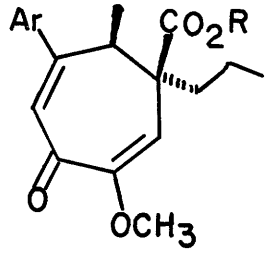
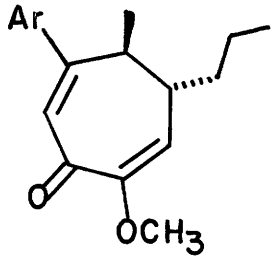


12, R = CH_3

13, R = H



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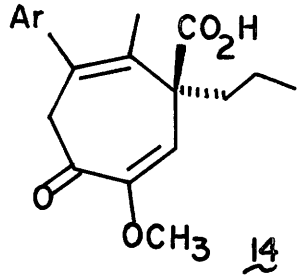
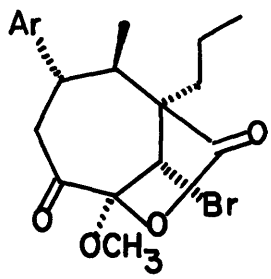


14

Attempts were then undertaken to prepare the halogenated derivatives of 7 and 8 in the hope that dehydrohalogenation would give 10. Treatment of enone 7 with varying amounts of N-bromosuccinimide (NBS) gave complex mixtures of products; when the crude keto-acid was treated with 1.1 equivalents of NBS in chloroform, a rather unexpected bromide 15 was obtained quantitatively. The infrared spectrum showed two 'high' carbonyl absorptions at 1790 and 1740 cm^{-1}. The structure and relative stereochemistry of the product, on the basis of ^1H NMR, mass spectrum, and mechanistic consideration was assigned to be the bromo-γ-lactone 15. Electrophi-

lic attack of bromine on the enol-ether was probably favored because of "neighboring group participation" by the carboxyl group. Since the carboxylic acid group is on the β-face of the molecule, the bromonium ion would have to be formed on the α-face and cyclization, to yield the γ-lactone, would give the indicated stereochemistry.



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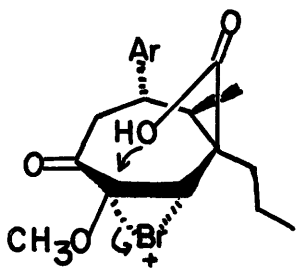
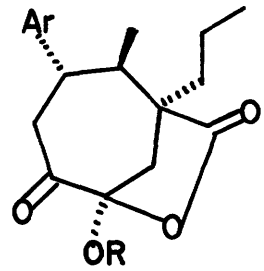
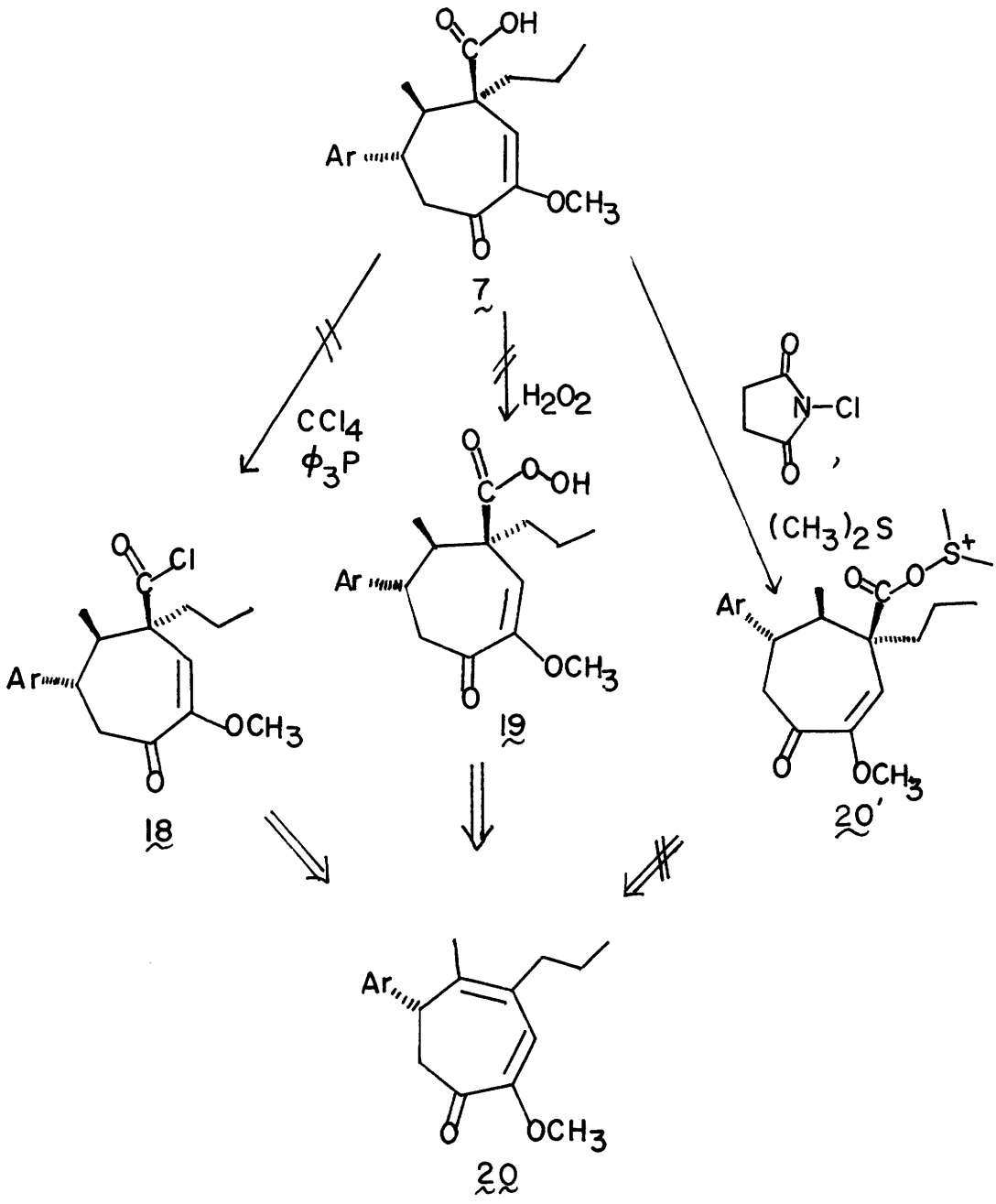




16, R = CH_3
17, R = H

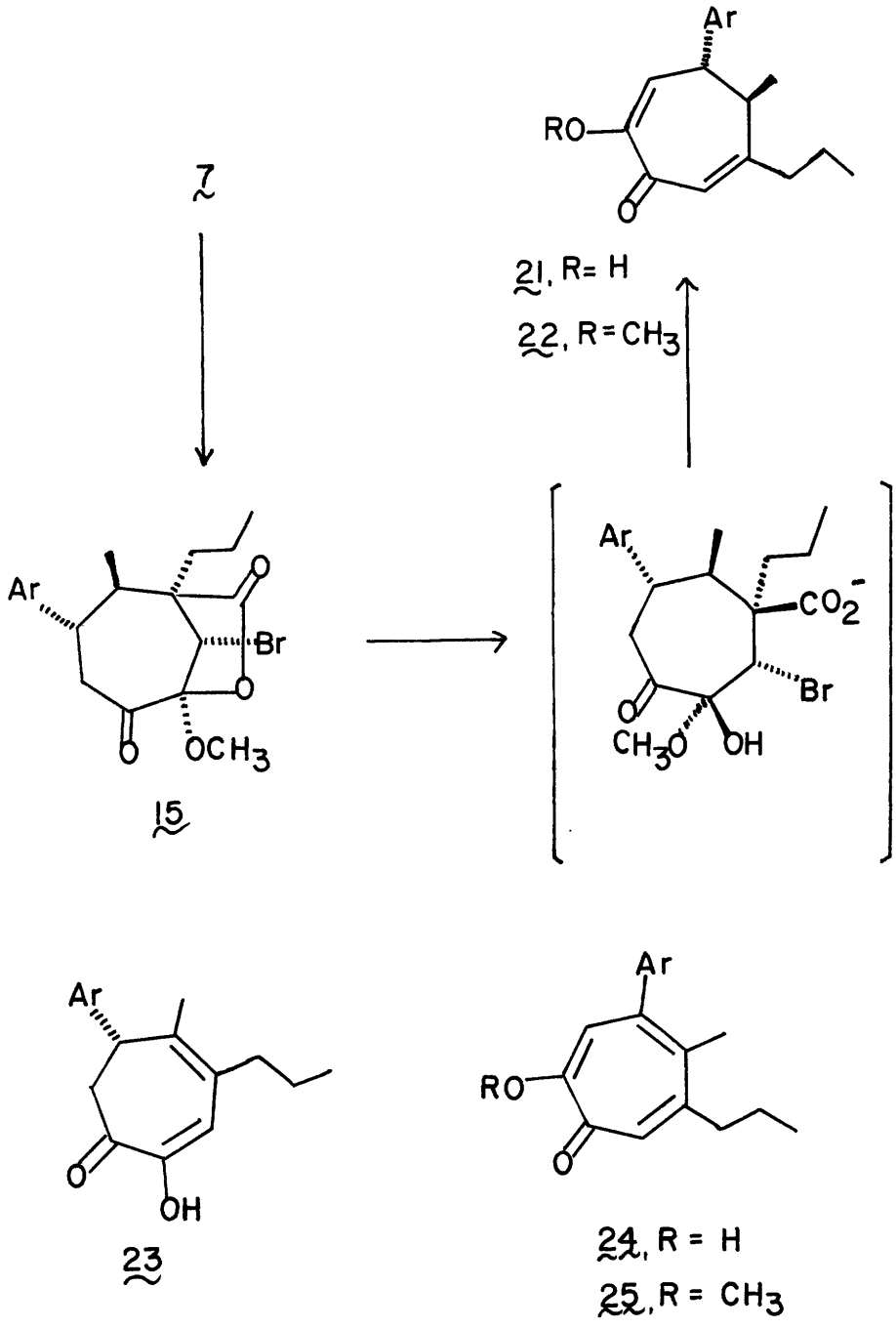
The ease of formation of the γ-lactone ring was emphasized when we attempted to derivatize the keto-acid 7. In an effort to prepare the acyl chloride 18, keto-acid 7 was heated in boiling carbon tetrachloride with one equivalent of triphenyl phosphine.[7] No desired chloride was obtained; instead, γ-lactone 16 was isolated in 90% yield. The same lactone was produced in lesser amounts (68%) when we subjected keto-acid 7 to an oxidative decarboxylation produre employing dimethyl sulfide and N-chlorosuccinimide followed by triethylamine.[8] In the presence of a stronger acid, the corresponding hydroxy-lactone 17 was isolated. The condi-



Scheme III

ion[9] used in the latter instance was originally designed to prepare the peracid 19, in the hope of its further transformation to the dienone 20. Undoubtedly, lactone ring formation is an extremely facile process; hydrochloric acid was liberated *in situ* when either NCS/DMS or Ph_3P/CCL_4 was employed and this was sufficient to promote the transformation.

However, a slight modification of the Corey-Kim procedure[8] did give some interesting results. In view of the fact that the free acid would be a proton source for lactone formation, the quarternary ammonium salt of 7, prepared by mixing of the keto-acid with excess triethyl amine in methylene chloride, was used instead. After careful separation from the complex mixture of products, a compound corresponding to enol 21 was isolated in less than 10% yield. The compound also seems to be in equilibrium with the keto-form as indicated by its ^{1}HNMR and IR spectra. A slighty better yield (10-15%) of 21 was obtained when 7 was treated with lead tetraacetate under a variety of conditions.[10] Other unidentifed products usually consisted of polyacetylated derivatives. The most efficient route for the preparation of 21 involved treatment of bromo-lactone 15 with aqueous potassium hydroxide in tetrahydrofuran. Hydrolysis of the lactone followed by rapid decarboxylation and debromination would give 21. (Scheme IV) However, owing to its instability on silica


7
Ar
RO
O
21, R= H
22, R=CH3
Ar
Br
O
OCH3
15
Ar
CO2-
Br
O
CH3O
OH
Ar
O
OH
23
Ar
RO
O
24, R = H
25, R = CH3

Scheme IV

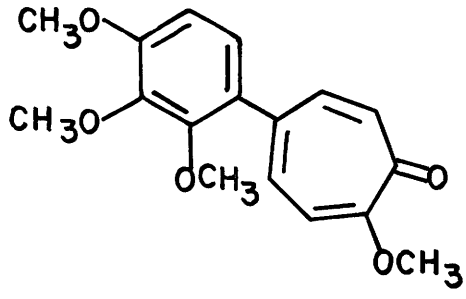
gel, the crude oil was methylated with methyl iodide and silver(I) oxide to give a 68% overall yield of the crystalline methyl ether 22. The secondary methyl group in 22, appearing as a doublet (J = 7 Hz) at δ1.33 in NMR, instead of a singlet (i.e., there was no adjacent vinyl proton!) could conclusively rule out 20 (see Scheme III) as a possible structure. This further confirms the identity of 21 (and not 23) as the correct structure.[12]

Tropolone 24 was still beyond our reach when we tried to oxidize enol 21 directly. However, tropolone methyl ether 25 was obtained in 80% yield after chromatography, as an oily solid when methyl ether 22 was treated with DDQ in refluxing benzene. One recrystallization gave pure tropolone methyl ether which was characterized by its NMR, IR, UV, and mass spectra, as well as elemental composition. Conversion of tropolone methyl ethers to the corresponding tropolones has been demonstrated in many systems.[13] It has been achieved either by base or acid treatment; they are usually isolated as the copper salts.

Conclusion

The preparation of tropolone methyl ether 25 constitutes a novel approach to the synthesis of the tropolone ring. The availability of varingly substituted quinone ketals and their facile cycloaddition reactions with different

olefins can lead to a general and versatile route to many tropolone derivatives. The preparation of tetracyclic intermediate B is now being investigated in this laboratory as an alternate route to tropolone 2, and subsequently to colchicine. In addition, tropolone methyl ether 25 is being examined for antimitotic activity similar to that of colchicine. It was reported[15] recently that the activities of colchicine could be manifested by compounds with simpler structures. For example, methyl ether 27 was found to be as active as colchicine in all tests performed. A convenient synthesis of this class of tropolones would then be valuable for a continuing study of structure-activity relationships in colchicine class compounds.



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Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are corrected. Proton magnetic resonance (^{1}HNMR) spectra (90 MH_z) were recorded on a Perkin-Elmer R-22 spectrometer and are reported in parts per millon (δ) downfield from tetramethylsilane as internal standard. Mass spectra were determined on a Varian mat 44 instrument. Ultraviolet (UV) spectra were obtained on a Perkin-Elmer 202 spectrometer. Infrared (IR) spectra were taken with a Perkin-Elmer 247 or 237B grating spectrometer. Elemental analyses were performed by Robertson Laboratory, Florham Park, New Jersey.

3-Methoxy-7β-methyl-6α-(3',4'-methylenedioxyphenyl)-4-oxo-1α-propyl-2-cycloheptene-1β-carboxylic acid Methyl Ester (9). A solution of bicyclooctanone 4 (342 mg, 1 mmol) and potassium hydroxide (1.5 g) in methanol (12 mL) was stirred at room temperature under an argon atmosphere for one h. The solution was then diluted with sat. sodium bicarbonate and washed twice with ether. Aqueous solution was then acidified with dilute hydrochloric acid and extracted thoroughly with ether. Combined organic layer was dried ($MgSO_4$) and concentrated to give 360 mg (100%) of the keto-acid 7 as a foam. This was again taken up in 5 mL of ether and treated with excess diazomethane, followed by the usual work-up to afford

370 mg (100%) of the foamy methyl ester 9: NMR (CCl_4) δ 0.80-1.58 (m, 8), 1.73-2.26 (m, 3), 2.60-3.08 (m, 3), 3.62 (s, 3), 3.68 (s, 3), 5.73 (s, 1), 5.90 (s, 2), 6.46-6.72 (m, 3); IR ($CHCl_3$) 1752, 1685, 1510, 1490, 1445, 1250, 1040 cm^{-1}; UV (95% EtOH) 240, 280 nm; mass spectrum (70 eV) m/e (rel instensity) 374 (M^+, 11), 232 (15), 167 (38), 162 (12), 155 (52), 41 (100).

2-Methoxy-5β-methyl-6α-(3,4-methylenedioxyphenyl)-4α-propyl-2-cycloheptenone (8). Bicyclooctanone 4 (50 mg, 0.146 mmol) and potassium hydroxide (0.3 g) was dissolved in 5 mL of methanol and the resulting solution was heated at reflux under an argon atmosphere for one h. After cooled to ambient temperature, the mixture was diluted with sat. sodium bicarbonate and extracted thoroughly with ether. Organic layers were combined and washed once with brine, dried ($MgSO_4$) and concentrated to an oil, which was then chromatographed on a 20 cm × 20 cm × .05 cm silica gel plate with 25% ethyl acetate in hexane as solvent. This provide 8 (27 mg, 58%) as a viscous oil: NMR (CCl_4) δ 0.78 (d, 3, J = 7 Hz), 0.87-1.11 (m, 3), 1.20-2.00 (m, 5), 2.25-3.07 (m, 4), 3.56 (s, 3), 5.04 (d, 1, J = 7 Hz), 5.91 (s, 2), 6.47-6.73 (m, 3); IR ($CHCl_3$) 1685, 1630, 1520, 1505, 1455, 1260, 1160, 1140, 1125, cm^{-1}; UV (95% EtOH) 236, 277 nm; mass spectrum (70 eV) m/e (rel intensity) 316 (M^+, 11), 168 (14), 162 (9), 148 (26), 55 (100).

3-Methoxy-7β-methyl-6α-(3,4-methylenedioxyphenyl)-4-oxo-1α-propyl-cyclohepta-2,5-diene-1β-carboxylic acid Methyl Ester (12). A mixture of methyl ester 9 (370 mg, 1 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (625 mmol, 2.5 mmol) in dry benzene (15 mL) was heated at reflux under nitrogen atmosphere for 5 h. This was cooled, diluted with ether, and then washed twice with sat. $NaHCO_3$, once with brine, and dried ($MgSO_4$). Evaporation of solvent in vacuo gave 400 mg of foam, which was filtered through a short column of silica gel (4 g, 2 : 1/hexane : ethyl acetate) to give 334 mg (90%) of pure 12 as foam. Crystallization from ether followed by one recrystallization from ether-hexane gave pale yellow crystals: mp 132-3°C; NMR ($CDCl_3$) δ 0.84 (br. t, 3, J = 7 Hz), 1.0-1.58 (m, 2), 1.10 (d, 3, J = 7 Hz), 1.80-2.10 (m, 2), 3.46 (br. q, 1, J = 7 Hz), 3.73 (s, 3), 3.82 (s, 3), 6.02 (s,2), 6.27 (br. s, 1), 6.35 (s, 1), 6.82 (d, 1, J = 8 Hz), 6.99 (br. s, 1), 7.03 (d, 1, J = 8 Hz, with fine splittings); IR ($CHCl_3$) 1740, 1620, 1515, 1500, 1450, 1260, 1230, 1200 cm^{-1}; UV (95% EtOH) 247 nm (sh, ε 9800), 259 (10, 400), 295 (5500), 352 (9800); mass spectrum (70 eV) m/e (rel intensity) 372 (M^+, 6), 242 (12), 155 (30), 141 (18), 59 (100).

Bromo-γ-lactone 15. To a solution of the crude keto-acid 7 (803 mg, 2.23 mmol) in chloroform (15 mL) was added N-bromosuccinimide (440 mg, 2.47 mmol). After stirring at room

temperature for 30 min, solvent was evaporated in vacuo and the residue was taken up in ether; this was washed three times with sat. sodium bicarbonate and then dried ($MgSO_4$). Ether was again removed under reduced pressure and 921 mg (94%) of 15 was obtained as a solid. Recrystallization from methylene chloride-heptane gave white rods: mp 152-4°C; NMR ($CDCl_3$) δ 0,70-1.10 (m, 6), 1.22-1.95 (m, 4), 2.47-2.87 (m, 3), 3.05-3.40 (m, 1), 3.72 (s, 3), 4.58 (s, 1), 5.98 (s, 2), 6.50-6.80 (m, 3); IR ($CHCl_3$) 1790, 1740, 1515, 1500, 1450 cm^{-1}; UV (95% EtOH) 235 nm (ε 4800), 288 (4500); mass spectrum (70 eV) m/e (rel Intensity) 440 (M^+ + 2, 8), 438 (M^+, 8), 299 (26), 175 (92), 167 (33), 155 (87), 148 (96), 41 (100). Anal. ($C_{20}H_{23}BrO_6$) C,H.

γ-Lactone 16. A mixture of crude keto-acid 7 (55 mg, 0.15 mmol) and triphenyl phosphine (50 mg, 0.15 mmol) in 5 mL of carbon tetrachloride was first heated at 45°C for 24 h, and then at reflux for 6 h. Solvent was then removed in vacuo to give a foamy residue, which was dissolved in ether and sat. sodium bicarbonate. After layers were separated, organic fraction was dried ($MgSO_4$) and then concentrated to give an oil. This was chromatographed on a 20 cm × 20 cm × .1 cm silica gel plate with 25% ethyl acetate in hexane as solvent. γ-Lactone 16 was then isolated (48 mg, 87%) as an oil which crystallized on standing. Recrystallization from methylene chloride-heptane gave white needles: mp 126-8°C;

NMR ($CDCl_3$) δ 0.82 (d, 3, J = 7 Hz); 0.96-1.70 (m, 7), 1.90-2.20 (m, 1), 2.53 (br. s, 2), 2.51-3.20 (m, 3), 3.62 (s, 3), 6.00 (s, 2), 6.59 (d, 1, J = 8 Hz), 6.62 (br. s, 1), 6.80 (d, 1, J = 8 Hz); IR ($CHCl_3$) 1785, 1740, 1515, 1500, 1455, 1260 cm^{-1}; Mass spectrum (70 eV) m/e (rel instensity) 360 (M^+, 7), 176 (20), 162 (9), 149 (32), 148 (100). Anal. ($C_{20}H_{24}O_6$) C, H.

γ-Lactone 17. A solution of the crude keto-acid 7 (36 mg, o.1 mmol), 30% hydrogen peroxide (20 μL), and concentrated sulfuric acid (1 drop) in dioxane (5 mL) was stirred under argon for 45 h. The resulting mixture was diluted with ether, washed successively with sat. sodium bisulfite, sat. sodium bicarbonate, and brine, and then dried ($MgSO_4$). After removal of the solvent in vacuo, the oil obtained was chromarographed on a 20 cm × 20 cm × .05 cm silica gel plate with 20 % ethyl acetate in hexane as solvent. γ-Lactone 17 was obtained (11.4 mg, 33%) as an oil which crystallized on standing. Recrystallization from methylene chloride-heptane gave white needles which exhibit the following properties: mp 199-202°C; NMR ($CDCl_3$) δ 0.84 (d, 3, J = 7 Hz), 1.0-1.90 (m, 7), 2.09-2.24 (m, 1), 2.57 (br. s, 2), 2.62-307 (m, 3), 5.26 (s, 1, exchangable with D_2O), 6.00 (s, 2), 6.57 (d, 1, J = 8 Hz), 6.62 (br. s, 1), 6.87 (d, 1, J = 8 Hz); IR ($CHCl_3$) 3500, 1780, 1735, 1515, 1500, 1450, 1260 cm^{-1}; mass spectrum (70 eV) m/e (rel intensity) 346 (M^+, 11), 176 (23),

175 (20), 149 (32), 148 (100).

2-Methyoxy-5β-methyl-4α-(3,4-methylenedioxyphenyl)-6-propyl-cyclohepta-2,6-dienone (22). A solution of the bromo-γ-lactone 15 (439 mg, 1 mmol) and 0.5 N potassium hydroxide (16 mL) in tetrahydrofuran (10 mL) was stirred under nitrogen blanket for one h, and then diluted with brine. The aqueous mixture was extracted thoroughly with ether; combined ethereal solution was dried ($MgSO_4$) and evaported in vacuo to give 271 mg of oily enol 21: NMR ($CDCl_3$) δ 3.76 (d of d, 1, J = 4 Hz, 9 Hz); IR ($CHCl_3$) 3400, 1645, 1600; mass spectrum (70 eV) m/e (rel intensity) 300 (M^+, 16), 135 (100).

The crude product was dissolved in 7 mL of dimethylformamide and to this was added excess silver (I) oxide (0.8 g) and methyl iodide (1 mL). The resulting suspension was stirred vigorously at room temperature for 20 h; insoluble materials were filtered and washed thoroughly with ethyl acetate, and then water. After layers were partitioned, organic phase was washed three times with water and then dried ($MgSO_4$). Removal of solvent gave a pale oil. Filtration through a short column of silica gel with 25% ethyl acetate in hexane gave dienone 22 (213mg, 68% from 15) as an oil which crystallized on standing. Recrystallization from ether-hexane gave analytical sample: mp 75-7°C; NMR (CCl_4) δ 0.69 (br. t, 3, J = 7 Hz), 0.81-1.22 (m, 2), 1.33 (d, 3, J = 7 Hz), 1.84 (br. t, 2, J = 7 Hz), 2.40-2.73 (m, 1),

3.62 (s, 3), 3.66 (d of d, 1, J = 4 Hz, 9 Hz; one set is underneath the methyl signal), 5.42 (d, 1, J = 9 Hz), 5.81 (br. s, 1), 5.93 (s, 2), 6.64 (br. s, 3); IR ($CHCl_3$) 1655, 1640, 1510, 1495, 1260 cm^{-1}; UV (95% EtOH) 255 nm (ε 11,900) 287 (6500), 315 (sh, 3100); mass spectrum (70 eV) m/e (rel intensity) 314 (M^+, 69), 300 (10), 299 (49), 271 (28), 175 (100). Anal. ($C_{19}H_{22}O_4$) C, H.

2-Methoxy-5-methyl-4-(3,4-methylenedioxyphenyl)-6-propyltropone (25). A mixture of the dienone 22 (43 mg, 0.137 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (37 mg, 0.16 mmol) in dry benzene (8 mL) was heated at reflux for 6 h under an atmosphere of nitrogen. After cooled, ether was added and this was washed successively with sat. sodium bicarbonate and brine, and then dried ($MgSO_4$). Evaporation of solvent gave an oil which was chromatographed on a 20 cm × 20 cm × 0.1 cm silica gel plate with 50% ethyl acetate in methylene chloride as solvent. Pure tropone 25 (33.9 mg, 80%) was isolated as an oily solid. Further recrystallization from ether-hexane-methylene chloride gave small plates: mp 148-50°C; NMR ($CDCl_3$) δ 1.02 (br. t, 3, J = 7 Hz), 1.46-1.80 (m, 2), 2.09 (s, 3), 2.62 (br. t, 2, J = 7 Hz), 3.84 (s, 3), 6.07 (s, 2), 6.58-6.73 (m, 3), 6.90 (d, 1, J = 8 Hz), 7.30 (s, 1); IR ($CHCl_3$) 1605, 1595, 1560, 1510, 1500, 1480, 1440, 1245, 1200 cm^{-1}; UV (95% EtOH) 248 nm (ε 35,000) 320 (sh, 10,600), 348 (11,600); mass spectrum (70 eV) m/e

(rel intensity) 312 (M^+, 47), 285 (21), 284 (100). Anal. ($C_{19}H_{20}O_4$) C, H.

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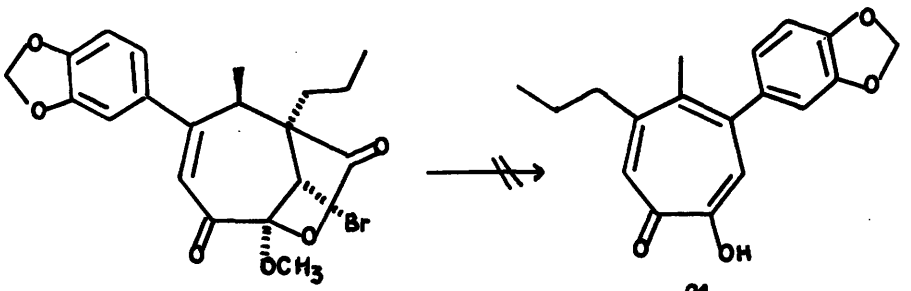
11. Treatment of the mixture of dienone-acids 13 and 14 with one equiv of NBS in chloroform gave 20% yield of a crystalline bromo-γ-lactone 26 after chromatography: mp 137-8°C (CH_2Cl_2-heptane); FT-NMR (CCl_4) δ1.07 (d, 3,

J = 7 Hz), 0.90-2.00 (m, 7), 2.92-3.20 (m, 1), 3.77 (s, 3), 4.51 (s, 1), 5.97 (s, 2), 6.71 (br. s, 3); IR ($CHCl_3$) 1785, 1680, 1500, 1485, 1245, 1030 cm^{-1}; mass spectrum (70eV) m/e (rel intensity) 438 (M^++2, 3.5), 436 (M^+, 3.5), 410 (5), 408 (5), 297 (100); UV (95% EtOH) 241 nm (ε 11,000), 255 (sh, 10,100), 298 (sh, 4900), 325 (6800). Further treatment of this compound failed to provide any tropolone derivative.



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12. The presence of enol-keto tautomers makes it difficult to identify all the signals in the NMR spectrum.
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Biographical Note

The author, son of Yan-Duen Mak and Wai-Yung Choi, was born on September 28, 1952 in Hong Kong. After completion of his secondary school education in Raimondi College in June 1970, he came to the United States and attended the University of Wisconsin-Eau Claire, where he graduated with a Bachelor of Science degree in May 1974, majoring in Chemistry and Biology. That Fall, he entered the Massachusetts Institute of Technology and studied in Professor George Buchi's research group. In January 1975, he is married to Kwan-Ling Lock. In May 1978, the author has completed the requirements for the degree of Doctor of Philosophy, and will be a Visiting Fellow at the National Institute of Health in Bethesda, Maryland.