APPROACHES FOR THE TOTAL SYNTHESIS OF MIROESTROL

by

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Department of Chemistry, January 1976

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The encouragement and patient understanding of my wife, Ann, made this thesis possible. It is dedicated to her with the hope that someday I may repay her for these years of hardship and sacrifice.

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ABSTRACT

Approaches directed toward the total synthesis of the novel nonsteroidal estrogen, miroestrol, are investigated. Studies describing the preparation of a number of highly substituted isoflavones and the Grignard addition of isopentenyl magnesium chloride to isoflavones as well as coumarins is reported. Attempts to cyclize olefins with various para-quinones, and the application of this approach for closure of the miroestrol skeleton are also discussed.

Thesis Supervisor: George H. Büchi
Title: Camille Dreyfus Professor of Chemistry

INTRODUCTION

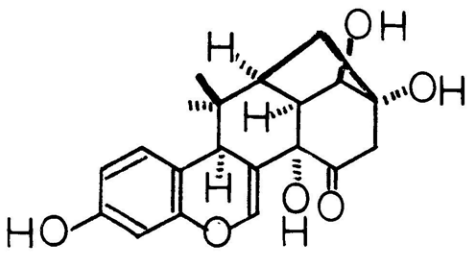
Throughout history man's desires to alleviate suffering and communicate with the supernatural have been at the very center in his quest for knowledge. After hundreds of years of haphazard experiences, tribal preparations and folk medicines were developed to extend man's capabilities and overcome his weaknesses. Even as the search continues today, many of these crude concoctions have lead to the discovery of potent biologically active agents which have not only directed the development of new medicinals but also advanced our understanding of experimentally difficult areas of biochemistry.

In 1932 Kerr[1] reported that a preparation derived from the tuberous roots of a woody vine found in northern Thailand was used by the local population as a rejuvenator of the elderly. Later Vatna[2] reported the presence of an estrogenic substance in this same plant, Pueraria mirifica, and the active principle, subsequently named miroestrol, was first isolated in crystalline form by Schoeller[3] in 1940.

Pharmacological evaluation[4] by the Allen-Doisy assay revealed that miroestrol, when administered subcutaneously, was one-fourth as active as estradiol and twice as active as estrone. When introduced orally, it surprisingly surpassed the activity of both animal hormones by sixty to seventy times. The limited human testing and early history of miroestrol have been reviewed.[5]

Early chemical degradation studies by Butenandt[6] resulted in complete failure with the establishment of an erroneous empirical formula. In 1960 Bounds and Pope[7] assigned the correct empirical

formula and prepared a mono-bromo derivative 2 possessing spectral and physical properties similar to miroestrol which was submitted to X-ray crystallographic analysis by Hodgkin, et al.[8] leading to the establishment of 1 as the structure of miroestrol.



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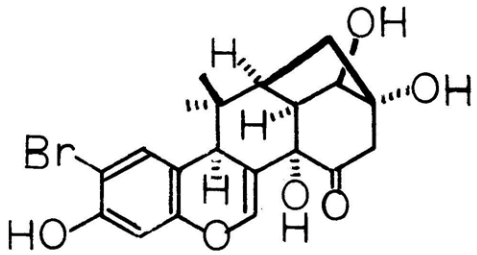

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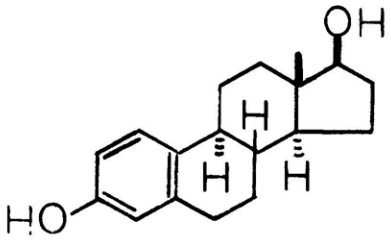

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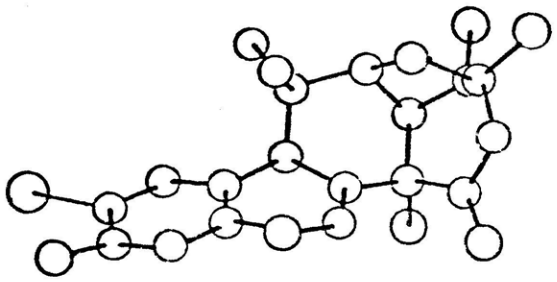
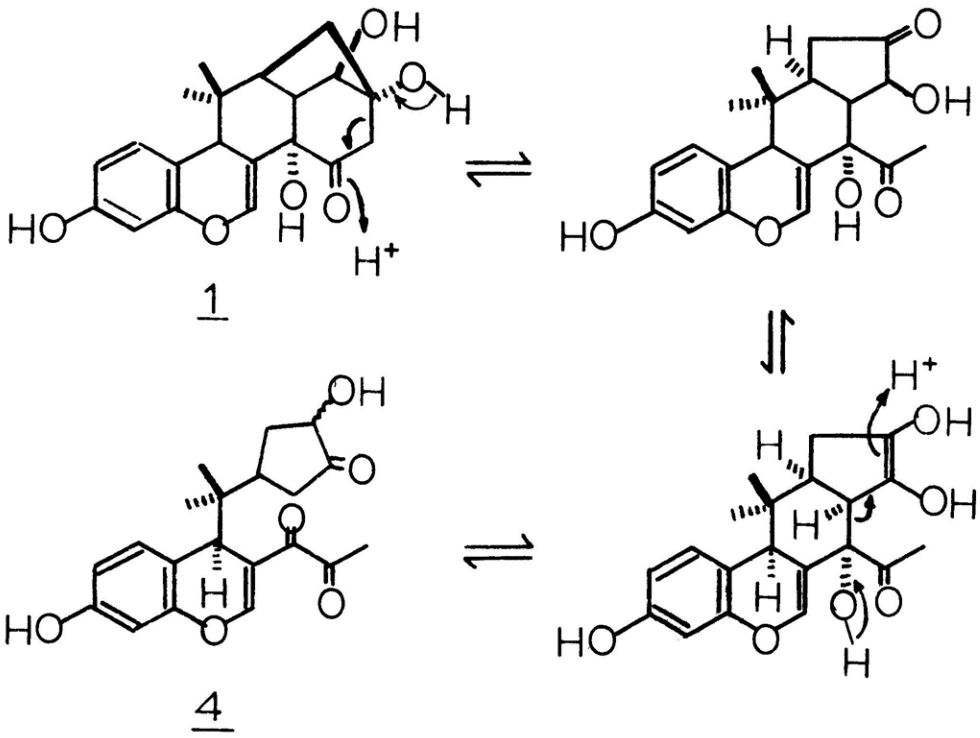
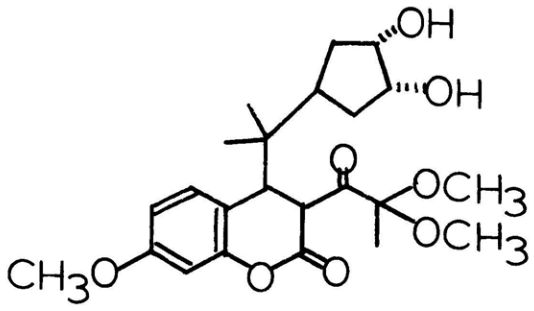


The exceptionally high estrogenic activity and most unique carbon skeleton provide a rather interesting addition to the structure-activity relationships already established for the estradiol system. Hodgkin has postulated that the estrogenic activity of miroestrol is a result of the geometrical constraint which positions the 3-hydroxy and 18-hydroxy at a distance which is very similar to that of estradiol (3). Since only small amounts of material have been available,

the clarification of the specificity and determination of the mechanism of action of this novel natural product have not been undertaken. The biochemistry of estradiol as well as other steroidal hormones is currently the subject of intensive investigations in many laboratories, and certainly miroestrol could provide some exciting results.

Several groups have reported a number of unsuccessful attempts directed toward the total synthesis of miroestrol. Professor Muxfeldt and coworkers[9, 10], while at Wisconsin, spent many years approaching the synthesis by visualizing the complex retro-aldol cleavage product 4 as a key intermediate for the formation of miroestrol. Progress towards "seco-miroestrol" 4 ended with the preparation of the dihydrocoumarin 5.





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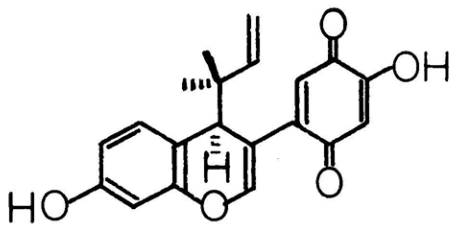
Minard[11] envisioned the synthesis of the intermediate para-quinone 6; however, his work terminated upon preparation of the ortho-quinone 7. Likewise Matsumoto[12] failed to condense the chromene 8 with 2, 5-dihydroxy-1, 4-benzoquinone to form the pentacyclic diketone 9. The tedious preparation of model compounds 10 and 11 have been published in detail by Miyano and Dorn[13] of G. D. Searle and Co., but their methods cannot be successfully applied to the entire molecule. More recently Minster[14] in these laboratories attempted the synthesis of the key intermediate 12 which had been designed to undergo an intramolecular Diels-Alder reaction to complete the miroestrol skeleton 13.



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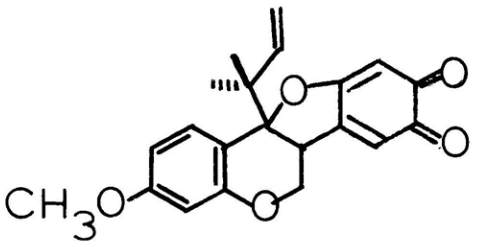

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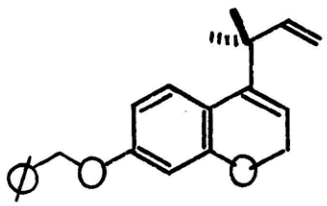

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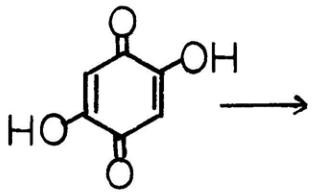

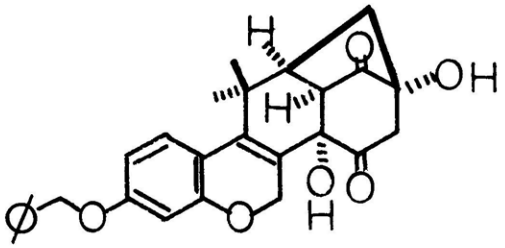

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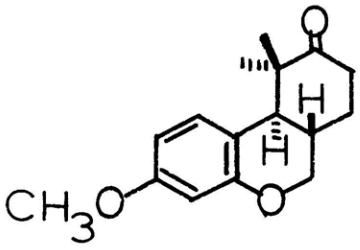

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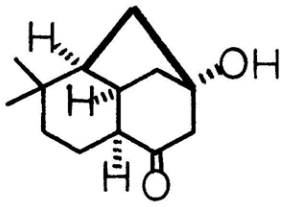

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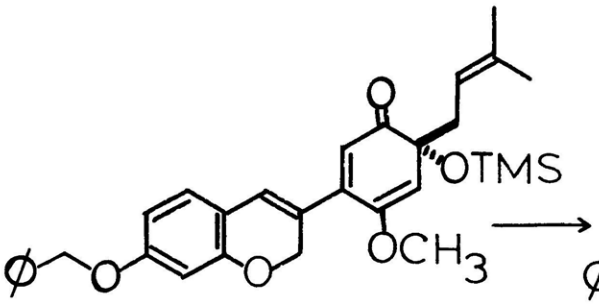

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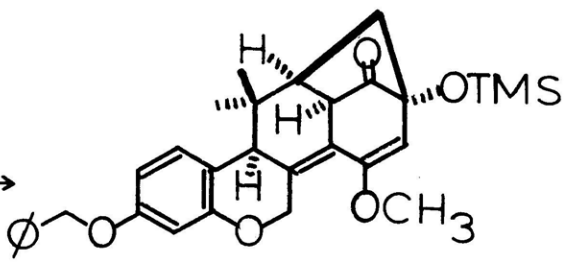

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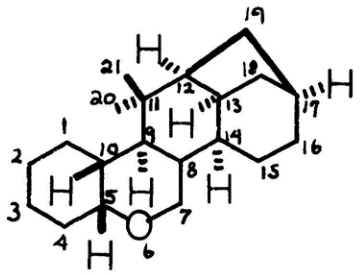
DISCUSSION

The nomenclature of miroestrol and its derivatives as proposed by Bounds and Pope,[7] is based on the hypothetical miroestran (14) with numbering and configurations as shown.



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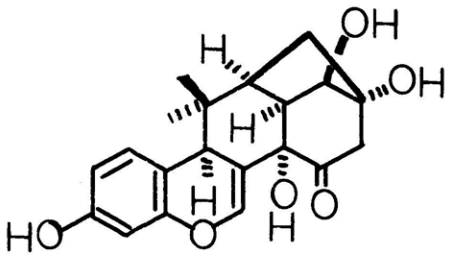
Factors which must be anticipated when designing a synthetic plan include an instability of miroestrol towards alkali and its insolubility in most organic solvents (soluble in acetone, dioxane and methanol). Treatment with dilute hydrogen chloride in aqueous dioxane under nitrogen affords isomiroestrol in good yield. Based on spectral changes, structure 15 is assumed for isomiroestrol as the consequence of an acid-catalyzed allylic rearrangement. A monomethyl ether 16 is formed on treatment of the hemiacetal 15 with anhydrous methanolic hydrochloric acid, but it is also obtained directly from miroestrol under similar conditions. The methyl ether is readily hydrolyzed back to 15 in an aqueous acid environment.



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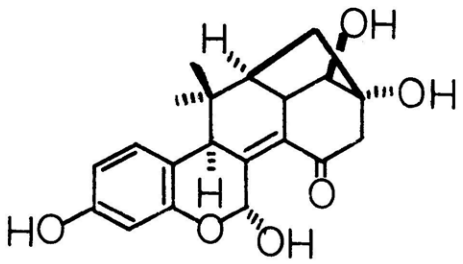
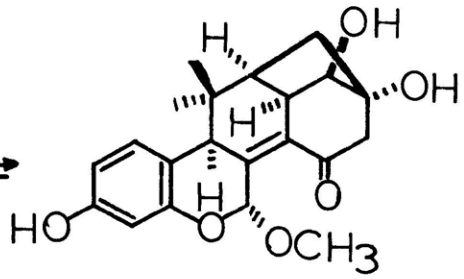
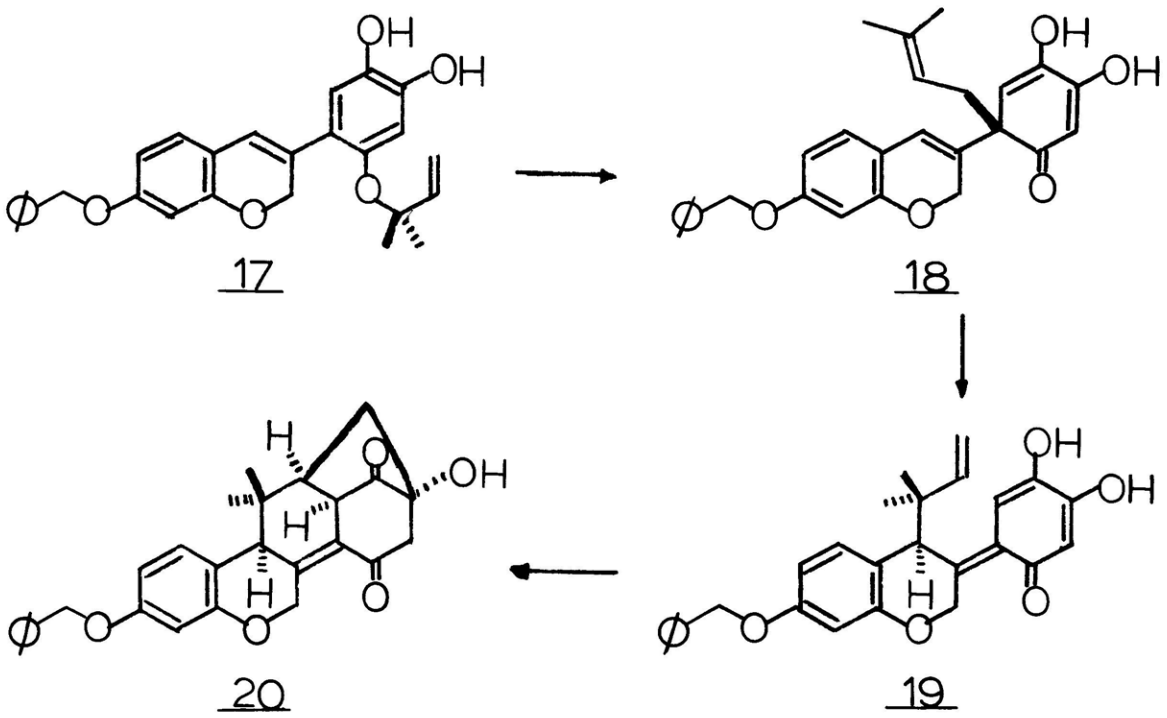




15 16

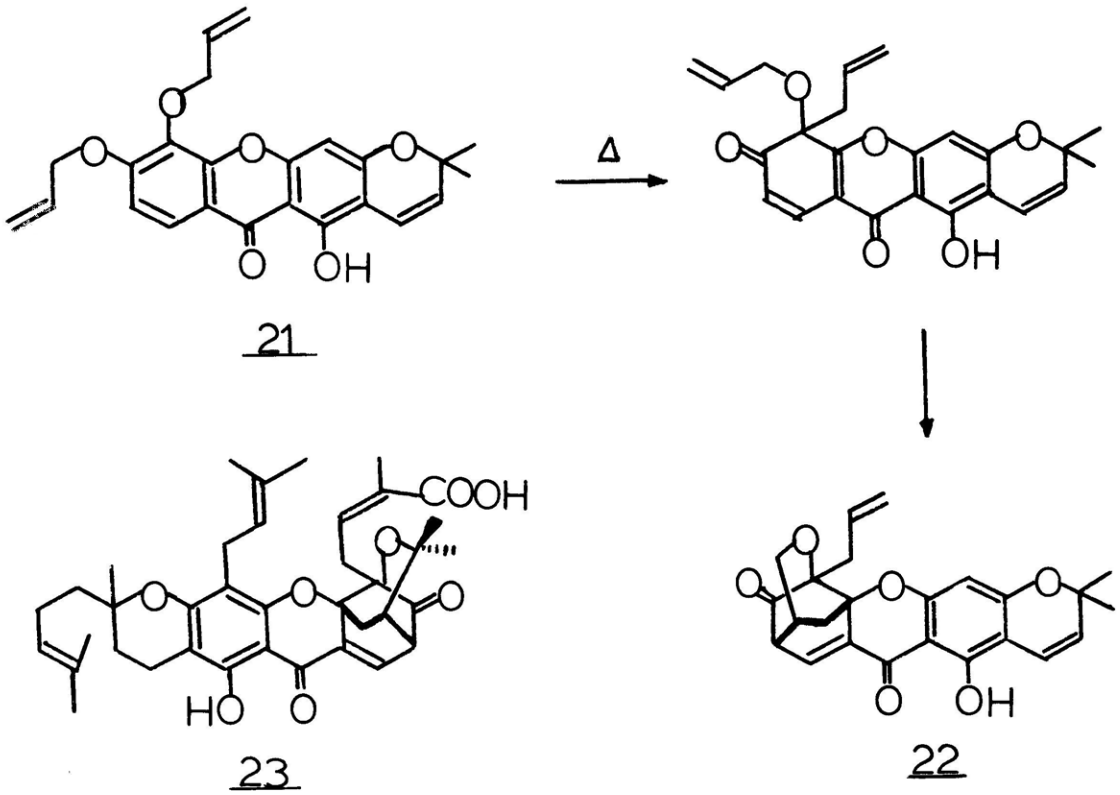
Our efforts are primarily aimed at developing some new and interesting chemistry which demonstrates a concern for biosynthesis and provides substantial material for biological studies. Miroestrol has six centers of asymmetry, and the introduction of the proper stereochemistry is clearly a major obstacle of any synthetic approach. Therefore, establishing all of the stereochemistry of this rigid carbon skeleton in a single step from a simple intermediate is highly desirable.

The first approach was directed toward preparation of chromene 17 as a possible precursor which fulfills these requirements. Upon heating 17 may undergo a Claisen rearrangement, forming intermediate 18, followed by Cope rearrangement to 19, and finally ring closure to the pentacyclic diketone 20, which may be easily transformed into miroestrol.



Regiospecific Claisen migrations to an apparently more hindered ortho position have been reported for a number of cases.[15,16,17] The influences which control these as well as similar migrations and electrophilic substitutions are factors providing the more thermodynamically stable cyclohexadienone transition state.[18] Furthermore the rearrangement of allyl ethers to an ortho position already bearing a substitutent are not unprecedented.[19,20] The facile conversion of the 5,6-diallyl ether of jacareubin 21 to bicyclic product 22 provides an elegant illustration.[21] Here a regiospecific Claisen rearrangement to the more hindered and substituted ortho-position is followed by an intramolecular Diels-Alder cyclization trapping the cyclohexadienone intermediate. This same sequence most probably accounts for the

biosynthesis of gambogic acid (23).[22]



21 22 23

Since allyl ethers of sesamol 24 are known to undergo Claisen rearrangements giving a single isomer 25 in high yield,[23] the methylenedioxy bridge is an ideal protecting group for the catechol moiety of 17 which may be selectively removed with boron trichloride at low temperature.[24]

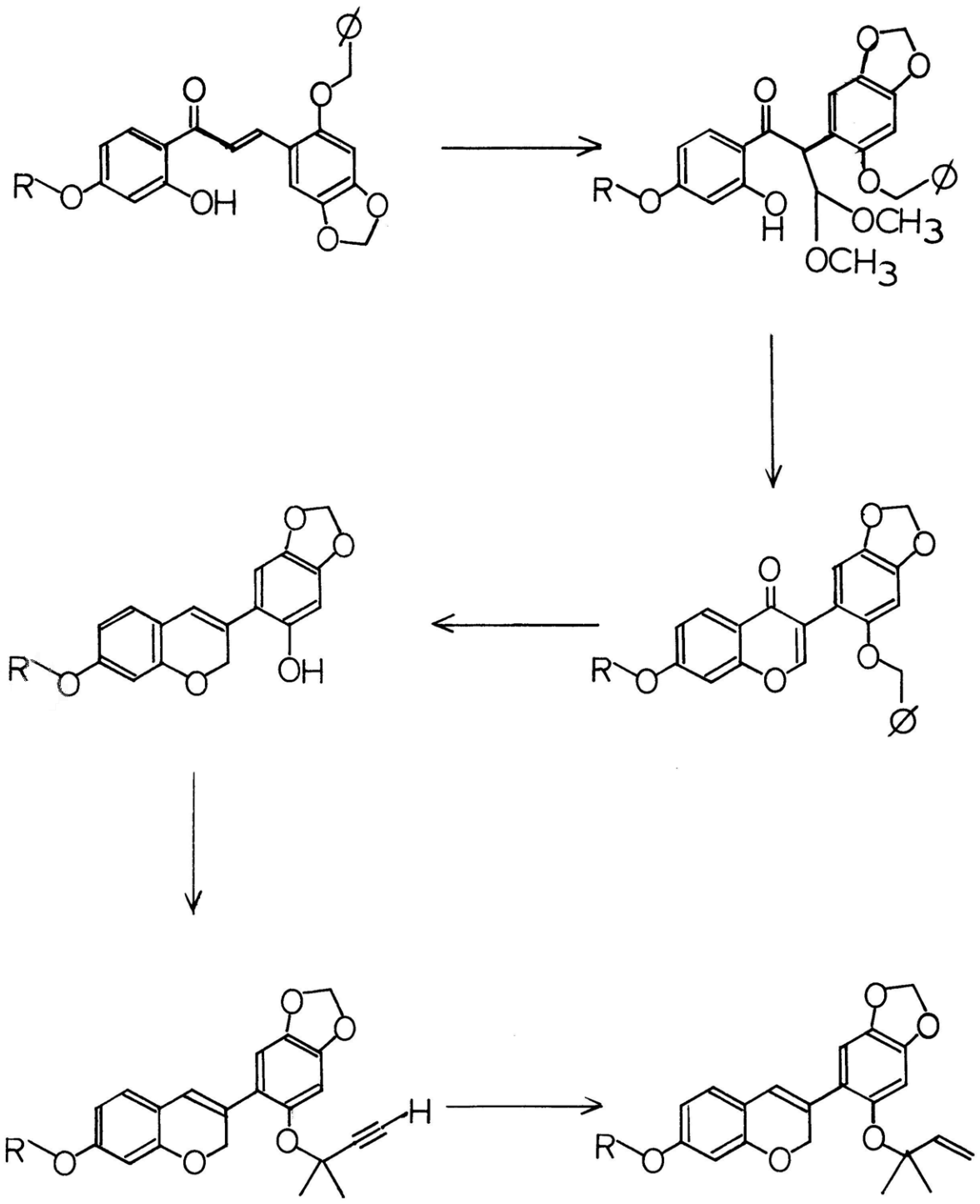
24 25

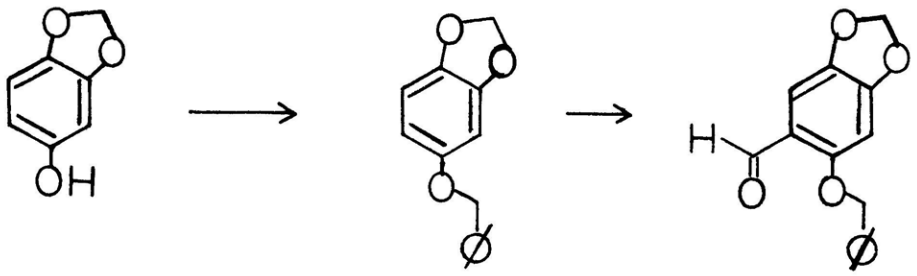
A major difficulty which must be overcome, however, is the economically feasible and convenient preparation of the isoflav-3-ene

nucleus. The enamine condensation method reported by Paquette[25] provides isoflavylium salts which may be selectively reduced at the 2-position.[26] Unfortunately this procedure requires an aryl acetaldehyde precursor the preparation of which would be laborious, particularly on a large scale. Since isoflavones can be easily transformed to 3-chromenes,[27] a general isoflavone synthesis was considered. The classical methodology[28] requires a Friedel-Craft acylation of resorcinol with the appropriate aryl acetic acid which is most often prepared from the corresponding benzaldehyde by transformation into the azlactone, hydrolysis to the pyruvic acid with formation of its oxime, and oxidative decarboxylation to the nitrile which is then hydrolyzed to the acid.[29,30,31] Consequently a more direct procedure involving the oxidative rearrangement of chalcones,[32,33] readily derived from a variety of acetophenones and benzaldehydes, was investigated.

The basic approach chosen for preparation of the key intermediate 17 is outlined in Scheme I. Sesamol (26) was prepared from commercially available piperonal by peracid oxidation in glacial acetic acid as reported by Orphanos and Taurins.[34] The benzyl aryl ether 27 was obtained in the usual way from a mixture of the phenol, benzyl chloride, sodium hydride, and glyme, and subsequent Vilsmeier reaction of freshly distilled benzyl ether yielded only the desired 2-benzyloxy-4,5-methylenedioxybenzaldehyde (28) in good yield.

SCHEME I





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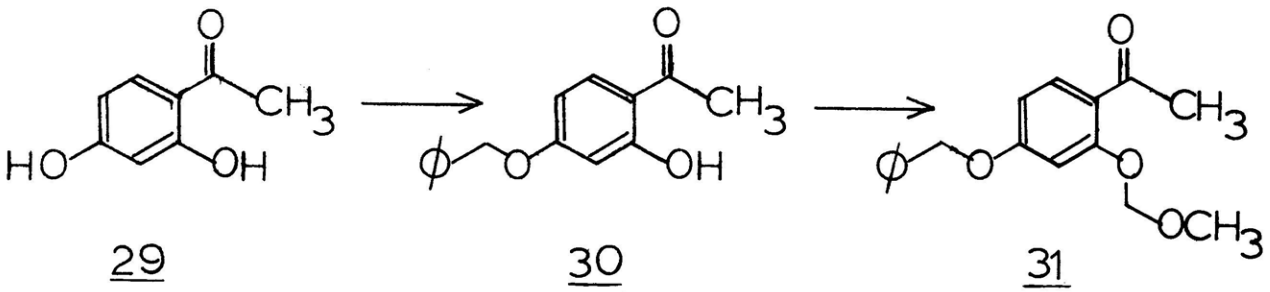
The sensitive acetophenone 31 was prepared by selective O-alkylation of 2,4-dihydroxyacetophenone (29) with one equivalent of benzyl chloride,[35] and subsequent reaction with chloromethyl methyl ether.



29 30 31

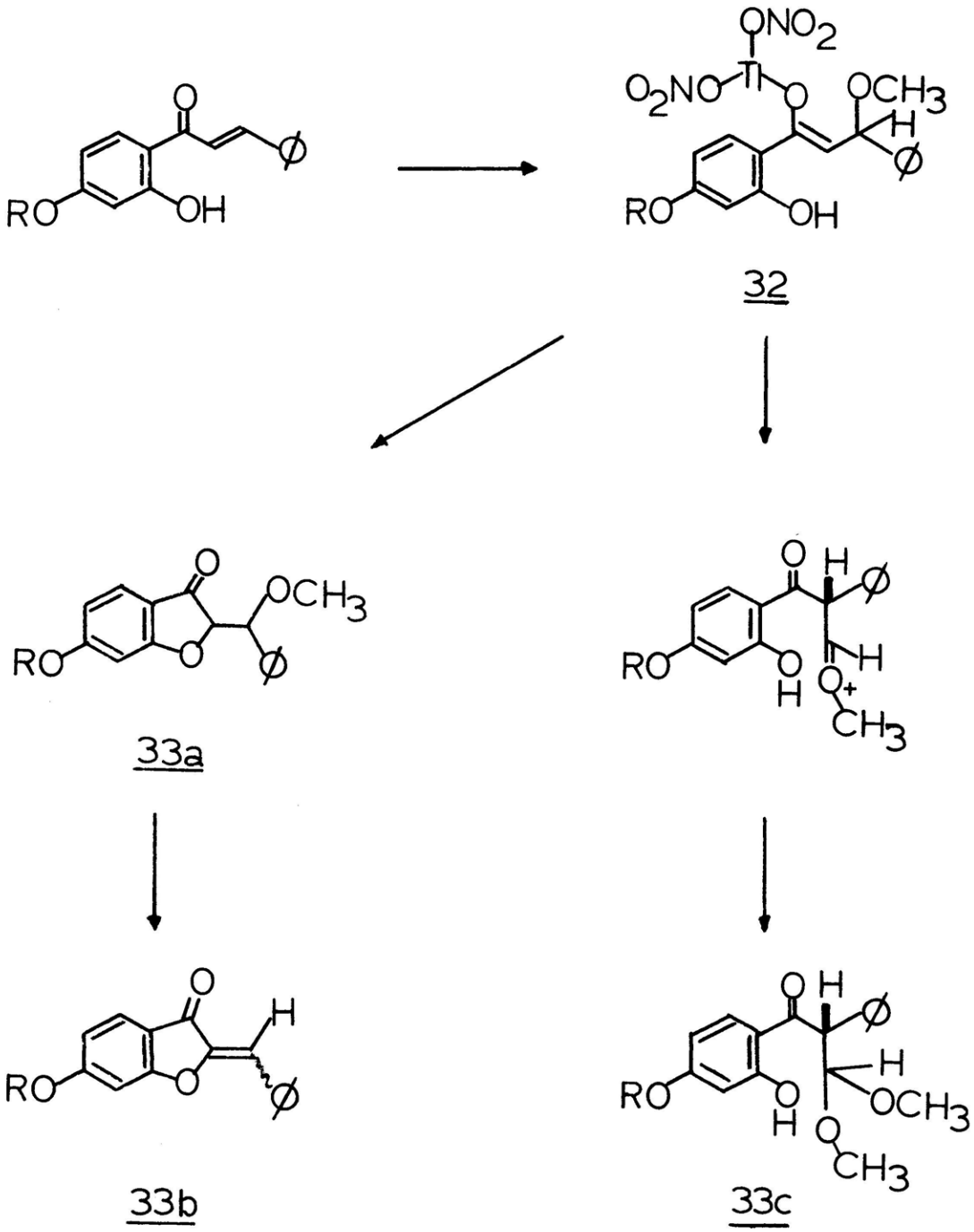
Selection of the methoxymethyl ether as a base-stable, acid-labile, protecting group for the 2'-hydroxyl was made to perform several functions. Chalcone formation generally proceeds more cleanly and in higher yield when the phenol is adequately blocked, but it is not known whether this is due to moderate insolubility of the starting material or the decreased reactivity of the methyl ketone toward enolate formation. More importantly the oxidative rearrangement utilizing thallium (III) nitrate requires the use of methanol not only to participate in the mechanism of the reaction as shown in Scheme II, but also to dissolve the inorganic reagent. Unfortunately many highly oxygenated chalcones bearing a 2'-hydroxyl are obstinately insoluble in methanol or any combination of methanol and cosolvent

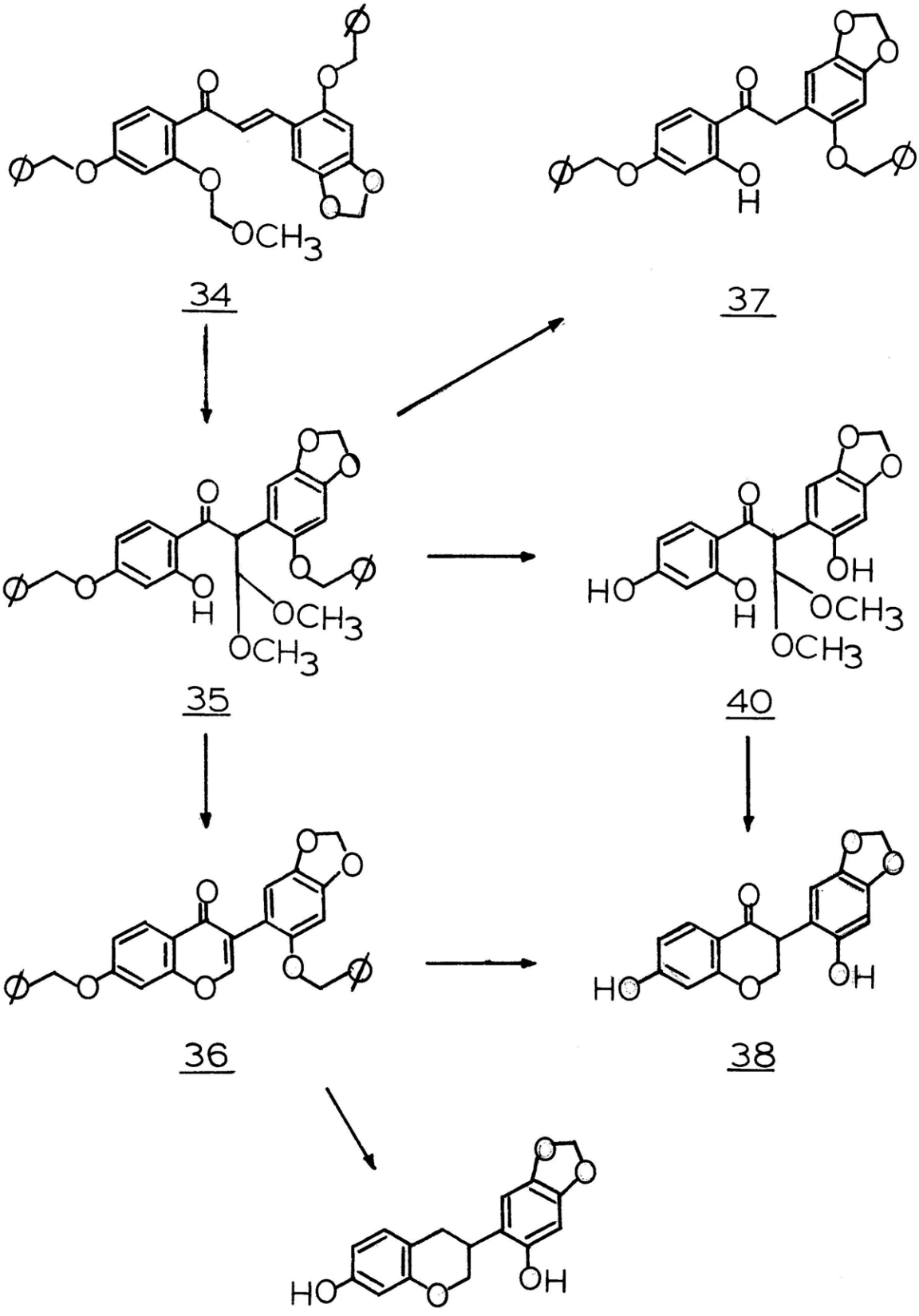
which also maintains the solubility of thallium (III) nitrate. Moreover, phenols have been oxidized to quinone derivatives[36,37] upon treatment with thallium (III) nitrate, and hydroxyl participation in the cylization of intermediate 32 giving the ketones 33 has been encountered in the analogous use of thallium (III) acetate.[38]

Base-catalyzed condensation of the protected acetophenone 31 and benzaldehyde 28 in refluxing ethanol afforded the desired chalcone 34 in 75% yield as bright yellow needles. Rearrangement upon treatment with thallium (III) nitrate proceeded smoothly in methanol-methylene chloride (1:1 by volume) at room temperature yielding the hydroxyacetal 35. The acid-sensitive methoxymethyl ether was also removed as two equivalents of nitric acid were produced for each equivalent of oxidized substrate. Cyclization resulted on treatment with a catalytic amount of para-toluenesulfonic acid in refluxing dioxane affording isoflavone 36 in good overall yield. Several drops of concentrated hydrochloric acid in dioxane at reflux also gave the desired isoflavone together with a small amount of deoxybenzoin 37 resulting from hydrolysis and retro-aldol cleavage of the acetal moiety.

Catalytic hydrogenation of the isoflavone to isoflavanone 38 was not accomplished in good yield, confirming literature reports[39] concerning the difficulties of catalytic reduction for this class of compounds. After three equivalents of hydrogen had been absorbed, isoflavanone 38 was isolated by preparative thin-layer chromatography as the major component in a complex mixture of debenzylated isoflavone and over-reduced products. On the other hand, complete reduction

SCHEME II

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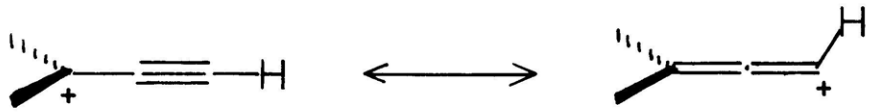
39

rapidly occurred using 10% palladium on charcoal in methanol under one atmosphere of hydrogen affording a quantitative yield of the chroman 39. Hydrogenolysis of the benzyl ketone 35 did not occur even upon prolonged treatment under these same conditions giving only the deprotected acetal 40 in high yield. Attempts at selective monoalkylation of 39 at the less hindered phenol were extremely sensitive to solvent effects owing to the insolubility of the starting material; however, a mixture of dimethylformamide and tetrahydrofuran (1:1 by volume) resulted in a 3:1 ratio of chroman 41 and dibenzylated product 42. Thus, introduction of the dimethylallyl moiety, followed by formation of the chromene double bond via any of a number of oxidative methods, and subsequent cleavage of the methylenedioxy bridge was to provide the desired intermediate 17 needed for future cyclization studies.

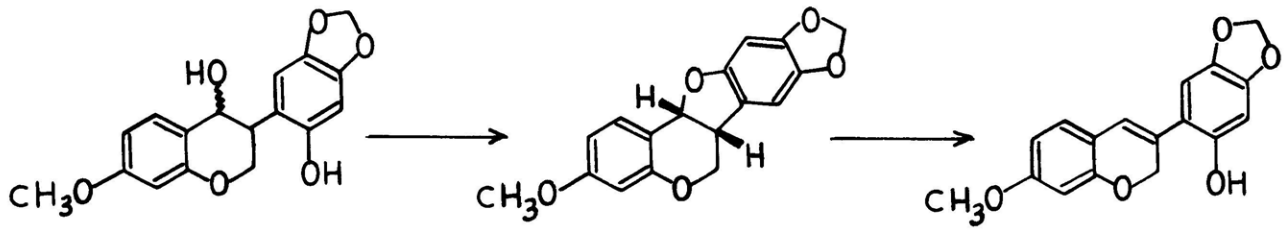
The most reliable method for addition of the prenyl side chain was discovered by Iwai and Ide.[40] In this, the acetylenic alcohol is converted into 3-chloro-3-methylbutyne[41] which is solvolyzed in the presence of the phenol with potassium carbonate and iodide catalyst. Mild reduction[42] of the acetylenic ethers provide the dimethylallyl ethers in good to excellent yield without contamination of allenic products resulting from reaction with vinyl carbocation 46b.[43]



46a 46b

Unfortunately, chroman 41 did not react with an excess of 3-chloro-3-methylbutyne in refluxing acetone or dry dimethoxyethane. Steric factors have been reported to unfavorably affect the success of this reaction;[44,45,46] however, the insolubility of the starting material may have also contributed to its failure.

It was hoped that O-alkylation of 2'-hydroxyisoflavones with 3-chloro-3-methylbutyne would proceed in the desired fashion because of the decreased steric hindrance compared to chroman 41. Chromene 49 also offers the same advantage; however closures of 2'-hydroxyisoflavan-4-ols 47 to yield pisatin 48 have been noted to occur under both acidic[47] and basic[48] conditions. These types of compounds are widely known in nature, and attempts to convert them into Δ^3-isoflavenes 49 have recorded limited success.[49]

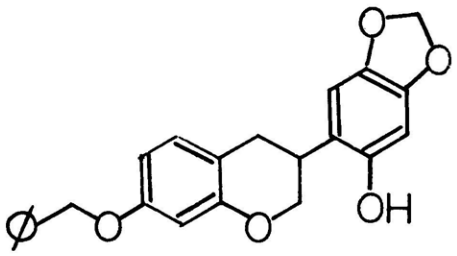


47 48 49

Birch and coworkers[50] have reported this transformation in moderate yield under carefully controlled conditions; however, it was advisable to avoid these problems. Chromenes are inherently unstable and undergo photochemical and acid-catalyzed dimerizations,[51,52,53,54] as well as disproportionation by hydride transfer to form chromans and pyrylium salts.[55]

Therefore, the desired 2'-hydroxy-7-methoxy-4',5'-methylenedioxy isoflavone was successfully prepared as shown in Scheme IV.

SCHEME III



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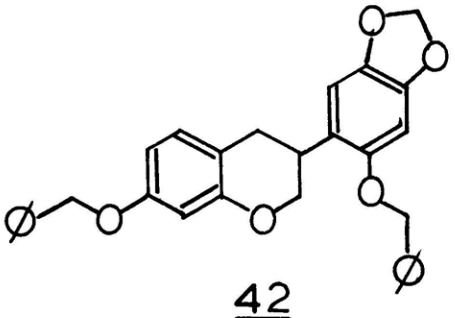

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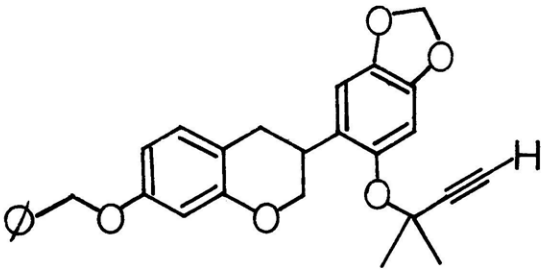

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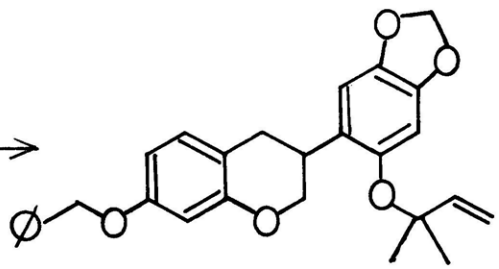

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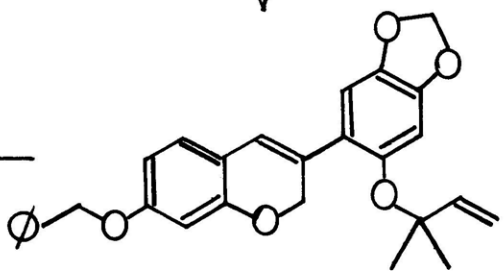

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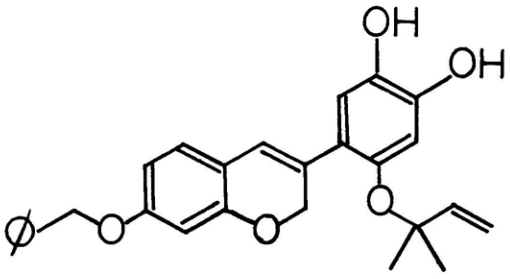

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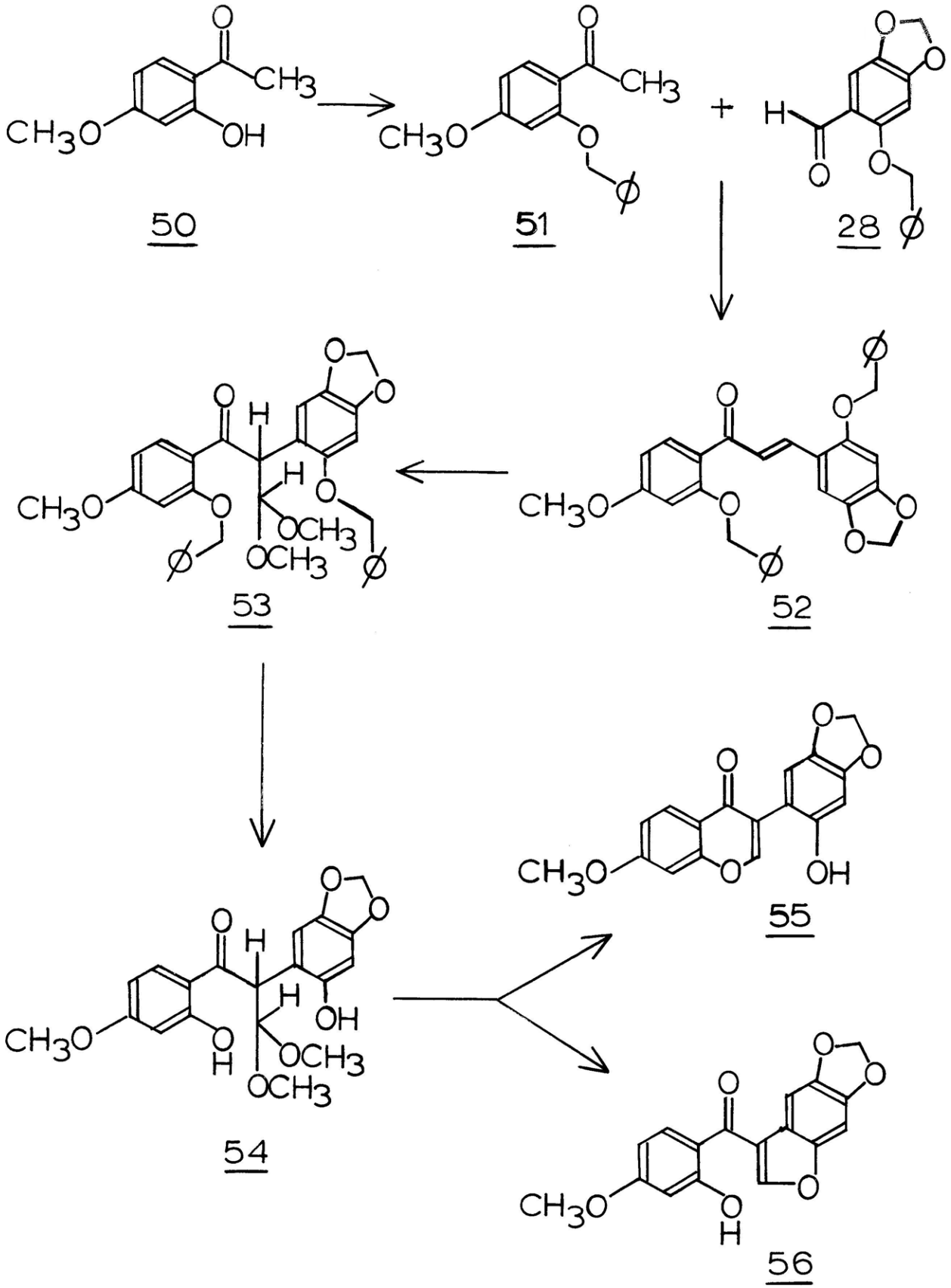
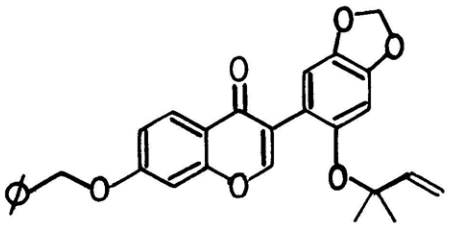
SCHEME IV



Commercially available 2,4-dihydroxyacetophenone was selectively alkylated with dimethylsulfate as previously reported by Simpson and Wright,[56] and the benzyl ether 51 was then prepared in the usual way from a mixture of the phenol 50, benzyl chloride, potassium carbonate, and refluxing glyme.[57] Subsequent base-catalyzed condensation of the protected acetophenone 51 with benzaldehyde 28 gave the substituted chalcone 52, which was oxidatively rearranged at room temperature with thallium (III) nitrate affording the acetal 53 in 50% yield following careful column chromatography. Catalytic hydrogenation gave the dihydroxyacetal 54 which cyclized upon heating at 175° providing a mixture of the desired isoflavone 55 and the isomer, 3-(2-hydroxy-4-methoxybenzoyl)-5,6-methylenedioxybenzofuran (56), as well as a small amount of starting material. Separation was achieved by column chromatography on silica gel.

Recently Hungarian workers have reported the synthesis of isoflavone 55 by the same route.[37,58] Unfortunately O-alkylation of the isoflavone with 3-chloro-3-methylbutyne under various conditions resulted in the isolation of benzofuran 54 by a base-catalyzed isomerization. No other products besides starting material were detected.

Opportunities to prepare the isoflavone 57 by initiating the sequence with benzaldehyde 58 failed in the early stages.



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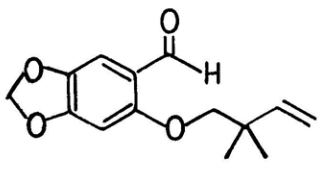


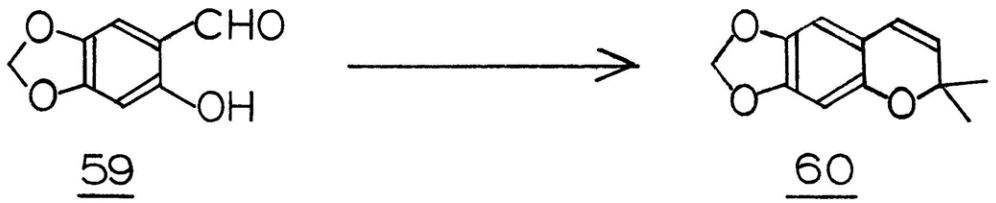
58

The ortho-hydroxybenzaldehyde 59 was prepared according to a series of known procedures beginning with commercially available piperonal.[59] Hydrogenolysis of benzyl ether 28 was unsuccessful because the desired product was inevitably contaminated with over-reduced materials, and the Vilsmeier formylation of sesamol proceeded in poor yield only at elevated temperatures with a large excess of reagent. O-alkylation of 59 with freshly distilled 3-chloro-3-methylbutyne unexpectedly gave the benzopyran 60 in 80% yield.

Two mechanisms for this transformation are illustrated in Scheme V. Although rearrangements of this type have been known to occur during the alkylation step,[60,61] no examples have been found with concomitant decarbonylation and most require high temperatures in refluxing diethylaniline or dichlorobenzene.[62] Recently catalysis by silver tetrafluoroborate or silver trifluoroacetate in benzene or chloroform has been discovered.[63]

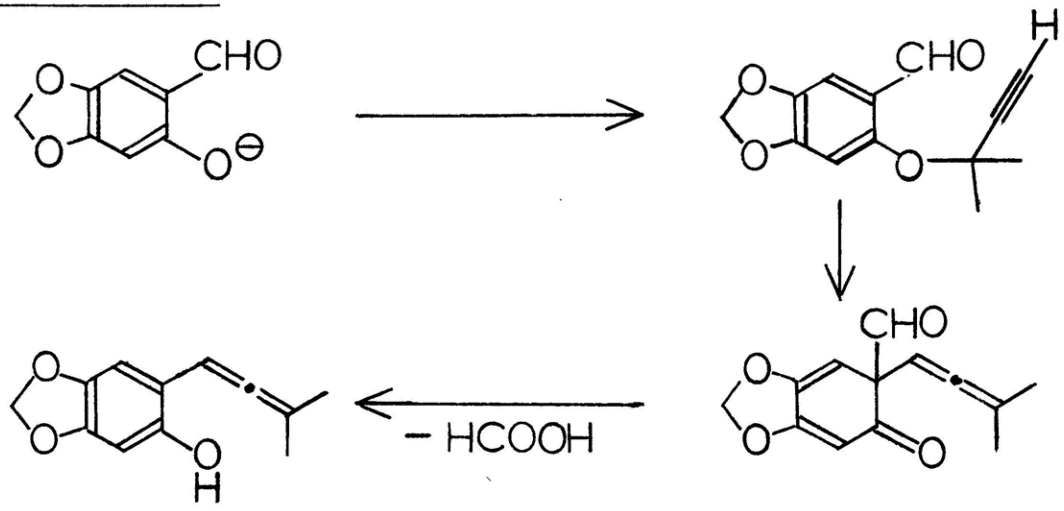
In separate studies designed to utilize the established accessibility of many coumarins, and avoid chromene formation until the final step, the synthesis of coumarin 61 was undertaken as an alternative approach to key intermediate 45. It was anticipated that diborane reduction[64,65] of the coumarin followed by oxidative workup would provide the isoflavan-3-ol 62 which could then be transformed into 45.

SCHEME V

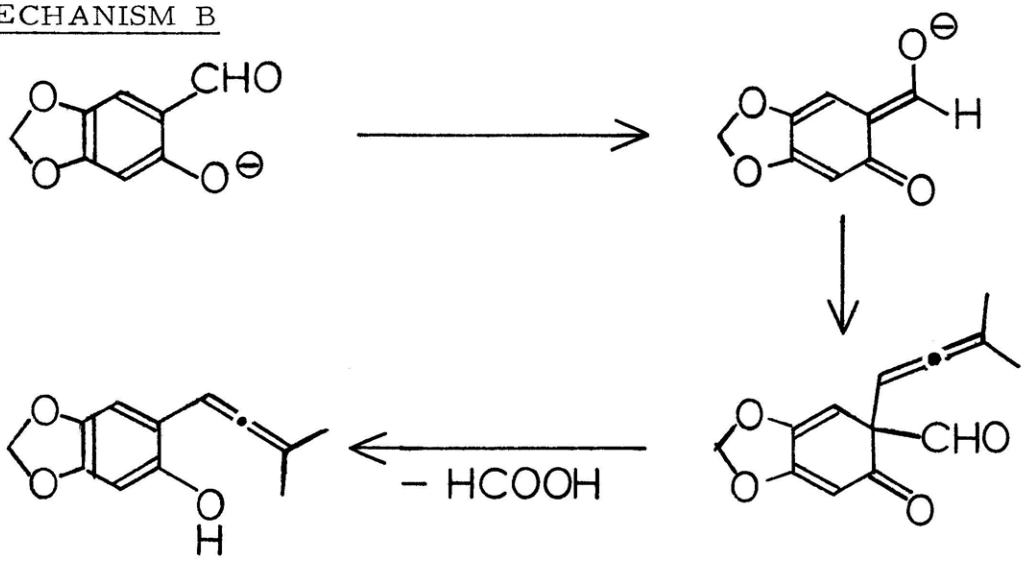


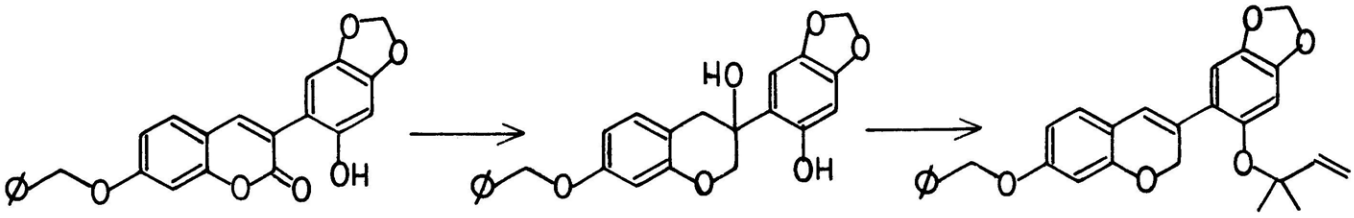
59 60

MECHANISM A



MECHANISM B



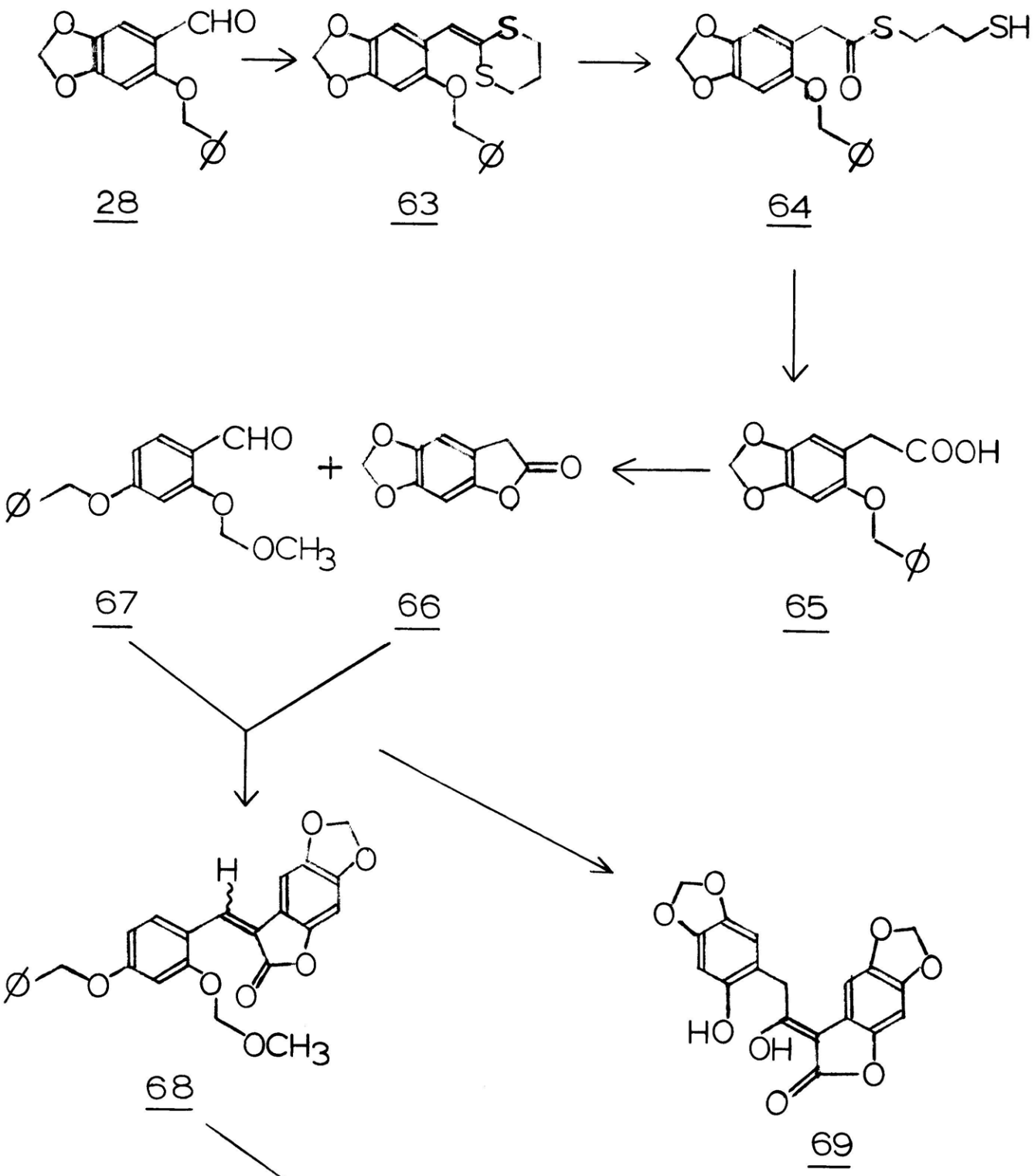


61 62 45

The attempted synthesis of 61 is visualized in Scheme VI. Transformation of aldehyde 28 to the homologous acid was achieved by preparation of the ketene thioacetal 63. Application of the Corey-Märkl method[66] involved generation of the phosphorous ylide from 1, 3-dithiacyclohexan-2-thione[67] in excess trimethylphosphite in the presence of the benzaldehyde 28. A second method developed by Seebach and coworkers[68] proved to be more convenient on the preparative scale. A solution of 2-litho-2-trimethylsilyl-1, 3-dithiane reacted cleanly with the aldehyde at -50° providing the highly crystalline ketene thioacetal in 81% yield.

The hydrolysis step proved to be more difficult than anticipated. Lewis acids known to promote hydrolysis of 1, 3-dithiane derivatives including mercuric chloride, acidic mercuric acetate, mercuric oxide-boron trifluoride etherate, silver nitrate, and cupric chloride-copper oxide gave extremely unfavorable results. Therefore a two step procedure[69] was successfully adopted by heating with aqueous methanolic para-toluenesulfonic acid to give the thiol ester 64 followed by base cleavage to the desired phenylacetic acid 65. debenzylation proceeded in high yield and lactonization to 66 occurred upon heating in tetralin under a stream of nitrogen. A direct

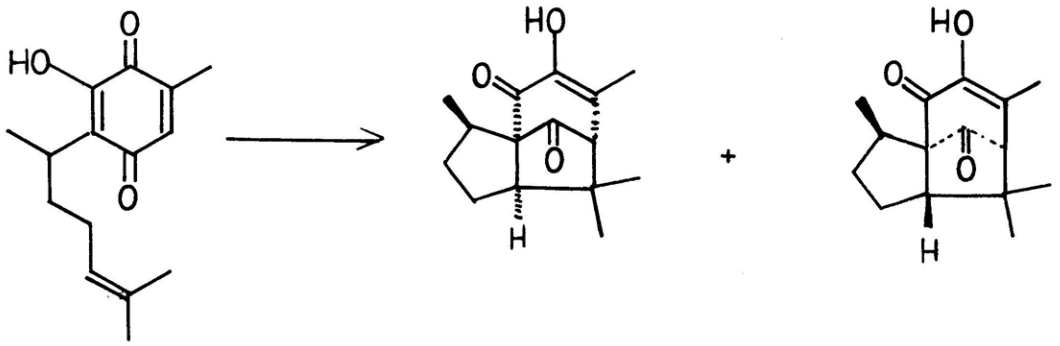
SCHEME VI



preparation by reaction of phenols with chloroacetyl chloride in the presence of Lewis acids was known to result in the exclusive formation of the undesired benzofuran-3-one.[70]

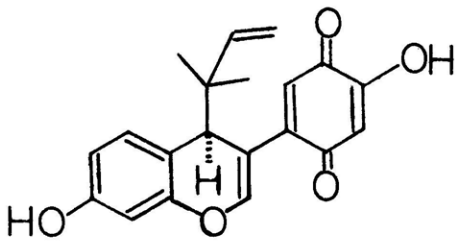
Guided by published precedent,[71] the preparation of 68 was undertaken with the hope that isomerization by mild acid catalysis would lead to the more stable coumarin 61. The necessary benzaldehyde was prepared by selective benzylation[72] followed by alkylation with chloromethyl methyl ether; however, all attempts at condensation of the benzofuran-2-one 66 with benzaldehyde 67 in tetrahydrofuran or dimethoxyethane at room temperature with a variety of bases resulted in isolation of the dimer 69 as the major product. These discouraging results led us to reevaluate our synthetic plan.

In 1965 Walls and coworkers determined the structures of α and β-pipitzol, (71) and (72), derived from the sesquiterpene, perezone (70), upon thermolysis.[73,74,75]



70 71 72

Two different mechanisms have been considered for this cyclization. Wagner[74] has proposed an acid-catalyzed process, whereas Woodward[76] has suggested a seven-centered, six electron, thermally allowed,



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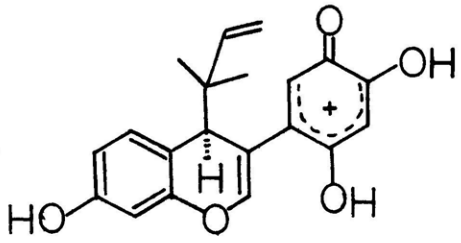

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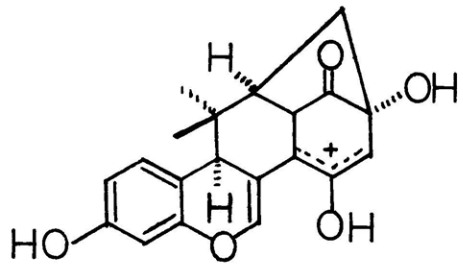

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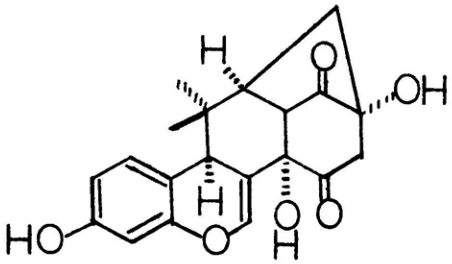

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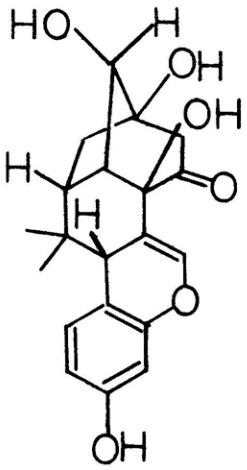


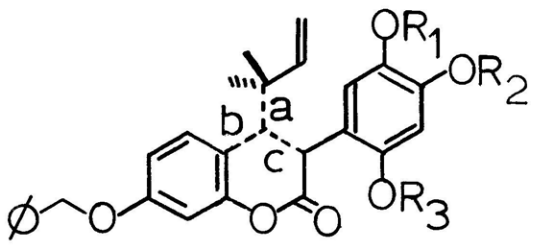
1

electrocyclic reaction. This type of intramolecular reorganization appeared to be quite applicable for the synthesis of miroestrol. Specifically the cycloaddition of para-quinone 73 via the intermediate pentadienyl cation 74 would produce the allylic system 75. The addition of water to yield 76 would complete the total synthesis of miroestrol upon reduction of the more reactive ketone. The feasibility of this approach was suggested by the close proximity of the interacting functions which would establish five of the six asymmetric centers in a single step. The remainder of the thesis concerns our progress along this route.

Three separate pathways have been devised for preparation of the aromatic precursor 77, which upon reduction with diisobutylaluminum hydride and elimination followed by oxidation would provide quinone 73. Each of these plans allows for the construction of the highly substituted β-ring by the formation of a different carbon-carbon bond as indicated in Scheme VII.

Route a involves the 1,4-addition of an allylic Grignard reagent to a coumarin nucleus. Workers have sporadically reported the 1,4-addition of Grignards to coumarins, and evidence indicates that increased steric hinderance of the magnesium reagent will encourage 1,4-addition.[77] Nothing has been reported concerning the effect of copper salts in these reactions, and organocuprates have not been reacted with coumarins, but it is well known that allylic Grignards attack through a six-centered transition state with allylic rearrangement and bonding to the more substituted terminus thus resulting in formation of the least substituted carbon double bond.[78]

SCHEME VII



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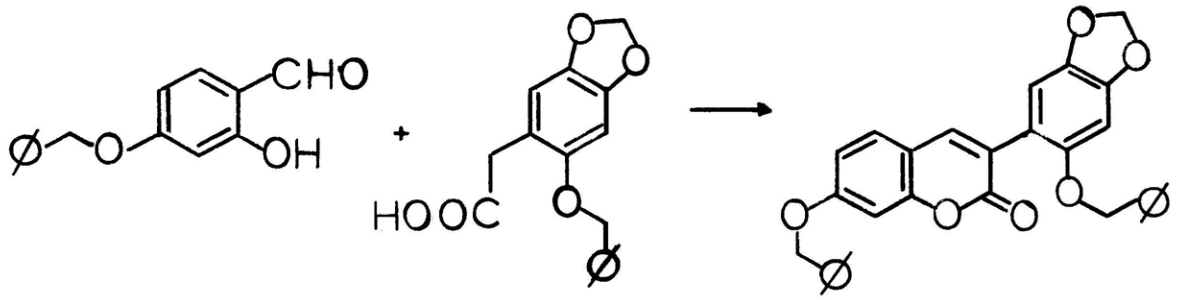
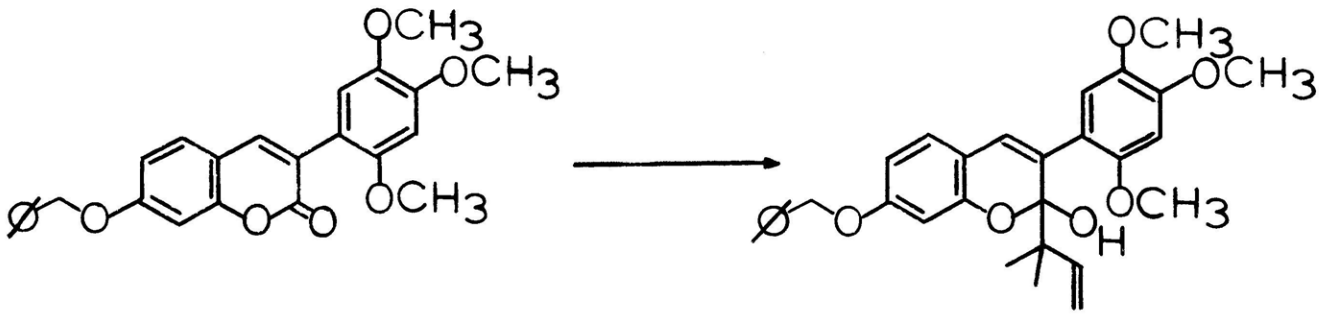
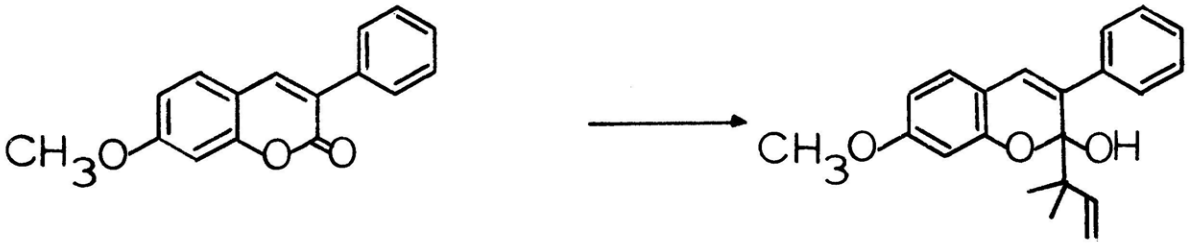


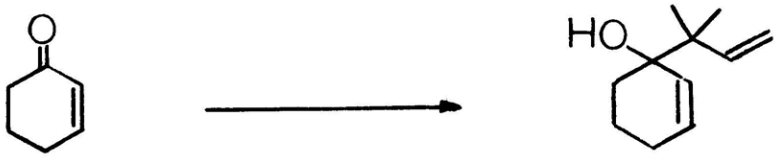
65 79



80 81



82 83

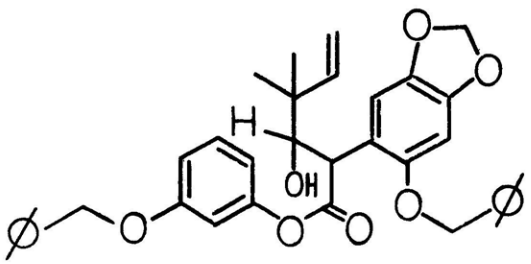


84

The desired coumarin 79 was synthesized from 4-benzyloxy-2-hydroxybenzaldehyde[72] and the phenylacetic acid 65 via the Perkin reaction using potassium acetate and acetic anhydride. The necessary isopentenyl magnesium reagent was prepared from 3-chloro-3-methylbutene[79] by a high dilution procedure using excess magnesium, and reacted with the coumarin 79 at -78°. Three major products were observed; however, structural elucidation was difficult due to the overlapping chemical shifts of many protons in the olefinic region. As a result, coumarin 80 was readily prepared and reacted at -78° under nitrogen atmosphere with the allylic Grignard providing the hemiacetal 81 in 50% yield by 1,2-addition to the carbonyl. Two minor products also formed appeared to have added two equivalents of Grignard, although complete structure assignments were not made. A small amount (10%) of starting material was also recovered. Interestingly cuprous iodide had no effect on the mode of addition or yields of products, and it was concluded that the electronic effects of the phenyl substituents substantially deactivated the double bond. To better understand the results, the Grignard was added to coumarin 82, as well as to cyclohexenone, with and without the presence of cuprous iodide in ether and in tetrahydrofuran at -78°, -10°, and room temperature. In all cases only 1,2-addition to the carbonyl was observed giving rise to a 70% yield of hemiacetal 83 as white needles and a nearly quantitative conversion to tertiary alcohol 84. To date no examples of the 1,4-addition of allylic Grignards to enone systems have been reported in the literature.[80,81]

The chemistry of route b was explored as shown in Scheme VIII.

SCHEME VIII



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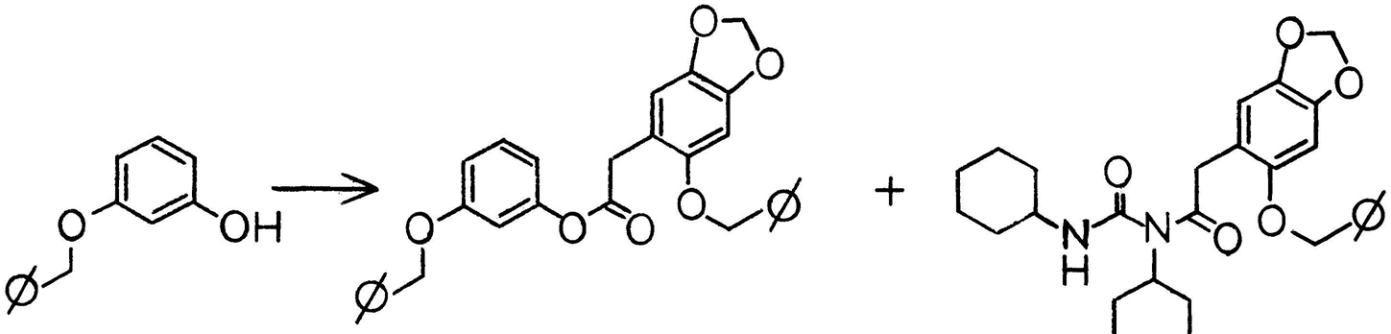
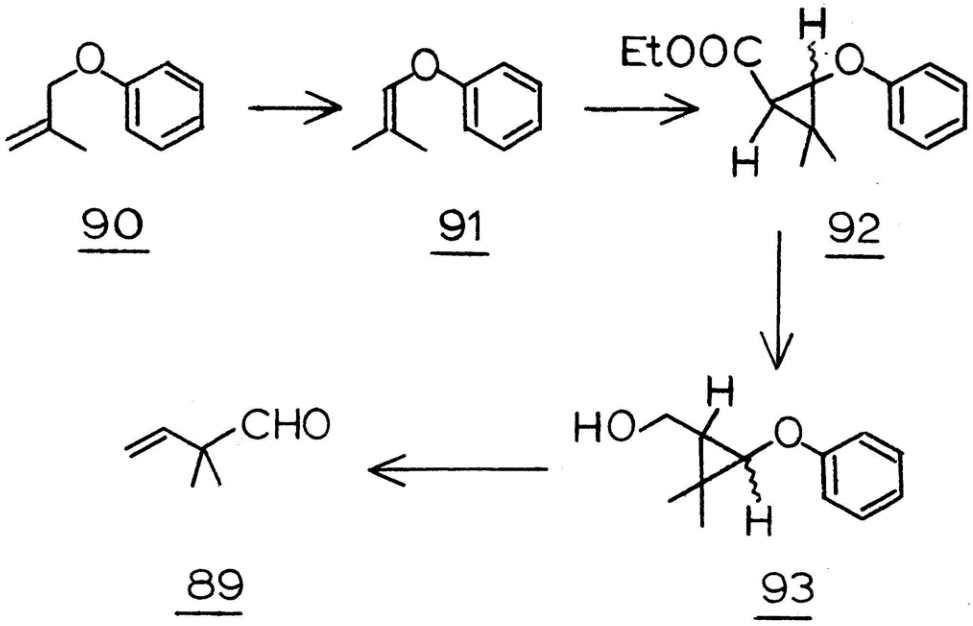
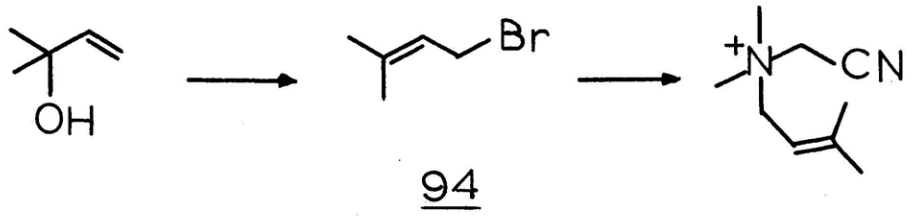


86 87 88



90 91 92 93 89

SCHEME VIII



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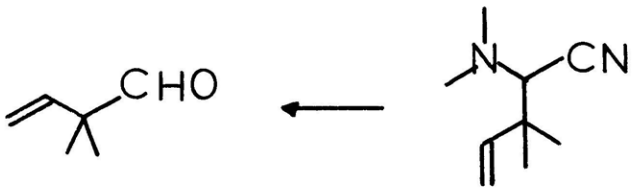

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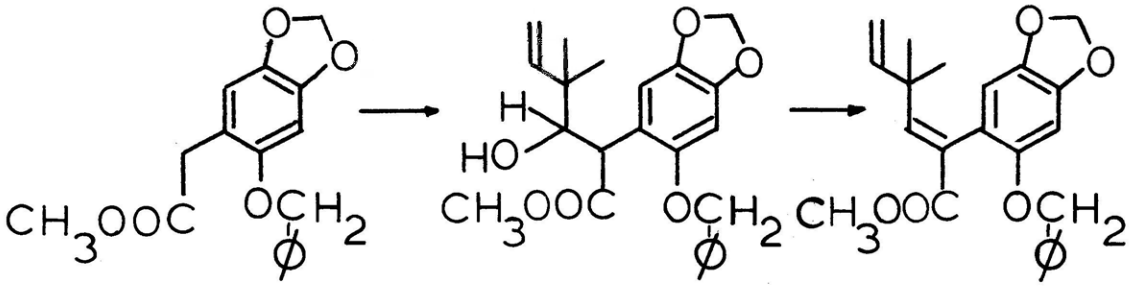


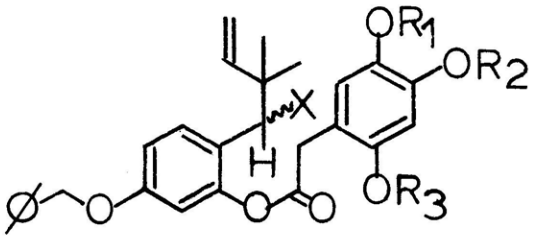
96 97 98

In this case, the dihydrocoumarin 77 would have been available by ring closure of intermediate 85. Resorcinol was monobenzylated providing the phenol 86 which was esterified with 2-benzyloxy-4,5-methylenedioxyphenylacetic acid using dicyclohexylcarbodiimide. The urea 88 was identified as a minor product. With the phenolic ester 87 in hand, preparation of the desired aldehyde 89 was undertaken. A preparative scheme previously demonstrated by French workers was utilized.[82,83] The ether 90 resulted from alkylation of phenol with methallyl chloride and double bond isomerization with potassium tert-butoxide gave enol ether 91. The addition of ethyl diazoacetate in the presence of copper powder at 135° resulted in cyclopropane formation, and reduction with lithium aluminum hydride afforded the cyclopropylcarbinol 93. Hydrolysis with 2 N sulfuric acid gave the desired nonenolizable aldehyde 89, but in spite of the fact that all intermediates were easily distillable and handled in preparative quantities, the sequence suffered from many steps. As a result, 2,2-dimethyl-3-butenal was conveniently prepared by a general method developed in these laboratories.[84] Allylic bromide 94 was combined with dimethylaminonitrile and the ammonium salt was rearranged *in situ* with potassium tert-butoxide. Subsequent hydrolysis of the crude aminonitrile 95 under neutral conditions with cupric sulfate provided the desired aldehyde in good yield. Since quantities of methyl ester 96 were on hand, preliminary experiments to investigate the Claisen condensation with aldehyde 89 indicated that adduct 97 was isolated only when kinetically-controlled conditions were used with lithium diisopropylamide as a base.

Presumably the lithium cation stabilized the anionic intermediate by chelation whereas sodium methoxide, potassium tert-butoxide, sodium hydride and piperidinium acetate were unable to prevent the favorable retro-aldol-type reaction.[85] Dehydration to prepare 98 under mildly acidic conditions produced several products, the major one of which was the starting methyl ester 96. Formation of the dihydrocoumarin 77 failed when the hydroxyester 97 was combined with resorcinol in the presence of aluminum chloride or fused zinc chloride. Although many products resulted, the major recoverable component was again methyl ester 96 while none of the desired adduct was observed. Since adducts of the hindered aldehyde 89 appeared to be sensitive materials which would probably not survive the conditions necessary to form bond b, further efforts along this pathway were terminated.

Investigations of plan c as summarized in Scheme IX involved construction of the dihydrocoumarin 77 by intramolecular displacement to form the six-membered lactone from intermediate 99. The synthesis of 99 was undertaken by Grignard addition to 4-benzyloxy-2-hydroxybenzaldehyde affording the hydroxyphenol 100. However, esterification with various phenylacetic acids using dicyclohexylcarbodiimide failed, and acid conditions resulted in formation of ester 101 by a solvolysis reaction. The structure assignment of 101 was based upon the position of carbonyl stretching in the infrared (1720 cm^{-1}), and the significant downfield shift (0.6 ppm) in the proton resonance spectrum for the secondary benzylic proton, as well as the isolation of the resorcinol derivative 102 upon hydrogenation with palladium on charcoal in ethanol.

SCHEME IX



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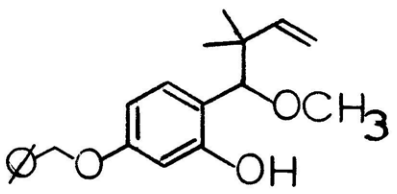

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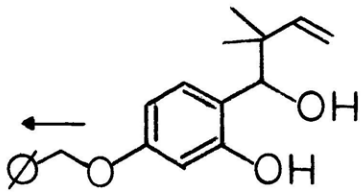

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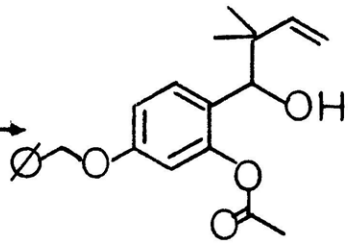

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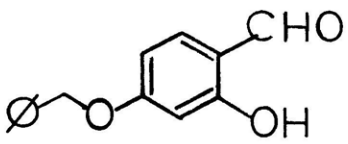

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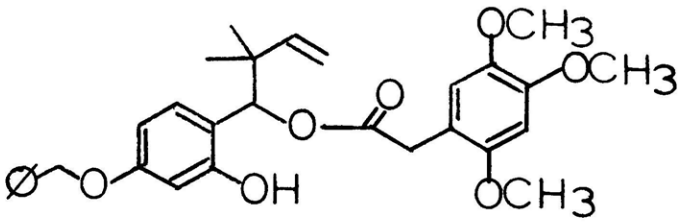

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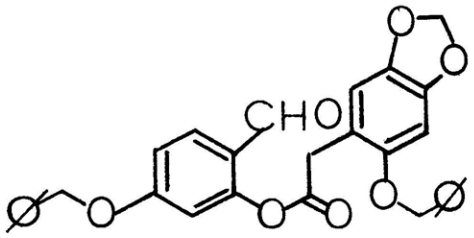

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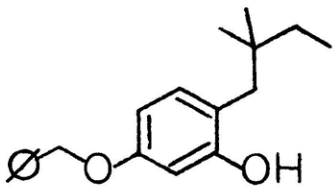

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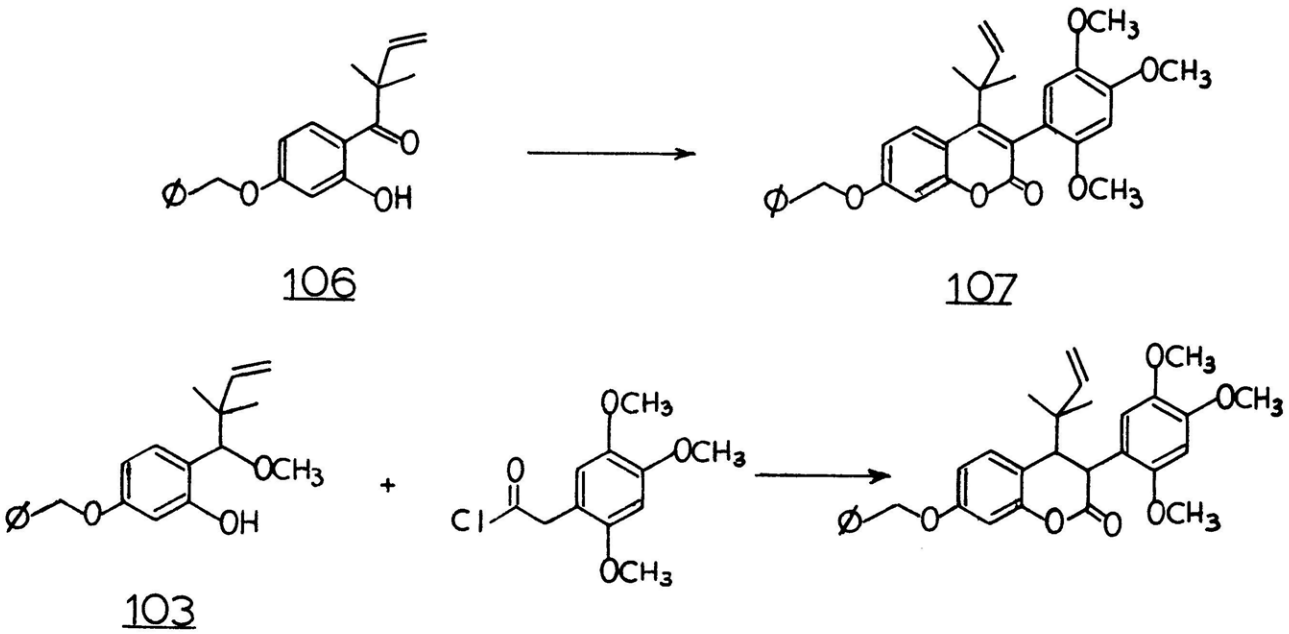
100

The outcome of this reaction was particularly characteristic of the chemistry of ortho-quinone methides, and as expected the elimination-addition sequence was greatly accelerated by traces of acid.[86,87] Thus the attempted crystallization of 100 from absolute methanol at room temperature for 2 days gave the methyl ether 103 as a yellow oil upon evaporation. The exchange was more efficiently undertaken in methylene chloride using a slight excess of methanol and a catalytic amount of acid.

When one equivalent of sodium hydride was used to generate the phenolate of 100, quenching with acetic anhydride was successful without subsequent O-acyl transfer affording acetate 104 as indicated by the diagnostic infrared carbonyl absorption at 1770 cm^{-1}. As anticipated, however, this material was prone to hydrolysis and underwent acyl-transfer upon storage. Introduction of the isopentenyl group after formation of the phenolic ester was also unsuccessful. The crystalline aldehyde 105 was easily prepared with dicyclohexylcarbodiimide; however, Grignard addition at -78° also cleaved the sensitive ester resulting in isolation of phenol 100.

Examination of these results suggested that if this approach were to succeed, closure to the dihydrocoumarin 77 had to be completed in a single step. Jones oxidation of 100 at 0° gave the hindered ketone 106 in rather poor yield, and the subsequent condensation with a phenylacetic acid to form coumarin 107 gave only starting materials. The attempted cyclization of methyl ether 103 with 2,4,5-trimethoxyphenylacetyl chloride with triethylamine in benzene at reflux gave 100 after aqueous workup; whereas, direct condensation of 100 with

2,4,5-trimethoxyphenylacetic acid and phosphorus oxychloride in refluxing dichloroethane resulted in a nonpolar derivative of 100 which was not an adduct and therefore not further characterized.



106 107

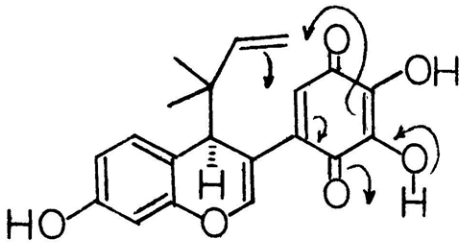
103

These investigations indicated that carbon bond formation by routes b and c were more difficult since these plans involved ring closure at a hindered neopentyl center. The difficulties proved insurmountable when intermediates along these paths were unable to survive the necessary reaction conditions. On the other hand, dimethylallyl Grignard reliably underwent 1,2-addition to several carbonyl compounds from the tertiary terminus. These results led us to utilize the isoflavone synthesis previously explored and undertake the Grignard addition to these compounds as well as the subsequent transformations leading to the desired para-quinone.

Closer examination and reports of further efforts in the pipitzol series[88] brought to our attention the necessity of proton

transfer in an intermediate, such as 108, to initiate the cyclization and facilitate direct formation of a neutral product 109. Then hydride reduction to triol 110 and allylic rearrangement upon hydrolysis of a vinyl ether or acetate would complete the miroestrol synthesis and demonstrate a biogenetic hypothesis.

Pyrogallol was chosen as an inexpensive and readily available starting material. Dimethylsulfate and potassium carbonate were used to prepare 1, 2, 3-trimethoxybenzene (111) by a known procedure,[89] and formylation via the Vilsmeier reaction also proceeded as previously reported,[90] giving benzaldehyde 112 as a colorless oil. Selective monodemethylation afforded the ortho-hydroxybenzaldehyde 113 in 58% yield after treatment with a one molar equivalent of reagent-grade aluminum chloride in dry toluene at reflux. This material was also prepared by formylation of pyrogallol giving insoluble 2, 3, 4-trihydroxybenzaldehyde[91] (115) followed by alkylation with iodomethane and potassium carbonate in acetone.[92]



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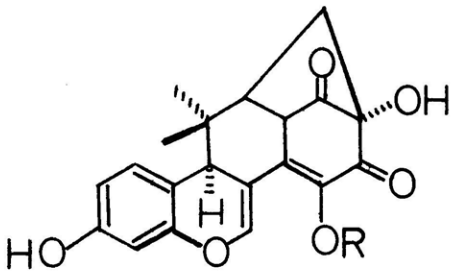

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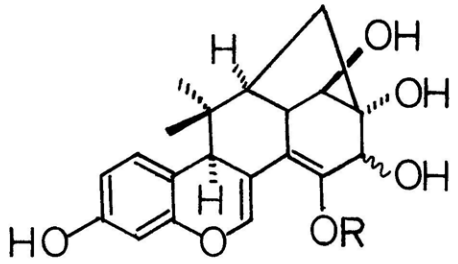

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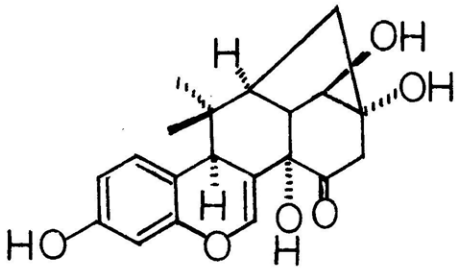

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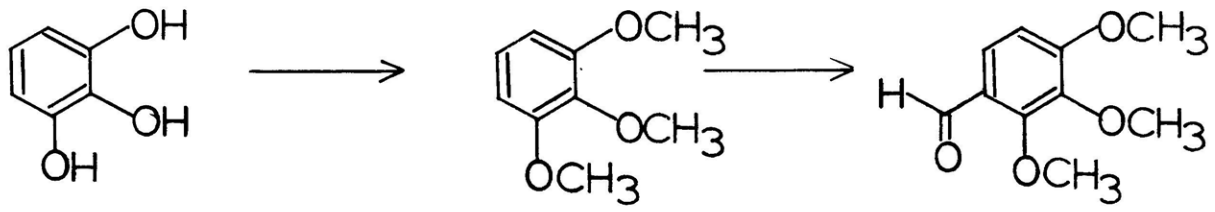
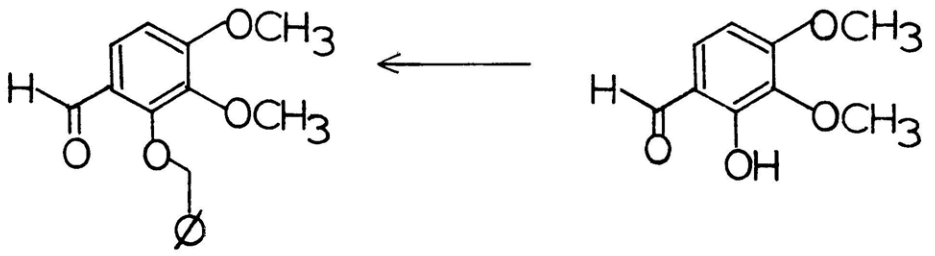
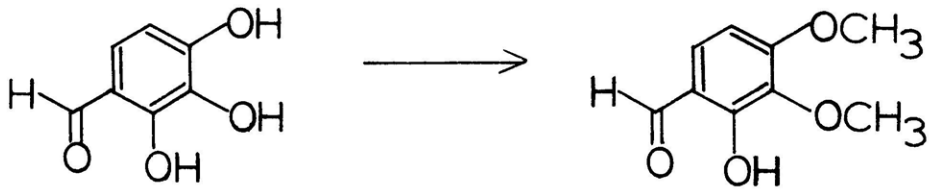


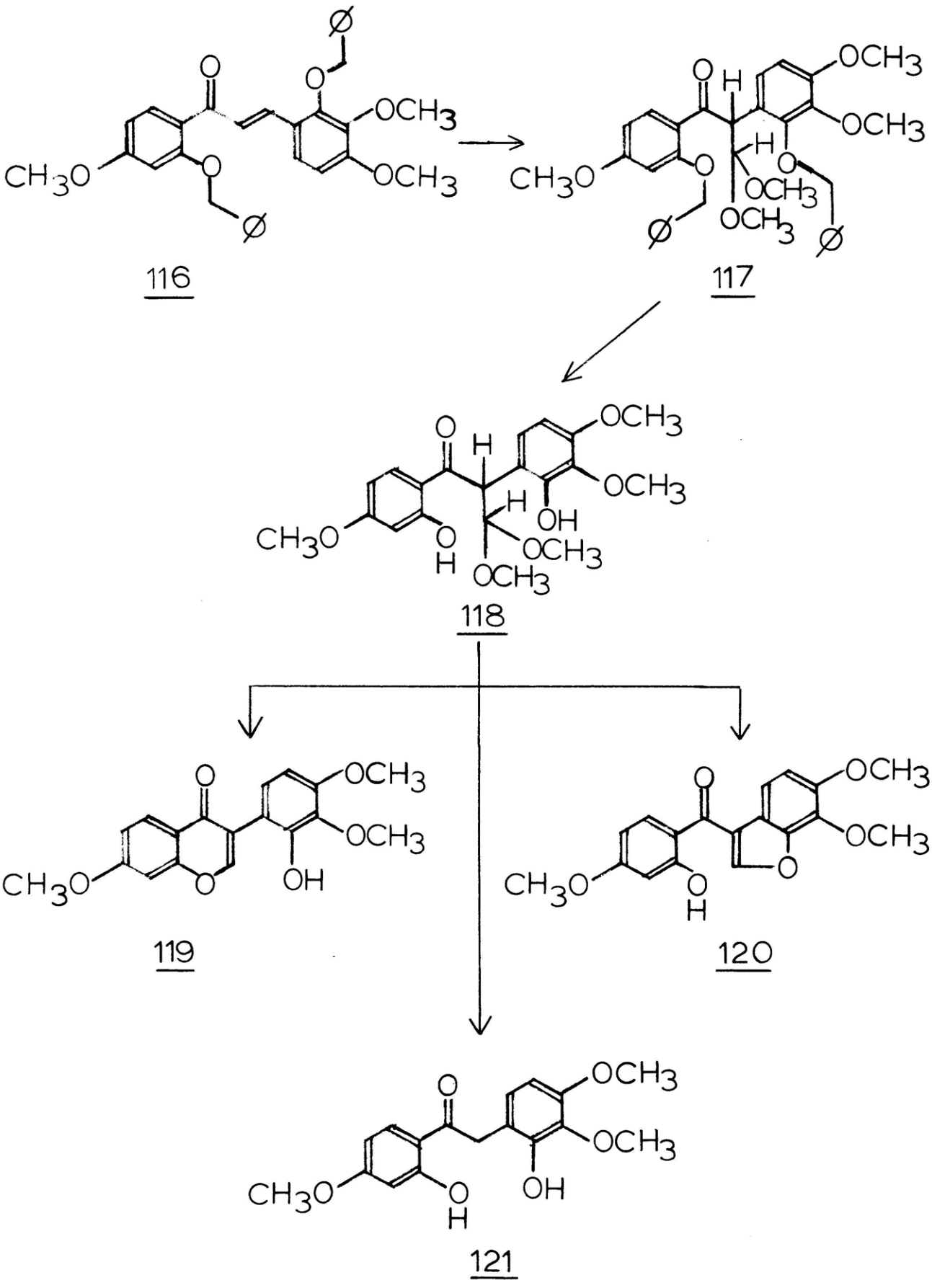
111 112



114 113

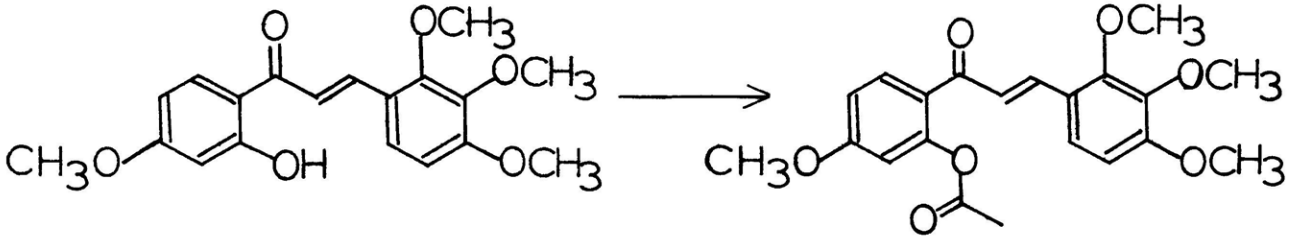


115 113


116
117
118
119
120
121

Benzylation in refluxing dimethylformamide gave the desired aldehyde 114 as a yellow oil isolated by distillation in vacuo. Subsequent base-catalyzed condensation with the protected acetophenone 51 gave the substituted chalcone 116, which was oxidatively rearranged at room temperature with thallium (III) nitrate affording the acetal 117 in 70% yield following silica gel chromatography. Catalytic hydrogenation gave a quantitative transformation to the dihydroxyacetal 118 which was cyclized upon heating at 175° under a stream of nitrogen providing 40% of the desired isoflavone 119 and 10% of the isomeric benzofuran 120. Approximately 5% of the deoxybenzoin 121 was also isolated and 40% of the reaction mixture was recovered as crystaline starting material. Separation was achieved by preparative thin-layer chromatography on silica gel.

Clearly a more efficient preparation of isoflavone 119 was needed if this sequence were to be useful. Chalcone 122 was obtained in 77% yield as bright yellow needles upon acidification of the crude reaction mixture following condensation of 2-hydroxy-4-methoxyacetophenone (50) with 2, 3, 4-trimethoxybenzaldehyde (112) in methanolic potassium hydroxide. The corresponding acetate 123 was formed quantitatively upon dissolving in acetic anhydride-pyridine with crystallization from hot methanol. Oxidative rearrangement proceeded under anhydrous conditions with thallium (III) nitrate in the presence of a small amount of trimethylorthoformate in methylene chloride-methanol, and the conversion appeared to be quantitative, as judged by thin-layer chromatography, without cleavage of the



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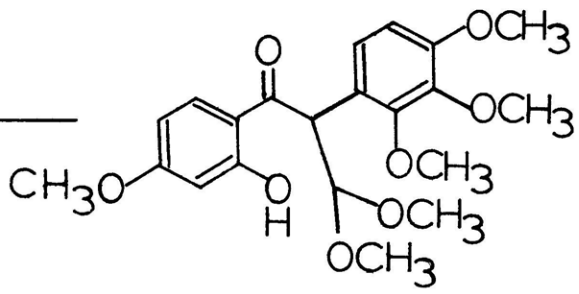
123



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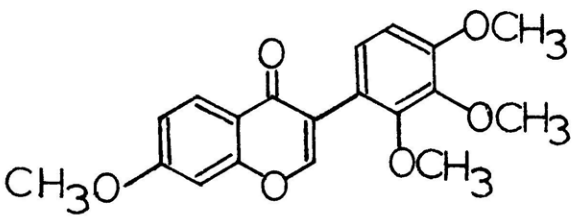
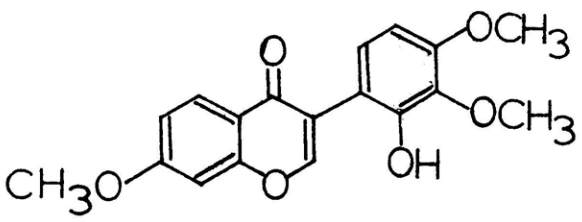
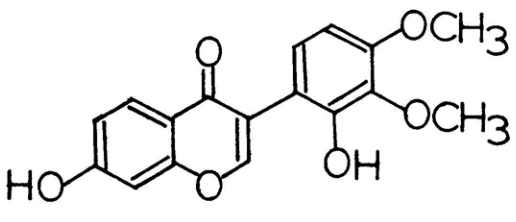


125

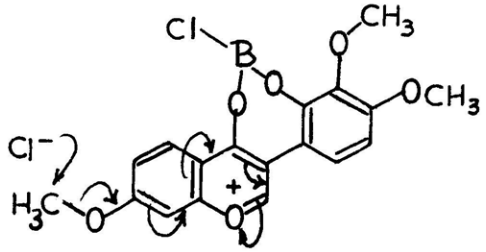


119



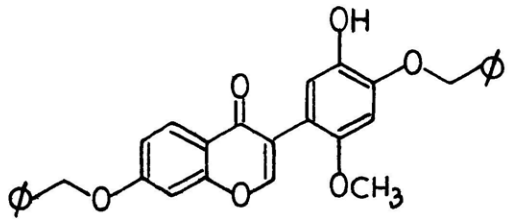
126

sensitive acetate. Also traces of yellow oxidation products which were seen in previous cases did not contaminate this reaction mixture. Neutralization with solid sodium bicarbonate followed by removal of the inorganic salts and hydrolysis with aqueous potassium carbonate led to the acetal 124 after filtration through a short column of silica gel. The thick yellow oil contained a small amount of the more polar isoflavone 125, and cyclization was completed in 89% overall yield from chalcone 123 upon heating in 1,4-dioxane in the presence of a catalytic amount of para-toluenesulfonic acid. Treatment of 125 with a one molar equivalent of boron trichloride in methylene chloride at low temperature gave the desired isoflavone 119 in 95% yield upon trituration with methanol. The addition of two equivalents of boron trichloride with stirring at room temperature surprisingly resulted in two highly selective demethylations affording isoflavone 126 in excellent yield. While it is well known that the initial reaction of a Lewis acid with a basic carbonyl predictably directs the cleavage of alkyl ethers within its immediate vicinity,[93] the selective cleavage of an aryl alkyl ether located para to the interacting carbonyl is apparently unprecedented. The driving force of this reaction may be neutralization of the positively charged species 127.



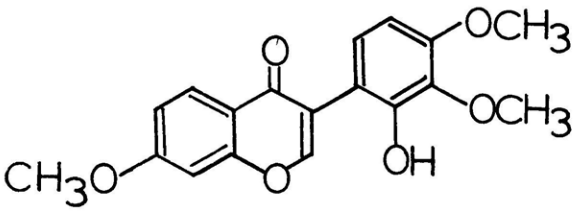
127

An ether solution of isopentenyl magnesium chloride, generated by a high dilution procedure, was rapidly added to the solid isoflavone 119 at room temperature under nitrogen atmosphere. Although the isoflavones prepared for this study were totally insoluble in ether, the magnesium phenolates quickly dissolved. This effect may be due to chelation with the carbonyl function since isoflavone 128 was recovered unreacted after stirring with excess Grignard owing to its complete insolubility in tetrahydrofuran as well as ether.

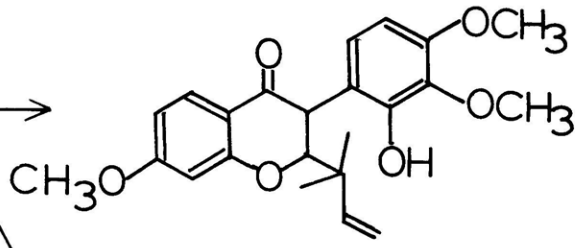


128

Upon quenching with saturated ammonium chloride, isoflavone 119 gave two products which were immediately separated by column chromatography on silica gel. Extensive decomposition occurred with exposure to light; therefore, the column and all flasks were wrapped with aluminum foil. The less polar component was obtained in 70% yield as a thick oil and subsequently identified as the sensitive alcohol 129 along with traces of dehydration product 130. The remainder of the reaction mixture proved to be the result of 1,4-addition yielding ketone 131 as ivory-colored clusters from ether-hexane. The benzofuranobenzopyran 130 was isolated in 50% yield as a thick oil from the starting isoflavone after dehydration of 129 by stirring in a slurry of silica gel under nitrogen atmosphere overnight.



119



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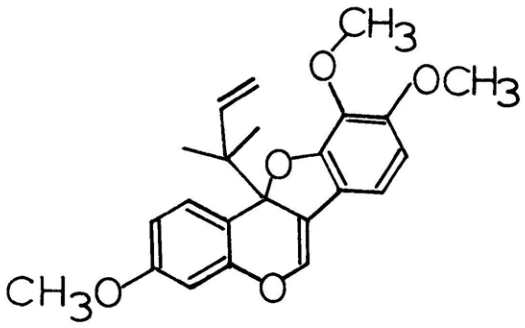

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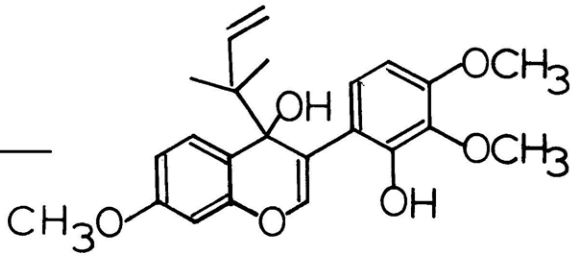

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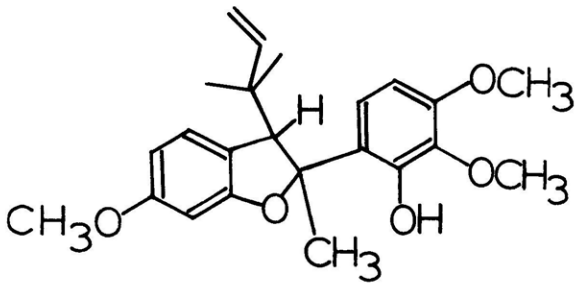

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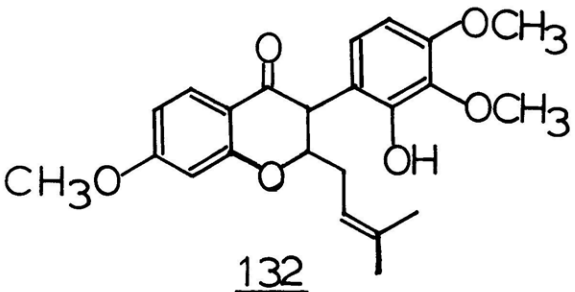
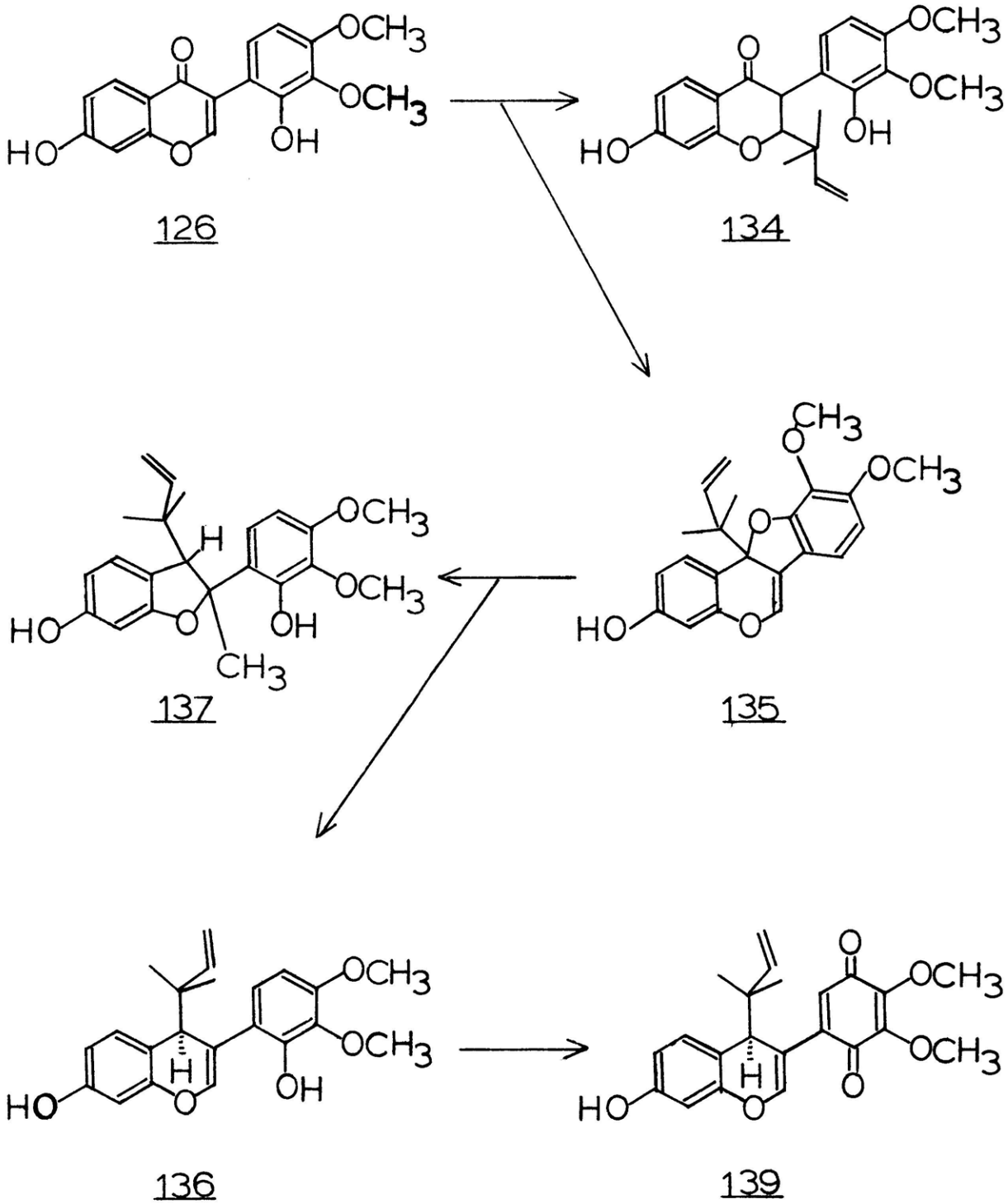


132

Although the reductive cleavage of benzylic alcohols and ethers is well documented in simple systems and proceeds with a variety of reagents, the tetracyclic ether 130 failed to react in the presence of sodium amalgam, Raney nickel, aluminum amalgam, and sodium in tert-butyl alcohol. Reports of successful reductions in similar steroidal derivatives[94,95,96] using lithium in liquid ammonia with the addition of aniline, ethylamine or methanol as a proton source encouraged a new series of experiments; however, when these conditions were applied to 130 only decomposition was observed.

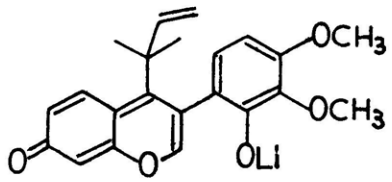
Investigators at Rutgers[97] recently reported the advantages of lithium-liquid ammonia and ammonium chloride as an effective means for the reduction of benzylic alcohols. However, Hall and coworkers were unable to reduce hindered tertiary benzylic alcohols and allylic-benzylic compounds often suffered over-reduction. Difficulties arose when Grignard adduct 129 proved to be only partially soluble in refluxing ammonia leading to the isolation of starting material in the form of ether 130 along with several new ketones, the major one of which appeared to be the result of a Cope rearrangement. On the other hand, the highly substituted compound 133 was the only product obtained when these conditions were applied to 130.

Fortunately the entire sequence above was simultaneously carried out with isoflavone 126. The addition of isopentenyl magnesium chloride resulted in a 70% yield of the unwanted 1,4-adduct 134 as fine white needles which selectively precipitated from ether solution following a standard workup procedure. The mother liquor was concentrated and chromatographed through silica gel affording the desired


OCH3
OCH3
O
HO
OH
O
126
134
135
137
136
139
H
CH3

tetracyclic ether 135 in 20% yield as dense white clusters from methylene chloride-hexane. This reaction mixture was more light-sensitive than the corresponding methoxy case, and the intermediate alcohol was never observed, but once crystalline the products were stable and conveniently stored. Direct Grignard addition to the carbonyl was apparently diminished due to the participation of the phenolate at the para position.

Lithium-liquid ammonia reduction of 135 utilizing ammonium chloride gave two major products which were separated by repeated preparative thin-layer chromatography affording the desired phenol 136 in 35% yield as a pale yellow air-sensitive oil and the product 137 in 38% yield as pale yellow needles from methylene chloride-hexane. The success of the reduction in this case may be attributed to an initial base-induced tautomerization to the quinone methide 138 which is subsequently reduced to the desired aromatic system.



138

Elaboration to the required quinone 139 was far more difficult than expected. Many reports are available concerning the advantages of Fremy's salt for the oxidation of phenols in excellent yield under mild conditions.[98,99] While introduction of an oxygen atom and continued oxidation to the quinone requires two equivalents of the stable radical in an aqueous medium, literature examples demonstrate a

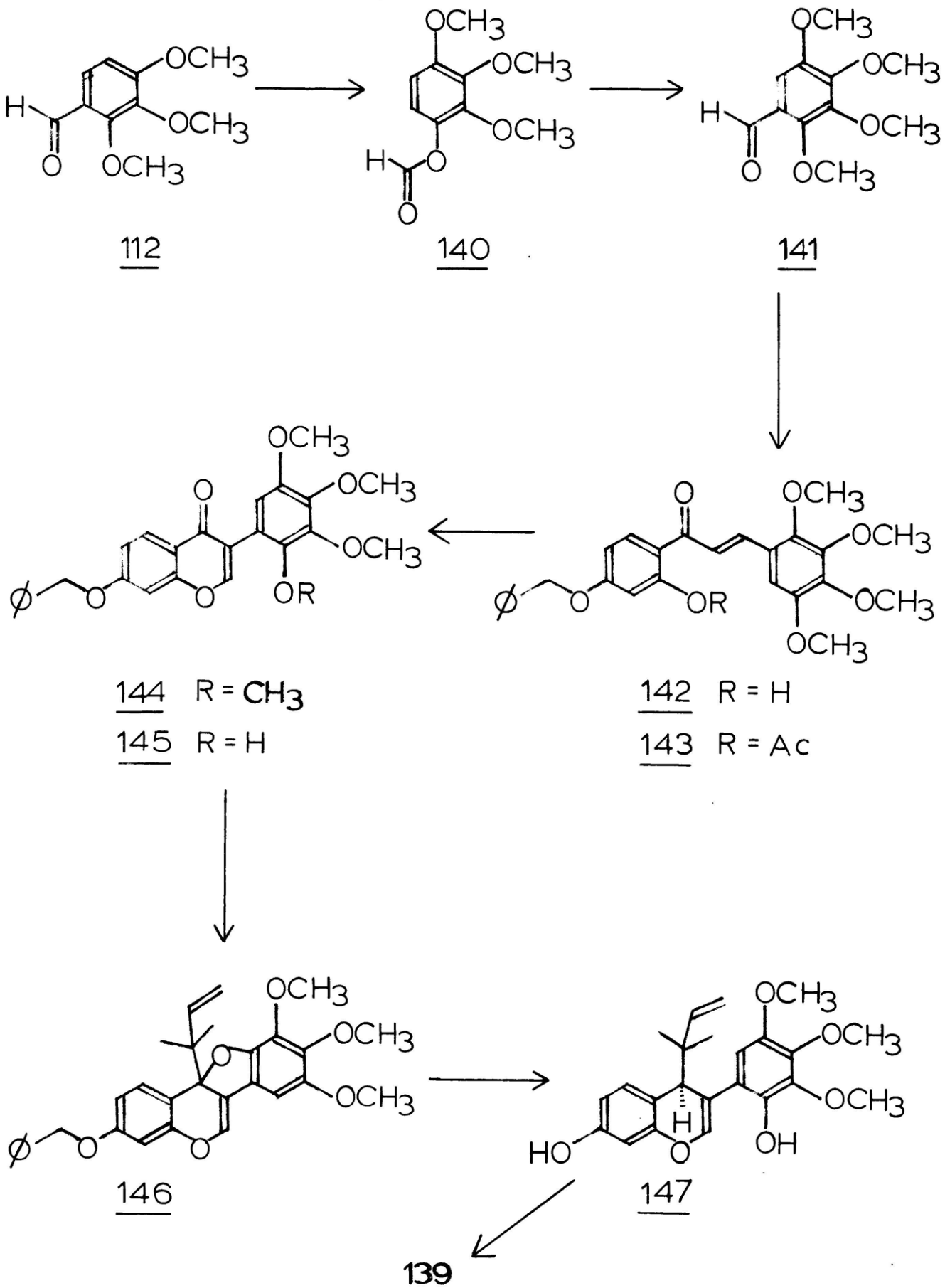
high selectivity favoring reaction at the para position rather than available ortho locations. This appeared to be the reagent of choice inspite of the reportedly large steric requirement.[100] However, when combined with phenol 136 at room temperature in aqueous methanol, aqueous acetone or a two-phase system of chloroform and water, the starting phenol was recovered unchanged even after vigorous stirring overnight. After the addition of three drops of 1 M potassium hydroxide followed by acidification, a new bright yellow product was produced together with substantial starting material. Isolation and nmr inspection revealed several complex proton absorptions which were totally uncharacteristic of any of the expected products, and very limited amounts of material discouraged further structure elucidation. When a dilute potassium carbonate solution of freshly prepared potassium nitrosodisulfonate[101] was shaken with phenol 136 in methylene chloride, the organic layer immediately became dark blue. After drying, the solution was concentrated at room temperature and a small amount of hexane was added to precipitate a dark blue solid which demonstrated the spectral characteristics required for the para-quinone 139. Further purification was impossible as the material quickly decomposed to no less than five new products upon standing in solution for several hours, and poor solubility properties prevented us from gathering vital nmr information concerning the substitution pattern of the A-ring. Although computer-assisted, high-resolution mass spectrometry confirmed preparation of the desired quinone 139 by recording the parent ion and a reasonable fragmentation pattern, the data also indicated the presence of

an impurity containing one additional oxygen. This over-oxidized material may be responsible for the instability of the product mixture. Also the reactivity, quality, and quantity of Fremy's salt was found to vary widely depending on the conditions of preparation, storage and age. Thus, the preparation of quinone 139 may be substantially improved upon further refinement of this reaction procedure. Hydrolysis of the quinone methyl ethers to give key intermediate 108 is a well known reaction for quinones, reported occurring under both acidic and basic conditions.[102,103,104]

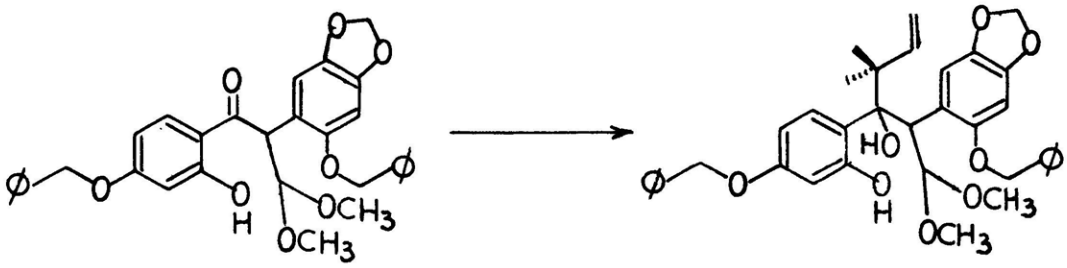
An analogous sequence was recently undertaken as illustrated in Scheme X. A benzyl protecting group was utilized to provide increased yields of the desired Grignard adduct 146. Then the reducing conditions could first cleave the benzylic ether providing a phenolate which would reduce as previously demonstrated. Since introduction of the hydroquinone moiety occurs at an early stage, conversion to the quinone can be accomplished with a variety of reagents which avoid competing A-ring oxidation. Thus, Baeyer-Villiger oxidation[105] of aldehyde 112 gave formate 140 in 68% yield and hydrolysis followed by methylation[106] and formylation[107] led to benzaldehyde 141. Chalcone formation with 4-benzyloxy-2-hydroxyacetophenone followed by acetylation at room temperature gave the highly crystalline acetate 143, which upon oxidative rearrangement and acid-catalyzed cyclization produced isoflavone 144 in good overall yield. The selective boron trichloride cleavage and subsequent transformations to 147 are currently underway.

A second alternative which was examined at an earlier date

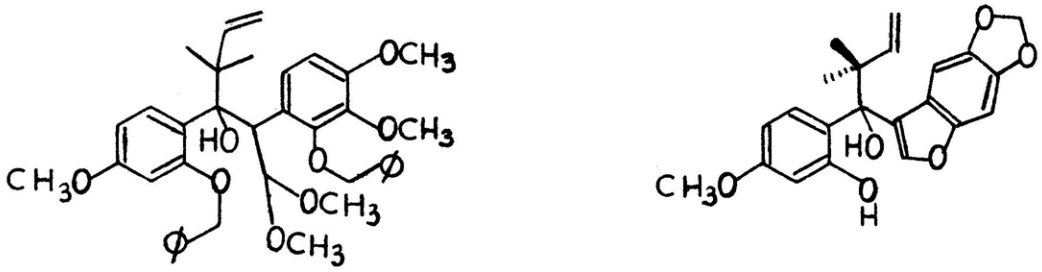
SCHEME X


OCH3
H
O
112
140
141
142 R = H
143 R = Ac
144 R = CH3
145 R = H
146
147
139
HO
OH
OR
Ø

has stimulated renewed interest. The addition of isopentenyl magnesium chloride to acetals 35 and 117 as well as benzofuran 56 occurred in regiospecific fashion without the formation of unwanted side products giving the tertiary alcohols 148, 149, and 150 respectively; however, all attempts at reduction also destroyed the acetal. As yet the reduction of these systems in lithium-liquid ammonia has not been investigated.

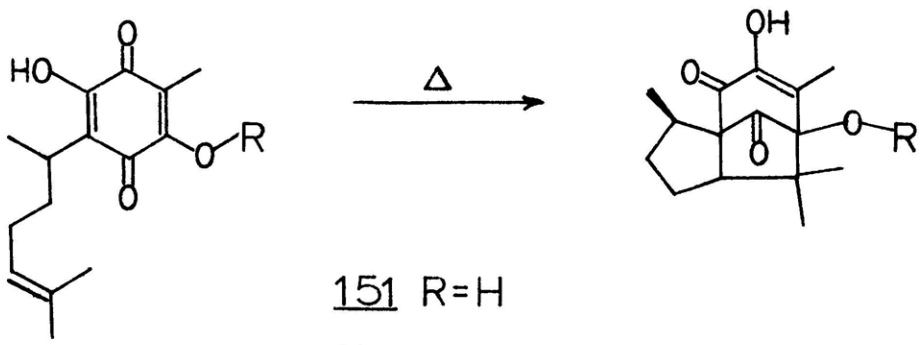


35 148



149 150

With the preparation of quinone 139 nearly in hand, a series of experiments was initiated to demonstrate the proposed cyclization. Although the perezone-pipitzol cycloaddition is a facile process, the same workers have recently reported that perezone derivatives 151-153 either failed to undergo the cyclization or proceeded in very low yield even after prolonged heating at high temperatures.[88]

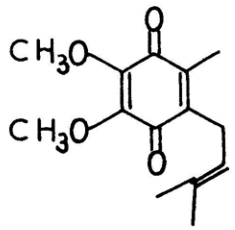


151 R=H

152 R=COCH$_2$iPr

153 R=CO

On the other hand, Pierre Mamont[108] has observed that the acid-catalyzed condensation of quinones such as 154 with styrene results in the formation of 155 in very good yield.



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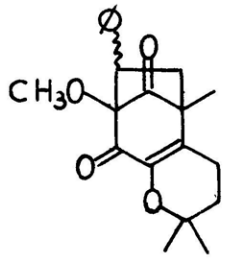
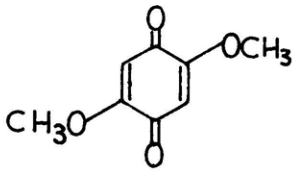
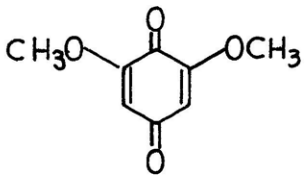


155

Thus, treatment of the readily available quinones 156-158 with 0.1 N perchloric acid or boron trifluoride etherate in the presence of a variety of olefins was attempted; however, no new ketones were detected with 2,4-dinitrophenylhydrazine. The lack of success may be attributed to the intermolecular nature of the reaction, but in most cases insolubility or instability of the starting quinone was observed.



156



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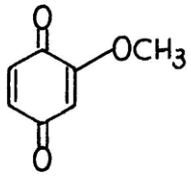
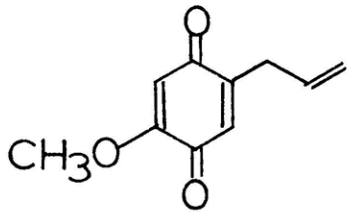


158

Finally our attention was focused on the structure elucidation of the neolignan, guianin 162.[109] Close inspection revealed that guianin could be synthesized via a short and elegant pathway utilizing the analogous intermolecular cyclization process as proposed for miroestrol. The required para-quinone 159 was prepared in excellent yield by DDQ oxidation of 2-allyl-4, 5-methylenedioxyphenol in aqueous acidic methanol; however, condensations with commercially available isosafrole 160 in methylene chloride containing 0.1 N perchloric acid or boron trifluoride etherate gave the same complex mixture of products which were separated after rigorous chromatography. Although several adducts were obtained, proton resonance and infrared spectra clearly confirmed the absence of ketones in an aromatized system in which the allyl moiety has also undergone cyclization. Unfortunately diketone 161 remained out of reach, but efforts in this direction will continue in these laboratories.

More importantly, the discovery of related neolignans,[110,111] whose formation can be rationalized via phenolic coupling mechanisms, has recently been reported. The demonstration of this process in vitro[112,113] has suggested utilization of the technique for cyclization of the miroestrol skeleton without demanding the preparation of a

sensitive quinone. Thus, several alternatives are available as future efforts to complete the total synthesis of miroestrol continue.



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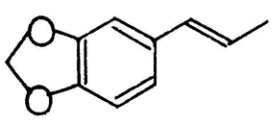

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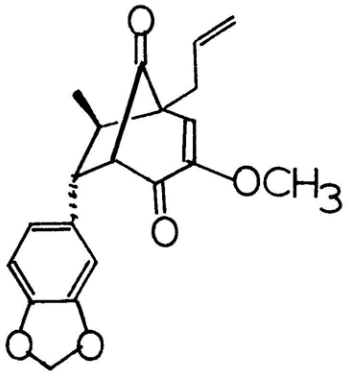

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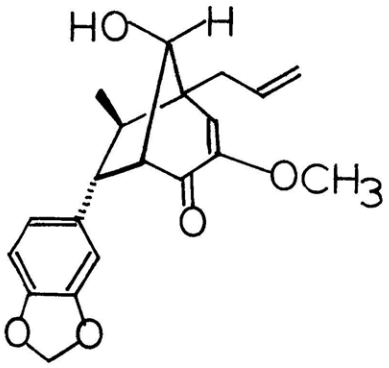

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EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected, as are boiling points. Infrared (ir) spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer, and ultraviolet (uv) spectra were measured on Perkin-Elmer 202 and Cary 14 instruments. Nuclear magnetic resonance spectra (nmr) were obtained with Varian T-60, HA-100, and Hitachi-Perkin-Elmer R-22 instruments, and are given in ppm (δ) downfield from an internal tetramethylsilane standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet respectively, and coupling constants (J) are given in Hertz. Mass spectra were determined on Hitachi RMU6D or RMU6L instruments, and the abbreviation (M^+) indicates the molecular ion. Dry solvents were routinely distilled freshly from lithium aluminum hydride or sodium-benzophenone ketyl, and purified nitrogen was used in all reactions requiring an inert atmosphere. The progress of most reactions was routinely followed by thin-layer or gas chromatography. Analytical thin-layer chromatography (tlc) was carried out on Bakerflex silica gel IB-F sheets with visualization by uv light, iodine vapors, and a variety of spray reagents including phosphomolybdic acid and 2,4-dinitrophenylhydrazine. Gas chromatographic (glpc) analyses were done on a Perkin-Elmer 990 instrument employing six foot glass columns packed with 15% SE-30, 3% OV-17, and 3% OV-225 adsorbents. Analtech silica gel GF plates (20 cm x 20 cm x 2 mm or 1 mm thick) were used for preparative separations, and

Merck PF_{254} or coarse silica gel (0.06-0.2 mm) were used for column chromatography. Microanalysis was performed by Midwest Microlab, LTD., Indianapolis, Indiana.

1-Benzyloxy-3,4-methylenedioxybenzene (27).

A solution of sesamol (8.0 g, 0.058 mol) in dry dimethoxyethane (60 ml) was added dropwise at room temperature to a stirring suspension of 57% sodium hydride (2.95 g) in dimethoxyethane (20 ml). After stirring for 30 min, benzyl chloride (8.8 g, 0.07 mol) was added and the mixture was heated to reflux for 24 hr. Upon cooling, dimethoxyethane was removed under reduced pressure and ether was added. After washing with 5% aqueous sodium hydroxide and water, the organic layer was dried, and ether was removed under reduced pressure. Distillation gave 12.0 g (90.9%) of the desired benzyl ether as a colorless liquid which occasionally solidified upon cooling: bp 133.5-139° (0.05 mm); mp 34.5-35.0° (1.3 ether-hexane); ir ($CHCl_3$) 2875, 1475, 1375, 1130, 1030, 935 cm^{-1}; nmr ($CDCl_3$) δ 4.96 (s, 2), 5.86 (s, 2), 6.20-6.75 (m, 3), 7.37 (s, 5).

2-Benzyloxy-4,5-methylenedioxybenzaldehyde (28).

The Vilsmeier reagent was formed by the dropwise addition of phosphorous oxychloride (8.46 g, 0.055 mol) to a roundbottom flask containing dimethylformamide (30 g) at 0° to 15°. The mixture was stirred for 15-20 min and the benzyl ether 27 (12.0 g, 0.0527 mol) was then added dropwise. The reaction mixture was immediately heated on a steam bath for 4 hr and subsequently poured into ice water

(200 ml). The dark aqueous mixture was made basic by the addition of 10% aqueous sodium hydroxide solution and extracted with ether. The combined ethereal layers were washed with water, dried ($MgSO_4$), decolorized with charcoal, and concentrated under reduced pressure. Crystallization from benzene-hexane afforded 11.75 g (0.0459 mol) (87.1%) of fine, cream-colored needles: mp 94°; ir ($CHCl_3$) 2875, 1665, 1620, 1500, 1475, 1440, 1260, 1155, 1035, 935 cm^{-1}; nmr ($CDCl_3$) δ 5.10 (s, 2), 5.99 (s, 2), 6.59 (s, 1), 7.26 (s, 1), 7.39 (s, 5), 10.34 (s, 1).

2',4-Benzyloxy-2-methoxymethylenoxy-4',5'-methylenedioxychalcone (34).

The acetophenone 30 (4.84 g, 0.020 mol) was O-alkylated using 57% sodium hydride (0.925 g) and chloromethyl methyl ether (1.77 g, 0.022 mol) in dimethoxyethane (20 ml). The reaction was complete after stirring 1 hr at room temperature generating the protected acetophenone 31 which proved to be extremely labile and not further characterized. The crude mixture was added to a round-bottom flask containing the benzaldehyde 28 (4.61 g, 0.018 mol), and the contents were dissolved by the addition of a solution of potassium hydroxide (36 g) in 80% aqueous ethanol (180 ml). The reaction mixture was heated to reflux for 2 hr and allowed to gradually cool to room temperature with continuous stirring. After cooling to 0°, the yellow precipitate was collected by vacuum filtration, redissolved in ethyl acetate, washed with water, dried, and evaporated under reduced pressure. Recrystallization from benzene-hexane gave 6.85 g (74.4%)

of the desired chalcone 34 as bright yellow needles: mp 148-149°; ir ($CHCl_3$) 1650, 1608, 1508, 1485, 1445, 1000, 940 cm^{-1}; nmr ($CDCl_3$) δ 3.42 (s, 3), 5.10 (s, 2), 5.06 (s, 2), 5.15 (s, 2), 5.92 (s, 2), 6.53 (s, 1), 6.75 (m, 2), 7.08 (s, 1), 7.35 (m, 11), 7.60 (d, 1, J = 4 Hz), 8.07 (d, 1, J = 7.5 Hz); uv max (95% EtOH) 385 (ϵ 16,300), 308 (ϵ 11,300), 248 (sh) (ϵ 14,700); mass spectrum (70 eV) m/e 524 (M^+), 91 (base peak).

1-(4-Benzyloxy-2-hydroxyphenyl)-2-(2-benzyloxy-4,5-methylenedioxyphenyl)-3,3-dimethoxypropan-1-one (35).

The dropwise addition of a saturated solution of thallium trinitrate (1.1 g, 2.5 mmol) in methanol to a solution of the chalcone 34 (1.24 g, 2.42 mmol) in methanol-methylene chloride (1:1 by volume) resulted in the rapid oxidative rearrangement of the chalcone and precipitation of thallium (I) nitrate. Water was added, methanol and methylene chloride were removed under reduced pressure, the aqueous mixture was extracted with chloroform, washed with water, dried, and concentrated to a reddish oil. Column chromatography on silica gel (50 g, 70-325 mesh) with benzene afforded 0.732 g (55.7%) of pale yellow crystals after recrystallization from benzene-hexane: mp 144-145°; ir ($CHCl_3$) 3000, 2840, 1635, 1510, 1490, 1435, 1290, 940, 840 cm^{-1}; nmr ($CDCl_3$) δ 3.28 (s, 3), 3.40 (s, 3), 5.00 (s, 4), 5.15 (d, 1, J = 8.5 Hz), 5.43 (d, 1, J = 8.5 Hz), 5.82 (m, 2), 6.30 (dd, 1, J = 2.0 and 8.5 Hz), 6.48 (d, 1, J = 2.0 Hz), 6.55 (s, 1), 6.97 (s, 1), 7.35 (m, 10), 7.85 (d, 1, J = 8.5 Hz), 12.70 (s, 1).

2', 7-Benzyloxy-4', 5'-methylenedioxyisoflavone (36).

Concentrated hydrochloric acid (1.0 ml) was added to a mixture of the acetal 35 (1.4 g, 2.58 mmol) in 1,4-dioxane (40 ml). After 3 hr at reflux hydrolysis was complete, and the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water, dried, and concentrated under reduced pressure. Column chromatography on silica gel (50 g, 70-325 mesh) with chloroform-benzene (80:20 by volume), and subsequent recrystallization from benzene-hexane gave 0.75 g (60.6%) of the desired isoflavone: mp 146-147°; ir ($CHCl_3$) 1625, 1485, 1440, 935, 835 cm^{-1}; nmr ($CDCl_3$) δ 4.97 (s, 2), 5.15 (s, 2), 5.90 (s, 2), 6.62 (s, 1), 6.82 (s, 1), 7.00 (m, 1), 7.28 (s, 5), 7.41 (s, 5), 7.82 (s, 1), 8.2 (d, 1); uv max (95% EtOH) 303 (ϵ 20,000), 280 (inflection), 265 (sh) (ϵ 14,500), 248 (ϵ 24,800), 238 (ϵ 26,200) nm.

3-(4,5-Methylenedioxy-2-hydroxyphenyl)-7-hydroxychroman (39).

Hydrogenation of the isoflavone 36 (1.01 g, 2.11 mmol) with 10% palladium on charcoal (200 mg) in ethanol (75 ml) under one atmosphere at room temperature was continued until hydrogen was no longer absorbed. The catalyst was removed and the filtrate was evaporated under reduced pressure. Crystallization from ether-hexane afforded 0.6050 g (2.11 mmol) of the chroman 39 as a white solid in 100% yield: mp 201-202°; ir (CH_3CN) 3380, 1630, 1590, 950 cm^{-1}; nmr (CD_3COCD_3) δ 2.90 (d, 2), 3.50 (m, 1), 4.10 (m, 2), 5.87 (s, 2), 6.30 (s, 1), 6.45 (d, 1), 6.53 (s, 1), 6.70 (s, 1), 6.92 (d, 1),

8.19 (s, 1) (exchanged with the addition of D_2O).

3,3-Dimethoxy-2-(2-hydroxy-4,5-methylenedioxyphenyl)-1-(2,4-dihydroxyphenyl)propan-1-one (40).

Palladium catalyst (10% on charcoal, 30 mg) was added to the acetal 35 (300 mg) in ethanol (50 ml), and the mixture was stirred under an atmosphere of hydrogen until hydrogen ceased to be absorbed. The catalyst was removed and the filtrate was evaporated under reduced pressure. The residue was then purified by preparative thin-layer chromatography on silica gel (20 x 20 cm x 2 mm) with benzene-ethyl acetate (70:30 by volume) affording a white powder which was recrystallized from benzene-ethyl acetate: mp 201-203°; ir (CH_3CN) 3330, 1635 cm^{-1}; nmr (CD_3COCD_3) δ 2.87 (s, 3), 3.00 (s, 3), 4.80 (d, 1), 5.03 (d, 1), 5.45 (m, 2), 6.06 (m, 3), 6.50 (s, 1), 7.80 (s, 1), 8.39 (br s, 1).

3-(4,5-Methylenedioxy-2-hydroxyphenyl)-7-benzyloxychroman (41).

A solution of the chroman 39 (605 mg, 2.11 mmol) in 5 ml of dry tetrahydrofuran was added dropwise with stirring to a round-bottom flask containing 50% sodium hydride in mineral oil dispersion (102 mg) and 10 ml of fresh dimethylformamide under nitrogen atmosphere. Hydrogen evolution occured immediately, and stirring was continued for 15 min after which a solution of benzyl chloride (268 mg) in 5 ml of dry tetrahydrofuran was added dropwise over 1 hr. Stirring was continued overnight followed by dilution with 10% aqueous hydrochloric acid (75 ml) and extraction with ethyl acetate. The combined

organic extracts were washed with 10% aqueous hydrochloric acid (75 ml), water (2 x 75 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Preparative thin-layer chromatography on silica gel (20 x 20 cm x 2 mm) with benzene-ethyl acetate (80:20 by volume) led to the isolation of the desired chroman 41 (406 mg, 1.08 mmol, 51.2%) as the more polar component. Recrystallization from methanol afforded fine white crystals: mp 160-161°; ir ($CHCl_3$) 3580, 1615, 1495, 1475, 1150, 1025, 935 cm^{-1}; nmr (d_6 acetone) δ 3.20 (m, 2), 3.62 (m, 1), 4.10 (m, 2), 5.13 (s, 2), 5.90 (s, 2), 6.63 (m, 5), 7.40 (d, 5), 8.09 (s, 1).

The faster-running component was isolated and identified as the dibenzyloxychroman 42. Recrystallization from ether-hexane gave 195 mg of 3-(4,5-methylenedioxy-2-benzyloxyphenyl)-7-benzyloxychroman as fine white crystals: mp 108-111°; ir ($CHCl_3$) 1620, 1585, 1500, 1490, 1150, 1035, 930 cm^{-1}; nmr ($CDCl_3$) δ 2.87 (m, 2), 3.30-4.40 (bm, 3), 5.03 (s, 4), 5.87 (s, 2), 6.4-6.9 (bm, 5), 7.38 (s, 10).

2',2-Benzyloxy-4-methoxy-4',5'-methylenedioxychalcone (52).

A roundbottom flask containing the benzaldehyde 28 (10.0 g; 0.039 mol) and the substituted acetophenone 51 (10.0 g; 0.039 mol) was equipped with a magnetic stirrer, and the contents were dissolved by the addition of a solution of potassium hydroxide (105 g) in 80% aqueous methanol (450 ml). The reaction mixture was stirred overnight at room temperature resulting in the formation of an insoluble, sticky brown mass. Methanol was removed under reduced

pressure, water (300 ml) was added, and the mixture was extracted with chloroform (3 x 150 ml). The combined organic extracts were washed with water (2 x 200 ml), dried ($MgSO_4$) and evaporated, giving a dark yellow oil which was dissolved in hot methanol (containing a few drops of water). Upon cooling, the desired chalcone 52 (11.66 g, 0.0236 mol) separated out of solution as yellow needles in 60.6% yield: mp 143-144° from methanol-chloroform); ir ($CHCl_3$) 1635, 1598, 1495, 1475, 1280, 1160, 1120, 1030 cm^{-1}; nmr ($CDCl_3$) δ 3.82 (s, 3), 4.97 (s, 2), 5.03 (s, 2), 5.91 (s, 2), 6.46 (s, 1), 6.55 (m, 2), 6.75 (s, 1), 7.37 (s, 10), 7.40 (d, 1, J = 16 Hz), 7.75 (d, 1, J = 9 Hz), 8.10 (d, 1, J = 16 Hz); uv max (95% EtOH) 387 (ϵ 14,700), 311 (ϵ 10,200), 277 sh, 254 (sh) nm.

1-(4-Methoxy-2-benzyloxyphenyl)-2-(2-benzyloxy-4,5-methylenedioxyphenyl)-3,3-dimethoxypropan-1-one (53).

To a suspension of chalcone 52, (4.95 g, 0.010 mol) in methanol (200 ml), thallium (III) nitrate trihydrate (4.5 g, 0.011 mol) was added in protions. After stirring 1.5 hr, the solution was neutralized with 10% aqueous sodium hydroxide, and methanol was evaporated under reduced pressure. Water was added and the residue was extracted with chloroform. After drying, solvent was evaporated leaving a yellow residue which was purified by column chromatography on silica gel (240 g, Brinkman 2:1 coarse grade to preparative grade) with chloroform. The desired major product 53 (2.78 g) (50%) was completely separated from other components and obtained as a yellow oil: ir ($CHCl_3$) 1670, 1605, 1500, 1480, 1160,

1110, 1025, 920 cm^{-1}; nmr ($CDCl_3$) δ 3.13 (s, 3), 3.37 (s, 3), 3.71 (s, 3), 4.85 (s, 2), 4.92 (s, 2), 5.12 (d, 1, J = 7 Hz), 5.83 (d, 1, J = 7 Hz), 5.83 (s, 2), 6.23-6.40 (m, 2), 6.50 (s, 1), 6.98 (s, 1), 7.27 (s, 10), 7.55 (d, 1, J = 7 Hz).

1-(2-Hydroxy-4-methoxyphenyl)-2-(2-hydroxy-4,5-methylenedioxyphenyl)-3,3-dimethoxypropan-1-one (54).

Catalytic reduction of 53 (2.78 g, 5.0 mmol) in acetone (75 ml) containing 300 mg of 10% palladium on charcoal under one atmosphere of hydrogen gave a single new product after 3 hr stirring at room temperature. Filtration through celite removed catalyst, and solvent was evaporated under reduced pressure leaving a yellow foam which could not be induced to crystallize with a variety of solvents: ir ($CHCl_3$) 3600, 3300 (br), 1625 cm^{-1}; lit.[36] mp 139-140° (MeOH). This material was efficiently carried on to the next step without further purification.

Thermolysis of the Dihydroxy-acetal 54.

A roundbottom flask containing the dihydroxy-acetal 54 (1.20 g, 3.20 mmol) was equipped with a stirring bar, placed under a stream of nitrogen, and plunged into an oil bath at 175°. Bubbling ceased after about 15 min with stirring, and upon cooling the major products were isolated by column chromatography on silica gel (30 g, 0.06-0.2 mm) with chloroform. Fractions containing the less polar component were combined and evaporated, and the residue was crystallized from hot methanol providing 223 mg (0.714 mmol, 22.4%)

of 3-(2-hydroxy-4-methoxybenzoyl)-5,6-methylenedioxybenzofuran (56) as fine pale yellow needles: mp 174-175°, ir ($CHCl_3$) 1635, 1580, 1540, 1515 cm^{-1}; nmr ($CDCl_3$) δ 3.87 (s, 3), 6.03 (s, 2), 6.50 (m, 2), 7.02 (s, 1), 7.37 (s, 1), 7.80 (d, 1, J = 9 Hz), 8.00 (s, 1), 12.57 (s, 1) (exchanged with D_2O); uv max (95% EtOH) 334 (sh), 300, 262 (inflection), 244 nm.

Fractions containing the more polar component were combined and evaporated, and the residue was crystallized from hot methanol affording 231 mg (0.740 mmol, 23.2%) of 2'-hydroxy-7-methoxy-4',5'-methylenedioxyisoflavone as a fine yellow powder: mp 204-205°, (lit.[36] mp 203-204°); nmr ($CDCl_3$) δ 3.97 (s, 3), 5.97 (s, 2), 6.62 (s, 1), 6.65 (s, 1), 7.00 (m, 2), 8.03 (s, 1), 8.25 (d, 1, J = 9 Hz), 8.77 (s, 1) (exchanged with D_2O).

Intermediate fractions were found to contain largely unreacted starting material 54 and isoflavone 55 and were evaporated (0.71 g) and recycled in the reaction as described above.

2,2-Dimethyl-6,7-methylenedioxy-2H-1-benzopyran (60).

A roundbottom flask equipped with a reflux condenser and magnetic stirrer was charged with 6-hydroxypiperonal (2.0 g, 0.01205 mol), potassium carbonate (1.67 g), and potassium iodide (0.33 g) and placed under nitrogen. Freshly distilled 3-chloro-3-methylbutyne[40] (2.5 g, 0.0241 mol) was dissolved in dry dimethoxyethane (25 ml), and the solution was added to the reaction flask under a stream of nitrogen. The mixture was heated to reflux with stirring for 96 hr. Upon cooling the mixture was diluted with ether, washed with water,

and dried over sodium sulfate. Solvent was removed under reduced pressure and the yellow residue was distilled by Kugelrohr oven (85-90°) at 0.05 mm affording 1.9 g (77.3%) of pale yellow liquid 60 which solidified upon cooling: ir ($CHCl_3$) 1505, 1480, 1270, 1160, 1115, 1040, 940, 900, 860 cm^{-1}; nmr ($CDCl_3$) δ 1.39 (s, 6), 5.43 (d, 1, J = 5.0 Hz), 5.82 (s, 2), 6.15 (d, 1, J = 5.0 Hz), 6.35 (s, 1), 6.46 (s, 1).

2-(2'-Benzyloxy-4',5'-methylenedioxybenzylidene)-1,3-dithiane (63).

A roundbottom flask equipped with magnetic stirring bar and reflux condenser, was charged with trimethylene trithiocarbonate[67] (6.42 g, 0.0427 mol), trimethylphosphite (60 g), and the benzaldehyde 28 (9.9 g, 0.0387 mol), and the yellow solution was heated to 55° under nitrogen atmosphere for 3 hr with continuous stirring. Excess trimethylphosphite was removed under reduced pressure at 40°, and the yellow residue was stirred overnight with a 4% aqueous sodium hydroxide solution (100 ml). The aqueous mixture was extracted with ether, and the combined ether extracts were washed with water and saturated sodium chloride solution, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallized from ether-hexane yielding 10.6 g (76.5%) of shiny yellow plates: mp 129-131°; ir ($CHCl_3$) 1610, 1495, 1470, 1425, 1155, 1030, 925 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (m, 2), 2.29 (m, 4), 5.01 (s, 2), 5.88 (s, 2), 6.52 (s, 1), 7.04 (s, 1), 7.21 (s, 1), 7.35 (s, 5); uv max (95% EtOH) 338 (14,700), 292 (11,900).

An alternate procedure involved the addition of a solution of

2-lithio-2-trimethylsilyl-1, 3-dithiane[68] (0.0325 mol) (prepared from 2-trimethylsilyl-1, 3-dithiane (6.25 g, 0.0325 mol) in dry tetrahydrofuran (60 ml) and 15 ml of a 2.2 M n-butyllithium solution in n-hexane at -30°) to a solution of the benzaldehyde 28 (8.0 g, 0.0325 mol) in tetrahydrofuran (80 ml) at -50° under nitrogen atmosphere. The temperature was allowed to rise to +20° within 1 hr, and after 14 hr at room temperature the solvent was removed under reduced pressure. Ether was added and the ethereal solution was washed with water, dried ($MgSO_4$); and evaporated under reduced pressure. Crystallization from ether-hexane afforded 9.35 g (81.8%) of the desired thioacetal.

2-Benzyloxy-4, 5-methylenedioxyphenylacetic acid (65).

A mixture of the ketene thioacetal 63 (8.0 g, 0.0223 mol) and p-toluenesulfonic acid monohydrate (2.0 g) in 200 ml of 80% aqueous methanol was heated to reflux for 18 hr. Upon cooling, methanol was removed under reduced pressure, water was added and the mixture was extracted with chloroform. The combined chloroform layers were washed with water, dried, and solvent was removed at reduced pressure leaving a yellow oil which appeared to be a single compound by thin-layer chromatography. Infrared data indicated the presence of the thioester 64: ir ($CHCl_3$) 1725, 1680, 1495, 1480, 1245, 1155, 1035, 935 cm^{-1}.

The crude thioester was dissolved in 200 ml of 80% aqueous methanol containing sodium hydroxide (4.0 g), and the mixture was stirred at reflux for 18 hr. After cooling, methanol was removed at

reduced pressure, ice water was added, the solution was acidified to pH 5 by the dropwise addition of concentrated hydrochloric acid, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried, and concentrated at reduced pressure leaving a yellow solid which upon trituration with small amounts of ether gave 4.82 g (75.5%) of a white powder. Crystallization from benzene-ethyl acetate afforded a high recovery of fine, white needles: mp 132-133.5°; ir (CH_3CN) 3600, 3525, 3230, 1750, 1635, 1170, 930 cm^{-1}; nmr (d_6 acetone) δ 3.72 (s, 2), 5.19 (s, 2), 6.04 (s, 2), 6.86 (s, 1), 6.92 (s, 1), 7.55 (m, 5).

5,6-Methylenedioxycoumaran-2-one (66).

Debenzylation by hydrogenation of the benzyl ether 65 (5.26 g; 0.0184 mol) under one atmosphere of hydrogen at room temperature using 10% palladium on carbon (0.50 g) in ethanol (100 ml) proceeded rapidly. When the uptake of hydrogen ceased, the catalyst was removed by filtration through a celite cake, and ethanol was evaporated at reduced pressure giving 3.5 g (97.0%) of a white, amorphous powder (mp 180-185°). Heating the solid in vacuo resulted in sublimation.

Dehydration of this hydroxyacid (0.97 g, 0.005 mol) to the desired lactone 66 occurred upon heating in refluxing tetralin (15 ml) under a stream of nitrogen for 15 min. Hexane was added upon cooling to room temperature, and further cooling to 0° gave 0.83 g (94.0%) of tan crystals. Filtration through a column of silica gel (25 g) with chloroform afforded the desired product as fine, white needles from ethyl acetate-hexane: mp 157-158°; ir ($CHCl_3$) 1810,

1480, 1465, 1305, 1150, 1105, 1040, 935, 880, 855 cm^{-1}; nmr ($CDCl_3$) δ 3.65 (s, 2), 5.98 (s, 2), 6.65 (s, 1), 6.73 (s, 1).

4-Benzyloxy-2-(α-methoxy)methoxybenzaldehyde (67).

A dry 100-ml roundbottom flask was charged with 280 mg of 57% sodium hydride in oil dispersion, and equipped with stirring bar and addition funnel and placed under nitrogen atmosphere. Pentane was introduced to free the sodium hydride of oil impurities and subsequently decanted via a syringe. Then 4-benzyloxy-2-hydroxybenzaldehyde (1.52 g, 6.66 mmol) in dry tetrahydrofuran (50 ml) was added dropwise with stirring as hydrogen evolution occurred immediately. After stirring for 10 min at room temperature, a solution of chloromethyl methyl ether (536 mg, 6.66 mmol) in 15 ml dry tetrahydrofuran was added dropwise to the dark mixture, and stirring was continued for 30 min. Since the product suffered hydrolysis under standard workup procedures, the inorganic salt was removed by filtration, and evaporation of solvent under reduced pressure gave the crude benzaldehyde 67 as a dark yellow oil: ir ($CHCl_3$) 1680, 1605, 1260, 1155, 1115, 1020 cm^{-1}; nmr ($CDCl_3$) δ 3.50 (s, 3), 5.12 (s, 2), 5.27 (s, 2), 6.75 (m, 2), 7.40 (s, 5), 7.83 (d, 1, J = 8 Hz), 10.36 (s, 1).

Preparation of Dimer 69.

A roundbottom flask, equipped with magnetic stirring bar, was charged with 1.18 g (6.66 mmol) of lactone 66 and one equivalent of the freshly prepared benzaldehyde 67 in 50 ml of dry tetrahydrofuran.

Sodium hydride (281 mg; 57% dispersion in mineral oil) was added with stirring at room temperature and hydrogen evolution occurred spontaneously. After 2 hr the reaction mixture was diluted with 5% aqueous hydrochloric acid and extracted with chloroform. An insoluble brown powder (0.6738 g) was collected by vacuum filtration. The chloroform extract was washed with water, dried, and concentrated in vacuo, resulting in further precipitation of light brown powder (0.1205 g). A portion of this material was purified by preparative thin-layer chromatography on silica gel (1 plate, 20 x 20 cm x 2 mm) with chloroform elution leading to the isolation of dimer 69 as a fine, cream-colored powder: mp = 188-190°; ir (KBr) 2940 (broad), 1715, 1630, 1440, 1300, 1110, 1025, 985, 920 cm^{-1}; nmr (d_6DMSO) δ 4.15 (s, 2), 5.90 (s, 2), 6.03 (s, 2), 6.53 (s, 2), 6.93 (s, 1), 7.26 (s, 1), 9.17 (br m, 2), (exchanged with D_2O).

7-Benzyloxy-3-(2'-benzyloxy-4',5'-methylenedioxy)coumarin (79).

A roundbottom flask containing 4-benzyloxy-2-hydroxybenzaldehyde (1.14 g, 5.0 mmol) and the sodium salt of phenylacetic acid 65 (generated from 1.43 g (5.0 mmol) of the free acid by precipitation from ether solution with one equivalent of sodium hydride) was equipped with stirring bar and condenser, and placed under nitrogen atmosphere. Freshly distilled acetic anhydride (4.0 ml) was added and the mixture was heated to reflux for 6 hr. Upon cooling the solidified mass was dissolved in chloroform and extracted several times with saturated sodium bicarbonate. After washing with aqueous sodium chloride, the organic layer was dried ($MgSO_4$),

and concentrated to a yellow oil. Thin-layer chromatography revealed as many as four products, but only the desired material displayed an intense spot under uv light, and purification by column chromatography on silica gel (70 g, 0.06-0.20 mm) with benzene-chloroform (6:4 by volume) led to the isolation of the coumarin 79 (435 mg) as fine white needles from ether-hexane: ir ($CHCl_3$) 1720, 1610, 1480, 1250, 1150 cm^{-1}; nmr ($CDCl_3$) δ 4.99 (s, 2), 5.10 (s, 2), 5.92 (s, 2), 6.60 (s, 1), 6.82 (m, 3), 7.25 (s, 5), 7.37 (s, 5), 7.60 (s, 1); uv max (95% EtOH) 330, 300, 269 (inflection), 245 nm.

7-Benzyloxy-3-(2',4',5'-trimethoxyphenyl)coumarin (80).

A roundbottom flask containing 4-benzyloxy-2-hydroxybenzaldehyde (2.28 g; 10.0 mmol), 2,4,5-trimethoxyphenylacetic acid (2.26 g; 10.0 mmol) and potassium acetate (1.0 g) was equipped with stirring bar and condenser and placed under nitrogen atmosphere. Freshly distilled acetic anhydride (6 ml) was added and the mixture was heated to reflux. After 5 hr the cooled reaction mixture was washed with 25 ml cold water and the aqueous layer was decanted from a thick residue which collected at the bottom of the flask. The precipitate was washed several times with water, dissolved in chloroform and extracted with saturated sodium bicarbonate solution followed by saturated aqueous sodium chloride solution. The organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure. Purification of the yellow residue by column chromatography on silica gel (100 g, 0.06-0.20 mm) with hexane-ethyl acetate (70:30 by volume) led to the isolation of coumarin 80 (2.45 g) as pale

yellow needles from ether-hexane: mp 158-161°; ir ($CHCl_3$) 1715, 1605, 1500, 1260, 1102, 1015 cm^{-1}; nmr ($CDCl_3$) δ 3.80 (s, 3), 3.85 (s, 3), 3.93 (s, 3), 5.13 (s, 2), 6.60 (s, 1), 6.93 (m, 3), 7.40 (m, 6), 7.65 (s, 1); uv max (95% EtOH) 330 (ϵ 17,100), 304 (inflection), 294 (ϵ 12,700), 278 (inflection), 245 (sh) nm.

Preparation of Isopentenyl Magnesium Chloride.

The required isopentenyl magnesium chloride was prepared by a high dilution procedure to minimize allylic coupling. A 300-ml roundbottom flask containing 100 ml of anhydrous ether, 5 g of magnesium turnings and magnetic stirring bar, was equipped with a 30 cm glass column (filled to the halfway point with reagent grade magnesium turnings) upon which was mounted a condenser which in turn was topped by an addition funnel. The entire system was placed under nitrogen atmosphere and 3-chloro-3-methyl-1-butene[79] (15 g) in 150 ml of anhydrous ether was slowly added dropwise over a period of 5 hrs while the ether was refluxing at the rate of 2 to 3 drops per second. In this way isopentenyl magnesium chloride was obtained in 90 to 95% yield, as determined by reactivity with excess benzaldehyde followed by gas chromatographic analysis. Ethereal solutions of active Grignard reagent were stored under nitrogen at room temperature for five days without significant loss of titer.

Grignard Addition to Coumarin 80.

A 100-ml roundbottom flask was charged with 400 mg (0.956

mmol) of coumarin 80 and 40 ml of dry tetrahydrofuran under nitrogen atmosphere. Upon cooling to -78° , an ether solution (20 ml, 4.0 mmol) of 0.2 M isopentenyl magnesium chloride was added dropwise via syringe with stirring. After 1.5 hr the reaction was quenched by pouring the cold solution into 100 ml of saturated aqueous ammonium chloride. The organic material was extracted into ether, washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to a yellow oil under reduced pressure. Thin-layer chromatography revealed two major products and three minor spots including a small amount of starting material. The major products were purified by preparative thin-layer chromatography on silica gel (4 plates, 20 x 20 cm x 2 mm) after two elutions with 20% ethyl acetate in hexane. The less polar component was isolated as a yellow oil (209 mg) which noticeably lacked carbonyl absorption in the infrared, but a complex proton resonance spectrum prevented the assignment of a suitable structure. The second component (232 mg) could not be crystallized but solidified upon storage of the neat oil giving a 50% yield of the hemiacetal 81: ir ($CHCl_3$) 3420, 1720 (weak), 1612, 1565, 1500, 1455, 1150, 1015, 900, 820 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (s, 6), 3.85 (m, 9), 4.90 (m, 4), 6.02 (s, 1), 6.00 (m, 1), 6.50 (m, 3), 6.78 (s, 1), 6.98 (d, 1, J = 8 Hz), 7.36 (s, 5).

Preparation of the Hemiacetal 83.

A solution of coumarin 82 (1.008 g; 4.0 mmol) in 25 ml of dry tetrahydrofuran was placed under nitrogen and cooled to -78° . An ethereal solution containing 1.2 equivalents of Grignard reagent was

added dropwise via syringe with continuous stirring. After 1 hr the yellow reaction mixture was quenched with saturated aqueous ammonium chloride (50 ml) and extracted with ether. The organic layer was washed twice with water, dried ($NaSO_4$), and evaporated under reduced pressure, to a yellow residue which crystallized upon the addition of hexane. Filtration and recrystallization from hot hexane afforded 900 mg (70.0%) of white crystals: mp 125-126°; ir ($CHCl_3$) 3570, 1708, 1602, 1490, 1140, 1095 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (s, 3), 1.06 (s, 3), 3.55 (s, 1) (exchanged with D_2O), 3.80 (s, 3), 4.75-5.10 (br m, 2), 6.05 (m, 1), 6.45 (m, 3), 7.00 (d, 1, J = 9 Hz), 7.40 (br m, 2).

3-(3-Methyl-1-buten-3-yl)-1-cyclohexen-3-ol (84).

A 50-ml roundbottom flask containing a solution of cyclohexenone (500 mg; 5.20 mmol) in 10 ml of dry tetrahydrofuran was placed under nitrogen atmosphere and cooled to -78°. A standardized ether solution containing 1.1 equivalents of isopentenyl magnesium chloride was slowly added dropwise via syringe with continuous stirring. After 30 min the reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure affording 814 mg (95%) of a pale yellow oil: ir ($CHCl_3$) 3615, 2950, 1060, 900 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (s, 6), 1.80 (m, 7), 4.82-5.20 (m, 2), 5.86 (m, 2), 6.10 (m, 1). Gas chromatographic analysis indicated only the presence of a single product with a variety of columns and temperatures.

3-Benzyloxyphenyl-2-benzyloxy-4,5-methylenedioxyphenylacetate (87).

A roundbottom flask equipped with stirring bar and addition funnel was charged with 4.0 g of dicyclohexylcarbodiimide, 1.43 g (5.0 mmol) of 2-benzyloxy-4,5-methylenedioxyphenylacetic acid, and 15 ml of tetrahydrofuran. After the mixture had stirred at room temperature for 1 hr, a solution of 3-benzyloxyphenol[114] (1.0 g; 5.0 mmol) in 15 ml of tetrahydrofuran was added dropwise and the mixture was stirred overnight. Upon the removal of solvent at reduced pressure, the residue was washed several times with 5% aqueous hydrochloric acid and extracted with ether. This treatment resulted in the precipitation of dicyclohexylurea which was removed by vacuum filtration. The organic layer was then washed with 5% aqueous sodium hydroxide solution followed by water, and finally dried over anhydrous magnesium sulfate. Solvent was evaporated under reduced pressure, and the residue was dissolved in ether, filtered to remove a small amount of insoluble urea 88, and crystallized upon addition of hexane and evaporation. Recrystallization from hot ether-hexane gave 1.85 g (79.2%) of the desired ester 87 as fine white crystals: mp 100-105°; ir ($CHCl_3$) 1760, 1605, 1590, 1500, 1485, 1130, 1030 cm^{-1}; nmr ($CDCl_3$) δ 3.80 (s, 2), 4.93 (s, 2), 5.01 (s, 2), 5.90 (s, 2), 6.60 (m, 5), 7.38 (m, 11).

2,2-Dimethyl-3-butenal (89).

After stirring a mixture of isopentenyl bromide (3.0 g; 20.0 mmol) and dimethylaminoacetonitrile (2.0 g; 20.0 mmol) in 10 ml of

dry tetrahydrofuran under nitrogen atmosphere overnight, the mixture was cooled to -35°, and a solution of 2.24 g (20.0 mmol) of freshly sublimed potassium tert-butoxide in tetrahydrofuran was added dropwise. Stirring was continued for 3 hrs while the temperature was maintained between -30 and -40° after which time the reaction mixture was allowed to warm to 0° followed by the addition of water and ether extraction. The ether layer was washed with water, dried over sodium sulfate, and solvent was evaporated leaving the dimethylaminonitrile 95 as a colorless liquid which was used for the subsequent hydrolysis without further purification.

A roundbottom flask equipped with condenser and stirring bar was charged with crude nitrile 95, copper (II) sulfate pentahydrate (15.4 mmol), and 95% aqueous methanol (30 ml). After 5 mins at reflux a brown precipitate had formed which upon cooling and dilution with 30 ml of ether was removed by gravity filtration. Solvent was evaporated under reduced pressure (>160 mm) at room temperature and the resulting liquid was dried over sodium sulfate in a small amount of ether. Isolation by Kugelrohr distillation at atmospheric pressure afforded 1.76 g (86%) of the desired aldehyde 89 as a colorless liquid: ir ($CHCl_3$) 2810, 2715, 1730, 1642, 995, 926 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (s, 6), 5.20 (m, 2), 5.80 (d of d, 1), 9.29 (s, 1).

Aldehyde 89 was also prepared by acid-catalyzed ring cleavage of 3-phenoxy-2,2-dimethylcyclopropylcarbinol (93) as documented by published procedures:[82,83] bp 97-103°.

Methyl-2-benzyloxy-4,5-methylenedioxyphenylacetate (96).

A 50-ml roundbottom flask, equipped with a stirring bar and condenser fitted with a calcium chloride drying tube, was charged with a solution of 2-benzyloxy-4,5-methylenedioxyphenylacetic acid (1.14 g; 4.0 mmol) in 30 ml of methylene chloride. Absolute methanol (500 mg) and 5 drops of concentrated sulfuric acid were added, and the mixture was heated to reflux overnight. Upon cooling the reaction mixture was washed with water, then with saturated sodium bicarbonate solution and again with water, and finally dried, and evaporated to a pale yellow oil which crystallized from hezane containing a small amount of ether. Recrystallization from hot hexane-ether gave 945 mg (78.7%) of the desired methyl ester 96 as cream-colored crystals: mp 65-66°; ir ($CHCl_3$) 1735, 1505, 1485, 1155 cm^{-1}; nmr ($CDCl_3$) δ 3.59 (s, 2), 3.63 (s, 3), 4.99 (s, 2), 5.90 (s, 2), 6.55 (s, 1), 6.70 (s, 1), 7.37 (s, 5).

2-(2-Benzyloxy-4,5-methylenedioxyphenyl)-4,4-dimethyl-3-hydroxy-5-hexenoic acid methyl ester (97).

A cold solution (-40°) of lithium diisopropylamide prepared at -10° from 1.1 mmol of n-butyllithium and diisopropylamine (120 mg; 1.20 mmol) in 3.0 ml of anhydrous ether containing 2,2'-bipyridyl as an indicator, was treated with 300 mg (1.0 mmol) of methyl ester 96 in 4.0 ml of dry ether. The resulting pale orange solution was stirred at -40° for 15 min and then treated with 109 mg (1.1 mmol) of aldehyde 87. The resulting light yellow solution was stirred at -50 to -60° for 5 min and then partitioned between ether and cold 5%

aqueous hydrochloric acid. The organic layer was washed with water, dried over sodium sulfate and evaporated to 382 mg of yellow oil: ir ($CHCl_3$) 3500, 1715, 1475, 1150, 1025 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (m, 6), 3.63 (s, 4), 4.00 (m, 1), 4.20-5.07 (m, 2), 4.98 (s, 2), 5.80 (m, 1), 5.83 (s, 2), 6.53 (s, 1), 7.00 (s, 1), 7.27 (s, 5).

4-(4-Benzyloxy-2-hydroxyphenyl)-3,3-dimethyl-4-hydroxy-1-butene (100).

The substituted benzaldehyde 29 (2.28 g; 10.0 mmol) was added in small portions as a solid to 2.1 equivalents of a standardized ether solution of isopentenyl magnesium chloride at room temperature with continuous stirring. After stirring for 15 min the reaction mixture was partitioned with cold saturated ammonium chloride and ether. The ether layer was washed with saturated ammonium chloride, then water, and finally dried over sodium sulfate. Solvent evaporation gave a yellow oil which was purified by column chromatography on silica gel (75 g, 0.06-0.20 mm) with chloroform-benzene (70:30 by volume). Like fractions were combined and evaporated under reduced pressure giving 2.1 g (70.5%) of a pale yellow liquid which became a waxy solid upon storage at room temperature: ir ($CHCl_3$) 3540, 3320, 2970, 1600, 1485, 1145, 1000 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (s, 6), 3.30 (d, 1) (exchanged with D_2O), 4.43 (d, 1) (singlet upon addition of D_2O), 4.94 (s, 2), 4.95 to 5.20 (m, 2), 5.80 (m, 1), 6.48 (m, 2), 6.77 (d, 2), 7.36 (s, 5), 8.52 (s, 1) (exchanged with D_2O).

A methylene chloride solution (30 ml) of hydroxyphenol 100 (600 mg, 2.0 mmol) containing absolute methanol (400 mg) and 1 drop of concentrated hydrochloric acid was stirred over 5 g of anhydrous sodium sulfate for 3 hr at room temperature. The solution was then decanted and evaporated at reduced pressure giving the methyl ether 103 as a pale yellow oil: nmr ($CDCl_3$) δ 1.02 (s, 6), 3.26 (s, 3), 4.42 (s, 1), 4.88 (s, 2), 5.05 (m, 2), 5.85 (m, 1), 6.45 (m, 3), 6.75 (d, 1, J = 8 Hz), 7.30 (s, 5).

Preparation of the Phenylacetic Acid Ester 101.

A 50-ml roundbottom flask containing the phenol 100 (600 mg; 2.0 mmol), 2,4,5-trimethoxyphenylacetic acid (550 mg; 2.0 mmol), 20 ml of methylene chloride and a trace of para-toluenesulfonic acid was stirred at room temperature overnight. The reaction mixture was then partitioned with saturated aqueous sodium bicarbonate and methylene chloride, and the organic layer was washed with water, dried, and evaporated under reduced pressure. The phenolic ester 101 was isolated as a pale yellow oil after purification by preparative thick-layer chromatography on silica gel (2 plates, 20 x 20 cm x 2 mm) with chloroform elution: ir ($CHCl_3$) 3550, 1720, 1605, 1500, 1450, 1150, 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (s, 6), 3.55 (s, 2), 3.63 (s, 3), 3.73 (s, 3), 3.81 (s, 3), 4.97 (m, 5), 5.80 (m, 1), 6.17 (s, 1), 6.50 (m, 3), 6.67 (s, 1), 7.00 (d, 1), 7.33 (s, 5).

4-(4-Benzyloxy-2-acetoxyphenyl)-3, 3-dimethyl-4-hydroxy-1-butene (104).

A 25-ml roundbottom flask equipped with magnetic stirring bar was charged with 48 mg (1.0 mmol) of 50% sodium hydride in mineral oil, and a solution of the phenol 100 (300 mg; 1.0 mmol) in 10 ml of dry tetrahydrofuran was added at room temperature with stirring. After 5 min one equivalent of freshly distilled acetic anhydride (102 mg) dissolved in 2.0 ml of dry tetrahydrofuran was added slowly via syringe. Stirring was continued for 4 hr. The reaction mixture was then quenched with water, extracted with ether, washed with saturated sodium bicarbonate solution followed by water, dried (Na_2SO_4), and finally evaporated under reduced pressure, to a yellow oil: ir ($CHCl_3$) 3540, 2960, 1770, 1610, 1500, 1450, 1155, 1010, 900 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (d, 6), 2.33 (s, 3), 5.00 (m, 4), 6.00 (m, 1), 6.55 (m, 3), 7.40 (s, 5).

Preparation of Phenolic Ester 105.

A solution of the benzaldehyde 29 (0.57 g; 2.50 mmol), 2-benzyloxy-4, 5-methylenedioxyphenylacetic acid (0.715 g; 2.50 mmol), and dicyclohexylcarbodiimide (1.03 g; 5.0 mmol) in 25 ml of dry tetrahydrofuran was stirred at room temperature overnight. Solvent was then removed under reduced pressure, and the residue was partitioned with 5% aqueous hydrochloric acid and chloroform. The organic layer was filtered to remove dicyclohexylurea, then washed with saturated sodium bicarbonate solution followed by water, dried ($MgSO_4$), and evaporated. The residue was dissolved in ether (15 ml)

and hexane was added dropwise (15 ml) precipitating 448 mg of pale yellow solid: ir ($CHCl_3$) 1770, 1690, 1610, 1100 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 2), 4.97 (s, 2), 5.03 (s, 2), 6.90 (s, 2), 6.50 to 7.00 (m, 4), 7.37 (s, 10), 7.78 (d, 1, J = 8 Hz).

4-(4-Benzyloxy-2-hydroxyphenyl)-3, 3-dimethyl-4-oxo-1-butene (106).

Chromic anhydride (6.7 g) was dissolved in 6 ml of concentrated sulfuric acid and carefully diluted with distilled water (50 ml). The dropwise addition of 1.5 ml of this reagent by pipette to a stirred solution of the hydroxyphenol 100 (600 mg, 2.0 mmol) in reagent-grade acetone (10 ml) at room temperature resulted in the instantaneous production of green chromous salts. After 15 min the mixture was diluted with water and extracted with ether. The ether layer was washed with aqueous sodium bisulfite, then twice with water, dried over sodium sulfate and evaporated to a yellow oil which contained two products. Separation by preparative thin-layer chromatography (silica gel, 2 plates, 20 x 20 cm x 2 mm) with chloroform elution resulted in isolation of the faster moving band giving 302 mg of the desired ketone 106 as a pale yellow oil: ir ($CHCl_3$) 1620, 1500, 1375, 1310, 1235, 1110, 900 cm^{-1}; nmr ($CDCl_3$) δ 1.43 (s, 6), 5.03 (s, 2), 5.20 (m, 2), 6.00-6.67 (m, 3), 7.36 (s, 5), 7.94 (d, 1, J = 8 Hz).

2-Benzyloxy-3,4-dimethoxybenzaldehyde (114).

A roundbottom flask equipped with reflux condenser, magnetic stirrer, and drying tube was charged with the ortho-hydroxybenzaldehyde 113[115] (21.0 g, 0.1158 mol), anhydrous potassium carbonate

(16.6 g, 0.12 mol), and benzyl chloride (15.2 g, 0.12 mole) dissolved in 70 ml of fresh dimethylformamide. The mixture was heated to reflux for 1.5 hr with continuous stirring giving a dark brown solution which upon cooling was carefully diluted with 10% aqueous hydrochloric acid (550 ml) and extracted twice with ether. The combined ether layers were washed with 10% aqueous hydrochloric acid (5 x 200 ml), then once with water and twice with 5% aqueous sodium hydroxide. The organic layer was again washed with water, dried ($MgSO_4$), and evaporated to a dark brown oil which was purified by a shortpath distillation yielding 18.15 g (57.5%) as a yellow oil: bp 162-178° at 0.05 mm, (lit.[116] bp 199-201° at 3.0 mm; mp 42-44°); nmr ($CDCl_3$) δ 3.92 (s, 3), 5.22 (s, 2), 6.75 (d, 1, J = 8.5 Hz), 7.36 (s, 5), 7.57 (d, 1, J = 8.5 Hz), 9.94 (s, 1).

2,2'-Dibenzyloxy-3 ,4',4-trimethoxychalcone (116).

A roundbottom flask containing the benzaldehyde 114 (3.70 g, 13.6 mole) and the substituted acetophenone 51 (3.45 g, 13.4 mole) was equipped with a magnetic stirrer and reflux condenser, and the contents were dissolved by the addition of a solution of potassium hydroxide (10 g) in 80% aqueous ethanol (100 ml). The reaction mixture was heated to reflux for 2 hr and allowed to gradually cool to room temperature with continuous stirring. Water was added and ethanol was removed under reduced pressure. The mixture was extracted twice with ether and the combined organic layers were washed with water (2 x 200 ml), dried ($MgSO_4$), and evaporated to a thick yellow oil. Column chromatography on silica gel (150 g) with

chloroform led to the isolation of 6.51 g of the desired product as a yellow oil: ir ($CHCl_3$) 1655, 1600, 1490, 1240, 1080 cm^{-1}; nmr ($CDCl_3$) δ 3.84 (s, 6), 3.77 (s, 3), 5.00 (s, 4), 6.55 (m, 3), 7.00 (d, 1, J = 8 Hz), 7.35 (m, 11), 7.60 (d, 1, J = 8 Hz), 8.00 (d, 1, J = 16 Hz).

1-(4-Methoxy-2-benzyloxyphenyl)-2-(2-benzyloxy-3,4-dimethoxyphenyl)-3,3-dimethoxypropan-1-one (117).

To a solution of chalcone 116 (2.50 g, 4.90 mmol) in methylene chloride- methanol (100 ml, 1:1 by volume), thallium(III)nitrate trihydrate (2.17 g, 4.95 mmol) was added in portions as a solid. After stirring 1.5 hr the solution was neutralized with saturated aqueous sodium bicarbonate and concentrated under reduced pressure. Saturated sodium chloride solution was added and the mixture was extracted with ether. The ethereal layer was washed with saturated sodium chloride solution, then twice with water, dried ($MgSO_4$), and evaporated under reduced pressure to a yellow oil which was purified by preparative thin-layer chromatography (silica gel, 20 x 20 cm x 2 mm, 6 plates) with chloroform elution affording 2.15 g (77.8%) of pure 117 as a pale yellow foam: ir ($CHCl_3$) 1665, 1600, 1490, 1245, 1085 cm^{-1}; nmr ($CDCl_3$) δ 3.16 (s, 3), 3.40 (s, 3), 3.62 (s, 3), 3.76 (s, 3), 3.79 (s, 3), 4.95 (m, 4), 5.15 (d, 1, J = 8 Hz), 5.70 (d, 1, J = 8 Hz), 6.33 (m, 2), 6.63 (d, 1, J = 9 Hz), 7.30 (m, 11), 7.64 (d, 1, J = 9 Hz).

1-(2-Hydroxy-4-methoxyphenyl)-2-(2-hydroxy-3,4-dimethoxyphenyl)-3,3-dimethoxypropan-1-one (118).

Catalytic reduction of 117 (2.2 g, 3.77 mmol) in acetone (100 ml) containing 200 mg of 10% palladium on charcoal under one atmosphere of hydrogen gave a single new product after 4 hr with stirring at room temperature. Filtration through celite removed the catalyst and solvent was evaporated under reduced pressure leaving 1.30 g (92.7%) of a pale yellow foam: ir ($CHCl_3$) 3600, 3300 (br), 1625 cm^{-1}; nmr ($CDCl_3$) δ 3.26 (s, 3), 3.41 (s, 3), 3.76 (s, 6), 3.84 (s, 3), 5.21 (s, 2), 6.25-6.65 (m, 4) (1 proton exchanged with D_2O), 7.10 (d, 1, J = 8 Hz), 8.00 (d, 1, J = 0 Hz), 12.80 (s, 1) (exchanged with D_2O).

Thermolysis of the Dihydroxy-acetal 118.

A roundbottom flask containing the dihydroxy-acetal 118 (4.20 g, 11.3 mmol) was equipped with a stirring bar, placed under a stream of nitrogen and plunged into an oil bath at 175°. Bubbling ceased after 15 min, but heating and stirring were continued an additional 10 min. Upon cooling the resulting glassy solid was digested in 200 ml of hot acetone and after cooling, filtered to remove 1.01 g of a white precipitate identified as the desired isoflavone 119. The mother liquors were evaporated and the residue was submitted to column chromatography on silica gel (150 g, 0.06-0.20 mm) with chloroform elution. The least polar component was crystallized from hot ether-hexane providing 75 mg of 3-(2-hydroxy-4-methoxybenzoyl)-6,7-dimethoxybenzofuran (120) as

bright yellow needles: mp 133-4°; ir ($CHCl_3$) 1620, 1495, 1250, 1090, 855 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 3), 3.97 (s, 3), 4.20 (s, 3), 6.45 (m, 2), 7.03 (d, 1, J = 9 Hz), 7.60 (d, 1, J = 9 Hz), 7.77 (d, 1, J = 9 Hz), 8.01 (s, 1), 12.76 (s, 1) (exchanged with D_2O); uv max (95% EtOH) 336 (ε 10,300), 287 (ε 14,900), 247 (ε 16,500), upon basification, 295 (ε 13,400), 265 (sh) (ε 17,100), 246 (sh) (ε 25,000), 235 (sh) (ε 27,900); mass spectrum (70 eV) m/e 328 (M^+), 151 (base peak).

The second fraction was crystallized from hot ether-hexane giving 186 mg of the deoxybenzoin 121: mp 149-150°; ir ($CHCl_3$) 3530, 1618, 1500, 1460, 1335, 1220, 1120, 1080 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s, 3), 3.92 (s, 3), 4.18 (s, 2), 6.20 (s, 2), 6.20 (s, 1) (exchanged with D_2O), 6.43 (m, 3), 6.86 (d, 1, J = 8 Hz), 7.86 (d, 1, J = 9 Hz), 12.63 (s, 1) (exchanged with D_2O).

Elution of the third component resulted in the crystallization of 1.50 g of the starting acetal as dense white plates: mp 139-140° ($CHCl_3$-hexane). Successive fractions containing mixtures of acetal 118 and 119 were combined and evaporated, and this material (0.9 g) was recycled in the reaction as described above. The most polar component was crystallized from chloroform-hexane as a fine white, insoluble powder affording an additional 265 mg of 119; thus giving a total yield of 1.28 g (30%) of the desired isoflavone: mp 210-212°; ir ($CHCl_3$) 1615, 1435, 1280, 1250, 1085 cm^{-1}; nmr (d_6 acetone) δ 3.94 (s, 3), 4.00 (s, 3), 4.12 (s, 3), 6.74 (d, 1, J = 9 Hz), 7.20 (m, 3), 8.27 (d, 1, J = 9 Hz), 8.41 (s, 1); uv max (95% EtOH) 304 (sh), 262 (ε 21,900), 247 (26,400), 238 (sh) nm; mass spectrum (70 eV) m/e 328 (M^+), 151 (base peak).

2 -Hydroxy-2, 3, 4, 4 -tetramethoxychalcone (122).

A one liter roundbottom flask containing the benzaldehyde 112 (33 g, 0.169 mol) and acetophenone 50 (28 g, 0.169 mol) was equipped with a magnetic stirrer and reflux condenser, and the contents were dissolved by the addition of a solution of potassium hydroxide (90 g) in 85% aqueous methanol (800 ml). After stirring at room temperature overnight (15 hr), the reddish solution was heated to reflux for 4 hr. Upon cooling the reaction mixture was poured into a 4 l Erlenmeyer flask containing 600 g of ice, and concentrated hydrochloric acid was added in 20 ml portions with swirling and cooling until the mixture was acidic, producing large amounts of bright yellow precipitate. After cooling to 5°, the precipitate was collected by vacuum filtration and rinsed with cold water followed by 50% aqueous methanol. The bright yellow needles were dried in a vacuum oven at 55° for 48 hr affording 44.4 g (76.5%) of the desired chalcone: mp 126-128°; ir ($CHCl_3$) 1630, 1565, 1355, 1120, 1085 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s, 3), 3.94 (s, 6), 3.98 (s, 3), 6.43 (m, 2), 6.75 (d, 1, J = 9 Hz), 7.30-7.90 (m, 3), 8.10 (d, 1, J = 15 Hz), 13.6 (s, 1) (exchanged with D_2O); uv max (95% EtOH) 377 (ϵ 33,300), 305 (sh), 255 (ϵ 10,700), upon basification, 247 (ϵ 16,400), 344 (ϵ 20,000) nm.

2'-Acetoxy-2, 3, 4, 4'-tetramethoxychalcone (123).

Chalcone 122 (30.0 g, 0.873 mol) was suspended in excess acetic anhydride (40 ml) and pyridine (20 ml) and heated on a steam bath for 2 hr. The resulting yellow solution was quenched with cold water (250 ml), diluted with 100 ml of ether, and vigorously stirred

for 30 min in an ice bath. The crystalline product was collected by vacuum filtration, rinsed with water, and recrystallized from hot methanol affording 27.3 g (80.6%) of the acetate 123 as shiny yellow crystals after drying in a vacuum oven overnight at 55°: mp 147-148°, ir ($CHCl_3$) 1760, 1605, 1580, 1485, 1455, 1080, 1000 cm^{-1}; nmr ($CDCl_3$) δ 2.30 (s, 3), 3.90 (m, 12), 6.60-7.95 (m, 7); uv max (95% EtOH) 342 (ϵ 20,500), 310 (sh), 285 (sh), 270 (inflection), 248 (sh) (ϵ 12,100) nm.

1-(2-Hydroxy-4-methoxyphenyl)-2-(2,3,4-trimethoxyphenyl)-3,3-dimethoxypropan-1-one (124).

To a solution of chalcone 123 (11.1 g, 28.7 mmol) in methylene chloride-methanol (1:1 by volume) (200 ml) containing 20 ml of trimethylorthoformate, thallium (III) nitrate trihydrate (15.0 g, 33.8 mmol) was added in portions as a solid. Precipitation of thallium (I) nitrate began almost immediately, and after 2.5 hr the solution was neutralized with solid sodium bicarbonate (15 g), filtered, and concentrated under reduced pressure. The yellow oil was stirred with 10 g potassium carbonate in 80% aqueous methanol at room temperature for 1 hr. The brown mixture was neutralized with 5% aqueous hydrochloric acid and extracted with methylene chloride. The organic layer was washed once with dilute hydrochloric acid, then twice with aqueous sodium chloride, dried and evaporated to an orange oil. Column chromatography on silica gel (200 g, 0.06-0.2 mm) with chloroform elution gave 10.9 g (26.8 mmol, 93.2%) of the desired acetal 124 as a thick yellow oil: ir ($CHCl_3$) 2825, 1625, 1485,

1460, 1365, 1080 cm^{-1}; nmr ($CDCl_3$) δ 3.24 (s, 3), 3.45 (s, 3), 3.74 (s, 3), 3.78 (s, 3), 3.86 (s, 3), 4.02 (s, 3), 5.05 (d, 1, J = 8 Hz), 5.33 (d, 1, J = 8 Hz), 6.40 (m, 2), 6.60 (d, 1, J = 9 Hz), 7.15 (d, 1, J = 9 Hz), 7.95 (d, 1, J = 9 Hz), 12.8 (s, 1) (exchanged with D_2O).

Also a small amount (750 mg) of isoflavone 125 was obtained upon further elution and identified as the more polar component of the hydrolysis mixture.

2', 3', 4', 7-Tetramethoxyisoflavone (125).

Cyclization of acetal 124 (10.9 g, 26.8 mmol) occurred upon heating in dry 1,4-dioxane (100 ml) at reflux with 50 mg of para-toluenesulfonic acid in a 250-ml roundbottom flask equipped with stirring bar and condenser under an inert atmosphere for 15 hr. Upon cooling, solvent was removed under reduced pressure at 50°, and the residue was crystallized from hot methanol giving 8.2 g (24.0 mmol, 89.4%) of isoflavone 125 as fine white crystals after drying in vacuo overnight: mp 168-169°; ir ($CHCl_3$) 1640, 1625, 1610, 1495, 1465, 1440, 1260, 1110, 1090, 1025, 1005, 830 cm^{-1}; nmr ($CDCl_3$) δ 3.80 (s, 3), 3.86 (s, 9), 6.57-7.10 (m, 4), 7.84 (s, 1), 8.15 (d, 1, J = 8 Hz); uv max (95% EtOH) 304 (sh), 296 (ε 11,900), 264 (sh), 248 (ε 29,400), 240 (ε 29,000) nm.

2'-Hydroxy-3', 4', 7-trimethoxyisoflavone (119).

The tetramethoxyisoflavone 125 (3.40 g, 10 mmol) was added to 100 ml of methylene chloride in a 250-ml roundbottom flask equipped with stirring bar, and cooled to -78° under nitrogen atmosphere.

Boron trichloride (1.0 ml, 11.6 mmol) was collected in a calibrated addition funnel containing methylene chloride (6 ml) by means of a dry ice condenser, and then added dropwise to the reaction mixture. The cooling bath was removed and stirring was continued for 15 min as the mixture became bright yellow with precipitation of a solid. The flask was again cooled to -78° and the reaction was quenched by the addition of absolute methanol (25 ml). After warming to room temperature, solvent was removed under reduced pressure, and the solid residue was heated in absolute methanol. Upon cooling the white crystals were collected and dried in vacuo at 50° overnight yeilding 3.02 g (9.22 mmol, 92.2%) of isoflavone 119: mp 210-212°; ir ($CHCl_3$) 1615, 1435, 1280, 1250, 1085 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 3), 3.93 (s, 3), 3.96 (s, 3), 6.55 (d, 1, J = 9 Hz), 7.00 (m, 3), 8.00 (s, 1), 8.18 (s, 1) (exchanged with D_2O), 8.20 (d, 1, J = 9 Hz); uv max (95% EtOH) 303 (sh), 293 (sh), 262 (ε 21,900), 247 (ε 26,400), 238 (sh) nm; mass spectrum (70 eV) m/e 328 (M^+), 151 (base peak).

2',7-Dihydroxy-3',4'-dimethoxyisoflavone (126).

Tetramethoxyisoflavone 125 (6.8 g, 20.0 mmol) was added to 200 ml of methylene chloride in a 300-ml roundbottom flask equipped with stirring bar and cooled to -78° under nitrogen. Boron trichloride (4.0 ml, 46.5 mmol) was collected in a calibrated addition funnel containing methylene chloride (4.0 ml) by means of a dry ice condenser, and this solution was then added dropwise to the reaction mixture. The cooling bath was removed and stirring was continued for 2.5 hr with gradual warming to room temperature as a

solid precipitated from the red solution. After cooling to -78°, excess reagent was destroyed by the addition of absolute methanol (40 ml). Then solvent was removed under reduced pressure, and the solid residue was triturated with hot methanol. Filtration gave 5.5 g (17.5 mmol, 87.5%) of the desired isoflavone 126 as a white powder after drying in vacuo overnight: mp 220-222°; ir (KBr) 3500 (br), 1615, 1080 cm^{-1}; nmr (d_6DMSO) 3.82 (s, 3), 3.93 (s, 3), 6.50 (d, 1, J = 9 Hz), 6.67 (d, 1, J = 9 Hz), 7.10 (m, 2), 8.00 (d, 1, J = 8 Hz), 8.10 (s, 1), 8.44 (br s, 2).

Treatment with excess acetic anhydride in pyridine at room temperature followed by aqueous workup and methylene chloride extraction led to the isolation of 2',7-diacetoxy-3',3'-dimethoxy-isoflavone as pale yellow prisms from methylene chloride-hexane: mp 168-170°; nmr ($CDCl_3$) δ 2.15 (s, 3), 2.31 (s, 3), 3.86 (s, 3), 3.92 (s, 3), 6.80-7.36 (m, 4), 7.80 (s, 1), 8.20 (d, 1, J = 9 Hz).

Grignard Addition to 2'-Hydroxy-3',4',7-trimethoxyisoflavone (119).

The isoflavone 119 (5.0 g, 15.2 mmol) was weighted into a 500-ml roundbottom flask with 150 ml of anhydrous ether, and a 0.46 M ether solution (80 ml, 36 mmol) of isopentenyl magnesium chloride was introduced as rapidly as possible via a 50 ml syringe at room temperature with stirring under nitrogen. After 30 min the clear solution was quenched by careful addition to saturated aqueous ammonium chloride. The organic phase was washed once with aqueous ammonium chloride, then twice with water, dried ($MgSO_4$), and evaporated under reduced pressure to a yellow oil which was carefully

protected against light. The less polar component, which was visualized as a bright yellow spot after thin-layer chromatography and treatment with 2,4-dinitrophenylhydrazine spray, was separated by column chromatography on silica gel (200 g, 0.06-0.2 mm) with 30% ethyl acetate in hexane elution. Upon evaporation, 3.55 g (9.0 mmol, 60.0%) of the unstable alcohol 129 was obtained as a pale yellow foam: ir ($CHCl_3$) 3500, 3250, 1620, 1575, 1500, 1460, 1280, 1160, 1090 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (s, 6), 3.77 (s, 3), 3.83 (s, 6), 4.4 (s, 1) (exchanged with D_2O), 4.9 (m, 2), 6.00 (q, 1), 6.45 (d, 1, J = 9 Hz), 6.70 (m, 2), 6.66 (s, 1), 6.95 (d, 1, J = 9 Hz), 7.40 (s, 1) (exchanged with D_2O), 7.52 (d, 1, J = 8 Hz).

When isoflavone 119 (2.75 g, 8.38 mmol) was reacted with Grignard reagent (24.0 mmol) as previously described, the mixture was dehydrated directly by quenching with solid ammonium chloride (30 g) followed by the addition of a slurry of silica gel (50 g) in anhydrous ether with continuous stirring at room temperature for 18 hr. The flask was wrapped in aluminum foil to shield the mixture from light. Vacuum filtration gave a pale yellow ether solution which was concentrated to a yellow oil under reduced pressure and submitted to column chromatography on silica gel (200 g, 0.06-0.20 mm) with 30% hexane in chloroform elution. Fractions of the least polar component were combined and evaporated giving 1.60 g (4.20 mmol, 50.2%) of the desired cyclic ether 130 as a nearly colorless oil: ir ($CHCl_3$) 1615, 1490, 1435, 1105, 1085, 1020, 955 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (s, 6), 3.78 (s, 3), 3.83 (s, 3), 4.03 (s, 3), 4.80 (m, 2), 5.80 (m, 1), 6.40 (d, 1, J = 8 Hz), 6.65 (m, 2), 6.85 (d, 1, J = 8 Hz),

7.16 (s, 1), 7.45 (d, 1, J = 8 Hz).

Intermediate fractions contained mixtures of minor by-products which were not investigated. However, the most polar component was eluted in high purity as a yellow oil which crystallized giving 0.74 g (1.86 mmol, 22.2%) of the 1,4-adduct 131 upon slow evaporation of an ether-hexane solution at room temperature: mp 120-122°; ir ($CHCl_3$) 3520, 1670, 1600, 1495, 1455, 1435, 1250, 1150, 1102, 1085 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (s, 6), 3.75 (s, 3), 3.81 (s, 3), 3.87 (s, 3), 3.95 (m, 1), 4.35 (m, 1), 4.80 (m, 2), 5.80 (m, 1), 6.23 (d, 1, J = 9 Hz), 6.43 (s, 1) (exchanged with D_2O), 6.60 (m, 3), 7.85 (d, 1, J = 9 Hz).

Grignard Addition to 2',7-Dihydroxy-3',4'-dimethoxyisoflavone (126).

The isoflavone 126 (5.27 g, 16.8 mmol) was weighed into a 500-ml roundbottom flask, and a 0.5 M ether solution (200 ml, 0.10 mol) of isopentenyl magnesium chloride was added as rapidly as possible via a 50 ml syringe at room temperature with stirring under nitrogen atmosphere. After 45 min the clear colorless solution was quenched by careful addition to 300 ml of cold 5% aqueous hydrochloric acid. The ethereal layer was washed once with dilute hydrochloric acid, twice with water, dried ($MgSO_4$), and evaporated to a dark yellow oil. The workup procedure was completed as quickly as possible since the product mixture became increasingly dark with exposure to light. Crystallization occurred from dry ether (40 ml) giving 2.90 g of white crystals which were identified as 1,4-adduct 134. The mother liquors were evaporated, constantly shielded from

light, and submitted to column chromatography on silica gel (170 g, 0.06-0.20 mm) with 30% ethyl acetate in hexane. The least polar component was evaporated and crystallized from methylene chloride-hexane giving 1.12 g (3.06 mmol, 18.2%) of the desired product 135 as a dense tan solid. Recrystallization from methylene chloride-hexane afforded pure 135 as white clusters: mp 151-153°; ir ($CHCl_3$) 3550, 1620, 1580, 1495, 1365, 1280, 1160, 1080, 965 cm^{-1}; nmr ($CDCl_3$) δ 0.91 (s, 6), 3.76 (s, 3), 3.80 (s, 3), 4.80 (m, 2), 5.85 (m, 2), (1 proton exchanged with D_2O), 6.37 (d, 1, J = 9 Hz), 6.70 (m, 3), 7.20 (s, 1), 7.47 (d, 1, J = 8 Hz); uv max (95% EtOH) 318 (ϵ 7,900), 309 (ϵ 7,980), 297 (inflection), 280 (ϵ 13,500), 257 (inflection) nm; mass spectrum (70 eV) m/e 366.15 (M^+), 297.08 (base peak).

Anal. Calcd. for $C_{22}H_{22}O_5$: C, 72.12%; H, 6.05%; Found: C, 71.98; H, 6.06.

Successive fractions led to the isolation of 0.55 g of a dark brown oil which contained at least two minor reaction products; however, this material was not further investigated. Isolation of the most polar component gave an additional 0.46 g of crystalline ketone 134 from ether-hexane along with 1.20 g of 134 as a yellow oil. The total yield of ketone 134 was 3.36 g (52.0%) as fine white needles: mp 172-175°; ir ($CHCl_3$) 3540, 3300, 1665, 1602, 1500, 1435, 1250, 1155, 1105, 1090 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (s, 6), 3.75 (s, 3), 3.90 (s, 3), 4.37 (m, 2), 4.90 (m, 2), 5.90 (m, 3) (two protons exchanged with D_2O), 6.23 (d, 1, J = 9 Hz), 6.60 (m, 3), 7.90 (d, 1, J = 9 Hz); uv max (95% EtOH) 312 (ϵ 7,950), 274 (16,600), 249 (inflection), 230

(ε 21,400), upon basification, 498 (ε 5,600), 455 (ε 6,450), 308 (ε 9,450), 273 (ε 13,800), 230 (ε 19,600) nm.

Reduction of Benzofuranobenzopyran 135.

A 3-necked, 100-ml, roundbottom flask was equipped with a dry ice condenser, gas inlet adapter, rubber stopper and magnetic stirring bar, and flame-dried under a stream of nitrogen. After cooling to room temperature the phenol 135 (293 mg, 0.80 mmol) was introduced, and upon further cooling to -78°, ammonia (70 ml) was distilled into the flask. The dry ice bath was then removed allowing the liquid ammonia to reflux, and several pieces of freshly-cut lithium wire (containing 1% sodium) (42 mg, 6×10^{-3} gram-atoms) were added under a stream of nitrogen into the clear colorless solution which soon became deep violet. After stirring for 4 min, the reaction was quenched by the careful addition of ammonium chloride (3 g) in small portions with rapid disappearance of the violet color. The flask was sheltered from direct light as the liquid ammonia was allowed to evaporate, but the mixture still became yellow and finally turned dark. Small amounts of anhydrous ether were occasionally added, and after warming to room temperature the ether solution was washed twice with saturated sodium chloride solution, then twice with water, dried ($MgSO_4$), and evaporated at reduced pressure to a yellow oil containing two products. Separation was achieved by careful preparative thin-layer chromatography on silica gel (2 plates, 20 x 20 cm x 2 mm) following two elutions using 25% ethyl acetate in hexane. Thus, the desired phenol 136 (101 mg, 0.275 mmol)

(34.4%) was isolated as a pale yellow oil which quickly decomposed on storage: ir ($CHCl_3$) 3530, 3390, 1625, 1500, 1465, 1360, 1160, 1090 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (s, 6), 3.76 and 3.85 (d, 7), 4.77 (m, 2), 5.58 (s, 2) (exchanged with D_2O), 5.75 (m, 1), 6.33-7.18 (m, 6).

The more polar component was detected as a deep red spot upon thin-layer chromatography after treatment with 2,4-dinitrophenylhydrazine spray and heating. This bright yellow oil (113 mg, 0.305 mmol) (38.1%) was assigned structure 137 and subsequently obtained as pale yellow needles from methylene chloride-hexane: mp 137-139°; ir ($CHCl_3$) 3540, 3440, 1625, 1575, 1502, 1485, 1465, 1440, 1315, 1285, 1150, 1090, 900 cm^{-1}; nmr ($CDCl_3$) δ 0.94 (s, 3), 1.07 (s, 3), 1.67 (s, 3), 3.83 (s, 4), 3.90 (s, 3), 4.60 (m, 2), 5.85 (m, 3) (two protons exchanged with D_2O), 6.57 (m, 4), 7.03 (d, 1, J = 8 Hz); uv max (95% EtOH) 278, 260 (inflection), 227 nm; mass spectrum (70 eV) m/e 370 (M^+), 301 (base peak).

Preparation of the para-quinone 139.

To a solution of potassium carbonate (1.0 g) in 70 ml of distilled water was added 500 mg of potassium nitrosodisulfonate. A solution of methylene chloride (30 ml) and phenol 136 (168 mg, 0.457 mmol) was introduced into the violet mixture, and the separatory funnel was vigorously shaken for 5 min as the organic phase immediately became dark blue. The methylene chloride layer was washed twice with water, dried ($MgSO_4$), and evaporated at room temperature under reduced pressure. The residue was dissolved in methylene

chloride (15 ml) and precipitated by the addition of hexane yielding 66 mg (0.173 mmol) (37.9%) of quinone 139 as a dark blue solid which quickly decomposed upon standing in solution at room temperature: mp 162-164° (decomp); ir ($CHCl_3$) 1690, 1670, 1620, 1500, 1165, 1060 cm^{-1}; nmr ($CDCl_3$) δ 0.90(d, 6), 3.59 (s, 1), 3.80 (s, 6), 4.80 (m, 2), 5.80 (m, 2) (one proton exchanged with D_2O), 6.50-7.20 (m, 5); uv max ($CHCl_3$) 620, 550, 282, 266 nm; mass spectrum (70 eV) m/e 382 (M^+).

2'-Acetoxy-4'-benzyloxy-2,3,4,5-tetramethoxychalcone (143).

A 250-ml roundbottom flask containing 2,3,4,5-tetramethoxybenzaldehyde (141) (5.7 g, 25 mmol) and 4-benzyloxy-2-hydroxyacetophenone (30) (6.1 g, 25 mmol) was equipped with a magnetic stirrer and reflux condenser. A methanolic solution (175 ml) of potassium hydroxide (25 g) was added with stirring, and the mixture was heated to reflux for 4 hr. After cooling the reddish solution was poured onto ice (400 g), acidified by the careful addition of concentrated hydrochloric acid, and extracted with methylene chloride. The organic phase was washed once with 5% aqueous hydrochloric acid, twice with water, dried ($MgSO_4$), and evaporated to a yellow oil which was identified as chalcone 142 by its spectral characteristics: ir ($CHCl_3$) 1625, 1570, 1480, 1460, 1275, 1120, 990 cm^{-1}; nmr ($CDCl_3$) δ 3.93 (, 12), 5.08 (s, 2), 6.56 (m, 2), 6.92 (s, 1), 7.40 (s, 5), 7.55 (d, 1, J = 15 Hz), 7.85 (d, 1, J = 9 Hz), 8.13 (d, 1, J = 15 Hz), 13.56 (s, 1) (exchanged with D_2O).

Acetylation of crude 142 proceeded directly by heating the

neat oil with acetic anhydride (10 ml) and pyridine (5ml) on a steam bath for 2 hr. The resulting yellow solution was quenched with 150 ml of ice water, diluted with 50 ml of ether and vigorously stirred for 30 min in an ice bath. The yellow crystalline product was collected by vacuum filtration, rinsed with water, and recrystallized from hot methanol affording 7.65 g (15.6 mmol, 62.1%) of the desired acetate 143: mp 130°; ir ($CHCl_3$) 1765, 1650, 1600, 1475, 1455, 1400, 1280, 1115, 990 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (s, 3), 3.90 (m, 12), 5.13 (s, 2), 6.88 (s, 1), 6.90 (m, 2), 7.22 (d, 1, J = 16 Hz), 7.43 (s, 5), 7.80 (d, 1, J = 9 Hz), 7.90 (d, 1, J = 16 Hz).

7-Benzyloxy-2',3',4',5'-tetramethoxyisoflavone (144).

Thallium (III) nitrate trihydrate (10.1 g, 23.0 mmol) was added as a solid at room temperature to a solution of chalcone 143 (10.7 g, 21.7 mmol) in 200 ml of methylene chloride-methanol (1:1 by volume) containing 20 ml of trimethylorthoformate. After 3 hr the solution was neutralized with solid sodium bicarbonate (15 g), filtered to remove inorganic salts, and concentrated under reduced pressure. Hydrolysis of the acetate was achieved by stirring with 10 g of potassium carbonate in 80% aqueous methanol at room temperature overnight. The dark mixture was neutralized with 5% aqueous hydrochloric acid and extracted with methylene chloride. The organic phase was washed once with dilute hydrochloric acid, then twice with aqueous sodium chloride, dried ($MgSO_4$), and evaporated to a dark yellow oil. Column chromatography on silica gel (200 g, 0.06-0.2 mm) with chloroform elution gave the expected

rearranged acetal as a yellow oil: nmr ($CDCl_3$) δ 3.30 (s, 3), 3.46 (s, 3), 3.80 (s, 3), 3.85 (s, 3), 3.92 (s, 3), 3.98 (s, 3), 5.00 (s, 2), 5.13 (d, 1, J = 8 Hz), 5.44 (d, 1, J = 8 Hz), 6.50 (m, 2), 6.83 (s, 1), 7.30 (s, 5), 8.04 (d, 1, J = 9 Hz), 12.8 (s, 1) (exchanged in D_2O).

Cyclization was completed upon heating in dry 1,4-dioxane (100 ml) at reflux overnight with 50 mg of para-toluenesulfonic acid in a 250-ml roundbottom flask equipped with stirring bar and condenser under nitrogen atmosphere. Upon cooling, solvent was removed at reduced pressure, and the remaining oil was crystallized from methanol with cooling to 0° yielding 7.1 g (15.85 mmol, 73.1%) of the complex isoflavone 144 as fine white crystals: mp 122-123°; ir ($CHCl_3$) 1620 (broad), 1485, 1455, 1435, 1400, 1300, 1260, 1110, 1055, 1000 cm^{-1}; nmr ($CDCl_3$) δ 3.85 (s, 3), 3.73 (s, 3), 3.96 (s, 3), 3.98 (s, 3), 5.16 (s, 2), 6.70 (s, 1), 7.10 (m, 2), 7.42 (s, 5), 7.97 (s, 1), 8.23 (d, 1, J = 9 Hz).

Formation of the Hydroxyacetal 148.

A 50-ml roundbottom flask was equipped with magnetic stirring bar, flame-dried and placed under nitrogen atmosphere. Upon cooling, the flask was charged with 537 mg (0.99 mmol) of ketone 35 followed by 20 ml of dry tetrahydrofuran. The resulting solution was cooled to -10°, and an ether solution (7 ml, 3.0 mmol) of freshly prepared 0.44 M isopentenyl magnesium chloride was added via syringe. After stirring for 20 min, the reaction was quenched with saturated aqueous ammonium chloride, and extracted with ether. The organic

layer was washed once with saturated ammonium chloride, then once with water, dried over sodium sulfate, and evaporated to a pale yellow oil, which was purified by preparative thin-layer chromatography on silica gel (2 plates, 20 x 20 cm x 2 mm) following two elutions with 20% ethyl acetate in hexane. Solvent evaporation gave 496 mg (82%) of the desired product 148 as a white foam: ir ($CHCl_3$) 3280, 1625, 1585, 1500, 1480, 1162, 1105, 1075, 1030, 925 cm^{-1}; nmr ($CDCl_3$) δ 1.00 (s, 3), 1.17 (s, 3), 3.36 (s, 3), 3.43 (s, 3), 4.57 (m, 1), 4.70-5.20 (m, 6), 5.75 (s, 2), 5.80-6.70 (m, 6), 6.83 (d, 1), 7.40 (d, 10), 10.2 (s, 1) (exchanged with D_2O).

Grignard Addition to the Benzylic Ketone 149.

An ether solution of excess isopentenyl Grignard, prepared as previously described, was combined with 400 mg (0.72 mmol) of ketone 117 in 10 ml of anhydrous ether, and the resulting solution was stirred at room temperature for 10 min. The reaction mixture was partitioned with 5% aqueous hydrochloric acid and the organic phase was separated, washed once with dilute acid, then twice with distilled water, dried ($MgSO_4$), and evaporated to a dark yellow oil. The desired product was separated from an oily nonpolar impurity by preparative thin-layer chromatography on silica gel (2 plates, 20 x 20 cm x 2 mm) with 50% ethyl acetate in hexane, and crystallized from ether-hexane yielding 313 mg (70%) of white needles identified as a diastereomeric mixture of 149: ir ($CHCl_3$) 3475, 1605, 1490, 1450, 1275, 1090 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (d, 6), 3.30 (s, 3), 3.46 (s, 3), 3.57 (s, 3), 3.73 (s, 6), 4.50 (m, 1), 4.80-5.46 (m, 7),

6.00-6.70 (m, 5), 6.90 (d, 1), 7.42 (s, 10). Further recrystallizations from ether-hexane led to substantial enrichment; however, complete separation was not achieved.

Preparation of the Isopentenylbenzofuran 150.

The required isopentenyl magnesium chloride was prepared by a high dilution procedure as previously described. The benzofuran 150 (147 mg, 0.471 mmol) was dissolved in 30 ml of dry dimethoxyethane and 75 ml (1.57 mmol) of a 0.02 M isopentenyl magnesium chloride solution in ether was added all at once at room temperature with continuous stirring. The clear yellow solution was stirred an additional 20 min, then decomposed with dilute hydrochloric acid and extracted with ether. The ether layer was washed with 5% aqueous hydrochloric acid, then twice with water, dried ($MgSO_4$), and evaporated to a yellow oil. Isolation by preparative thin-layer chromatography on silica gel (1 plate, 20 x 20 cm x 2 mm) with two successive chloroform elutions gave 42 mg of an unidentified less polar component and 114 mg of 150 as a pale yellow oil which was crystallized from hexane-ether affording 86.4 mg (48.2%) of fine white crystals: mp 138-139°; ir ($CHCl_3$) 3580, 3325, 1615, 1575, 1500, 1455, 1300, 1150, 1030, 935 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (s, 6), 3.43 (s, 1), (exchanged with D_2O), 3.73 (s, 3), 5.25 (m, 2), 5.80 (s, 2), 6.00-6.63 (m, 5), 6.80 (s, 1), 7.80 (s, 1), 9.53 (s, 1) (exchanged with D_2O).

2-Allyl-5-methoxy-*para*-benzoquinone (159).

A 50-ml roundbottom flask, equipped with magnetic stirring bar, was charged with a methanolic solution (20 ml) of 2-allyl-4,5-methylenedioxyphenol[23] (264 mg, 1.48 mmol) followed by the addition of 340 mg (1.50 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Three drops of concentrated sulfuric acid were introduced into the yellow solution and stirring was continued for 35 min. Solvent was evaporated under reduced pressure, and the solid residue was purified by column chromatography on silica gel (25 g, 0.06-0.20 mm) with 50% ethyl acetate in hexane. Fractions containing the least polar component were combined and evaporated, and the residue was dissolved in ether (40 ml). A small amount of brown precipitate which did not dissolve was removed by filtration, and the yellow filtrate was concentrated to 10-15 ml which upon cooling afforded 209 mg (79.2%) of the desired quinone 159 as large gold plates: mp 109-111°; ir (Nujol) 1670, 1650, 1605, 975 cm^{-1}; nmr ($CDCl_3$) δ 3.23 (d, 2), 3.78 (s, 3), 5.20 (m, 2), 5.80 (m, 1), 5.96 (s, 1), 6.50 (br s, 1).

BIBLIOGRAPHY

1. A. J. Kerr, J. Siam. Nat. Hist. (Supp.), 8, 336 (1932).
2. S. Vatna, Thai Sci. Bull., 4, 3 (1939).
3. W. Schoeller, M. Dohrn and H. Hohlweg, Naturwiss., 28, 532 (1940).
4. H. E. H. Jones and G. S. Pope, J. Endocrinology, 22, 303 (1961); ibid., 20, 299 (1960).
5. J. C. Cain, Nature, 188, 774 (1960).
6. A. Butenandt, Naturwiss., 28, 533 (1940).
7. D. G. Bounds and G. S. Pope, J. Chem. Soc., 3696 (1960).
8. D. C. Hodgkin, J. S. Rollett and N. E. Taylor, J. Chem. Soc., 3685 (1960).
9. M. Weigele, Diss. Abst., 25, 6245 (1965).
10. V. H. Van Rheenan, Diss. Abst., 27B, 1103 (1966).
11. R. D. Minard, Diss. Abst., 30B, 133 (1969).
12. K. E. Matsumoto, Ph.D. Thesis, M.I.T. (1971).
13. C. R. Dorn and M. Miyano, J. Org. Chem., 37, 257, 268 (1972).
14. D. K. Minster, Ph.D. Thesis, M.I.T. (1975).
15. J. Hlubucek, E. Ritchie and W. C. Taylor, Tetrahedron Lett., 1369 (1969).
16. R. D. H. Murray, M. M. Ballantyne and K. P. Mathai, Tetrahedron Lett., 243 (1970).
17. V. Chandrashekar, M. Krishnamurti and T. R. Seshadri, Tetrahedron, 23, 2505 (1967).

18. D. G. Clarke, L. Crombie and D. A. Whiting, J. Chem. Soc. (I), 1007 (1974).

19. M. Mülly, J. Zsindely and H. Schmid, Helv. Chim. Acta, 58, 610 (1975).

20. A. Jefferson and F. Scheinmann, Quart. Rev., 22, 391 (1968).

21. A. J. Quillinan and F. Scheinmann, Chem. Commun., 966 (1971).

22. W. D. Ollis, M. V. J. Ramsay, I. O. Sutherland and S. Mongkolsuk, Tetrahedron, 21, 1453 (1965).

23. B. H. Alexander, S. I. Gertler, R. T. Brown, T. A. Oda and M. Beroza, J. Org. Chem., 24, 1504 (1959).

24. S. Teitel, J. O'Brien and A. Brossi, J. Org. Chem., 37, 3368 (1972).

25. L. A. Paquette and H. Stucki, J. Org. Chem., 31, 1232 (1966).

26. J. W. Clark-Lewis and M. I. Baig, Aust. J. Chem., 24, 2581 (1971).

27. K. H. Dudley, R. C. Corley, H. W. Miller and M. E. Wall, J. Org. Chem., 32, 2312 (1967).

28. F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963. L. Jurd, "The Chemistry of Flavonoid Compounds", T. A. Geissman (ed.), Pergamon, Oxford, 1962.

29. P. Rajagopalan and A. I. Kosak, Tetrahedron Lett., 5 (1959).

30. K. Fukui and M. Nakayama, Nippon Kagaku Zasshi, 821, 606 (1963).

31. H. Suginome, Bull. Chem. Soc. Japan, 39, 1525 (1966).

32. W. D. Ollis, K. L. Ormand and I. O. Sutherland, J. Chem. Soc. (C), 119 (1970).

33. A. McKillop, B. P. Swann and E. C. Taylor, J. Amer. Chem. Soc., 95, 3641 (1973).

34. D. G. Orphanos and A. Taurins, Canad. J. Chem., 44, 1875 (1966).

35. K. C. Gulati, S. R. Seth and K. Venkataraman, J. Chem. Soc., 1765 (1934).

36. A. McKillop, B. P. Swann and E. C. Taylor, Tetrahedron, 26, 4031 (1970).

37. A. Antus, L. Farkas, A. Gottsegen and M. Nogradi, J. Chem. Soc. (I), 305 (1974).

38. O. W. Ollis, K. L. Ormand, B. T. Redman, R. J. Roberts, and I. O. Sutherland, J. Chem. Soc. (C), 125 (1970).

39. R. A. Micheli, A. N. Booth, A. L. Livingston and E. M. Bickoff, J. Chem. Soc., 4448 (1954).

40. I. Iwade and J. Ide, Chem. Pharm. Bull. (Japan), 10, 926 (1962); ibid., 11, 1042 (1963).

41. G. F. Hennion and K. W. Nelson, J. Amer. Chem. Soc., 79, 2142 (1957).

42. R. D. H. Murray, M. M. Ballantyne and K. P. Mathai, Tetrahedron, 27, 1247 (1971).

43. H. G. Richey, J. C. Philips and L. E. Rennick, J. Amer. Chem. Soc., 87, 1381 (1965).

44. R. D. H. Murray, M. M. Ballantyne, T. C. Hogg and P. H. McCabe, Tetrahedron, 31, 2960 (1975).

45. R. D. H. Murray, M. Sutcliffe and H. Hasegawa, Tetrahedron, 31, 2966 (1975).

46. H. Heingartner, J. Zsindely, H.-J. Hansen and H. Schmid, Helv. Chim. Acta, 55, 1113 (1972).

47. M. Uchiyama and M. Matsui, Agr. Biol. Chem. (Tokyo), 31, 1490 (1967).

48. W. Cocker, T. B. H. McMurray and P. A. Staniland, J. Chem. Soc., 1034 (1965).

49. A. J. Birch, B. Moore, and S. K. Mukerjee, Tetrahedron, 15, 673 (1962).

50. C. W. L. Beran, A. J. Birch, B. Moore and S. K. Mukerjee, J. Chem. Soc., 5991 (1964).

51. R. Braz Filho, M. de J. Coutinho Lemos and O. R. Gottlieb, Phytochemistry, 12, 947 (1973).

52. C. S. Barnes, M. T. Strong and J. L. Occolowitz, Tetrahedron, 19, 839 (1963).

53. W. D. Cotterill, R. Livingstone, K. D. Bartle and D. W. Jones, Tetrahedron, 24, 1981 (1968).

54. T. R. Kasturi, E. M. Abraham and P. Brown, J. Chem. Soc. (I), 2468 (1973).

55. B. D. Tilak and Z. Muljiani, Tetrahedron, 24, 949 (1968).

56. T. H. Simpson and R. S. Wright, J. Org. Chem., 26, 4686 (1961).

57. L. Jurd and L. A. Rolle, J. Amer. Chem. Soc., 80, 5527 (1958).

58. A. Antus, L. Farkas, A. Gottsegen and M. Nagradi, Chem. Commun., 825 (1972).

59. K. Campbell, P. Hopper and B. Campbell, J. Org. Chem., 16, 1736 (1951).

60. J. W. Huffmann and T. M. Hsu, Tetrahedron Lett., 141 (1972).

61. A. J. Quillinan and F. Scheinmann, J. Chem. Soc. (I), 1382 (1972).

62. M. Harfenist and E. Thom, J. Org. Chem., 37, 841 (1972).

63. U. Foch-Pomeranz, H.-J. Hansen and H. Schmid, Helv. Chim. Acta, 56, 2981 (1973).

64. W. Clark-Still and D. J. Goldsmith, J. Org. Chem., 35, 2281 (1970).

65. B. S. Kirkiacharian and D. Raulais, Bull. Soc. Chim. Fr., 1139 (1970).

66. E. J. Corey and G. Märkl, Tetrahedron Lett., 3201 (1967).

67. W. E. Mills and B. O. Saunders, J. Chem. Soc., 537 (1931).

68. D. Seebach, B.-Th. Grobel, A. K. Beck, M. Braun and K.-H. Geiss, Angew. Chem. Internat. Edit., 11, 443 (1972).

69. J. A. Marshall and J. L. Belletire, Tetrahedron Lett., 871 (1971).

70. K. Horváth, Monatsh., 82, 901 (1951); T. A. Geissman and E. Hinreiner, J. Amer. Chem. Soc., 73, 782 (1951).

71. R. Walter, H. Zimmer and T. C. Purcell, J. Org. Chem., 31, 3854 (1966).

72. J. Daly, L. Horner and B. Witkop, J. Amer. Chem. Soc., 83, 4787 (1961).

73. F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar and J. Romo, Tetrahedron, 22, 2387 (1966).

74. E. R. Wagner, R. D. Moss, R. M. Brooker, J. P. Heeschen, W. J. Potts, M. L. Dilling, Tetrahedron Lett., 4233 (1965).

75. D. A. Archer and R. H. Thomson, J. Chem. Soc. (C), 1710 (1967).

76. R. B. Woodward and R. Hoffmann, Angew. Chem. Internat. Edit., 8, 817 (1969).

77. R. W. Tickle, T. Melton and T. A. Elvidge, J. Chem. Soc. (I), 569 (1974).

78. G. W. Whitesides, J. E. Nordlander and J. D. Roberts, Discuss. Faraday Soc., 34, 185 (1962).

79. W. J. Jones and H. W. T. Chorley, J. Chem. Soc., 832 (1946).

80. H. O. House and W. F. Fischer, J. Org. Chem., 34, 3615 (1969).

81. L. Mandall and J. M. Broadmann, J. Org. Chem., 31, 591 (1966).

82. M. Julia and M. Baillarge, Bull. Soc. Chim. Fr., 734 (1966).

83. W. Sucrow and W. Richter, Chem. Ber., 103, 3771 (1970).

84. G. Büchi and H. Wüest, J. Amer. Chem. Soc., 96, 7573 (1974).

85. H. O. House, D. S. Crumrine, A. Y. Teranishi and H. D.

Olmstead, J. Amer. Chem. Soc., 95, 3310 (1973).

86. K. Freudenberg and H.-K. Werner, Chem. Ber., 97, 579 (1964).

87. C. D. Cook and B. E. Norcross, J. Amer. Chem. Soc., 78, 3797 (1956).

88. P. Joseph-Nathan, Ma. P. Gonzales, E. Garcia, G. H. Barrios and F. Walls, Tetrahedron, 30, 3461 (1974).

89. H. J. King, R. H. Holland, F. P. Reed and A. Robertson, J. Chem. Soc., 1672 (1948).

90. P. K. Sharma, M. K. Menon and P. C. Dandiya, J. Pharm. Soc., 53, 1055 (1964).

91. H. Gross, A. Reiche and G. Matthey, Chem. Ber., 96, 308 (1963).

92. W. Baker, J. Chem. Soc., 1683 (1934).

93. F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price and N. Somvichien, Tetrahedron Lett., 4153 (1966).

94. R. V. Coombs, J. Koletar, R. P. Danna and H. Mah, J. Chem. Soc. (I), 792 (1975).

95. P. N. Rao, E. J. Jacob and L. R. Axelrod, J. Chem. Soc. (C), 2855 (1971).

96. G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, J. Chem. Soc., 5072 (1963).

97. S. S. Hall and F. J. McEnroe, J. Org. Chem., 40, 271 (1975).

98. H. J. Teuber and W. Rau, Chem. Ber., 86, 1036 (1953).

99. H. J. Teuber and G. Staiger, Chem. Ber., 88, 802 (1955).

100. H. Zimmer, D. C. Lankin and S. W. Horgan, Chem. Rev., 71, 229 (1971).

101. R. P. Singh, Canad. J. Chem., 44, 1994 (1966).

102. R. D. Johnson, A. Haber, K. L. Rinehart, Jr., J. Amer. Chem. Soc., 96, 3316 (1974).

103. Y. Inouye and H. Kakisawa, Bull. Chem. Soc. Japan, 44, 563 (1971).

104. K. T. Finley, "The Addition and Substitution Chemistry of Quinones", The Chemistry of the Quinonoid Compounds, Vol. 2, S. Patai (ed.), Wiley (1974), 877.

105. R. Hüe, A. Jubier, J. Andrieux and A. Resplandy, Bull. Soc. Chim. Fr., 10, 3617 (1970).

106. W. Baker, J. Chem. Soc., 665 (1941).

107. F. Benington, R. D. Morin and L. C. Clark, J. Org. Chem., 20, 102 (1955).

108. P. Mamont, Bull. Soc. Chim. Fr., 1557, 1564, 1568 (1970).

109. M. V. von Bülow, N. C. Franca, O. R. Gottlieb and A. M. P. Suarez, Phytochemistry, 12, 1805 (1973).

110. C. J. Aiba, R. B. Filho and O. R. Gottlieb, Phytochemistry, 12, 413 (1973).

111. K. Matsui and K. Munakata, Tetrahedron Lett., 1905 (1975).

112. O. L. Chapman, M. R. Engel, J. P. Springer and J. C. Clardy, J. Amer. Chem. Soc., 93, 6697 (1971).

113. L. Merlini and A. Zanarotti, Tetrahedron Lett., 3621 (1975).

114. H. J. Hopwood and J. A. Stock, J. Chem. Soc., 4972 (1965).

115. T. Reichstein, R. Oppenauer, A. Grüssner, R. Hirt, L. Rhyner and C. Glatthaar, Helv. Chim. Acta, 18, 816 (1935).

116. T. Kametani, S. Kano and Y. Watanabe, Yakugaku Zasshi, 86, 417 (1966).

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