SYNTHESIS AND SELECTIVE DEMETHYLATION OF CATECHOL ETHERS DURING ACID-CATALYZED CYCLIALKYLATION

By

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CHAPTER I

INTRODUCTION AND HISTORICAL

Acid-catalyzed cyclialkylation of aromatic ethers is an example of the more broadly defined Friedel-Crafts reaction.[1] The Friedel-Crafts reaction is generally considered to be a process for the formation of carbon-carbon bonds through an electrophilic substitution reaction catalyzed by strongly acidic metal halides such as aluminum chloride and boron tribromide.[2] However, the formation of carbon-phosphorus, carbon-oxygen, carbon-sulfur, carbon-nitrogen, carbon-halogen, carbon-boron, and carbon-deuterium bonds also conform to the general Friedel-Crafts definition. Currently the definition of Friedel-Crafts reactions has expanded to include any reaction taking place under the catalytic influence of Lewis acids, including proton acids.[3]

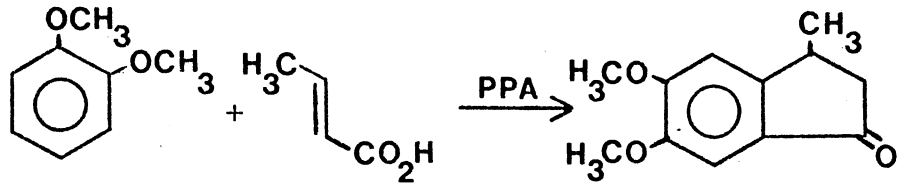
Since the Friedel-Crafts reaction covers a broad area of chemistry,[4] discussion in this work will be limited to a brief description of the cyclialkylation of aromatic ethers and the conditions required to effect these reactions.

Acid-catalyzed cyclialkylation of aromatic ethers is a reaction in which the electrophilic attack of an alkyl cation (or a highly polarized bond) with an aromatic ether forms a new ring. This attack can take place either on the aromatic nucleus to form a new alkyl-aryl bond or on the nucleophilic oxygen atom to form a cyclic ether. The

cation is formed by the action of a Lewis acid (including proton acids) with an alkyl halide, olefin, or alcohol.[1]

Acid-catalyzed cyclialkylation can be either intermolecular or intramolecular. In the intermolecular process, a bifunctional molecule reacts with the aromatic ether to form both of the bonds which comprise the new ring as shown in Scheme I.[5] In the intramolecular process, a side chain containing one of the functional groups described earlier reacts with the aromatic ether to form only one new bond as shown in Scheme II.[6]

Scheme I



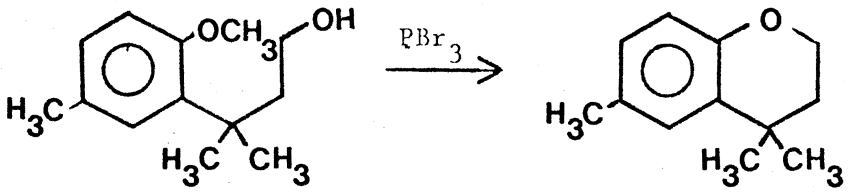
1a 2a 3a

The bifunctional molecule involved in the intermolecular reaction can be either one of two types. In the first, both functional groups of the molecule must be either an alkyl halide, olefin, or alcohol. These molecules must involve a cyclialkylation reaction.

The second contains an alkyl halide, alkene, or alcohol as one of the functionalities and a carboxylic acid or acid halide as the other

functionality. Reactions of this group of molecules could involve either alkylation followed by cycliacylation or acylation followed by cyclialkylation.

Scheme II



4 5

When benzene is allowed to react with crotonic acid (2a) the reaction is believed to involve alkylation followed by cycliacylation.[7] However, when aromatic ethers are allowed to react with crotonic acid (2a), crotonyl chloride (2b), or cinnamic acid (12) the reaction is believed to involve acylation followed by cyclialkylation.[5,8] Several examples of cyclialkylation reactions with aromatic ethers are shown in Table I.

The acidic cleavage of alkyl-aryl ethers is another reaction of importance to the synthetic organic chemist. Ethers are frequently used as protecting groups for phenols and are prevalent in natural products.

A number of natural products contain an ortho-dihydroxy aromatic nucleus (catechol) or its mono- or dimethyl ethers. The structures of

TABLE I

CYCLIALKYLATION OF AROMATIC ETHERS

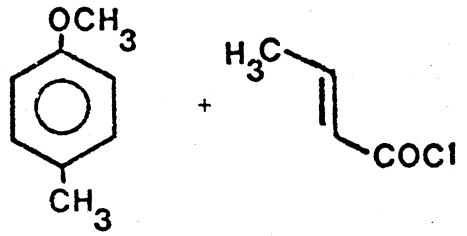
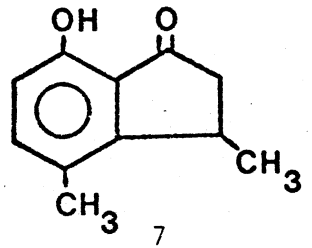
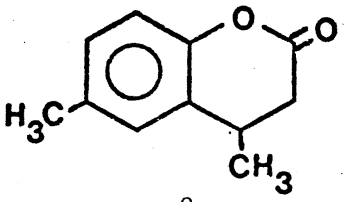
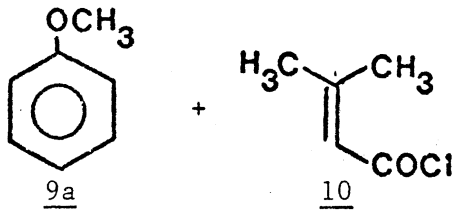
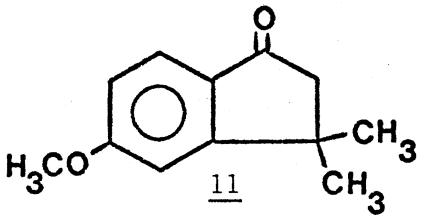
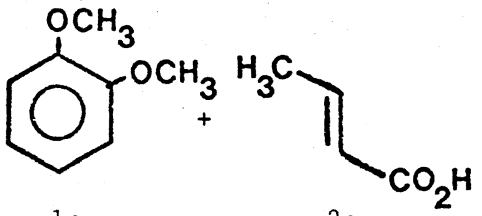
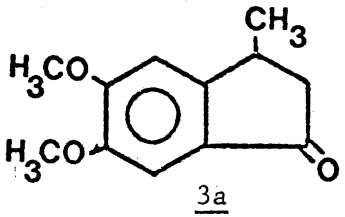
Reactant(s)	Catalyst	Product(s)	Ref.
 6 + 2b	$AlCl_3$	 7  8	8
 9a + 10	$AlCl_3$	 11	9
 1a + 2a	PPA	 3a	5

TABLE I (Continued)

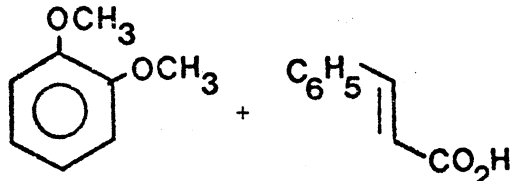
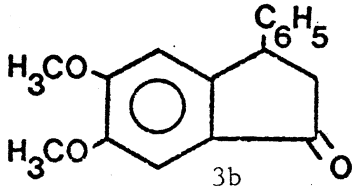
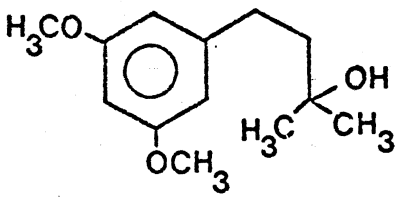
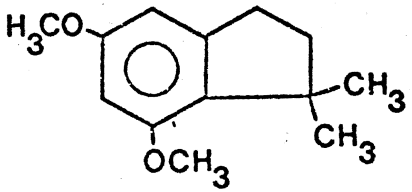
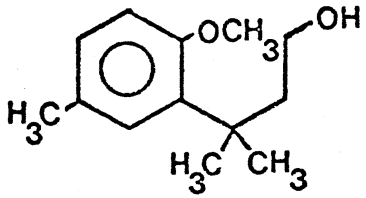
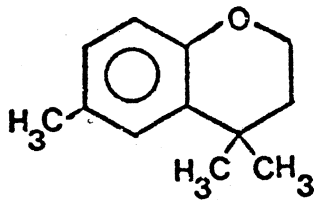
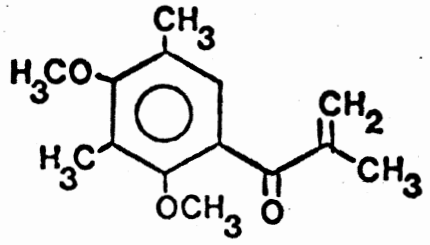
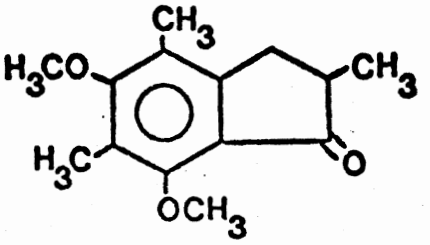
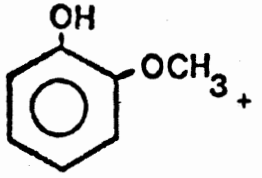
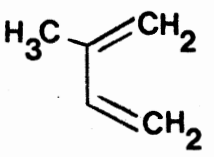
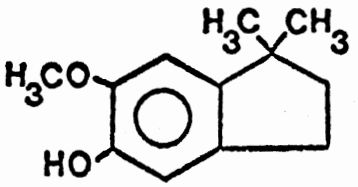
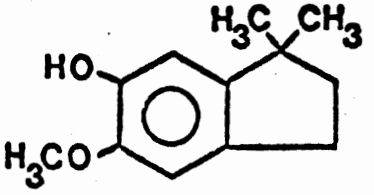
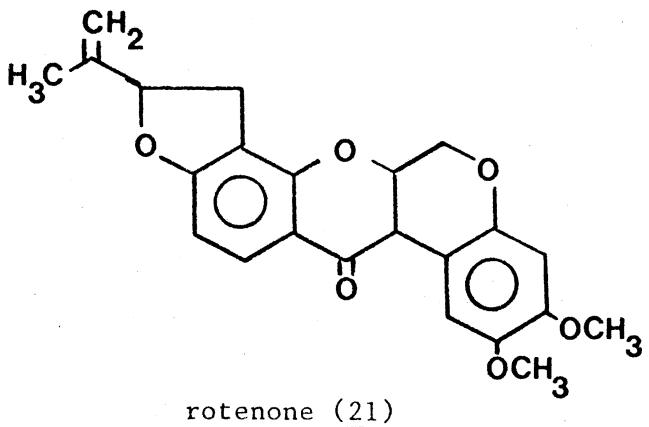
Reactant(s)	Catalyst	Product(s)	Ref.
 1a + 12	PPA	 3b	5
 13	H_2SO_4	 14	10
 4	PBr_3	 5	6

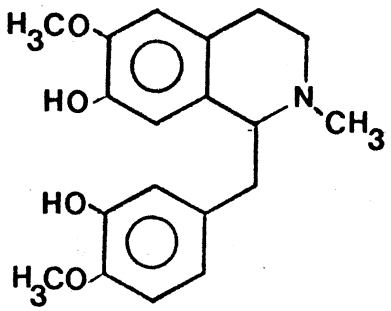
TABLE I (Continued)

Reactant(s)	Catalyst	Product(s)	Ref.
 15	H_2SO_4	 16	11.
 1b +  17	H_2PO_4	 18a  18b + three cyclic ethers (19, 20a, and 20b)	12

two examples (21 and 22) are shown below. The selective



rotenone (21)



reticulene (22)

interconversion between the catechols and their mono- and dimethyl ethers is of importance in their total synthesis.

In the past, a variety of acidic reagents have been used in these conversions. A few of the most frequently used acidic reagents are aluminum chloride, boron tribromide, hydriodic acid, and pyridine hydrochloride. In 1967 a comparison of some of the most frequently used acids was made in the demethylation of veratraldehyde (23a).[13] By varying the acid concentration, veratraldehyde (23a) was selectively demethylated to either vanillin (23b), isovanillin (23c), or 3,4-dihydroxybenzaldehyde (23d) as shown in Scheme III. The results of this study are shown in Table II. Four other examples of selective demethylations are shown in Table III.

Since 1975 trimethylsilyl iodide, a Lewis acid, has been used in a variety of organic reactions. This includes ether cleavage,[17-24] ester hydrolysis,[23-27] the condensation of ketones,[28-29] and the conversion of ketals to ketones,[30] alcohols to iodides,[31] sulfoxides

TABLE II

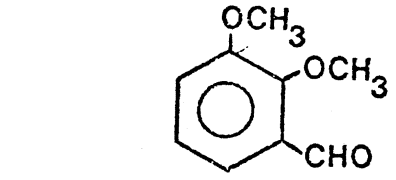
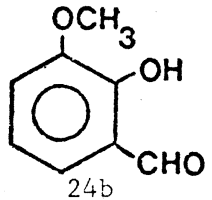
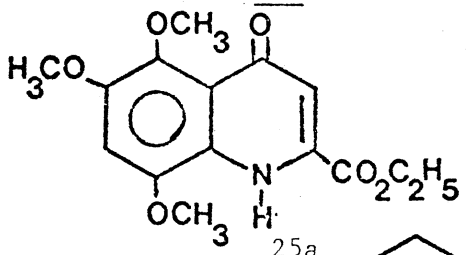
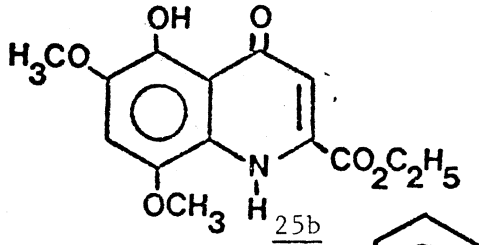
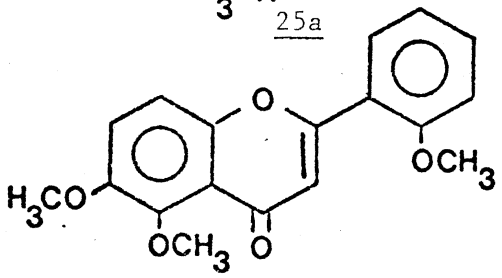
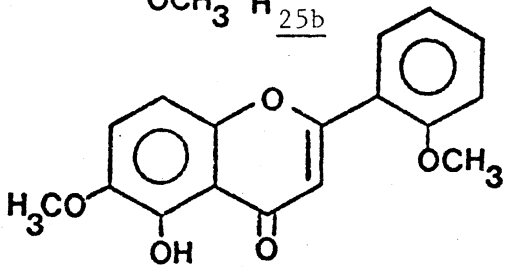
DEMETHYLATION OF VERATRALDEHYDE (23a) WITH LEWIS ACIDS

Reagent		Relative %[a]		
		23b	23c	23d
$AlCl_3$[b]	0.5 moles[c]	--	100	--
"	0.7 "	5	95	--
"	1.0 "	35	55	10
"	1.5 "	78	3	19
"	2.0 "	65	2	33
BCl_3[d]	0.5 "	--	100	--
"	1.5 "	84	7	9
BBr_3[e]	0.5 "	5	95	--
"	1.5 "	50	--	50
pyridine·HCl[f]	0.25 "	46	54	--
"	0.5 "	42	39	19
"	1.0 "	--	--	100

[a]Determined by GLC on a 6' SE-100 column at 180°. [b]In benzene, 40 min at 90°. [c]Relative to veratraldehyde (23a). [d]In light petroleum 3 h at 10°. [e]In benzene, 3 h at 80°. [f]Five min at 180°.

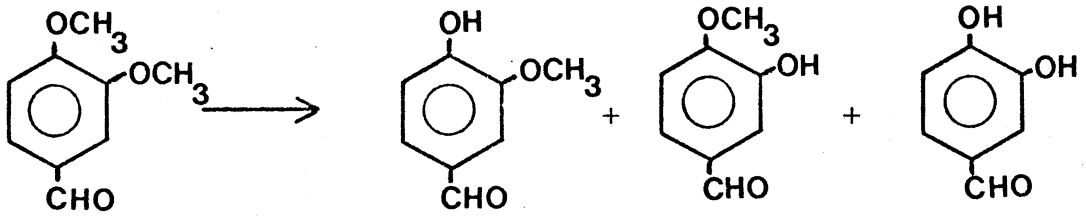
TABLE III

SELECTIVE DEMETHYLATION OF CATECHOL ETHERS

Reactant	Acid	Product	Ref.
 24a	BCl_3	 24b	14
 25a	BBr_3	 25b	15
 27a	HCl	 27b	16

to sulfides,[32] and aldehydes to geminal diiodides.[33] Specific examples of these reactions are given in Table IV.

Scheme III



23a 23b 23c 23d

In 1962, Kruerke observed the formation of 4-iodobutyl trimethylsilyl ether in 96% yield from the reaction of trimethylsilyl iodide with tetrahydrofuran.[19] This work was repeated in 1975 and since then trimethylsilyl iodide has been used to cleave tetrahydropyran, alkyl-alkyl, and alkyl-aryl ethers.[17] The mechanism proposed by Jung for this cleavage is shown in Scheme IV.[21]

Scheme IV

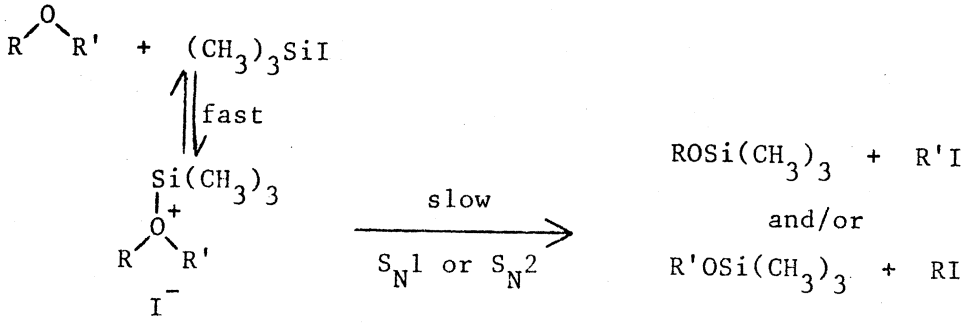
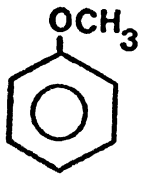
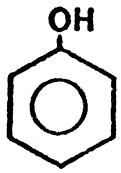
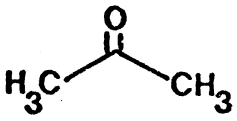
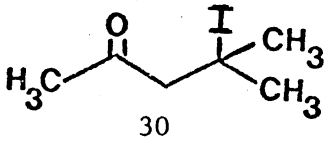
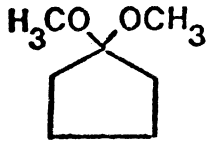
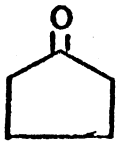


TABLE IV

REACTIONS USING TRIMETHYLSILYL IODIDE

Reactant	Product	% Yield	Ref.
 9a	 9b	100	21
$C_6H_5CO_2CH_3$ 28a	$C_6H_5CO_2H$ 28b	80	23
 29	 30	82	29
$C_{15}H_{31}CH_2OH$ 33a	$C_{15}H_{31}CH_2I$ 33b	88	31
$n\text{-}C_4H_9S(O)C_5H_{11}\text{-}n$ 34a	$n\text{-}C_4H_9SC_5H_{11}\text{-}n$ 34b	82	32
C_6H_5CHO 35	$C_6H_5CHI_2$ 36	51	33
 31	 32	87	30

A study of the trimethylsilyl iodide cleavage of a variety of ethers led to the following conclusions: (1) trityl, benzyl, and tert-butyl ethers are cleaved much faster than other alkyl ethers, thus permitting selective hydrolysis of trityl, benzyl, and tert-butyl ethers in the presence of other alkyl ethers; (2) alkyl-aryl ethers react more slowly than dialkyl ethers so that dialkyl ethers can, in general, be cleaved completely under conditions which cause only 5-10% cleavage of phenolic ethers; (3) alkyl-methyl ethers can be cleaved cleanly in the presence of methyl esters; (4) many functional groups (e.g. alkyl esters, acetylenes, olefins, ketones, amines, aromatic halides) are stable to the conditions for ether cleavage; and (5)methyl ethers of straight-chain secondary alcohols are cleanly demethylated.[21]

CHAPTER II

RESULTS AND DISCUSSION

It was previously noted that the cyclization of 4,5-dimethoxy-2-methylcrotonophenone (38a) with Amberlyst-15[34] in refluxing xylene gives a phenolic product in 40% yield.[35] The ^{13}C NMR spectrum of this phenol showed it to be isomerically pure, and to contain twelve carbon atoms (four aliphatic, one methoxyl, six aromatic, and one carbonyl carbon).[36] Therefore, only one of the methoxyl groups is cleaved during the cyclization. In order to clearly establish the factors involved in the formation of this keto phenol, the cyclization was carried out under a variety of acidic conditions, as shown in Table V.

Since no attempt had previously been made to exclude water from the reaction mixture, the cyclization was repeated with A-15 under anhydrous conditions. Most of the water was removed by azeotropic distillation and any remaining water was removed using a four Å molecular sieve. These reaction conditions gave no change in either the product or the yield.

Since xylene is receptive to electrophilic attack, it was thought that xylene could become involved in the reaction. Therefore, the cyclization was repeated using chlorobenzene as the solvent instead of xylene. There was no change in either the product or the yield.

There still remained the possibility that the cleavage resulted from a peculiarity of the A-15 catalyst. However, when methanesulfonic

acid was used in place of A-15 for the cyclization,[37] the same keto phenol was formed. Thus the reaction seems to be a simple acid-catalyzed process.

TABLE V

REACTION CONDITIONS FOR THE CYCLIZATION OF 38a

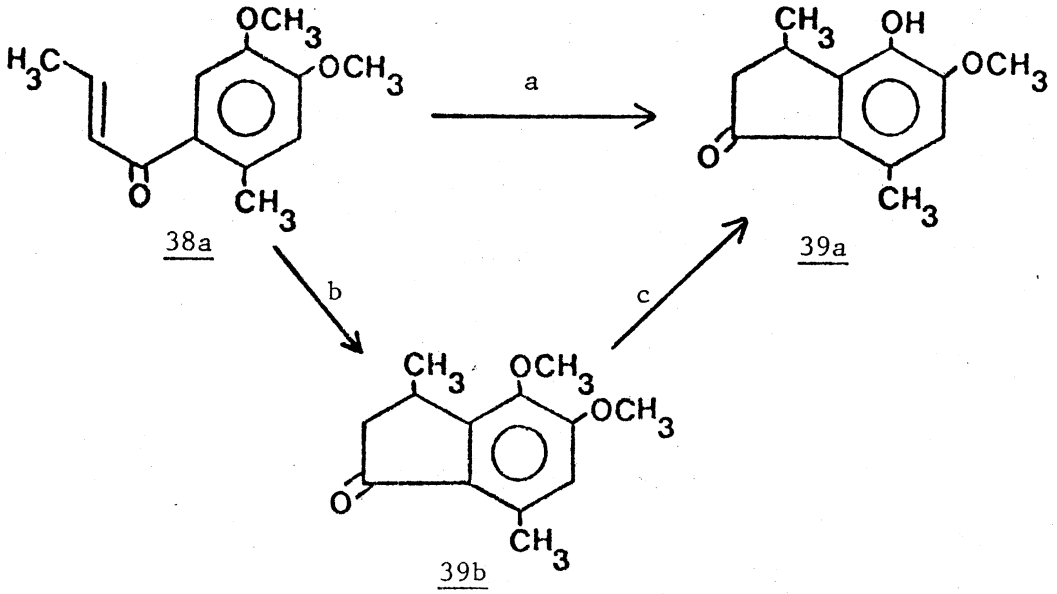
Acid	Conc. of Acid	Hours	°C	Yield
A-15[a] + water[b]	10g/L	42	138	40% of 39a
A-15 (anh.)[b]	10g/L	42	138	40% of 39a
A-15[c]	10g/L	42	132	40% of 39a
CH_3SO_3H[c]	neat	2	130	30% of 39a
CH_3SO_3H[c]	50% by vol.	4	132	40% of 39a
CH_3SO_3H[c]	4.4g/L	24	132	38% of 39a
PTSA[c]	8g/L	24	132	no reaction
XN-1010[c,d]	10g/L	42	132	40% of 39b

[a]Amberlyst-15. [b]Xylene. [c]Chlorobenzene. [d]Amberlyst XN-1010.

Further changes in the reaction conditions revealed that other strong acids seem to cause the cyclization. However, para-toluene-sulfonic acid (PTSA) failed to cause a reaction and Amberlyst XN-1010 only caused cyclization but without cleavage to the keto phenol.[34]

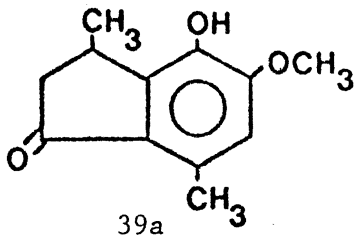
It is likely that the keto phenol may be formed in two ways. It could be formed during the cyclization, by a Fries-type rearrangement mechanism and/or after the cyclization by a selective acid-catalyzed demethylation reaction. In order to determine whether the latter process could occur, the diether 39b obtained in the Amberlyst XN-1010 cyclization was allowed to react with A-15 in refluxing xylene. This reaction provided the keto phenol which was shown to be identical with the one obtained in the cyclization of 38a. All of the above mentioned reactions are summarized in Scheme V.

Scheme V

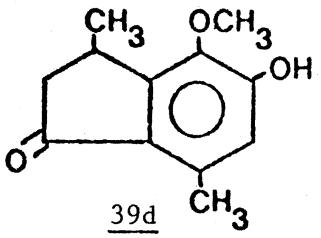


[a]Various acids. [b]Amberlyst XN-1010. [c]A-15.

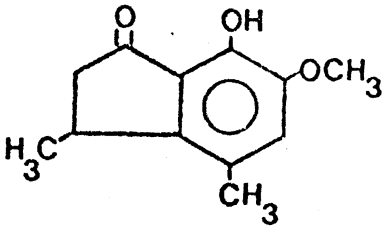
The structure of the product from the cyclization of 38a has been postulated to be either 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (39a) or 3,7-dimethyl-5-hydroxy-4-methoxy-1-indanone (39d).[35] However, there was no spectroscopic or chemical evidence presented to support this postulate. It was possible that the keto phenol could also be 3,4-dimethyl-7-hydroxy-6-methoxy-1-indanone (40a) or 3,4-dimethyl-6-hydroxy-7-methoxy-1-indanone (40b). These four structures are shown in Figure 1. Structure 40a is the only one capable of showing intramolecular hydrogen bonding.



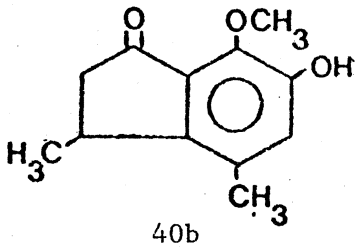
39a



39d



40a



40b

Figure 1. Possible Structures of the Keto Phenol

Intramolecular hydrogen bonding for the keto phenol was dismissed by observing the IR absorption shifts due to dilution.[38] If hydrogen bonding were present, a shift of the hydroxyl absorption to longer wavelength would have been observed. Since none occurred, structure 40a is eliminated.

The use of a shift reagent in the ^{1}H NMR spectrum of the keto phenol gave some evidence about the basic carbon skeleton 39a, 39d, or 40b.[39] Sievers' reagent is known to complex with oxygen producing a change in resonance position of the ^{1}H NMR spectrum in which the magnitude of the shift would be proportional to the distance from the complexation site; the change in resonance of the protons α to the complexation site would be greater than the change in resonance of the protons β to the complexation site.[40-43] This shift reagent was used in the ^{1}H NMR analysis of the keto phenol. The results are shown in Table VI.

If the keto phenol were 40a or 40b the change in resonance of the aromatic methyl protons would be approximately the same as the change in resonance of the aliphatic methyl protons. However, if the keto phenol were 39a or 39d, the change in resonance of the aromatic methyl protons would be larger than the change in resonance of the aliphatic methyl protons.

As can be seen in Table VI, the change in resonance of the aromatic methyl protons is approximately three times larger than the change in resonance of the aliphatic methyl protons. This indicates that the keto phenol is either 39a or 39d. However, the shift reagent complexed to some extent with the phenol as can be seen by the large change in

resonance (60 Hz) of the phenolic proton. Since two complexation sites complicate the analysis, the shift reagent analysis was repeated on the phenol 41a, prepared by the catalytic hydrogenolysis of the keto phenol as shown in Scheme VI, in order to determine the extent of phenol complexation. The results of this analysis are shown in Table VII.

TABLE VI

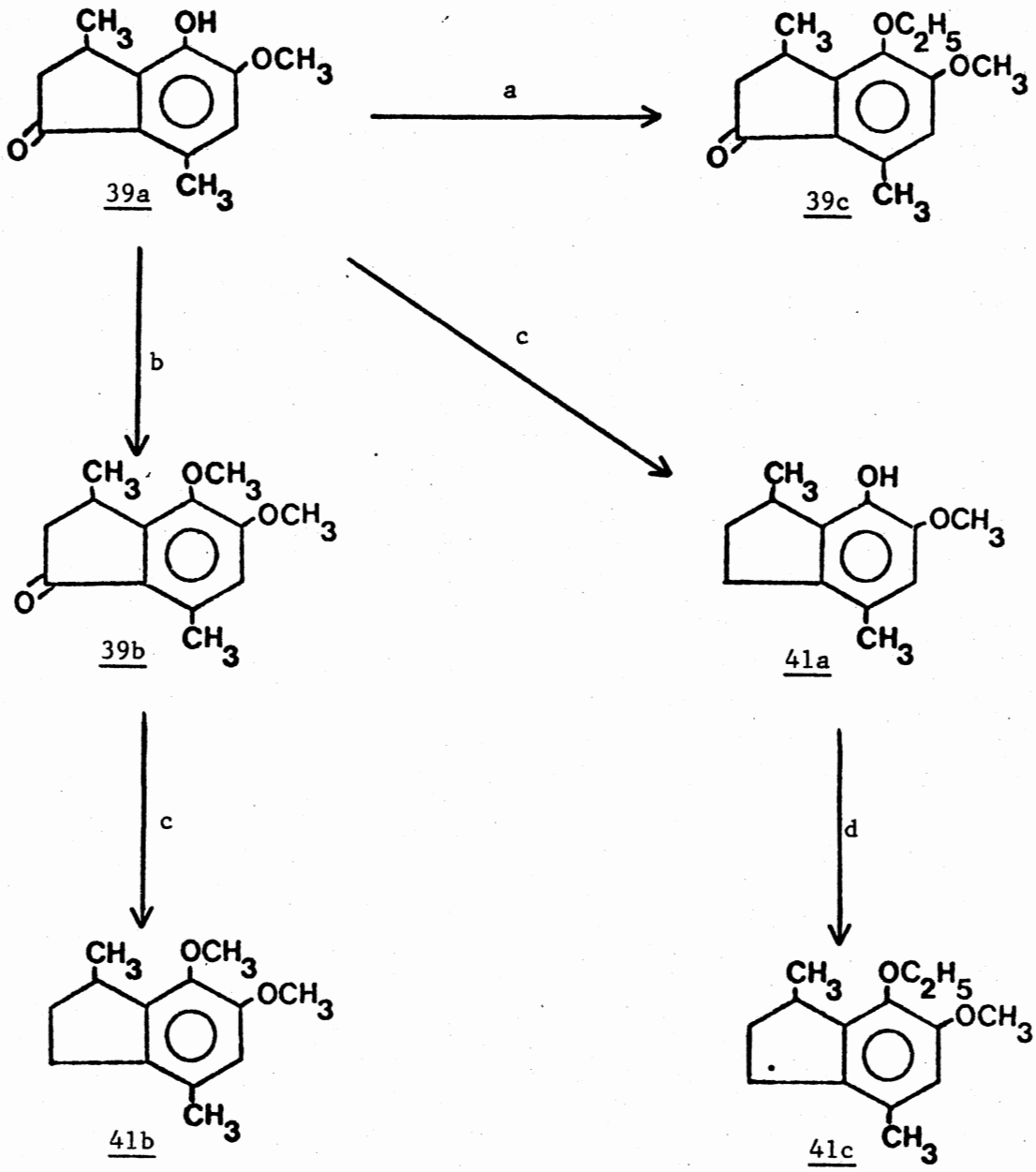
EFFECT OF SIEVERS' REAGENT ON THE ^1H NMR SPECTRUM OF 39a

Proton	ν (Hz)[a,b]
CCH_3	26
ArCH	60
$COCH_2$	121 and 169
$ArCH_3$	87
ArH	38
$ArOCH_3$	18
ArOH	60

[a] $\nu = \nu_{compound+shift\ reagent} - \nu_{compound}$.

[b] 2.32% Sievers' reagent, 3.25% 39a in $DCCl_3$.

Scheme VI



[a] $(C_2H_5)_2SO_4$, K_2CO_3, acetone. [b] $(CH_3)_2SO_4$, K_2CO_3, acetone. [c] H_2, Pd/C, acetic acid. [d] NaOH, $(C_2H_5)_2SO_4$.

TABLE VII

EFFECT OF SIEVERS' REAGENT ON THE ^{1}H NMR SPECTRUM OF 39b, 39c, and 41a

Compound	Proton	ν (Hz)[a,b]
39b	CCH_3	33
	ArCH	79
	$COCH_2$	152 and 162
	$ArCH_3$	102
	ArH	42
	$ArOCH_3$	24 and 23
39c	CCH_3	22
	ArCH	57
	$COCH_2$	141 and 140
	$ArCH_3$	98
	ArH	40
	$ArOCH_3$	18
	$ArOCH_2$	22
	$OCCH_3$	22
41a	CCH_3	20
	ArCH	49
	$ArCCH_2$	25
	$ArCH_2$	37
	$ArCH_3$	38
	ArH	120
	$ArOCH_3$	115
	ArOH	342

[a] $\nu = \nu_{\text{compound+Sievers' Reagent}} - \nu_{\text{compound}}$.

[b] 2.32% Sievers' Reagent, 3.25% 39b, 39c, or 41a in $DCCl_3$.

Treatment of 41a with Sievers' reagent causes a change in resonance of 342 Hz for the phenolic proton. This indicates that the effect on the change in resonance due to complexation with the phenol of the keto phenol is 18% of the corresponding change in resonance of 41a. This effect was compensated for by the shift reagent analysis of two alkyl derivatives (39b and 39c) of the keto phenol, which were prepared as shown in Scheme VI.

These results, presented in Table VII, show that the change in resonance of the aromatic methyl protons is indeed three to four times the change in resonance of the aliphatic methyl protons. Also the change in resonance of the alkoxyl protons are the smallest in the spectrum. These data confirm the keto phenol to be either 39a or 39d.

The above data failed to distinguish structures 39a and 39d. In order to determine the correct structure of the keto phenol, the ^{13}C NMR spectra of the keto phenol, its methyl and ethyl ethers (39b and 39c respectively), and the phenol 41a were obtained. These spectra all have a methoxyl absorption at approximately 56 ppm. However, one of the methoxyl absorptions in 39b was shifted downfield to approximately 60 ppm and the ethoxyl methylene carbon in 39c was at approximately 68 ppm. Both of these shifts are approximately four ppm farther downfield than the expected values of 55-57 ppm for methoxyl and 63-65 ppm for the methylene of an ethoxyl.[44] In order to determine whether this downfield shift was general for the carbon skelton or due to the position of the carbonyl, the methyl and ethyl ethers (41b and 41c respectively) of the phenol 41a were prepared as shown in Scheme VI and their ^{13}C NMR spectra were attained. These compounds

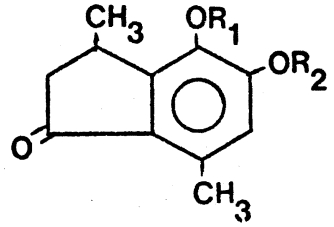
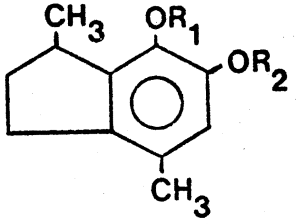
also show unexpected downfield shifts for the alkoxyl carbons. Therefore, the shift is thought to be a factor of the position of methoxyl groups on the carbon skeleton and not resulting from the position of the carbonyl. All the methoxyl shifts for the above compounds are shown in Table VIII.

Similar types of shifts have been observed previously for the methoxyl carbons of substituted aromatic methyl ethers.[44] These shifts have been assigned to sterically hindered methoxyls in ortho-disubstituted anisoles, substituted vanillins, and certain xanthones.[45-48] This downfield shift is thought to be caused by steric interactions that force the methoxyl carbon out of the plane of the aromatic ring, thereby reducing the resonance contribution of the methoxyl group and producing the downfield shift.[48]

In order to determine whether this steric effect is the cause of the observed shifts, a series of model compounds were prepared. The model compounds were chosen because it was felt the effect in the indan series should also be exhibited in the 3-alkyl substituted catechol methyl or ethyl ethers. The catechol derivatives were prepared by the alkylation of 2-methoxyphenol (1b). Monoalkyl derivatives of 3-methylcatechol and 3-isopropylcatechol were prepared by the alkylation of 3-methylcatechol (42a) or 3-isopropylcatechol (45a) with one equivalent of the appropriate dialkyl sulfate. The monophenols thus formed were isolated using 10% sodium hydroxide and then separated from each other by extraction with dilute sodium hydroxide (0.5-2%). A summary of the preparation of these model compounds is shown in Scheme VII.

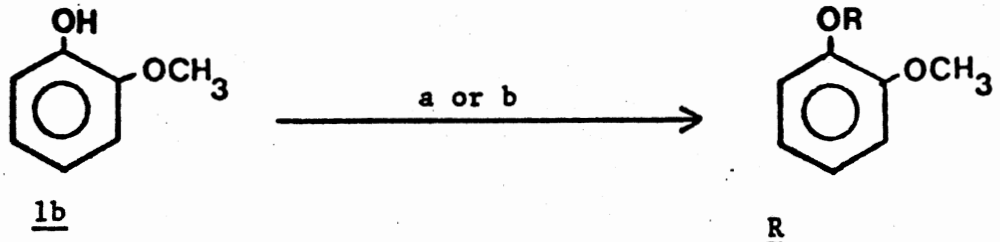
TABLE VIII

^{13}C NMR SHIFTS FOR ALKOXYL CARBONS IN
39a, 39b, 39c, 41a, 41b, AND 41c

Carbon Skeleton	Compound	R_1	Shift for R_1[a]	R_2	Shift for R_2[a]
	39a	H	----	CH_3	56.3
	39b	CH_3	60.5	CH_3	56.0
	39c	$\underline{C}H_2CH_3$	68.5	CH_3	56.0
	41a	H	----	CH_3	56.3
	41b	CH_3	60.3	CH_3	56.1
	41c	$\underline{C}H_2CH_3$	68.2	CH_3	56.0

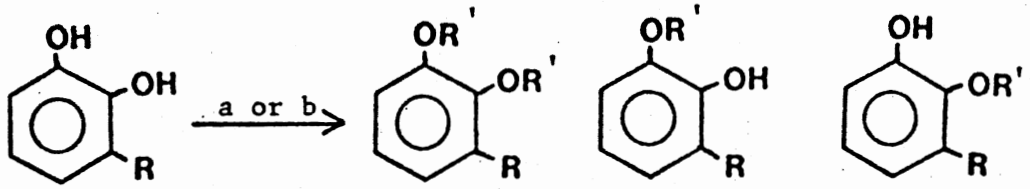
[a]Values are given in ppm downfield from TMS.

Scheme VII

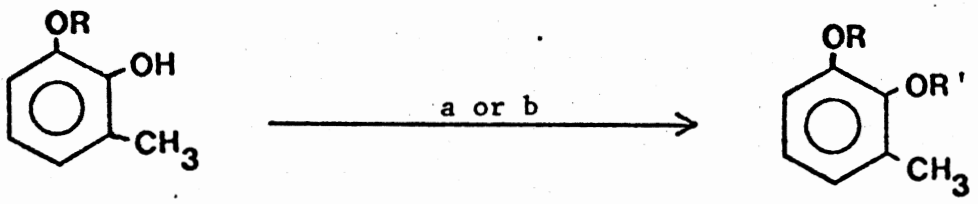


1b

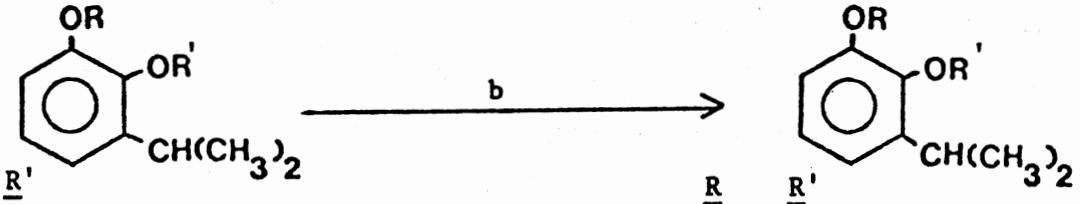
R	
CH_3	1a
C_2H_5	1c



R	R'			
CH_3	CH_3	42b	42c	42d
CH_3	C_2H_5	43a	43b	43c
$CH(CH_3)_2$	CH_3	45b	45c	45d



R		R'	
CH_3	42c	C_2H_5	44a
C_2H_5	43b	CH_3	44b



R	R'		R	R'	
CH_3	H	45c	CH_3	C_2H_5	46a
H	CH_3	45d	C_2H_5	CH_3	46b

[a] $(CH_3)_2SO_4$, NaOH. [b] $(C_2H_5)_2SO_4$, NaOH.

The ^{13}C NMR spectra of the model compounds revealed that a methoxyl with only one ortho substituent absorbs at 55.4 to 55.7 ppm and an ethoxyl with only one ortho substituent absorbs at 63.9 to 64.3 ppm. When the alkoxyl is ortho to two substituents the resonance is shifted downfield four to five ppm; 59.6 to 60.6 ppm for methoxyl and 68.0 to 68.6 ppm for ethoxyl. These shifts are summarized in Table IX. Based on the consistency of the ^{13}C NMR data and the other data already presented, the structure of the keto phenol obtained from the cyclization of 38a is 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (39a).

There still remained the possibility that the other phenolic isomer 39d was produced during the cyclization but was subsequently destroyed. In order to determine whether this does indeed occur, a sample of 39d was prepared using the reactions which are summarized in Scheme VIII.

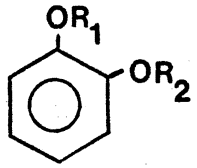
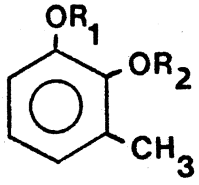
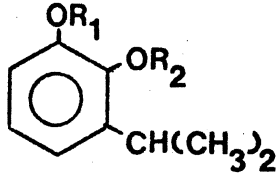
In order to determine whether 39d would be destroyed by acidic conditions, it was allowed to react with A-15 in refluxing xylene. Upon workup, 39d was recovered unchanged in 40% yield (80% by GC).[49]

We considered that 39d could have been destroyed during cyclization. Therefore a mixture of 39d and the crotonophenone 38a was allowed to react with methanesulfonic acid (neat). Upon workup, the base soluble fraction showed the presence of both phenolic isomers in the ratio (39a:39d, 2:1) as evidenced by the ^{1}H NMR spectrum of this mixture which contained two phenolic resonances, two methoxyl resonances, and two aromatic methyl resonances.

Since it has been shown that 39b will react under acidic conditions to form 39a, 39a may be formed by selective demethylation of the intermediate diether 39b during the cyclization of 38a. In order

TABLE IX

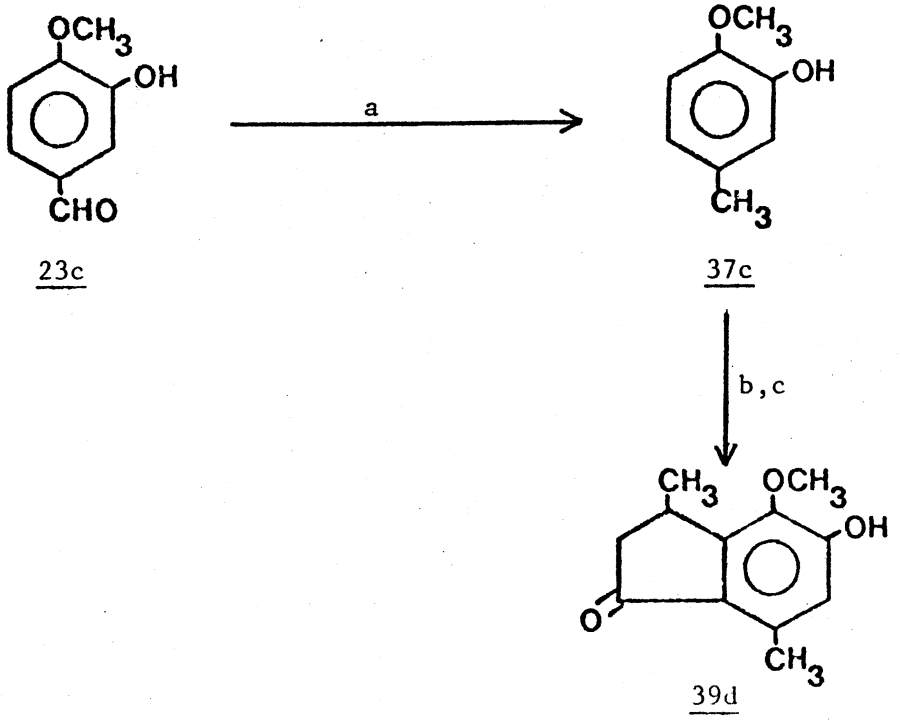
^{13}C NMR SHIFTS FOR ALKOXYL CARBONS IN MODEL COMPOUNDS

Carbon Skeleton	Compound	R_1	Shift for R_1[a]	R_2	Shift for R_2[a]
	1a	CH_3	55.6	CH_3	55.6
	1b	H	----	CH_3	55.7
	1c	$\underline{C}H_2CH_3$	64.1	CH_3	55.6
	42b	CH_3	55.4	CH_3	59.7
	42c	CH_3	55.7	H	----
	43b	$\underline{C}H_2CH_3$	64.3	H	----
	44a	CH_3	55.5	$\underline{C}H_2CH_3$	68.0
	44b	$\underline{C}H_2CH_3$	64.0	CH_3	59.6
	45b	CH_3	55.4	CH_3	60.5
	45c	CH_3	55.7	H	----
	45d	H	----	CH_3	61.5
	46a	CH_3	55.4	$\underline{C}H_2CH_3$	68.6
	46b	$\underline{C}H_2CH_3$	63.9	CH_3	60.6

[a]Values are given in ppm downfield from TMS.

to determine whether 39a could be prepared from 39b under acidic conditions which would not be conducive to molecular rearrangements, trimethylsilyl iodide was chosen as the Lewis acid catalyst for cleavage of 39b to 39a. When 39b was treated with 2.2 equivalents of trimethylsilyl iodide, the product was shown to be 39a. Further treatment with 4.2 equivalents of boron tribromide, which is known to convert keto diethers to keto catechols,[13] gave only recovered 39a.

Scheme VIII



23c 37c 39d

[a] H_2, Pd/C, acetic acid. [b] PPA, crotonic acid.

[c] Methanesulfonic acid.

Since 4,5-dihydroxy-3,7-dimethyl-1-indanone could not be produced from either 39a or 39b, 41b was allowed to react with 2.2 equivalents of trimethylsilyl iodide in an attempt to form 41d. The only product that could be isolated from this reaction was monophenol 41a previously formed through hydrogenolysis of 39a. Further treatment with 8.1 equivalents of boron tribromide gave 41d in 97% yield. A summary of these demethylation reactions is given in Scheme IX.

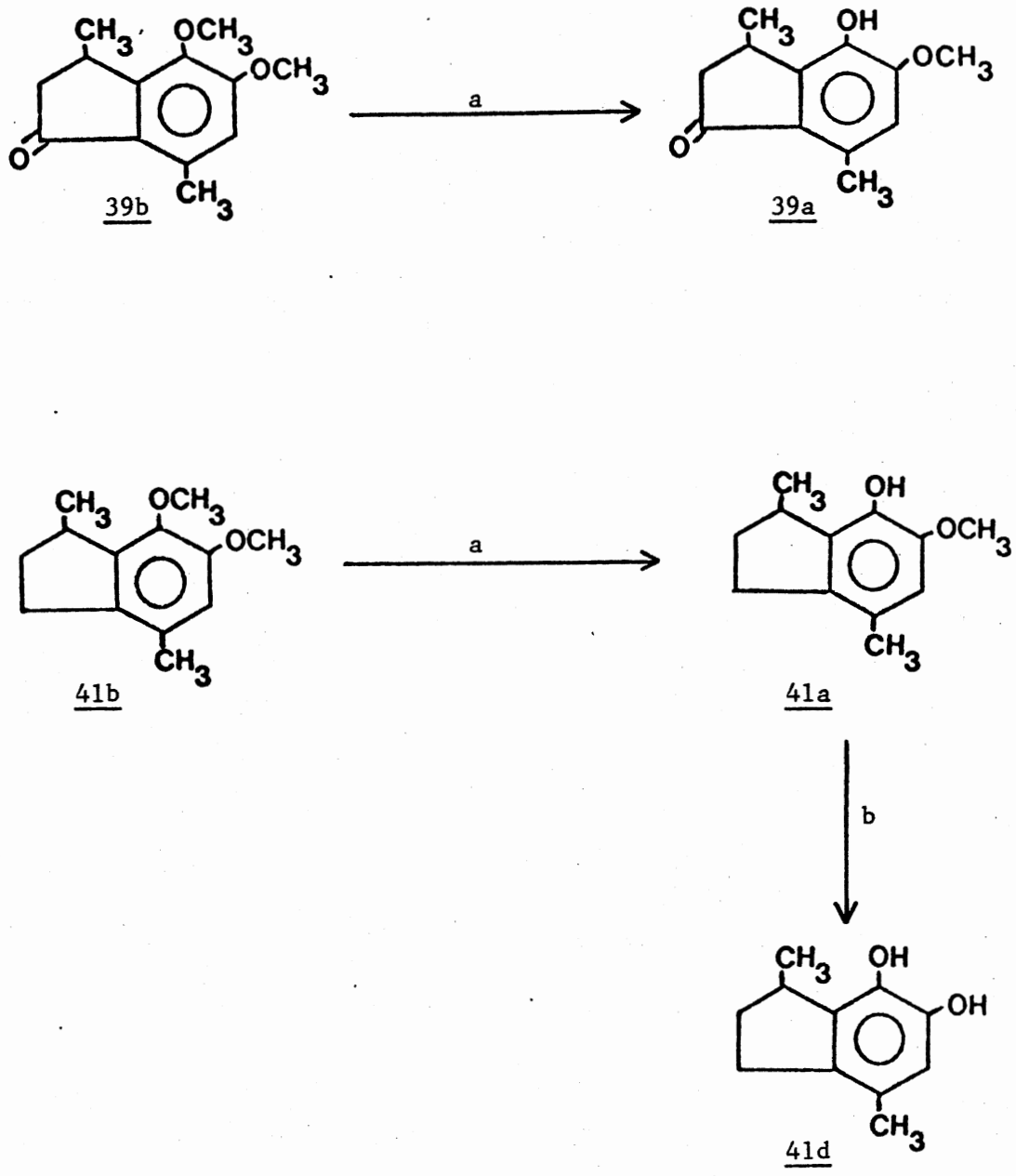
The selective demethylation of 39b to 39a is predictable from the cyclization data and literature precedents.[13,50] However, there are no literature precedents for the selective demethylation of aromatic ethers which don't contain a conjugated carbonyl. Therefore the selectivity which was observed in the demethylation of 41b was unexpected. This leads to the conclusion that the selective demethylation observed in the cyclization is determined by the position of the carbonyl and also a result of the steric environment of the methoxyl group.

In order to determine whether the observed sterically controlled selective demethylations are general in nature, the model compounds prepared for the ^{13}C NMR study were subjected to cleavage.

Treatment of 1,2-dimethoxybenzene (1a) with 1.1 equivalents of either trimethylsilyl iodide or boron tribromide gave approximately a statistical ratio of starting material (1a), 2-methoxyphenol (1b), and 1,2-benzenediol (1d). However treatment of 1a with 2.2 equivalents of trimethylsilyl iodide or boron tribromide gave a quantitative yield of 1d.

Treatment of either 1,2-dimethoxy-3-methylbenzene (42b) or 1,2-dimethoxy-3-(1-methylethyl)benzene (45b) with 1.1 equivalents of

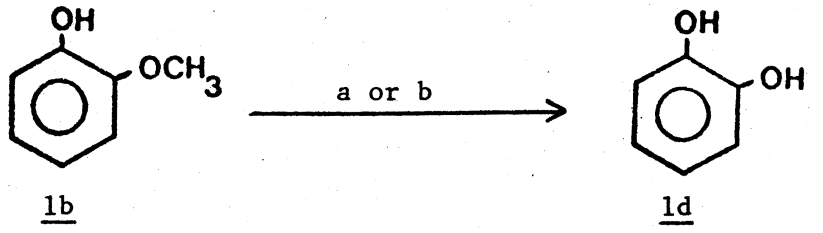
Scheme IX



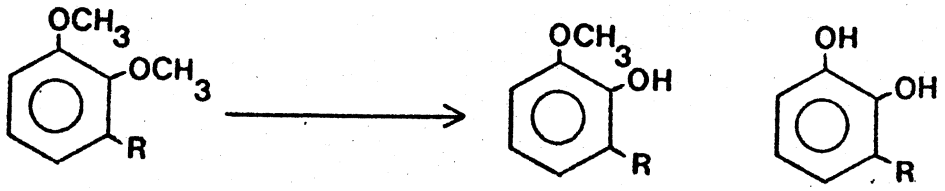
[a]Excess trimethylsilyl iodide. [b]Excess boron tribromide.

trimethylsilyl iodide gave only the monophenol corresponding to cleavage of the 'hindered' methoxyl group of 42c or 45c as shown in Scheme X. Even though treatment with 1.1 equivalents of boron tribromide gave a mixture of products, the only monophenol formed in the reaction was again the one corresponding to cleavage of the 'hindered' methoxyl group. Treatment of 42b or 45b with 3.3 equivalents of trimethylsilyl iodide gave a mixture of monophenol 42c or 45c and catechol 42a or 45a. However treatment of 42b or 45b with 3.3 equivalents of boron tribromide gave only catechol 42a or 45a. The product ratios from the above demethylations are shown in Table X.

Scheme X



1b 1d



R			
H	1a	1b	1d
CH_3	42b	42c	42a
$CH(CH_3)_2$	45b	45c	45a

[a]Trimethylsilyl iodide. [b]Boron tribromide.

TABLE X

DEMETHYLATION OF 1a, 1b, 42b, AND 45b

Starting Material	Equiv. TMSI[a]	Equiv. BBr_3	Products (%)		
			1a	1b	1d
1a	1.1		21	64	15
1a		1.1	18	60	22
1a	3.3		0	0	100
1a		3.3	0	0	100
			1b	1d	
1b	1.1		33	67	
1b		1.1	0	100	
			42a	42b	42c
42b	1.1		0	6	94
42b		1.1	18	40	42
42b	3.3		70	0	30
42b		3.3	100	0	0
			45a	45b	45c
45b	1.1		4	0	96
45b		1.1	46	30	24
45b	3.3		53	0	47
45b		3.3	100	0	0

[a]Trimethylsilyl iodide (TMSI).

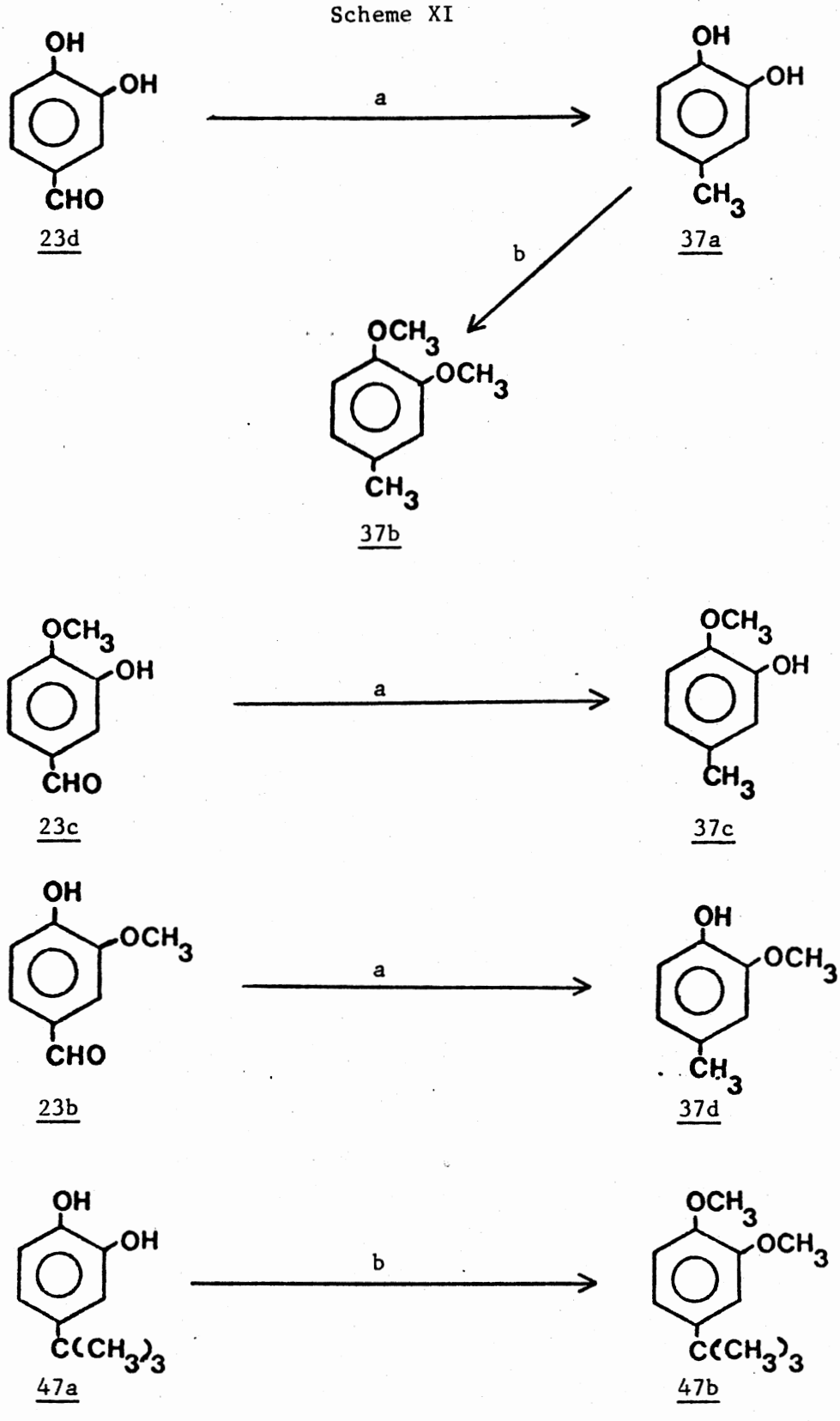
The above data led to the following conclusions: (1) both boron tribromide and trimethylsilyl iodide give selective demethylations, (2) trimethylsilyl iodide is the reagent of choice for monodemethylations, and (3) boron tribromide is the reagent of choice for the complete conversion of diether to catechol.

Since the methoxyl which is selectively demethylated in 42b and 45b is ortho to two electron releasing groups whereas the other methoxyl is ortho to one electron releasing group and meta to the other, there remained the possibility that the observed selective demethylations result from electronic and not steric effects. In order to resolve this the demethylations were repeated using 4-alkyl substituted 1,2-dimethoxybenzenes. The starting materials and standards were prepared as shown in Scheme XI.

This study showed no selectivity as evidenced by the formation of both possible monophenols as shown in Scheme XII in the ratio (37c:37d, 1.3:1). It also showed that 1.1 equivalents of either boron tribromide or trimethylsilyl iodide gave approximately a statistical ratio of products and that 3.3 equivalents gave the corresponding catechol in quantitative yield. The actual product ratios are given in Table XI. Therefore, the selectivity observed in the demethylations of 41b, 42b, and 45b is assumed to result from steric effects and not electronic effects.

It is interesting to note that the methoxyl group which is selectively cleaved is also the one which appears approximately four ppm downfield from the expected value in the ^{13}C NMR spectrum. However, when there is less than 0.2 ppm difference of the methoxyl resonances

Scheme XI



[a] H_2, Pd/C, acetic acid. [b] $(CH_3)_2SO_4$, NaOH.

in the ^{13}C NMR spectrum, as in 37b (55.6 and 55.8 ppm) and 47b (55.7 ppm), there also is no selectivity in the demethylations. It would seem that the downfield shift in the ^{13}C NMR spectrum and the selective demethylations are related in origin.

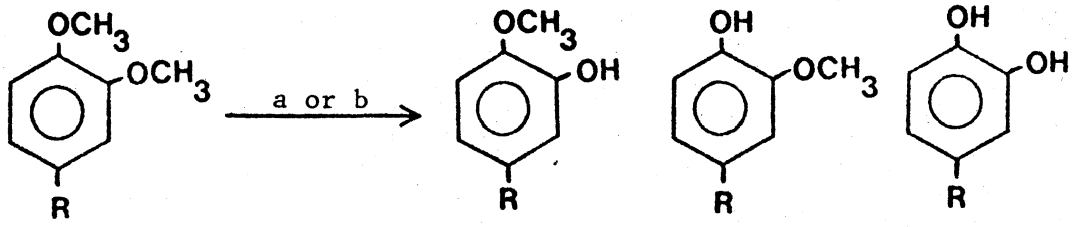
TABLE XI

DEMETHYLATION OF 37b

Starting Material	Equiv. TMSI[a]	Equiv. BBr_3	Products (%)			
			37a	37b	37c	37d
37b	1.1		13	28	33	26
37b		1.1	22	31	26	21
37b	3.3		100	0	0	0
37b		3.3	100	0	0	0

[a]Trimethylsilyl iodide (TMSI).

Scheme XII



R				
CH_3	37b	37c	37d	37a
$C(CH_3)_3$	47b	47c	47d	47a

[a]Trimethylsilyl iodide. [b]Boron tribromide.

Since the cause of the observed downfield shifts had earlier been attributed to steric interactions forcing the methoxyl carbon out of the plane of the benzene ring,[48] CNDO calculations were carried out on the various conformations of 1,2-dimethoxy-3-methylbenzene (42b) in order to determine the most stable conformation.[51] A molecular model was made using the known interatomic distances of 1,4-dimethoxybenzene and toluene.[52,53] The x, y, and z coordinates for each atom were manually obtained for each 45° rotation of both methoxyl groups through all possible conformations. The data thus obtained (Table XII) shows the most stable conformation to be the one in which the 1-methoxyl carbon is in the plane of the benzene ring with the carbon atom away from the adjacent methoxyl group. The 2-methoxyl carbon lies 45° out of the plane of the benzene ring and toward the 1-methoxyl group. This conformer is more stable than the next most stable conformer by a difference in total energies of 0.08 atomic units (approximately 50 Kcal). A drawing of this conformer is shown in Figure 2.

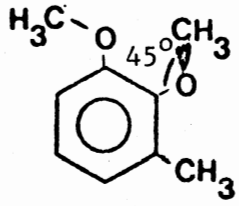


Figure 2. Most Stable Conformer of 42b

TABLE XII

CALCULATED TOTAL ENERGIES FOR THE CONFORMATIONS OF 42b[a]

θ (deg)[b]	φ (deg)[b]	E_{total}[c]
0	0	-109.39
	45	-109.52
	90	-109.26
	135	-107.93
	180	-109.44
45	0	-109.15
	45	-109.29
	90	-109.03
	135	-107.70
	180	-109.21
	-135	-107.75
	-90	-109.08
	-45	-109.34
90	0	-109.18
	45	-109.31
	90	-109.08
	135	-107.74
	180	-109.26
	-135	-107.74
	-90	-109.07
	-45	-109.33
135	0	13.08
	45	12.03
	90	-109.22
	135	-107.91
	180	-109.42
	-135	-109.28
	-90	-109.06
	-45	-107.73

TABLE XII (Continued)

θ (deg)[b]	φ (deg)[b]	E_{total}[c]
180	0	21.63
	45	13.24
	90	-109.17
	135	-107.86
	180	-109.37

[a]These energies were calculated using a CNDO (Complete Neglect of Differential Overlap) computer program.[51] [b]Starting with the molecule as shown in Figure 2, positive angles correspond to a rotation above the plane of the benzene ring and negative angles correspond to a rotation below the plane of the benzene ring. The angle of the 1-methoxyl carbon with the benzene ring is designated as θ and the angle of the 2-methoxyl carbon with the benzene ring is designated as φ (i.e. the exact conformation shown in Figure 2 would have a value of θ = 0 and a value of φ = 45. [c]These values are given in atomic units (one atomic unit equals 627.5 kilocalories) with the more negative numbers corresponding to less total energy.

The fact that the 'hindered' methoxyl group is forced out of the plane of the benzene ring is not only in agreement with Stothers' theories about the downfield shift in the ^{13}C NMR spectrum but it also explains the selective demethylations.[48] The non-bonded electrons of the 1-methoxyl oxygen are sterically hindered to electrophilic attack because of the close proximity of the adjacent methoxyl group. On the other hand, the non-bonded electrons of the 2-methoxyl oxygen atom have a greater electron density due to decreased resonance contributions,[48] as well as being more readily accessible to an electrophile because of their out-of-plane conformation. These electrons are therefore selectively attacked by Lewis-acid catalysts. Consequently, both the steric environment of the methoxyl groups and the electronic contribution due to the position of the carbonyl facilitate the selective formation of 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (39a) from the acid-catalyzed cyclialkylation of 4,5-dimethoxy-2-methylcrotonophenone (38a).

CHAPTER III

EXPERIMENTAL

1,2-Dimethoxybenzene (1a). To a 300 mL flask equipped with magnetic stirrer, nitrogen inlet, reflux condenser, and dropping funnel were added 1b (12.4 g, 0.1 mol) and 50 mL of 10% NaOH. Dimethyl sulfate (16.0 g, 0.13 mol) was added slowly (15 min) and the mixture was heated on a steam bath for 15 min. Fifty mL of 10% NaOH was again added, followed by dimethyl sulfate (16.0 g, 0.13 mol), and the reaction mixture was then heated for 1 h. NaOH (50 mL of 10%) was again added, the mixture was allowed to cool to room temperature, and then extracted with ether. The extract was washed with 10% NaOH, then with water, dried ($MgSO_4$), and concentrated to give 11.3 g (81.9%) of 1a, bp 206°C (lit[54] bp 205°C); IR (thin film) 1128 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 3.70 (s,6,$ArOCH_3$), 6.78 (s,4,ArH); ^{13}C NMR ($DCCl_3$) ppm 55.6 (q), 111.6 (d), 120.8 (d), 149.1 (s).

1-Ethoxy-2-methoxybenzene (1c). The procedure was the same as in the preparation of 1a except diethyl sulfate (18.5 g, 0.12 mol) was substituted for dimethyl sulfate. This process gave 14.0 g (92%) of 1c, bp 60°C at 0.25 mm (lit[55] 207-209°C); IR (thin film) 1130 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.34 (t,3,$OCCH_3$), 3.70 (s,3,$ArOCH_3$), 3.94 (q,2,$ArOCH_2$), 6.78 (s,4,ArH); ^{13}C NMR ($DCCl_3$) ppm 14.9 (q), 55.6 (q), 64.1 (t), 111.9 (d), 113.1 (d), 120.7 (d), 148.4 (s), 149.5 (s).

4-Methyl-1,2-benzenediol (37a). A mixture of 23d (10 g, 0.07 mol), 250 mL of acetic acid, and 2 g of 5% Pd/C was hydrogenated at 50 psig and 55°C until hydrogen uptake ceased. This was filtered through Dicalite, concentrated, diluted with salt water, and extracted with ether. The extract was washed with sodium carbonate, then with salt water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 6.5 g (72%) of 37a, mp 59-63°C (lit[56] mp 65°C); IR (KBr) 3027 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 2.20 (s,3,$ArCH_3$), 5.42 (s,2,ArOH), 6.48-6.84 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 20.5 (q), 115.5 (d), 116.4 (d), 121.5 (d), 131.0 (s), 140.7 (s), 143.0 (s).

1,2-Dimethoxy-4-methylbenzene (37b). A mixture of 37a (125 g, 1.0 mol), 10% NaOH, and dimethyl sulfate were reacted as in the preparation of 1a to give 143 g (93%) of 37b, bp 220-222°C (lit[54] bp 220-222°C); IR (thin film) 1030 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 2.20 (s,3,$ArCH_3$), 3.65 (s,6,$ArOCH_3$), 6.60 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 20.9 (q), 55.6 (q), 55.8 (q), 111.4 (d), 112.5 (d), 120.7 (d), 130.1 (s), 146.8 (s), 148.7 (s).

2-Methoxy-5-methylphenol (37c). A mixture of 23c (50 g, 0.33 mol), 250 mL of acetic acid, and 5 g of 5% Pd/C was hydrogenated and worked up as in the preparation of 37a to give 34.5 g (76%) of 37c, mp 34-35°C (lit[57] mp 35-36°C); IR (KBr) 3400 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 2.22 (s,3,$ArCH_3$), 3.76 (s,3,$ArOCH_3$), 5.75 (s,1,ArOH), 6.48-6.80 (m,3, ArH); ^{13}C NMR ($DCCl_3$) ppm 20.7 (q), 55.9 (q), 110.7 (d), 115.5 (d), 120.2 (d), 130.9 (s), 144.5 (s), 145.3 (s).

2-Methoxy-4-methylphenol (37d). A mixture of 23b (100 g, 0.66 mol), 1 L of acetic acid, and 10 g of 5% Pd/C was hydrogenated and

worked up as in the preparation of 37a to give 78.5 g (86%) of 37d, bp 38-39°C at 0.2 mm (lit[58] bp 219-221°C); IR (thin film) 3480 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 mHz) δ 2.21 (s,3,$ArCH_3$), 3.66 (s,3,$ArOCH_3$), 5.92 (s,1,ArOH), 6.50-6.88 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 20.9 (q), 55.6 (q), 111.8 (d), 114.3 (d), 121.4 (d), 129.4 (s), 143.3 (s), 146.4 (s).

3,7-Dimethyl-4-hydroxy-5-methoxy-1-indanone (39a). A. To a 2 L flask equipped with magnetic stirrer and reflux condenser were added 38a (10 g, 46 mmol), 1 L of o-xylene, and 10 g of A-15.[34] The reaction mixture was heated at reflux (132°C) for 42 h until the starting material was consumed as evidenced by GC analysis.[67] The black mixture was then cooled, filtered, and steam distilled to remove the o-xylene. The ether extract of the steam distillation residue was dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 4 g (40%) of a pale yellow liquid which solidified after a few hours. Two recrystallizations from boiling isohexane[68] gave pale yellow crystals of 39a, mp 92.5-93.5°C; IR (KBr) 3200, 2900, 1670, 1585, 1500, 1450, 1350, 1300, 1145, 1080, 1000, 880, 835 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.35 (d,3,CCH_3), 2.20 (q,1,methylene proton in an unsymmetrical environment), 2.55 (s,3,$ArCH_3$), 2.85 (q,1, methylene proton in an unsymmetrical environment), 3.50 (m,1,ArCH), 3.90 (s,3,$ArOCH_3$), 5.65 (s,1,ArOH), 6.95 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.0 (q), 20.4 (q), 29.9 (d), 46.5 (t), 56.3 (q), 112.5 (d), 127.7 (s), 131.0 (s), 140.4 (s), 145.7 (s), 150.9 (s), 206.7 (s); MS (70-eV) M/z (rel. intensity) M^+ 206 (81), 181 (85), 91 (18), 18 (100), 17 (29), 15 (31). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.86.

B. To a 2 L flask equipped with magnetic stirrer and Dean-Stark trap were added 1 L of o-xylene and 10 g of A-15. This mixture was refluxed overnight in order to remove any water that would azeotrope from the mixture. Ketone 38a (10 g, 46 mmol) was then added and a Dean-Stark trap which had been modified such that the solvent passed over 15 g of 4 Å molecular sieve was substituted. The remainder of the reaction was identical with that described for A. The yield and isolated product were also identical.

C. To a 500 mL flask equipped as in A were added 39b (3.0 g, 14 mmol), 300 mL of o-xylene, and 3.0 g of A-15. This mixture was refluxed for 48 h and processed as in A. This gave 2.0 g (69.4%) of a phenol which was shown to be identical with the phenol formed in A.

4,5-Dimethoxy-3,7-dimethyl-1-indanone (39b). A. To a 250 mL flask equipped with reflux condenser, dropping funnel, and magnetic stirrer were added 39a (6.5 g, 31 mmol), 150 mL of anhydrous acetone, and potassium carbonate (4.8 g, 34 mmol). Dimethyl sulfate (3.7 g, 24 mmol) was added, the mixture was refluxed for 3 h, allowed to cool to room temperature, filtered, and concentrated. This concentrate was dissolved in ether, passed through a plug of neutral alumina, washed with 10% NaOH, then with water, concentrated, and Kugelrohr distilled to give 3.5 g (51%) of 39b, mp 64.5-65.5°C; IR (thin film) 2950, 1700, 1590, 1500, 1460, 1390, 1340, 1308, 1260, 1235, 1195, 1138, 1035, 986, 843, 827, 775, 754, 700, 662 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.38 (d,3, CCH_3), 2.21 (q,1,methylene proton in an unsymmetrical environment), 2.58 (s,3,$ArCH_3$), 2.88 (q,1,methylene proton in an unsymmetrical environment), 3.48 (m,1,ArCH), 3.88 (s,3,$ArOCH_3$), 3.92 (s,3,$ArOCH_3$),

6.68 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.1 (q), 21.3 (q), 30.2 (d), 46.5 (t), 56.0 (q), 60.5 (q), 114.2 (d), 128.3 (s), 135.3 (s), 143.8 (s), 152.9 (s), 157.1 (s), 205.5 (s); MS (70-eV) M/z (rel. intensity) M^+ 220 (100), 205 (59), 177 (18), 91 (19), 77 (14), 31 (12). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.02; H, 7.31.

B. To a 500 mL flask were added ketone 38a (2.5 g, 11 mmol), 250 mL of chlorobenzene, and 2.5 g of Amberlyst XN-1010.[34] This mixture was refluxed for 48 h, filtered, concentrated, and Kugelrohr distilled to give 1.0 g (40%) of a solid which was found by melting point and ^1H NMR to be 39b.

Trimethylsilyl Iodine Cleavage of 4,5-Dimethoxy-3,7-dimethyl-1-indanone (39b) to 39a. To a 10 mL flask was added 39b (570 mg, 2.6 mmol) and 1.3 mL of chloroform. An inert atmosphere was established and maintained with use of a septum. Trimethylsilyl iodide (0.85 mL, 5.8 mmol) was added with a 1 mL syringe, the mixture was stirred at room temperature for 48 h, diluted with 10 mL of methanol, 20 mL of salt water was added, and this was extracted (2X) with 20 mL of ether. The extract was washed with sodium bisulfite, dried (Na_2SO_4), concentrated, and Kugelrohr distilled to give 473 mg (88%) of a solid which was shown by melting point and ^1H NMR to be 39a.

3,7-Dimethyl-4-ethoxy-5-methoxy-1-indanone (39c). To a 250 mL flask equipped with reflux condenser, magnetic stirrer, and dropping funnel were added 39a (0.5 g, 2.4 mmol), 150 mL of anhydrous acetone, and potassium carbonate (0.37 g, 2.6 mmol). Diethyl sulfate (0.35 g, 2.3 mmol) was added and the remainder of the procedure carried out as in the preparation of 39b to give 0.4 g (71%) of 39c, mp 58-60°C; IR

(KBr) 3330, 2950, 1700, 1550, 1490, 1450, 1345, 1305, 1270, 1230, 1045, 1005, 920, 875, 775, 710, 699 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.48 (t,3,$OCCH_3$), 1.49 (d,3,CCH_3), 2.20 (q,1,methylene proton in an unsymmetrical environment), 2.58 (s,3,$ArCH_3$), 2.87 (q,1,methylene proton in an unsymmetrical environment), 3.46 (m,1,ArCH), 3.90 (s,3,$ArOCH_3$), 4.08 (m,2,$ArOCH_2$), 6.66 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.8 (q) 18.1 (q), 21.2 (q), 30.4 (d), 46.5 (t), 56.0 (q), 68.5 (t), 114.1 (d), 127.6 (s), 135.1 (s), 142.8 (s), 153.2 (s), 157.2 (s), 205.5 (s); MS (70-eV) M/z (rel. intensity) M^+ 234 (93), 206 (73), 191 (100), 177 (33), 28 (60), 18 (67). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.49; H, 7.76.

3,7-Dimethyl-5-hydroxy-4-methoxy-1-indanone (39d). To a 500 mL 2-neck flask equipped with mechanical stirrer and drying tube were added 37c (20 g, 0.14 mol), 2a (12.5 g, 0.14 mol), and 350 g of PPA. This mixture was heated (60-70°C) and stirred for 2 h, hydrolyzed with ice water, and extracted with ether. The extract was washed with sodium carbonate, then with salt water, dried (Na_2SO_4), and concentrated to give 7.0 g of a brown oil. A mixture of 2.5 g of the oil and 250 mL of methanesulfonic acid was heated (100°C) for 45 min, diluted with water, and extracted with ether. The extract was washed with salt water, dried ($MgSO_4$), and concentrated to give a brown oil which was triturated with n-hexane. This solution, upon slow evaporation, gave 230 mg (2.3%) of pale brown crystals which were Kugelrohr distilled to give 39d, mp 131-133°C; IR (KBr) 3160, 2945, 1660, 1575, 1500, 1450, 1330, 1263, 1240, 1195, 1167, 995, 857, 749, 695 cm^{-1}; ^1H NMR ($DCCl_3$, 100 mHz) δ 1.39 (d,3,CCH_3), 2.21 (q,1,methylene proton in an

unsymmetrical environment), 2.54 (s,3,$ArCH_3$), 2.87 (q,1,methylene proton in an unsymmetrical environment), 3.48 (m,1,ArCH), 3.89 (s,3,$ArOCH_3$), 6.68 (s,1,ArOH), 6.71 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.1 (q), 20.7 (q), 30.5 (d), 46.2 (t), 60.4 (q), 118.2 (d), 127.0 (s), 136.2 (s), 141.8 (s), 152.8 (s), 154.9 (s), 206.0 (s); MS (70-eV) M/z (rel. intensity) M^+ 206 (12), 191 (10), 40 (7), 32 (100), 28 (83), 14 (19). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.99.

1,4-Dimethyl-7-hydroxy-6-methoxyindan (41a). A mixture of 39a (0.11 g, 0.5 mmol), 60 mL of acetic acid, and 0.1 g of 10% Pd/C was hydrogenated at 50 mm of Hg until pressure change ceased.[59] The mixture was then filtered through Dicalite, diluted with salt water, and extracted with ether. The extract was concentrated, diluted with isohexane, passed through a column of neutral alumina, and again concentrated to give 0.08 g (78%) of 41a, mp 58-60°C; IR (KBr) 3400, 2925, 1492, 1448, 1353, 1287, 1200, 1108, 1090, 1061, 1017, 894, 853, 837 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.26 (d,3,CCH_3), 1.67 (m,1,methylene proton in an unsymmetrical environment), 2.16 (s,3,$ArCH_3$), 2.22 (m,1,methylene proton in an unsymmetrical environment), 2.73 (t,2,$ArCH_2$), 3.39 (m,1, ArCH), 3.80 (s,3,$ArOCH_3$), 5.39 (s,1,ArOH), 6.50 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.7 (q), 19.6 (q), 29.5 (t), 34.0 (t), 37.7 (d), 56.3 (q), 110.5 (d), 123.7 (s), 133.4 (s), 135.7 (s), 139.9 (s), 145.0 (s); MS (70-eV) M/z (rel. intensity) M^+ 192 (100), 178 (11), 177 (79), 159 (7), 145 (9), 117 (13). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.72; H, 8.50.

6,7-Dimethoxy-1,4-Dimethylindan (41b). A mixture of 39b (0.76 g, 3.5 mmol), 75 mL of acetic acid, and 0.1 g of 10% Pd/C was hydrogenated

and worked up as in the preparation of 41a to give 0.59 g (83%) of 41b, mp 50-52°C; IR (KBr) 2880, 1695, 1580, 1490, 1451, 1337, 1298, 1256, 1228, 1216, 1188, 1130, 1109, 1089, 1062, 1030, 987, 970, 891, 847 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.25 (d,3,CCH_3), 1.44 (m,1,methylene proton in an unsymmetrical environment), 2.18 (s,3,$ArCH_3$), 2.20 (m,1,methylene proton in an unsymmetrical environment), 2.67 (t,2,$ArCH_2$), 3.39 (m,1, ArCH), 3.80 (s,6,$ArOCH_3$), 6.56 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.8 (q), 20.4 (q), 29.3 (t), 34.0 (t), 38.2 (d), 56.1 (q), 60.3 (q), 112.8 (d), 128.3 (s), 135.3 (s), 140.8 (s), 143.9 (s), 151.1 (s); MS (70-eV) M/z (rel. intensity) M^+ 206 (100), 192 (17), 191 (70), 175 (14), 160 (11), 159 (10). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.44; H, 8.82.

Trimethylsilyl Iodide Cleavage of 6,7-Dimethoxy-1,4-dimethylindan (41b) to 41a. To a 10 mL flask were added 41b (533 mg, 2.6 mmol) and 1.3 mL of chloroform. This mixture was reacted with trimethylsilyl iodide in the same manner as 39b to give 0.5 g (100%) of a white solid which was shown by melting point and ^1H NMR to be 41a.

1,4-Dimethyl-7-ethoxy-6-methoxyindan (41c). To a 250 mL 3-neck flask equipped with nitrogen inlet, reflux condenser, dropping funnel, and magnetic stirrer were added 41a (2.2 g, 10 mmol) and 50 mL of 10% NaOH. Diethyl sulfate (23.5 g, 0.15 mol) was added dropwise at room temperature, the mixture was warmed for 1 h, allowed to cool to room temperature, 50 mL of 10% NaOH was added, stirring was continued for 2 H, and the mixture was extracted with ether. The extract was washed with 10% NaOH, then with water, dried (Na_2SO_4), and concentrated to give 2.0 g (91%) of 41c, bp 90-91°C at 0.4 mm; IR (thin film) 2875,

1490, 1340, 1300, 1220, 1122, 1064, 1044, 920, 833 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.30 (t,3,CCH_3), 1.42-1.76 (m,1,methylene proton in an unsymmetrical environment), 1.98-2.32 (m,1,methylene proton in an unsymmetrical environment), 2.12 (s,3,$ArCH_3$), 2.38-2.44 (m,2,$ArCH_2$), 3.14-3.46 (m,1,ArCH), 3.65 (s,3,$ArOCH_3$), 3.80-4.18 (m,2,$ArOCH_2$), 6.46 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.9 (q), 18.8 (q), 20.3 (q), 29.3 (t) 34.1 (t), 38.4 (d), 56.0 (q), 68.2 (t), 112.7 (d), 128.0 (s), 135.2 (s), 141.1 (s), 143.0 (s), 151.3 (s); MS (70-eV) M/z (rel. intensity) M^++1 221 (18), M^+ 220 (100), 177 (8), 145 (6), 131 (6), 117 (6). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.27; H, 8.96.

6,7-Dihydroxy-1,4-dimethylindan (41d) from 41a. To a 25 mL flask was added 41a (600 mg, 3.1 mmol) and 10 mL of chloroform. An inert atmosphere was established and maintained with use of a septum. The mixture was cooled in a Dry Ice/2-propanol bath and boron tribromide (0.8 mL, 8.4 mmol) was added. This was stirred for 30 min, warmed to room temperature, poured into salt water, and extracted with ether. The extract was dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 0.54 g (97%) of 41d, mp 58-59°C; IR (KBr) 3320, 2910, 1600, 1490, 1455, 1345, 1300, 1180, 1080, 927, 840, 710 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.20 (d,3,CCH_3), 1.50-1.80 (m,1,methylene proton in an unsymmetrical environment), 1.84-2.30 (m,1,methylene proton in an unsymmetrical environment), 2.20 (s,3,$ArCH_3$), 2.44-2.96 (m,2,$ArCH_2$), 3.10-3.42 (m,1,ArCH), 6.04 (s,2,ArOH), 6.43 (s,1,ArH); ^{13}C NMR ($DCCl_3$) ppm 18.3 (q), 19.6 (q), 29.3 (t), 33.9 (t), 37.4 (d), 115.1 (d), 125.5 (s), 134.8 (s), 135.6 (s), 137.9 (s), 141.4 (s); MS (70-eV) M/z (rel. intensity) M^+ 178 (64), 163 (100), 145 (56), 112 (96), 82 (48), 39 (52);

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.30; H, 8.02.

1,2-Dimethoxy-3-methylbenzene (42b). To a 300 mL flask equipped with magnetic stirrer, nitrogen inlet, reflux condenser, and dropping funnel were added 42a (24.8 g, 0.2 mol) and 100 mL of 100% NaOH. Dimethyl sulfate (32.0 g, 0.26 mol) was added dropwise, the exothermic reaction mixture was stirred for 15 min, and 100 mL of 10% NaOH was added. The cooled mixture was extracted with ether, the extract was washed with 10% NaOH, then with water, dried (Na_2SO_4), concentrated, and Kugelrohr distilled to give 8.6 g (28%) of 42b, bp 45-47°C at 0.3 mm (lit[60] 200-202°C at 76 mm); IR (thin film) 1085 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 2.22 (s,3,$ArCH_3$), 3.70 (s,3,$ArOCH_3$), 3.74 (s,3,$ArOCH_3$), 6.58-6.96 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.7 (q), 55.4 (q), 59.7 (q), 110.2 (d), 122.7 (d), 123.5 (d), 131.6 (s), 147.4 (s), 152.7 (s).

2-Methoxy-6-methylphenol (42c). The aqueous layer from the preparation of 42b was acidified, extracted with ether, dried ($MgSO_4$), concentrated, and Kugelfohr distilled (45-50°C at 0.25 mm) to give 11.1 g (40.2%) of a clear liquid containing 42c and 42d. An ether solution of this mixture was washed with 113 mL of 2% NaOH, dried (Na_2SO_4), and concentrated to give 4.7 g (17%) of 42c, mp 39-41°C (lit[61] mp 42°C); IR (KBr) 3400 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 2.23 (s,3,$ArCH_3$), 3.60 (s,3, $ArOCH_3$), 6.14 (s,1,ArOH), 6.43-6.85 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.4 (q), 55.7 (q), 108.2 (d), 119.0 (d), 123.1 (d), 123.8 (s), 143.7 (s), 146.1 (s).

2-Ethoxy-6-methylphenol (43b). The procedure was the same as in the preparation of 42b except diethyl sulfate (42.4 g, 0.28 mol) was

substituted for dimethyl sulfate. The cooled reaction mixture was extracted with ether, the extract was washed with 10% NaOH, then with water, the combined aqueous layers were acidified, and extracted with ether. The extract was washed with water, dried (Na_2SO_4), concentrated, and Kugelrohr distilled to give 13.6 g (45%) of an orange liquid containing 43b and 43c. An ether solution of this liquid was washed with 2% NaOH, dried (Na_2SO_4), and concentrated to give 4.3 g (14%) of 43b, bp 49-51°C at 0.3 mm (lit[62] bp 101°C at 12 mm); IR (thin film) 3470 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.31 (t,3,$OCCH_3$), 2.24 (s,3,$ArCH_3$), 3.97 (q, 2,$ArOCH_2$), 5.88 (s,1,ArOH), 6.40-6.90 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 14.7 (q), 15.4 (q), 64.3 (t), 109.2 (d), 119.0 (d), 122.9 (d), 123.8 (s), 143.9 (s), 145.4 (s).

2-Ethoxy-1-methoxy-3-methylbenzene (44a). To a 500 mL flask equipped with magnetic stirrer, nitrogen inlet, reflux condenser, and dropping funnel were added 42c (2.3 g, 17 mmol) and 15 mL of 10% NaOH. This mixture was warmed, diethyl sulfate (62.4 g, 0.41 mol) was added dropwise, the mixture warmed for 2 h, 250 mL of 10% NaOH was added, the mixture cooled overnight, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 2.2 g (78%) of 44a, bp 46-47°C at 0.3 mm (lit[63] bp 72-74°C at 4 mm); IR (thin film) 1085 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.33 (t,3, $OCCH_3$), 2.24 (s,3,$ArCH_3$), 3.70 (s,3,$ArOCH_3$), 3.96 (q,2,$ArOCH_2$), 6.56-7.02 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.8 (q), 16.0 (q), 55.5 (q), 68.0 (t), 110.2 (d), 122.7 (d), 127.6 (d), 131.9 (s), 146.6 (s), 152.8 (s).

1-Ethoxy-2-methoxy-3-methylbenzene (44b). This procedure is the same as in the preparation of 44a except that 43b (2.3 g, 15 mmol) was

substituted for 42c and dimethyl sulfate (6.6 g, 53 mmol) was substituted for diethyl sulfate. This gave 2.2 g (88%) of 44b, bp 48-50°C at 0.25 mm (lit[62] 115°C at 24mm); IR (thin film) 1075 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.34 (t,3,$OCCH_3$), 2.20 (s,3,$ArCH_3$), 3.74 (s,3,$ArOCH_3$), 3.91 (q,2,$ArOCH_2$), 6.54-6.94 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.0 (q), 15.8 (q), 59.6 (q), 64.0 (t), 111.5 (d), 122.7 (d), 123.4 (d), 131.6 (s), 147.8 (s), 151.9 (s).

1,2-Dimethoxy-3-(1-methylethyl)benzene (45b). This procedure is the same as in the preparation of 42b except 45a (30.4 g, 0.2 mol) was substituted for 42b. This gave 10.7 g (30%) of 45b, bp 56-57°C at 0.33 mm (lit[64] bp 119-121°C at 24 mm); IR (thin film) 1055 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.19 (d,6,$C(CH_3)_2$), 3.16-3.54 (m,1,ArCH), 3.73 (s,3, $ArOCH_3$), 3.78 (s,3,$ArOCH_3$), 6.52-7.10 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 22.5 (q), 23.5 (q), 26.9 (d), 55.4 (q), 60.5 (q), 109.9 (d), 118.2 (d), 123.8 (d), 134.2 (s), 142.2 (s), 152.6 (s).

2-Methoxy-6-(1-methylethyl)phenol (45c). The combined aqueous layers from the preparation of 45b were treated in the same manner as in the preparation of 42c to give 3.8 g (11%) of 45c, bp 53-54°C at 0.3 mm (lit[65] bp 122°C at 24mm); IR (thin film) 1058 cm^{-1}; ^{1}H NMR ($DCCl_3$, 100 MHz) δ 1.23 (d,6,$C(CH_3)_2$), 3.10-3.68 (m,1,ArCH), 3.70 (s,3, $ArOCH_3$), 5.84 (s,1,ArOH), 6.50-6.90 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 22.5 (q), 27.2 (d) 55.7 (q), 108.0 (d), 118.6 (d), 119.3 (d), 134.3 (s), 142.8 (s), 146.2 (s).

2-Methoxy-3-(1-methylethyl)phenol (45d). The combined base layers from the preparation of 45c were acidified, extracted with ether, the extract washed with water, and then washed with 80 mL of 0.5% NaOH. The base layer was acidified, extracted with ether, the extract washed

with water, and then extracted with 40 mL of 0.5% NaOH. The base layer was acidified, extracted with ether, the extract washed with water, dried (Na_2SO_4), concentrated, and Kugelrohr distilled to give 1.0 g (3%) of 45d, bp 61-63°C at 0.25 mm; IR (thin film) 3400, 2950, 1460, 1270, 1195, 995, 955, 783, 733 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.20 (d,6,$C(CH_3)_2$), 3.10-3.44 (m,1,ArCH), 3.74 (s,3,$ArOCH_3$), 5.96 (s,1,ArOH), 6.54-7.08 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 23.7 (q), 26.6 (d), 61.5 (q), 113.2 (d), 117.9 (d), 125.0 (d), 141.6 (s), 141.9 (s), 148.5 (s); MS (70-eV) M/z (rel. intensity) M^+ 166 (53), 153 (16), 152 (100), 137 (8), 95 (9), 91 (19). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.54.

2-Ethoxy-1-methoxy-3-(1-methylethyl)benzene (46a). This procedure is the same as in the preparation of 44a except 45c (2.0 g, 12 mmol) was substituted for 42c. This gave 2.2 g (94%) of 46a, bp 45-46°C at 0.3 mm; IR (thin film) 2950, 1460, 1267, 1052, 902, 780, 741 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.19 (d,6,$C(CH_3)_2$), 1.35 (t,3,$OCCH_3$), 3.19-3.59 (m,1, ArCH), 3.74 (s,3,$ArOCH_3$), 3.78 (q,2,$ArOCH_2$), 6.60-7.06 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.8 (q), 23.6 (q), 26.8 (d), 55.4 (q), 68.6 (t), 109.7 (d), 118.1 (d), 123.6 (d), 142.4 (s), 145.4 (s), 152.6 (s); MS (70-eV) M/z (rel. intensity) M^+ 194 (100), 166 (79), 152 (34), 151 (18), 124 (18), 91 (16). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.06; H, 9.28.

1-Ethoxy-2-methoxy-3-(1-methylethyl)benzene (46b). This procedure is the same as in the preparation of 44a except 45d (0.6 g, 3.6 mmol) was substituted for 42c. This gave 0.4 g (57%) of 46b, bp 49-50°C at 0.25 mm; IR (thin film) 2950, 1480, 1275, 1060, 785, 745 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.19 (d,6,$C(CH_3)_2$), 1.40 (t,3,$OCCH_3$), 3.16-3.50 (m,1,

ArCH), 3.80 (s,3,$ArOCH_3$), 4.20 (q,2,$ArOCH_2$), 6.60-7.04 (m,3,ArH); ^{13}C NMR ($DCCl_3$) ppm 15.0 (q), 23.5 (q), 26.9 (d), 60.6 (q), 63.9 (t), 110.8 (d), 118.1 (d), 123.7 (d), 142.3 (s), 142.5 (s), 151.7 (s); MS (70-eV) M/z (rel. intensity) M^+ 194 (87), 179 (68), 165 (47), 151 (100), 149 (32), 137 (45). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.30; H, 9.46.

1,2-Dimethoxy-4-(1,1-dimethylethyl)benzene (47b). To a 500 mL 3-neck flask equipped with nitrogen inlet, magnetic stirrer, reflux condenser, and dropping funnel were added 47a (17 g, 0.12 mol) and 100 mL of 10% NaOH. Dimethyl sulfate (42.4 g, 0.28 mol) was added, the mixture warmed for 30 min, 100 mL of 10% NaOH added, dimethyl sulfate (42.4 g, 0.28 mol) was added, and the mixture warmed for 1 h. Then 200 mL of 10% NaOH were added, the mixture cooled, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to give 18.8 g (94%) of 47b, mp 31.5-32.5°C (lit[66] mp 36-37°C); IR (KBr) 1027 cm^{-1}; ^1H NMR ($DCCl_3$, 100 MHz) δ 1.30 (s,9, $C(CH_3)_3$), 3.78 (s,3,$ArOCH_3$), 3.82 (s,3,$ArOCH_3$), 6.66-6.98 (m,3,ArH): ^{13}C NMR ($DCCl_3$) ppm 31.5 (q), 34.3 (s), 55.7 (q), 109.2 (d), 110.8 (d), 117.0 (d), 143.7 (s), 146.7 (s), 148.3 (s).

Trimethylsilyl Iodide Cleavage: General Procedure. To a 10 mL flask were added reactant (2 mmol) and 1 mL of chloroform. An inert atmosphere was established and maintained through use of a septum. Trimethylsilyl iodide (0.32 mL, 2.2 mmol or 0.96 mL, 6.6 mmol) was added through the septum with a 1 mL syringe. This mixture was magnetically stirred at room temperature for 48 h, diluted with 10 mL of methanol, 20 mL of salt water were added, and this was extracted (2X)

with 20 mL of ether. The extract was washed with sodium bisulfite, then with salt water, dried (Na_2SO_4), and concentrated. This procedure was used for the cleavage of 1a, 37b, 42b, 45b, and 47b.

Boron Tribromide Cleavage: General Procedure. To a 10 mL flask were added reactant (3.6 mmol) and 5 mL dichloromethane. An inert atmosphere was established and maintained through use of a septum. This mixture was cooled in a Dry Ice/2-propanol bath and boron tribromide (0.38 mL, 4 mmol or 1.14 mL, 12 mmol) was added through the septum with a syringe. The cold bath was removed, the mixture stirred for 30 min, poured into ice water, stirred for 30 min, saturated with salt, and extracted with dichloromethane. The extract was dried ($MgSO_4$) and concentrated. This procedure was used for the cleavage of 1a, 37b, 42b, 45b, and 47b.

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36. ^{13}C NMR spectra were recorded at 25.2 MHz in the FT mode on a Varian XL-100A interfaced with a 12 K Nicolet 1080 computer system. Spectra were run in $DCCl_3$ using a deuterium lock and are reported in ppm downfield from TMS (δ $DCCl_3$ = 76.9 ppm).

37. Methanesulfonic acid was obtained as a gift from Pennwalt Corp., Philadelphia, PA 19102, and literature describing its use and properties may be obtained from this source.

38. IR spectra were obtained using a Beckman IR-5A instrument.

39. ^{1}H NMR spectra were recorded at 100.1 MHz on a Varian XL-100A. Spectra were run in $DCCl_3$ using a deuterium lock and are reported in terms of δ relative to internal TMS.

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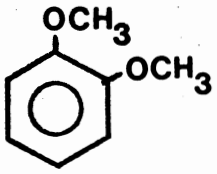
67. GC analyses were done on a Hewlett-Packard 5750 instrument with dual flame ionization detectors using a 6' x ¼" column packed with 5% UC W-98 coated on 80-100 mesh AW DMCS-treated Chromosorb G at 190°C.

68. Phillips Isohexanes, bp 61°C.

APPENDIX

GLOSSARY OF STRUCTURES



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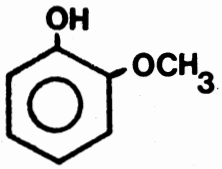

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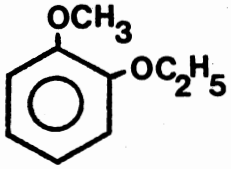

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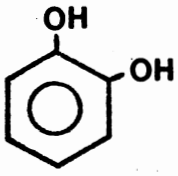

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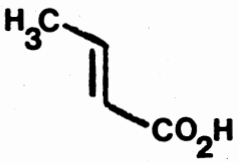

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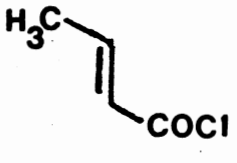

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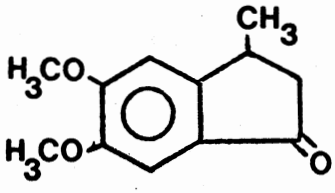

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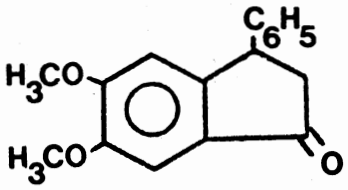

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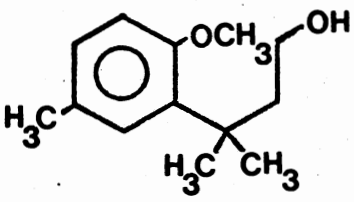

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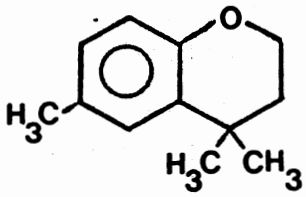

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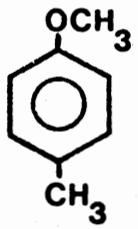

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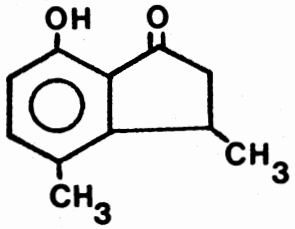

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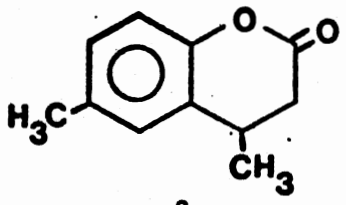

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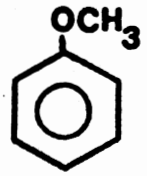

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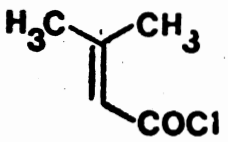

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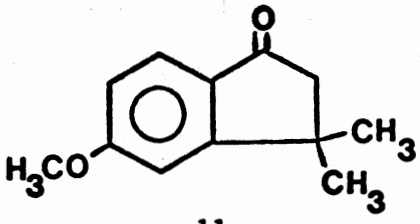

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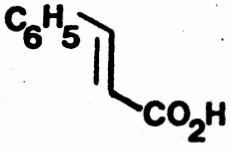

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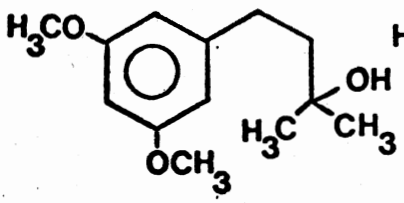

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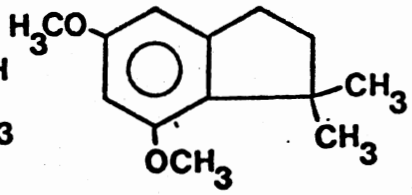

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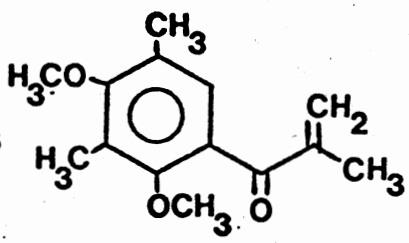

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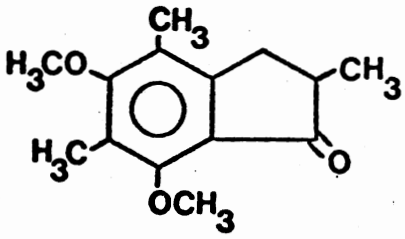

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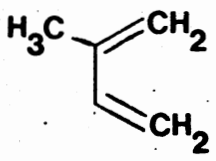

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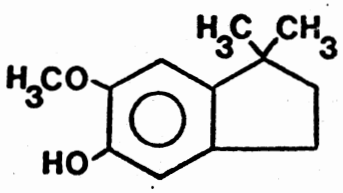

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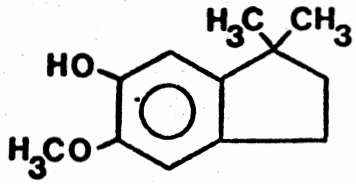

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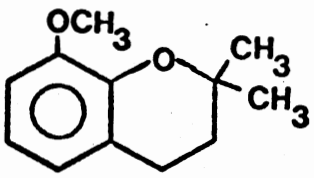

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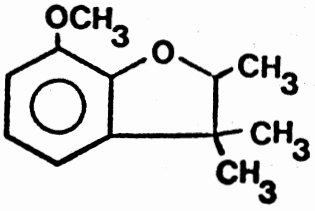

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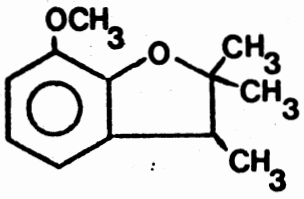

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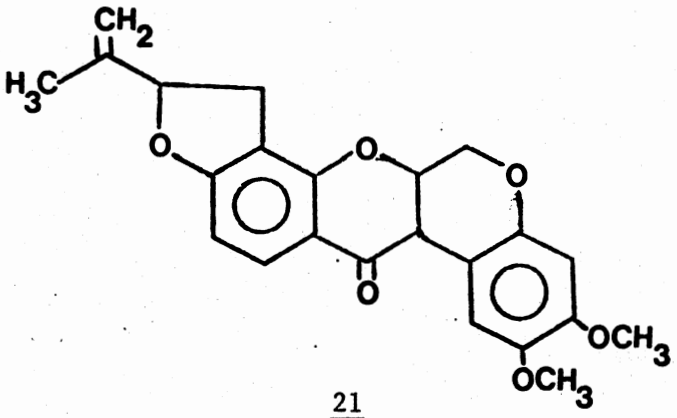

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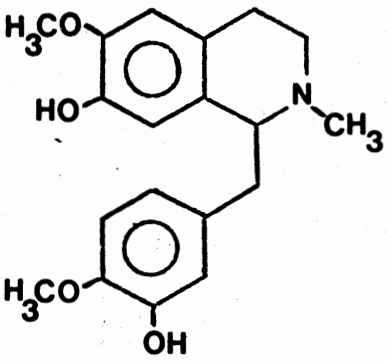

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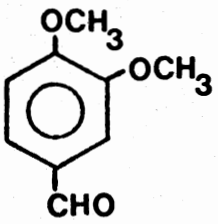

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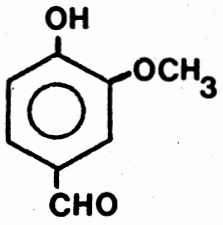

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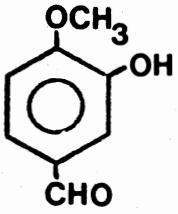

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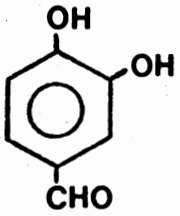

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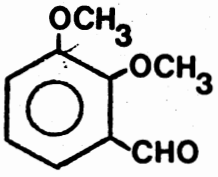

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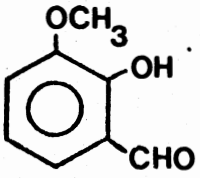

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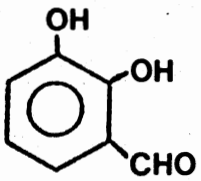

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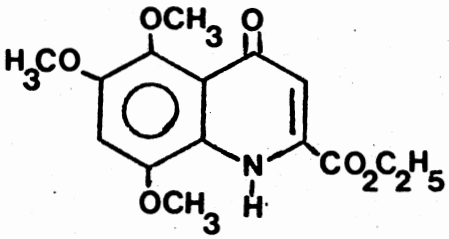

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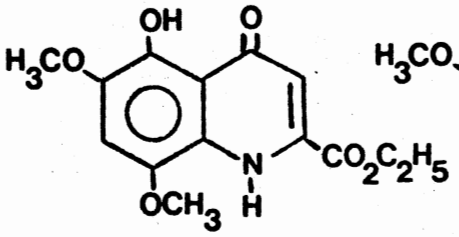

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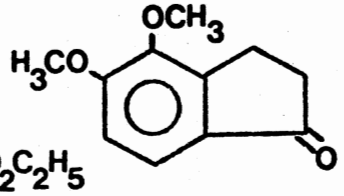

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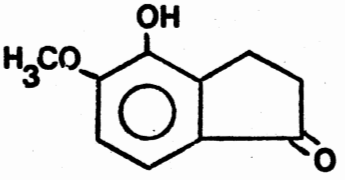

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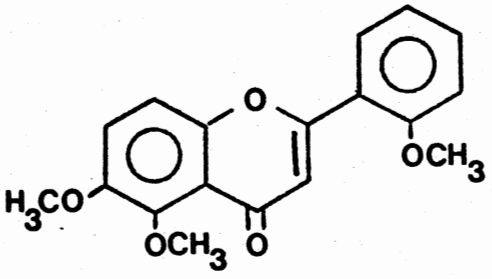

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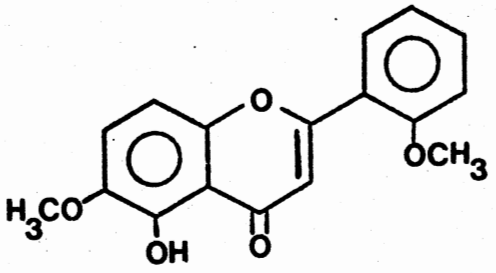

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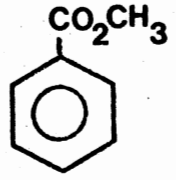

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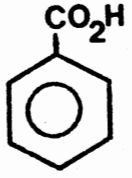

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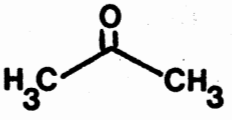

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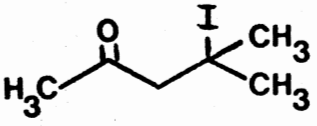

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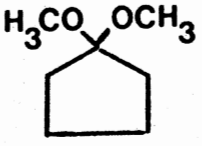

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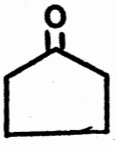

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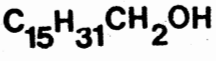

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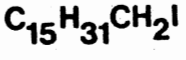

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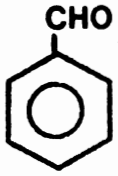

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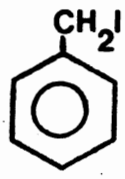

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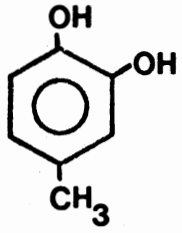

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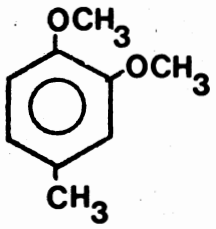

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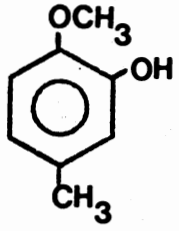

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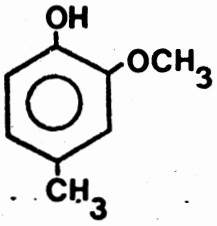

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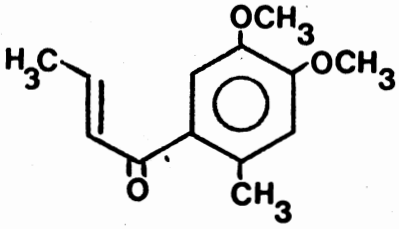

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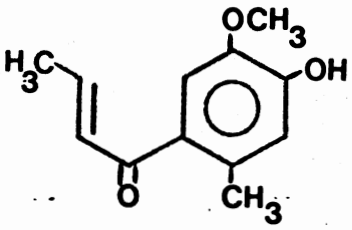

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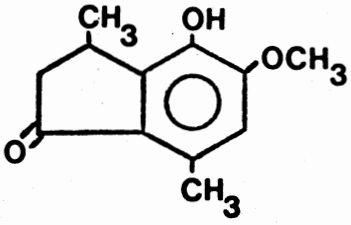

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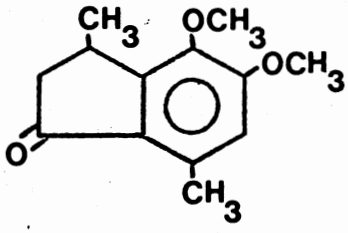

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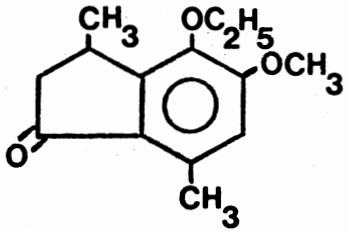

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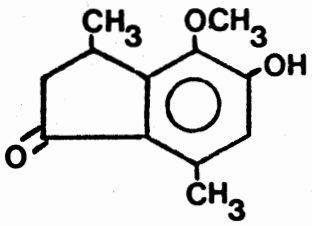

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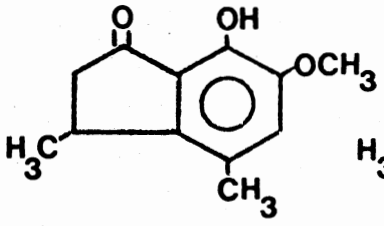

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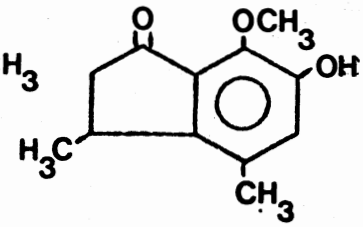

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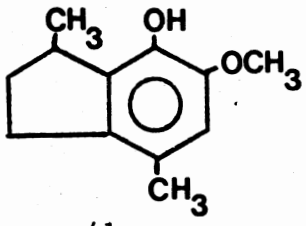

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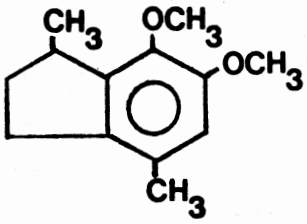

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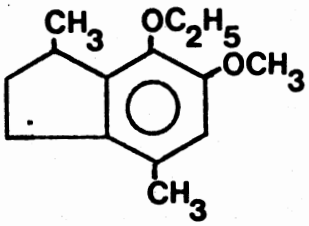

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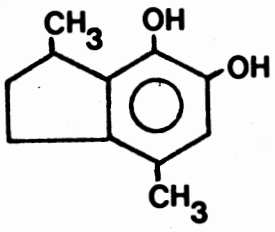

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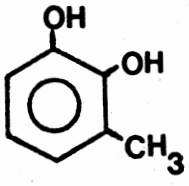

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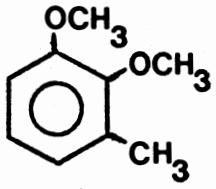

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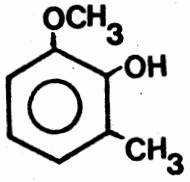

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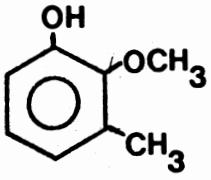

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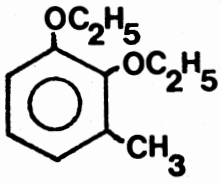

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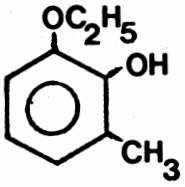

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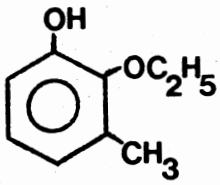

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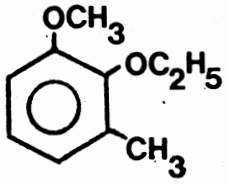

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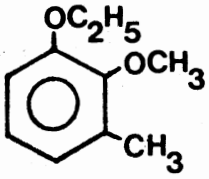

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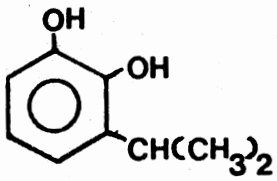

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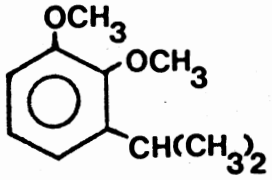

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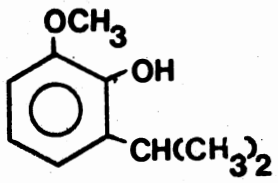

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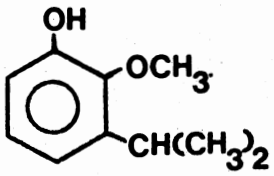

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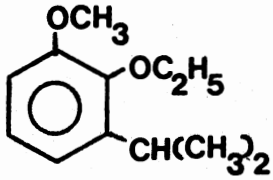

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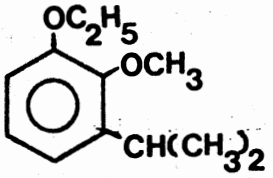

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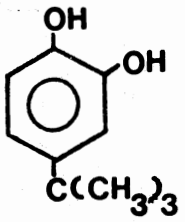

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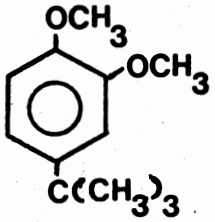

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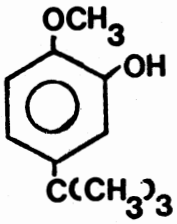

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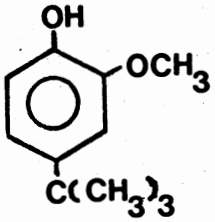

47d

VITA[2]

Euin Harold Vickery, Jr.

Candidate for the Degree of

Doctor of Philosophy

Thesis: SYNTHESIS AND SELECTIVE DEMETHYLATION OF CATECHOL ETHERS DURING ACID-CATALYZED CYCLIALKYLATION

Major Field: Chemistry

Biographical:

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Education: Received high school diploma from Union County High School, Morganfield, Kentucky, in 1971; received the Bachelor of Science degree from Campbellsville College in December 1974 with a major in chemistry and mathematics; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in May, 1979.

Professional Experience: Laboratory technician (Quality Control) Chappel's Dairy, Campbellsville, Kentucky, 1973-1974; Graduate Teaching Assistant, Oklahoma State University, 1975-1976; Alumni Summer Fellow, Oklahoma State University, 1975; Graduate Research Assistant, Environmental Protection Agency, Oklahoma State University, 1975, 1977, 1979; Graduate Research Assistant, Energy Research and Development Administration, Oklahoma State University, 1975-76; Dow Summer Fellow, Oklahoma State University, 1976; Graduate Research Assistant, National Institutes of Health, Oklahoma State University, 1976-78; Continental Oil Company Graduate Research Fellow, Oklahoma State University, 1978; Graduate Research Assistant, United States Department of Energy, Oklahoma State University, 1978. Member of Phi Lambda Upsilon and American Chemical Society.