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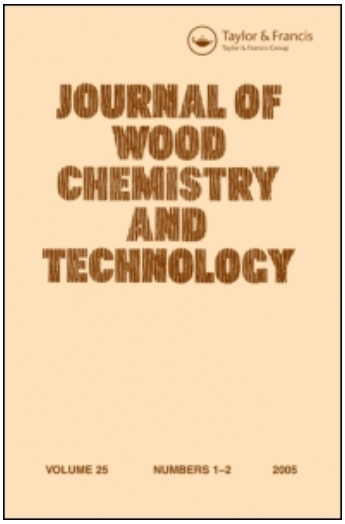

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Synthesis of Lignin Model Dimers by Novel Techniques

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JOURNAL OF WOOD CHEMISTRY AND TECHNOLOGY, 2(3), 297-315 (1982)

SYNTHESIS OF LIGNIN MODEL DIMERS BY NOVEL TECHNIQUES

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ABSTRACT

A new procedure has been developed for the synthesis of β-substituted β-aryl ether lignin model dimers: models capable of generating quinonemethides in alkaline solutions. The process involves selective alkylation of the β-carbon of an unprotected α-keto-β-aryl ether model, followed by borohydride reduction and treatment with acetylchloride. A sampling of different alkylating agents indicates that the process is limited to very simple electrophiles. Attempts to prepare α-hydroxy-β-aryl ether lignin models by stereospecific ring openings of styrene and substituted styrene oxides met with no success.

INTRODUCTION

Detailed mechanistic studies of lignin reactions have been hampered by the structural complexities of this random, cross-linked polymer. Although far from being perfect mimics, lignin model dimers have provided a wealth of information about the possible reactions of lignin during pulping and bleaching.[1,2] We have been interested in establishing if anthrahydroquinone dianion (AHQ^{-2}), a species present during anthraquinone (AQ) pulping,[3] could promote delignification reactions by electron-transfer mechanisms. Our attention has been initially directed at establishing the plausibility of this mechanism with lignin model studies.

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The models sought were ones with different bulky groups attached to the β-carbon of β-aryl ether models that could produce quinonemethides in alkali. Electron-transfer reactions are presumably insensitive to steric effects,[4] whereas actual bonding and dissociation of a quinonemethide-AHQ adduct[5,6] should be retarded by bulky groups near the bonding site. This paper describes the synthesis of models of the type 3-5 by some novel techniques.

RESULTS AND DISCUSSION

The usual procedure[7,8] for synthesizing β-aryl ether lignin models has been to start with an appropriate ketone, such as 1a, protect the phenolic hydroxylic group as a benzyl ether (1d), brominate to produce a β-bromoderivative (2c), displace the bromine with a guaiacolate ion to get a protected β-aryl ether ketone (3d), remove the protecting group by catalytic hydrogenation (3a), and reduce with hydride to obtain an α-hydroxy-β-aryl ether model (4a). To make a second model, such as 4b, the whole process must be repeated, but beginning with ketone 1b, which is not commercially available.

Three basic things were wrong with this approach for us. First, the exact conditions for bromination of ketones 1d and 1e varied with the amount of substrate used and was, therefore, difficult to control; our yields of 2d-e and subsequently 3d-e were rather low when done on a large scale. Second, with each model desired, many synthetic steps were required. Third, the displacement step (2 → 3) probably occurs by an S_N2 mechanism and, thus, would not be successful in the sterically hindered case where R_2 = R_3 = methyl.

The requirement to protect the phenolic hydroxyl group appears unwarranted. Large quantities of the simple β-aryl ether model 3a were easily prepared from acetovanillone (1a) by direct bromination (2a) and guaiacolate treatment.[9] Attempts were then made to introduce alkyl groups into the β-position of the already premade β-aryl ether model by selective alkylation of a dianion intermediate. The alkylation of polyanions has proven to be a useful

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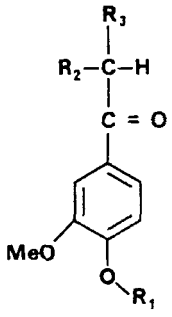

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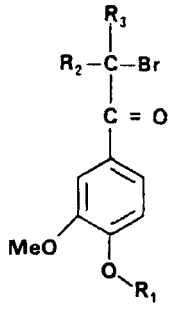

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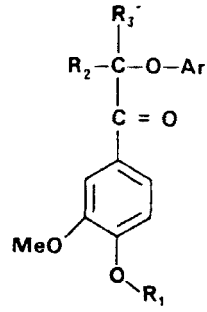

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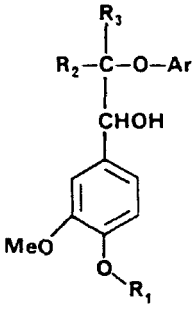

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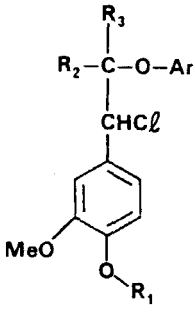

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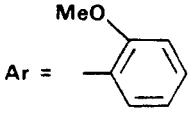

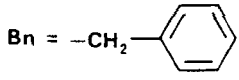

a. $R_1 = R_2 = R_3 = H$

b. $R_1 = R_2 = H$, $R_3 = Me$

c. $R_1 = H$, $R_2 = R_3 = Me$

d. $R_1 = Bn$, $R_2 = R_3 = H$

e. $R_1 = Bn$, $R_2 = H$, $R_3 = Me$

f. $R_1 = Ac$, $R_2 = R_3 = H$

g. $R_1 = Ac$, $R_2 = H$, $R_3 = Me$

h. $R_1 = Ac$, $R_2 = R_3 = Me$

i. $R_1 = R_2 = H$, $R_3 = CH_2OH$

j. $R_1 = Bn$, $R_2 = H$, $R_3 = CH_2OH$

way to introduce alkyl groups (electrophiles) into secondary acidic positions.[10] Advantage is taken of the greater reactivity of the last anion formed; one equivalent of electrophile per one equivalent of polyanion will lead to selective alkylation of the most reactive anion.

Lignin model 3a was treated with 2.2 equivalents of a strong base, lithium diisopropylamine (LDA), and then 1.1 equivalents of methyl iodide, followed by acidification. The desired alkylated model 3b was, indeed, formed - but at a somewhat low conversion

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(equation 1). The conversion could be substantially improved by using an excess of methyl iodide reagent. This was a surprising result, since one would expect that the phenolate ion would also be methylated; yet 3, $R_1 = R_2 = Me$, $R_3 = H$, was not observed. Treatment of either guaiacol (o-methoxyphenol) or phenol under these conditions also led to no methylation. The lack of reactivity of lithium phenolate groups greatly simplifies the alkylation procedure, eliminating several nuisance by-products.

Even with an excess of methyl iodide, the conversion of 3a to 3b was not complete (generally 50-65%). However, the two materials could easily be separated by column chromatography, presumably because the β-methyl group interferes with absorption of the α-carbonyl group on the silica gel surface. The isolated yield of pure 3b (based on consumed 3a), following chromatography, was very high. Treatment of 3b with LDA and excess methyl iodide, followed by chromatography led to the β,β-dimethyl model ketone 3c, a material which would be extremely difficult to prepare by other means.

In an attempt to define the scope of these alkylations, we treated the dilithio species 6 with a variety of alkylating agents, including ethyl, propyl, and benzyl halides and formaldehyde. Only the latter reaction was successful, producing 3i. [Formaldehyde alkylations of benzyl-protected ketones, such as 3d, have been used to prepare protected ketones, such as 3j.[8]] The reasons why higher homologs of methyl iodide did not alkylate 6 are not known; however, these reagents have greater bulk and there is the possibility of competing elimination reactions (loss of HX to produce an olefin). Although extensive variations of reaction conditions were not examined, it appears that the alkylation of 1b is restricted to some simple, unhindered electrophiles. Two variations which were examined, employing n-butyllithium alone as the base and LDA/MeI treatment of the acylated ketone 3f, gave methylated product but in lower conversion than the typical procedure.

Another possible way to introduce a single alkyl group into the β-position of an existing β-aryl ether model would be to

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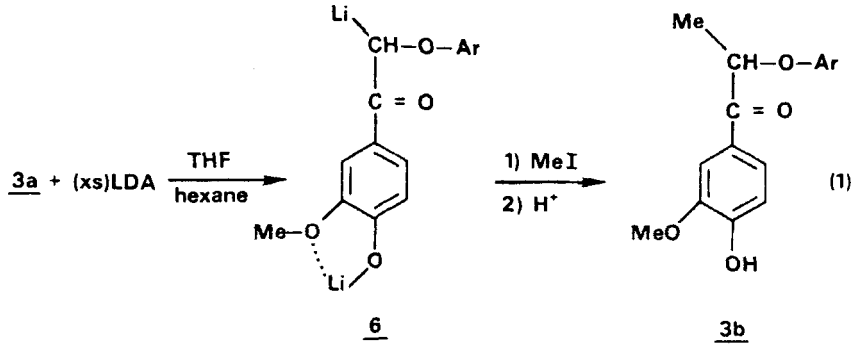

alkylate ketone 7a to 7b, followed by decarboxylation to 8b and deprotection of the phenolic hydroxyl group to 3, $R_1 = R_2 = H$, R_3 = alkyl.

The decarboxylation step was first attempted on a sample of 7a, which was obtained by the oxidation of 9.[11] Treatment of 7a with alkali, followed by heating in acid (the typical procedure for decarboxylation of β-keto esters), did not give 8a but rather fragmentation products 10 and 11 (equation 2). A direct acid hydrolysis of 7a also did not give 8a. The base-induced fragmentation reaction (equation 3) poses two problems: first, it interferes with decarboxylation attempts, and, second, similar reactions would probably also occur during attempted base-catalyzed alkylations of 7a.

Both lithium aluminum hydride and sodium borohydride were examined for the reduction of ketones 3a–c to the α-hydroxy models 4a–c. The latter gave better yields of a cleaner product and was the method of choice in large-scale reductions. Compound 4b was produced as a mixture of stereoisomers, which were not separated. The proton NMR spectrum of 4c showed two sharp signals in the 1.05-1.15 δ region indicative of nonequivalent β,β-dimethyl groups; this has been interpreted to mean that the C_α–C_β bond rotation is slow on an NMR time scale because of bulky substituents on these carbons.

The α-hydroxy lignin models were then each treated with acetyl chloride in attempts to prepare α-chloroacetate models 5f–h. The

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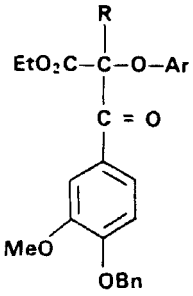

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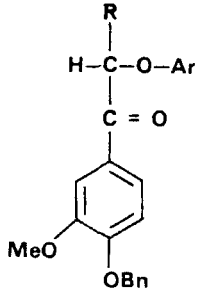

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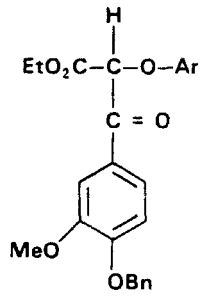

9

a. R = H

b. R = alkyl

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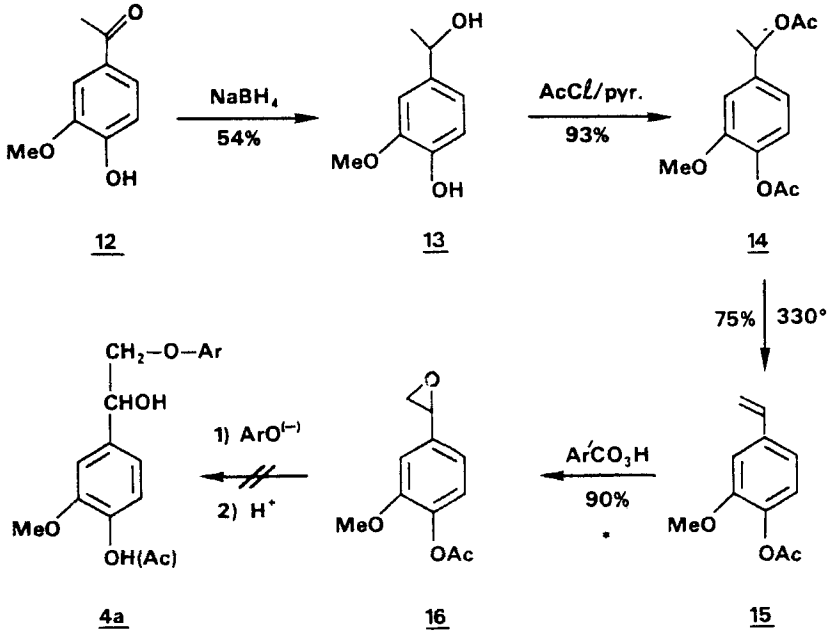
simple chloroacetate 5f was obtained in good yield and easily purified. The β-methyl analog 5g was also produced in good yield but existed as a pair of stereoisomers which were not separated. In contrast, however, the β,β-dimethyl analog 5h could not be obtained from 4c, presumably because of the crowded nature of the α and β-carbons and the probability for carbonium ion rearrangements. The chloroacetates were desired, because in alkali they should be converted to quinonemethides under very mild conditions.[6] The α-hydroxy models 4a-c will also give quinonemethides in alkali but the conditions have to be fairly severe.[12]

Another method examined for the production of α-hydroxy lignin models is outlined in Scheme I. The advantage of this sequence of reactions is in the final step where both the desired α and β-functionalities are produced simultaneously. There is also the likelihood that a β-substituted analog of epoxide 16 would open in a stereospecific manner to afford a single stereoisomer product.

The reactions outlined in Scheme I have all been run several times. The steps leading to the styrene derivative 15 were quite reproducible, and purification of each compound in the sequence was



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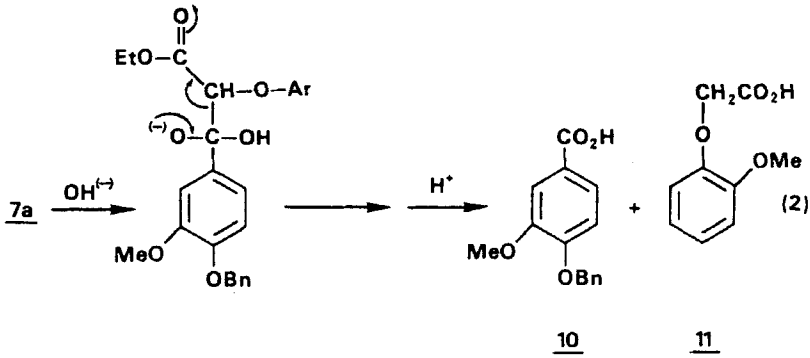
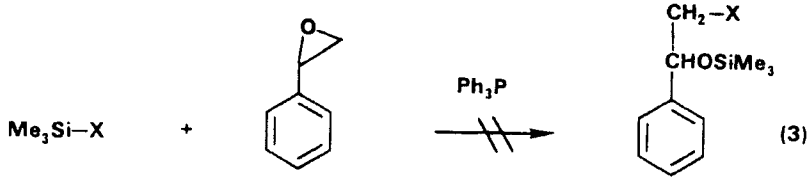
straightforward. Unfortunately, even though the epoxidation yield, 15 → 16, was high, the product was difficult to purify. The epoxide 16 was sensitive to heat and has only been successfully distilled once. The main impurities in the crude epoxidation product appeared to be aromatic acids and peracids related to the epoxidizing agent. Attempts to lessen these impurities by the use of KF were not successful.[13] Several attempts to convert crude mixtures of 16 to α-hydroxy-β-aryl ether products 4a failed.

Andrews and co-workers have recently reported that chlorotrimethylsilane (17a) adds to styrene oxide (18) in the presence of triphenylphosphine to afford 19a in high yield (equation 3).[14] If the concept of this chemistry could be extended to include the addition of silated phenols to substituted styrene oxides, α-silyloxy-β-aryl ether aromatics, such as 19b, would result. Trimethylsilyl guaiacol (17b) was synthesized and its reaction with styrene oxide examined; unfortunately, no reaction occurred over several days at room temperature or at 60°C for 2 hours.



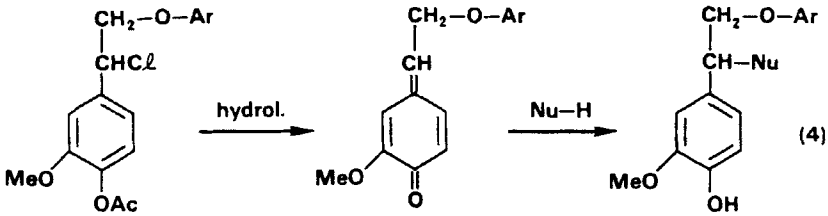
10 11



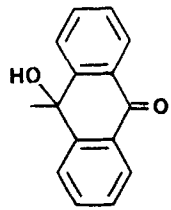
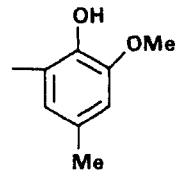
17 18 19

a, x = Cℓ

b, x = OAr



5f 20 21

a, Nu = OMe b, Nu =  c, Nu = 

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The chloroacetates discussed earlier readily afford quinonemethides upon hydrolysis. Under the proper conditions, the quinonemethides can be reacted with nucleophiles to afford desired lignin model derivatives (equation 4). Compounds 21a and 21b in pure forms and 21c in impure form have been synthesized by this technique. For 21a, chloroacetate 5f is simply placed briefly in MeONa/MeOH. For the other two compounds, a hydrolysis of 5f in $NaOH/H_2O$-dioxane in the presence of AHQ^{-2} or sodium creosolate was conducted. In these systems, hydroxide competes for the quinonemethide 20 - unsuccessfully in the case of AHQ^{-2}, but successfully in the case of sodium creosolate. Presumably, other derivatives of 21, such as Nu = SH or OAr, could probably also be synthesized with the proper choice of conditions.

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CONCLUSIONS

A new way to prepare β-aryl ether lignin model dimers, which can generate quinonemethides in alkali, has been developed. The process involves the selective alkylation of the β-carbon of an unprotected phenolic β-aryl ether α-keto model, followed by reduction with sodium borohydride and acetyl chloride treatment. The resulting chloroacetates serve as convenient sources of quinonemethides for the generation of other model compounds or for use in mechanistic studies. The alkylation process appears to be limited to very simple electrophiles.

Attempts to prepare α-hydroxy-β-aryl ether lignin models by stereospecific ring openings of styrene and substituted styrene oxides failed. Extensive variations of reaction conditions were not, however, pursued. Thus, the concept may succeed with the proper reaction conditions and the development of better procedures for isolating substituted styrene oxides.

Our results, together with that of Hosoya and co-workers,[9] suggest that the practice of protecting phenolic hydroxyl groups during lignin model synthesis may be unwarranted in many cases.

EXPERIMENTAL

The instrumentation used has been described previously.[15] All melting and boiling points are uncorrected. The details for the

preparation of methylated ketones 3b and 3c and hydroxymethylated ketone 3i can be found elsewhere.[16]

General Reduction Procedure. - A solution of 230 mmoles of sodium borohydride in 100 mL of water was added dropwise to a stirred solution of 40 mmoles of ketone in 100 mL of absolute ethanol at room temperature. Analysis by TLC indicated that reduction was instantaneous. After 30 minutes stirring, the solution was quenched by the dropwise addition of 6M HCl, diluted with more water, and extracted several times with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated. The crude residues, except in the case of 4b, were successfully recrystallized.

General Chloroacylation Procedure. - A few grams of α-hydroxyphenol model (4), slurried in $CHCl_3$, were added in small portions to an excess (ca. 25 mL) of fresh acetyl chloride, which was stirred and ice cooled. The mixture was allowed to warm to room temperature, stirred overnight, added to about one liter of saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4), and evaporated to afford the crude product.

β-Bromoacetoguaiacone (2a). - The procedure outlined here is a modification of the one reported by Hosoya and co-workers.[9] To a stirred, ice-cooled solution of 50 g (0.3 mole) of acetoguaiacone (1a) in 500 mL of anhydrous ether and 375 mL of anhydrous dioxane was slowly added (ca. 8 hours) 48 g, (0.3 mole) of bromine. Intermittent illumination with a UV lamp was applied in an attempt to decrease the bromine color (and concentration) in the solution. We were unable to eliminate the bromine color, as previously reported,[9] before the next drop of bromine was added. The reaction mixture was allowed to warm to room temperature while being stirred overnight.

A mixture of 750 mL of ether and 250 mL of ice water was added to the reaction mixture. The ether phase was separated, washed with cold saturated sodium thiosulfate and ice water, dried (Na_2SO_4), and gently evaporated under reduced pressure to afford

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75 g of purple oil, which crystallized upon refrigeration: IR (mull) cm^{-1} 3000-3600 (OH) and 1670 (C=O); ^{1}H-NMR ($CDCl_3$) δ 3.71 (dioxane), 3.92 (s, 3, OMe), 4.40 (s, 2, CH_2), 6.6 (broad s, 1, OH), 6.93 (d, 1, J = 8 Hz, C-4) and 7.5 (m, 2, C-2, and C-6); MS m/e (%) 244,246 (10%, M^+), 229,231 (50%, M-Me), and 151 (100%, C_α-C_β cleavage).

β-(2'-Methoxyphenoxy)acetoguaiacone (3a). - This procedure is a modification of an earlier one.[9] Anhydrous sodium guaiacolate was prepared by freeze-drying an aqueous solution of 1 equivalent of guaiacol and 1 equivalent of NaOH. A solution of 75 g of β-bromoacetoguaiacone (2a), which contained some residual dioxane, was dissolved in 350 mL of DMF and added dropwise to a stirred, 50° solution of sodium guaiacolate (6 equivalents) in 1500 mL of DMF. After stirring another 45 minutes at 50°C, the solution was added to 4 L of ice water, acidified with aqueous HCl, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4), and concentrated under mild vacuum.

The residue was mixed with 500 mL of xylene and vacuum distilled to remove the excess guaiacol, xylene, and DMF. The residue (100 g) was chromatographed on a short, wide, column of silica gel packed in toluene with a relatively fast flow rate of successive amounts of 25% (1500 mL) and 50% (500 mL) solutions of ethyl acetate-toluene. Twelve fractions were collected in open beakers; these were allowed to evaporate in a hood overnight. Fractions 3-8 were combined and recrystallized from toluene to afford 40 g of 3a: mp 89-92°; acetate (3f), mp 104-105° (toluene). The melting points, NMR and MS spectral data agree with previous reports[8,9] for both 3a and 3f. The two synthetic steps (1a → 3a) required about 4 days to obtain a 46% yield of crystallized material.

1-(4'-Hydroxy-3'-methoxyphenyl)-2-(2"-Methoxyphenoxy)-2-ethanol (4a). - The general reduction procedure when applied to ketone 3a gave (75%) alcohol 4a: mp 124-126° (benzene-pet. ether) (lit.[17] 129-130°); IR (mull) cm^{-1} 2600-3700 (broad OH); ^{1}H-NMR (DMSO) δ 3.74 (s, 3, OMe), 3.77 (s, 3, OMe), 3.95 (d, 2, J = 6 Hz,

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CH_2), 4.82 (m, 1, CH), 5.41 (d, 1, J = 4 Hz, OH), 6.7-7.0 (m, 7, aryl), and 8.80 (s, 1, ArOH); ^{13}C-NMR ($CDCl_3$) PPM 55.8 (q, both OMe), 72.2 (d, C_α), 76.0 (t, C_β), 108.9 (d), 112.0 (d), 114.2 (d), 115.4 (d), 119.3 (d), 121.1 (d), 122.3 (d), 131.5 (s), 145.4 (s), 146.7 (s), 147.9 (s), and 149.8 (s) (aryl); MS m/e (%) 290 (14, M^+), 166 (17), 153 (100), 138 (60), 137 (42), 125 (28), 124 (45), 109 (24), 93 (45), 77 (29), and 65 (20).

1-Chloro-1-(4'-acetoxy-3'-methoxyphenyl)-2-(2"-methoxyphenoxy)-ethane (5f). - The general chloroacylation procedure when applied to alcohol 4a gave a 98% yield of crude pink-colored solid: mp 88-90° (toluene or acetic acid); IR (mull) cm^{-1} 1760 (C=O); ^{1}H-NMR ($CDCl_3$) δ 2.31 (s, 3, OAc), 3.82 (s, 3, OMe), 3.84 (s, 3, OMe), 4.38 (d, 2, J = 7 Hz, CH_2), 5.20 (t, 1, J = 7 Hz, CH), and 6.9-7.1 (M, 7, aryl); ^{13}C-NMR ($CDCl_3$) PPM 20.6 (q, Me of acetate), 55.9 (q, OMe), 56.1 (q, OMe), 60.1 (d, C_1), 74.4 (t, C_2), 111.9 (d), 112.9 (d), 116.1 (d), 119.8 (d), 121.0 (s + d), 122.7 (d), 122.8 (d), 137.0 (s), 147.8 (s), 150.3 (s), and 151.1 (s) (aryl) and 168.7 (s, C=O); MS m/e (%) 350/352 (20, 3:1 ratio due to Cl), 308/310 (21, M-ketene), 185/187 (100), 184/186 (13), 153 (12), 150 (24), 135 (13), 125 (11), 124 (29), 122 (15), 77 (24), and 43 (34).

1-(4'-Hydroxy-3'-methoxyphenyl)-2-(2"-methoxyphenoxy)-1-propanol (4b). - The general reductive procedure when applied to ketone 3b gave an 85% crude yield of a glassy solid; attempts to recrystallize this from mixtures of benzene and pet. ether failed, even though others have been successful in crystallizing both the erythro and threo forms of 4b.[7] The spectral evidence indicated that the glassy solid was a mixture of stereoisomers in which one was considerably more abundant than the other: IR (neat) cm^{-1} 3000-3700(OH); ^{1}H-NMR ($CDCl_3$) δ 1.19 (d, 3, J = 6 Hz, Me), 3.88 (s, 6, OMe), 4.0-4.9 (m, 3, CH-CH and OH), 5.61 (s, 1, ArOH), and 6.8-7.1 (m, 7, aryl); ^{13}C-NMR ($CDCl_3$) PPM 13.4 (q, Me, major), 16.9 (q, Me, minor), 55.8 (q, OMe), 55.9 (q, OMe), 73.9 (d, C_1), major), 81.9 (d, C_2, major), 83.6 (d, C_2, minor), 109.1 (d), 112.2 (d), 114.0 (d), 119.1 (d), 119.4 (d), 121.3 (d), 123.1 (d), 131.9 (s), 144.8 (s), 146.5 (s), 146.7 (s), and 151.3 (s) (aryl); MS m/e

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(%) 304 (70, M^+), 287 (72), 180 (48), 163 (40), 153 (78), 152 (100), 151 (75), and 124 (55).

1-Chloro-1-(4'-acetoxy-3'-methoxyphenyl)-2-(2"-methoxyphenoxy) propane (5g). - The general chloroacylation procedure applied to 4b gave a quantitative yield of crude product, an oil, which resisted recrystallization from acetic acid or toluene. The spectral evidence indicated that the oil was approximately a 60:40 mixture of stereoisomers (the values for the more abundant isomer, where obvious, are underlined for the NMR results): IR (neat) cm^{-1} 1760 (C=O); ^{1}H-NMR ($CDCl_3$) δ 1.23/1.44 (d, 3, J = 6 Hz, Me), 2.29/2.30 (s, 3, Me of acetate) 3.77/3.79/3.83/3.83 (singlets, 6, OMe), 4.65 (m, 1, C_2-H), 5.07 (d, 1, J = 5.4 Hz, C_1-H) and 6.7-7.1 (m, 7, aryl), irradiation with a frequency corresponding to the 4.65 δ region caused the 1.23, 1.44, and 5.07 signals to collapse to singlets; ^{13}C-NMR ($CDCl_3$) PPM 16.5/16.8 (q, Me), 20.6 (q, Me of acetate), 55.9 (q, OMe groups), 65.0/65.3 (d, CHCl), 79.4/79.7 (d, CHO), 112.5/112.8 (d), 117.5, 118.6, 120.4, 120.9, 122.2, 122.4, 122.6, and 122.9 (aryl), 136.8/137.1 (s), 139.7/139.8 (s), 146.9/147.0 (s), and 150.8/151.0 (s) (aryl), and 168.6 (s, C=O); MS m/e (%) 364/366 (53, M^+ in a 3:1 ratio indicative of Cl), 329 (20, M-Cl), 199/201 (100, $Ar\overset{+}{C}HCl$), 153 (93), and 43 (20).

1-(4'-Hydroxy-3'-methoxyphenyl)-2-(2"-methoxyphenoxy)-2-methyl-1-propanol (4c). - The general reduction procedure when applied to 3c gave (100% yield) crude 4c: mp 106.5-7.5° (benzene-pet. ether); IR (mull) cm^{-1} 2900-3600 (OH); ^{1}H-NMR (DMSO-d_6) δ 1.06 (s, 3, Me), 1.12 (s, 3, Me), 3.72 (s, 3, OMe), 3.74 (s, 3, OMe), 4.56 (d, 1, J = 4 Hz, CH), 5.13 (d, 1, J = 4 Hz, OH, exchanged with D_2O addition), 6.6-7.0 (m, 7, aryl), and 8.76 (s, 1, ArOH, exchanged with D_2O addition); ^{1}H-NMR ($CDCl_3$) similar to above except roughly 0.1-0.15 δ larger chemical shifts; ^{13}C-NMR ($CDCl_3$) PPM 21.5 (q, Me), 22.8 (q, Me), 55.5 (q, OMe), 78.3 (d, C_1), 83.9 (s, C_2), 112.3 (d), 112.5 (d), 114.2 (d), 120.3 (d), 120.5 (d), 123.9 (d), 124.8 (d), 132.5 (s), 143.8 (s), 145.4 (s), 146.4 (s), and 153.4 (s) (aryl carbons); MS m/e (%) 318 (1, M^+), 316 (1), 194 (23), 165 (100), 151 (14), 125 (16), 124 (38), and 104 (15).

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Ethyl 3-(3'-methoxy-4'-benzyloxyphenyl)-3-oxo-2-(2"-methoxyphenoxy) propanoate (7a). - To a stirred, room-temperature solution of 31 g (69 mmoles) of ethyl 3-(3'-methoxy-4'-benzyloxyphenyl)-3-hydroxy-2-(2"-methoxyphenoxy)propanoate (9)[11] in acetone was slowly added Jones Reagent[18] until the orange color, indicative of excess chromic acid, persisted. Isopropanol was added to destroy the excess chromic acid. The solution was diluted with water and extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to leave 23.7 g (77%) of ketone 7a: mp 72-74° (EtOH); IR (mull) cm^{-1} 1750 (C=O, ester) and 1690 (C=O, conj. ketone); ^{1}H-NMR ($CDCl_3$) δ 1.22 (t, 3, Me), 3.78 (s, 3, OMe), 3.92 (s, 3, OMe), 4.25 (q, 2, CH_2), 5.22 (s, 2, CH_2Ph), 5.73 (s, 1, CH), 6.94, 7.39, and 7.70 (multiplets, 12, aryl); MS m/e (%) 450 (5%, M^+), 359 (2%, M-Bn), 241 (64%, BnO(MeO)Ph$\overset{+}{C}$ ≡ O) and 91 (100%, Bn^+).

Attempted Decarboxylation of Keto Ester 7a. - A suspension of 2.5 g (5.5 mmoles) of keto ester 7a in 50% aqueous ethanol containing 37.5 g (0.94 mole) of sodium hydroxide was stirred and refluxed under nitrogen for 5 hours. The clear solution was then cooled, acidified, and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to a low volume, which was principally composed of ethanol solvent. Fine yellow crystals of the benzyl ether of vanillic acid (10), precipitated from the solution: mp 170-172° (lit.[19] 169°); IR (mull) cm^{-1} 2600-3700 (OH of CO_2H) and 1675 (C=O of CO_2H); ^{1}H-NMR ($CDCl_3$) δ 3.94 (s, 3, OMe), 5.22 (s, 2, $-CH_2-$), 6.90 (d, 1, J = 9 Hz, C-5 aryl), 7.35 [m, 4-5, benzyl aryl and OH (?)] and 7.65 (m, 2, C-2 and C-6 aryl); MS m/e (%) 258 (10%, M^+), 91 (100%, $PhCH_2$), and 65 (12%).

Evaporation of the mother liquor which gave 10 afforded a reddish-brown solid, (*o*-methyoxyphenoxy)-acetic acid (11): IR (mull) cm^{-1} 2100-3700 (OH of CO_2H) and 1735 (C=O of CO_2H); ^{1}H-NMR ($CDCl_3$) δ 3.88 (s, 3, OMe), 4.69 (s, 2, $-CH_2-$), 6.93 (m, 4, aryl) and δ 8.87 (broad s, 1, CO_2H); MS m/e (%) 182 (100, M^+), 124 (24), 123 (84), 122 (36), 109 (38), 95 (81), and 77 (97). The material

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was identical to a sample of 11 obtained from the hydrolysis of ethyl (*o*-methoxyphenoxy)acetate (used to prepare compound 7a): mp 116-118° (lit.[20] mp 121°).

A direct acid-hydrolysis of 7a also did not give 8a.

α,4-Diacetoxy-3-methoxy-1-ethylbenzene (14). - To an ice-cooled flask containing 132 mL of acetyl chloride was added dropwise 43.2 mL of pyridine dissolved in an equal volume of chloroform. A solution of 30 g α-methylvanillyl alcohol (13)[21] in $CHCl_3$ was added dropwise. Stirring was continued for 2 hours at ice-bath temperature and 3 hours at room temperature. The mixture was then poured into water, the $CHCl_3$ layer separated, and the water layer washed with fresh $CHCl_3$. The combined $CHCl_3$ extracts were washed with 3M HCl, water, saturated aqueous $NaHCO_3$ and water, respectively, dried (Na_2SO_4), and evaporated to give 42 g (93%) of residue. The latter was distilled, and the fraction boiling at 146-164°/1 mm consisted of diacetate 14: mp 36-38°; IR (neat) cm^{-1} 1760 (C=O, acetate), 1725 (C=O, acetate), and 1170-1280 (C-O acetate); ^{1}H-NMR ($CDCl_3$) δ 1.51 (d, 3, J = 7 Hz, α-methyl), 2.05 (s, 3, aliphatic acetate), 2.27 (s, 3, aryl acetate), 3.81 (s, 3, OMe), 5.85 (q, 1, J = 7 Hz, CH), and 7.04 (s, 3, aryl); ^{13}C-NMR ($CDCl_3$) PPM 20.4 (q), 21.1 (q), 22.1 (q), 55.7 (q), 71.9 (d), 110.6 (d), 118.3 (d), 122.6 (d), 139.3 (s), 140.5 (s), 151.1 (s), 168.7 (s), and 169.9 (s); MS m/e (%) 252 (4, M^+), 210 (32), 168 (10), 151 (32), 150 (22), 135 (10), 91 (10), and 43 (100).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.90; H, 6.35. Found: C, 61.50; H, 6.31.

4-Acetoxy-3-methoxystyrene (15). - A 20% solution of 21.1 g of α,4-diacetoxy-3-methoxy-ethylbenzene (14) in toluene was dripped through a glass column packed with glass raschig rings, which was heated by a tubular electric furnace at 330°C. A slow stream of nitrogen carried the vapors down the column and into a side-armed test tube immersed in an ice bath. The collected condensate was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to give 18.8 g of residue, which by NMR analysis was a 2:1

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mixture of 15 (75% yield) and toluene. Vacuum distillation afforded pure 4-acetoxy-3-methoxystyrene (15): bp 94-108°/1 mm; IR (neat) cm^{-1} 1760 (C=O, acetate) and 1170-1280 (C-O, acetate); ^{1}H-NMR ($CDCl_3$) δ 2.24 (s, 3, acetate), 3.76 (s, 3, OMe), 5.18 (d, 1, J = 9 Hz, = CH_2), 5.64 (d, 1, J = 17 Hz, = CH_2), 6.55 (d of d, 1, J = 9 and 17 Hz, -CH=) and 6.94 (s, 3, aryl); ^{13}C-NMR ($CDCl_3$) PPM 20.6 (q), 55.8 (q), 109.9 (d), 114.0 (t), 118.8 (d), 122.7 (d), 136.2 (d), 136.6 (s), 139.4 (s), 151.0 (s) and 168.9 (s); MS m/e (%) 192 (8, M^+), 150 (100, M-ketene), 135 (48), 107 (18), 91 (7), 78 (10), 77 (16), and 43 (18).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.56; H, 6.35.

4-Acetoxy-3-methoxystyrene Oxide (16). - A solution of 10.1 g (59 mmoles) of m-chloroperbenzoic acid in $CHCl_3$ was added dropwise to an ice-cooled stirred solution of 8.0 g (42 mmoles) of 4-acetoxy-3-methoxystyrene (15) in about 150 mL of $CHCl_3$. After stirring for 2 1/2 hours more, the solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to afford 11.3 g of residue. A ^{1}H-NMR of the residue showed it to contain about 2 parts 16 (90% yield) and 1 part aromatic acids. An attempted vacuum distillation caused polymerization.

A smaller 2.0-g run was successfully distilled to give a clear liquid product: IR (neat) cm^{-1} 1755 (C=O, acetate) and 11.95 (C-O, acetate); ^{1}H-NMR ($CDCl_3$) δ 2.29 (s, 3, acetate), 2.74 (m, 1, HCH), 3.11 (m, 1, HCH), 3.81 (s, 3, OMe), 3.82 (?, 1, CH), and 6.8-7.1 (m, 3, aryl); ^{13}C-NMR ($CDCl_3$) PPM 20.6 (q), 51.1 (t), 52.0 (d), 55.8 (q), 109.0 (d), 118.0 (d), 122.7 (d), 136.6 (s), 139.6 (s), 151.3 (s), 168.8 (s), and several smaller impurity signals.

Additional runs with KF present,[13] either during the reaction or at the conclusion, gave epoxide 16, which was still contaminated. Attempts to purify the product mixture by silica-gel column chromatography led to decomposition of the epoxide.

Trimethylsilyl Guaiacolate (17b). - To a stirred, room-temperature solution of 100 g (0.8 moles) of guaiacol in about 150 mL of benzene was added dropwise 107.5 mL (5% excess) of

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chlorotrimethylsilane and then 68.4 mL of distilled pyridine. A vigorous reaction occurred upon pyridine addition. After refluxing for 2 1/2 hours, the solution was cooled and filtered. The collected salts were washed with benzene. The combined filtrates were evaporated and distilled to afford 17b: bp 212-7°; ^{1}H-NMR ($CDCl_3$) δ 0.24 (s, 9, Me_3Si), 3.79 (s, 3, MeO) and 6.85-6.87 (s, 4, aryl).

1-(4'-Hydroxy-3'-methoxyphenyl)-1-methoxy-2-(2"-methoxyphenoxy) ethane (21a). - To a stirred, room-temperature solution of 20 mL of anhydrous methanol was added 0.2 g (8.7 mg-atom) of sodium metal, followed by 1.0 g (2.8 mmoles) of chloroacetate 5f. After stirring for 2 hours, the solution was poured into 3M HCl (a precipitate formed) and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried (Na_2SO_4), and gently evaporated under reduced pressure to leave 1.3 g of residue, which upon several days exposure to air lost more solvent to give a quantitative yield of 21a: mp 62-66° (unrecrystallized); IR (mull) cm^{-1} 2900-3600 (OH); ^{1}H-NMR ($CHCl_3$) δ 3.32 (s, 3, ROMe), 3.81 (s, 3, ArOMe), 3.87 (s, 3, ArOMe), 4.1 (m, 2, CH_2), 4.53 (d of d, 1, J = 4 and 7 Hz, CH), 5.66 (s, 1, OH), and 6.85 (s, 7, aryl); ^{13}C-NMR ($CDCl_3$) PPM 56.0, 56.1, and 57.0 (quartets, OMe), 74.1 (t, C_2), 82.3 (d, C_1), 109.4, 112.7, 114,3, 115.0, 121.0, and 121.7 (doublets, CH aryl), 130.7, 145.6, 146.8, 148.7, and 150.1 (singlets, C aryl); MS m/e % 304 (8, M^+), 180 (8), 167 (100, $Ar'\overset{+}{C}HOMe$), and 77 (10). This compound has previously been reported as a colorless oil, with no spectral confirmation.[17]

Quinonemethide-AHQ Adduct 21b. - The red AHQ^{-2} species was generated by heating (60°C) a stirred solution of anthrahydroquinone diacetate (1.26 g, 4.3 mmoles) for 30 minutes with 1.14 g (28.5 mmoles) of NaOH in 30 mL of a 2:1 mixture of dioxane:water, under nitrogen. The solution was then cooled in ice and 1.0 g (2.85 mmoles) of chloroacetate 5f dissolved in 10 mL of dioxane was added dropwise. The ice bath was removed and the solution stirred for 30 minutes at room temperature and diluted with 6M HCl. The resulting precipitate was collected and washed with 2M

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NaOH containing sodium dithionite; the latter keeps AQ in its soluble AHQ^{-2} form. The filtrate was extracted with $CHCl_3$. The chloroform extracts were combined with the solid precipitate, washed with 6M HCl, dried (Na_2SO_4), and evaporated to leave 1.3 g (95%) of adduct 21b: mp 163-5° (90% ethanol) (lit.[5] 166-173° dec.); IR and NMR in agreement with literature values[5]; MS m/e (%) 274 (4), 273 (5), 272 (3), 210 (47, AHQ by quinonemethide elimination[22]), 209 (18), 150 (100), 149 (44), 135 (15), 124 (16), 123 (15), and 77 (19).

Quinonemethide-creosol Adduct 21c. - A room-temperature solution of 50 mg (0.14 mmoles) of 5f, 178 mg (1.4 mmoles) of guaiacol, and 114 mg (2.8 mmoles) of NaOH in 25 mL of 75% DMSO-water was stirred at room temperature for 1 hour, acidified with 3M HCl, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated. The residue was methylated with dimethyl sulfate,[15] and analyzed by GC/MS. The principal components of the reaction mixture were 4, R_1 = Me, R_2 = R_3 = H and its dehydration products (molecular weights 304 and 286). A minor long retention component displayed a mass spectrum indicative[22] of a diaryl methane condensation product [methylated 21c], namely: m/e (%) 424 (5, M^+) and 287 (100, Ar'_2CH^+).

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