THE TOTAL SYNTHESIS OF ARISTOLINDIQUINONE

a thesis submitted to the

UNIVERSITY OF CAPE TOWN

in partial fulfilment of the requirement

for the degree of

MASTER OF SCIENCE

by

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Finally, I would like to express my sincere gratitude to my parents, Jan and June, for their love, continued support and encouragement throughout my academic pursuits. Their kindness and unsurpassed generosity will not be forgotten. I could not have wished for more.

ABSTRACT

Aristolindiquinone (1), a novel natural compound possibly possessing anti-fertility activity, was synthesized via two independent routes. First, a Stobbe reaction unambiguously gave the naphthalene nucleus with the required substitution pattern (3,8-dioxygenated-2,5-dimethyl naphthalene), starting from 2-hydroxy-5-methylbenzaldehyde (31).

Second, a general synthesis of substituted C-5 oxygenated-1,4-naphthoquinones is applied to the synthesis of (1). The critical step in the synthesis is the reaction of the novel Diels-Alder partners, dienophile (90), synthesized from 2,6-dihydroxytoluene (56), and diene (109).

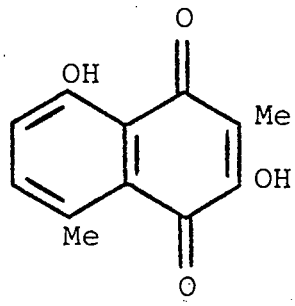
TO MY PARENTS

INTRODUCTION

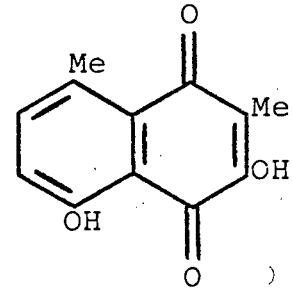
Compounds containing the quinone ring are widely distributed in nature[1] and have been isolated from plants, bacteria and throughout the animal kingdom including man. They have been shown to exhibit extensive biological activity,[2,3] including antibiotic and antineoplastic[16,5] properties. More specifically it has recently been inferred[6,7] that they may exhibit antifertility activity.

Indian folk medicine makes use of the roots of Aristolochia indica (Indian birthwort) as an abortifacient[8]. Recently, the medicinal property of this plant has been verified by the work of Pakrashi[9] who confirmed its contragestational activity. Further research by Cordell[6,7] has shown that the ethanol extracts of these roots show a marked decrease in the number of pregnancies in rats and hamsters when administered postcoitally. On partitioning of the ethanol extracts a new naphthoquinone, aristolindiquinone (1), was isolated as a bright orange crystalline pigment and its proposed structure was based on mass, u.v., i.r. and n.m.r. spectroscopic data. Due to its possible biological importance as an antifertility agent and in conjunction with its novel structure, we were keenly interested in its total synthesis.

It is clearly evident that the naturally occurring juglone derivative (1) with its regioisomer (2) is a classic example of a large group of naphthoquinones having the general regiochemistry illustrated by structures (3) and (4).



Aristolindiquinone (1)



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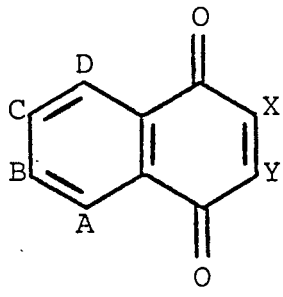

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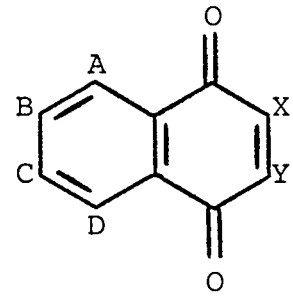
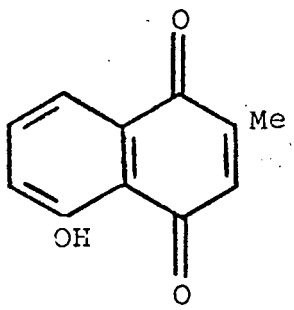


(4)

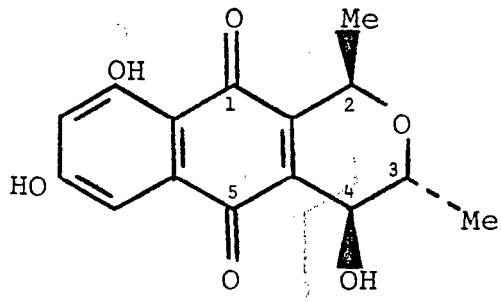
Structures (3) and (4) are different by virtue of the relative regiochemistry of the two rings. The two problems posed by such structures are: first, their identification, and secondly, a synthesis which takes into account the regiochemistry of the left hand ring with respect to the right hand ring. Well known examples exhibiting these problems are:

a) Plumbagin (5), whose methyl group location was finally settled by an unambiguous synthesis[10].

b) Quinone A (6), which was obtained by hydrogenolysis of protoaphin-*fb* followed by reoxidation to the quinonoid level, was undoubtedly a 5,7-dihydroxy-1,4-naphthoquinone according to spectroscopic studies. The stereochemistry of the aliphatic protons was determined by oxidation of (6), which yielded D,D-(+) dilactic acid, an acid of known absolute configuration[11]. Cameron[12] determined the regiochemistry by taking into account the chemistry of erythroaphin-*fb* (7) which contains no aliphatic hydroxyl group and by making the assumption, justified by spectroscopic and chemical similarities, that there is no significant difference between the non aromatic portions of Quinone A (6) and the erythroaphin-*fb* (7).

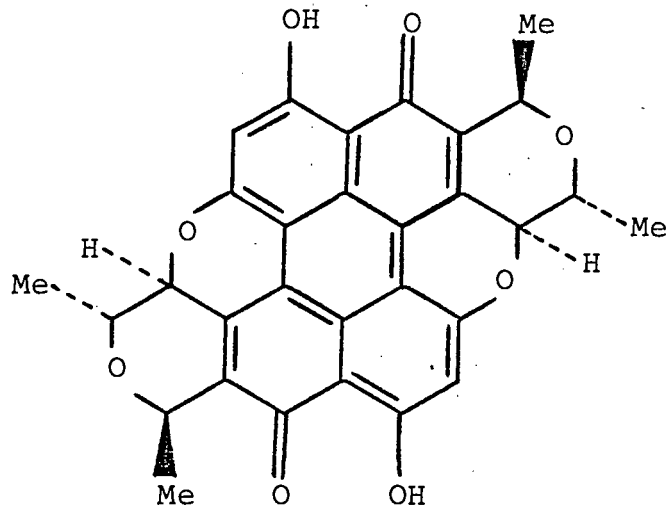


Plumbagin (5)



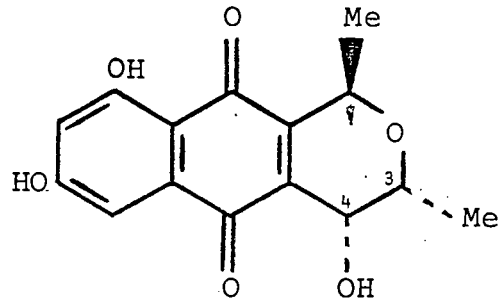
Quinone A (6)

The regiochemical assignment has recently been shown to be correct by the synthesis of the racemate of Quinone A in this laboratory[13].



Erythroaphin-*fb* (7)

c) Quinone A' (8), which differs from Quinone A (6) in the configuration of the carbon atom (C-4) bearing the alcoholic group as shown by the coupling constants of the pyran ring protons.



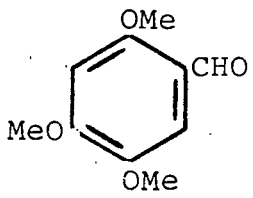
Quinone A' (8)

The general problem of identification of the regiochemistry of naphthoquinones can be elucidated by a total synthesis, spectroscopic studies, comparison with compounds of known absolute configuration and by an x-ray crystal structure. The general problem of regiochemical synthesis can be solved in a number of ways as

illustrated below by methods 1, 2 and 3. Accordingly we have supplied sufficient background information on each synthetic route to provide the reader with a sense of the terrain in which our explorations were conducted.

METHOD 1

One can synthesize a substituted naphthalene whose regiochemistry is known. A good example of this technique is the synthesis of naphthalenes via the Stobbe reaction. Harper[14] reported that the Stobbe condensation between 2,4,5-trimethoxy-benzaldehyde (9) and diethyl succinate (10) gave solely ethyl 4-acetoxy-5,6,8-trimethoxy-2-naphthoate (11) in 32% yield.



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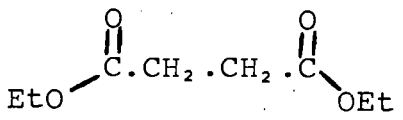

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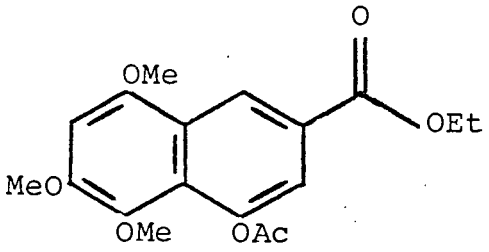
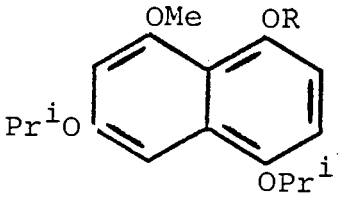


(11)

METHOD 2

The desired naphthalene system could be obtained via selective electrophilic substitution of aromatic compounds. Tedder[15] has shown that mixtures of trifluoroacetic-anhydride and carboxylic acids give good yields of ketones from polyalkylbenzenes. More specifically, Giles[16] has shown that the oxygenated naphthalene (12) undergoes

acylation at C-3 and the protected naphthalene (13) shows acylation at C-8 in the presence of premixed acetic acid and trifluoroacetic anhydride.



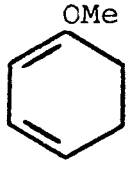
(12) R = H

(13) R = Ac

METHOD 3

The desired regiochemistry can be obtained via a regiospecific Diels-Alder reaction. The following examples illustrate this.

Giles[17] and Roos established the regiospecific addition of methoxycyclohexa-1,3-diene (14) to 2-methoxy-1,4-benzoquinone (15) which yielded the adduct (16) and not (17).



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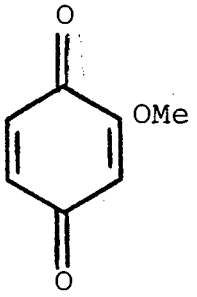

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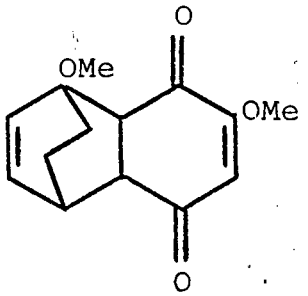

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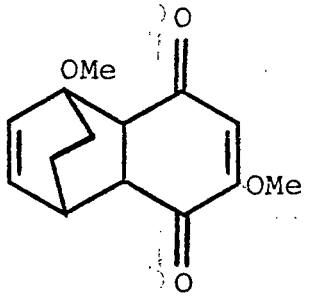
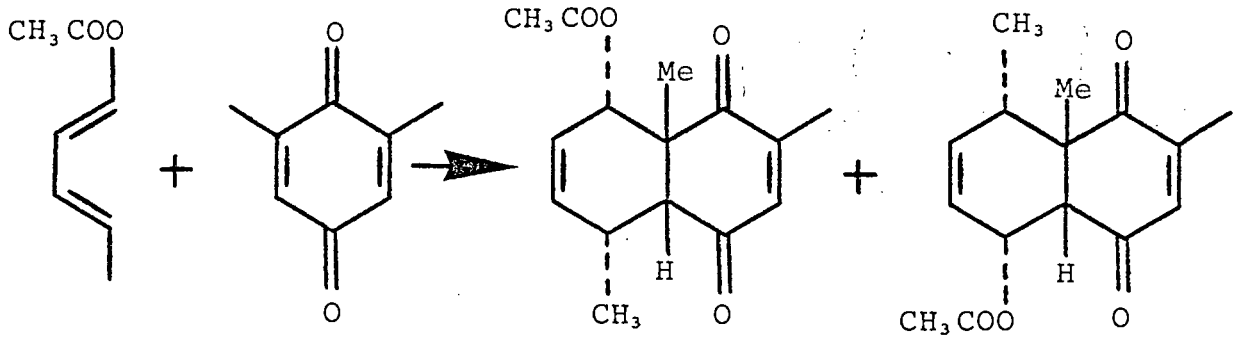


(17)

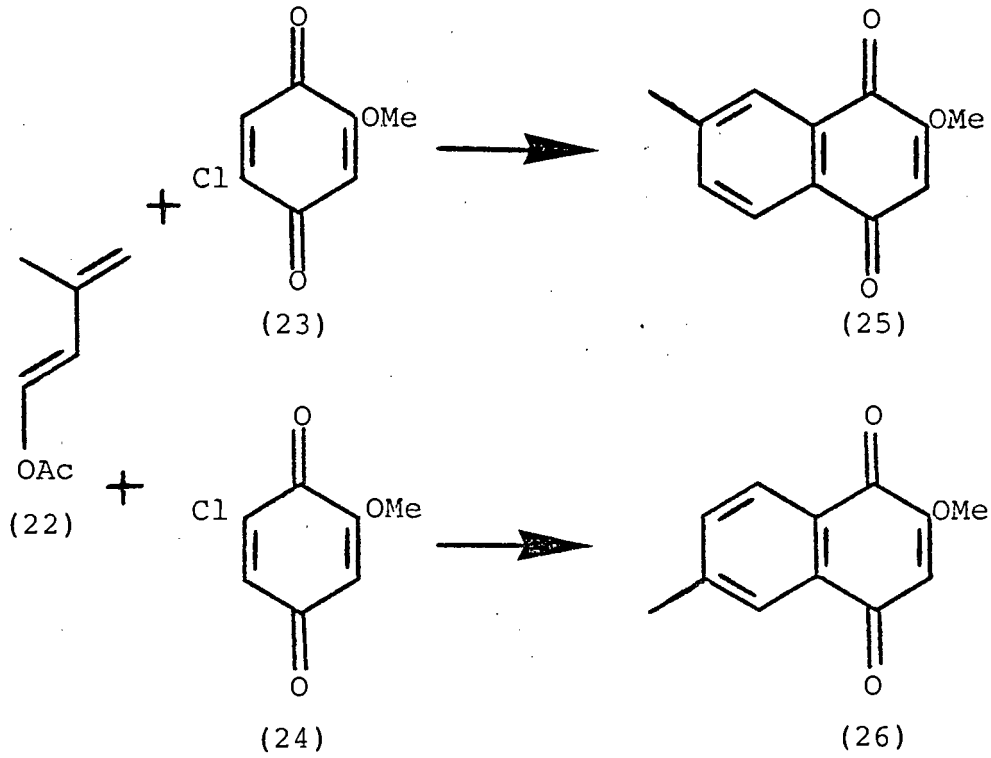
Danishefsky[18] has shown that the use of siloxy dienes can be a major source of simplification in total synthesis. However, the addition of dienes to unsymmetrical quinones are notorious for their lack of regiospecificity.[19] In this respect Schmidt[20] has shown that in the Diels-Alder reaction of 1-acetoxy-1,3-pentadiene (18) with 2,6-dimethyl-benzoquinone (19) this led to an 85% yield of (20) and (21) in a ratio of 4 : 1.



(18) (19) (20) (21)

This, however, can be overcome by using a substrate with functions having orientation controlling properties. It has been shown that in the Diels-Alder addition of siloxy dienes with haloquinones the regiochemistry is determined by the position of the halogen with the added advantage that the latter is removed upon aromatization of the adduct.

Brassard[19] showed that the reaction of the 1-acetoxy-butadiene (22) with 2-chloro-5-methoxybenzoquinone (23) and 2-chloro-6-methoxybenzoquinone (24) gave the corresponding isomers (25) and (26) regioselectively.

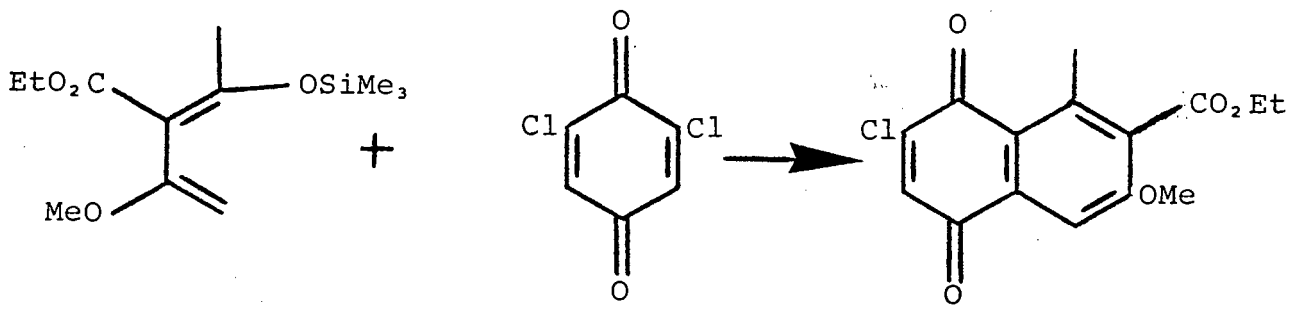


(23) (25)

(22)

(24) (26)

It has also been shown by Cameron[21] that the diene (27) added to 2,6-dichloro-1,4-benzoquinone (28) regiospecifically; the less nucleophilic terminus of the diene attacking the chlorinated carbon affording only isomer (29) in 80% yield.



(27) (28) (29)

Due to the biological interest of aristolindiquinone (1), we aimed at the investigation of its regiospecific synthesis using routes related to each of the above methods. The regiospecific synthesis of aristolindiquinone was successfully completed by two unrelated routes and all of the data of the synthetic compound were identical to those of the natural product, proving the proposed structure correct.[22] Subsequently a single crystal x-ray structure and an alternative synthesis[23] of aristolindiquinone (1) were achieved, further confirming the proposed structure.

It was also deemed pertinent to synthesize the regioisomer (2) as this could be used for direct comparison between physical and spectroscopic criteria and possibly anti-fertility activity, with that of aristolindiquinone (1).

DISCUSSION

In this project we decided to initially synthesize aristolindiquinone (1) via the Stobbe reaction route (Scheme 1, page 17) in order to be certain of obtaining the correct regiochemistry. Thereafter we aimed at its concomitant synthesis using electrophilic substitution (Scheme 3, page 34) and Diels-Alder (Scheme 8, page 53) methodology, the latter two potential routes being far more elegant and direct. The unambiguous regiochemical synthesis of the alternative isomer (2) was achieved using a slight modification of the Diels-Alder synthesis.

CHAPTER 1

THE SYNTHESIS OF ARISTOLINDIQUINONE VIA THE STOBBE REACTION

The reaction sequence that led to the successful synthesis of aristolindiquinone is illustrated in Scheme (1), (page 17).

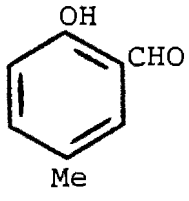
The desired aldehyde precursor (31) for the Stobbe reaction, with the requisite substitution pattern, was obtained via the Reimer-Tiemann formylation of para-cresol (30) in a yield of 37% according to a literature procedure [24,25] Due to the poor yield for this reaction introduction of the formyl group was investigated using the Vilsmeier-Haack formylation technique.

Sargent[26] has reported the successful preparation of aldehydes from methoxy-methyl benzene derivatives (see page 24). Consequently we attempted aromatic formylation of the commercially available methyl ether (32), using the prescribed method. Formylation was expected to occur ortho to the methoxy group due to its stronger directing influence, however, on its subjection to Sargent's formylation conditions a t.l.c. examination of the reaction product showed extensive degradation of the starting material with no characterisable product. Thus, synthesis

of aldehyde (33) remained routed via the Reimer-Tiemann reaction.

The methyl ether (33) was obtained in a 94% yield by refluxing the phenol (31) with dimethyl sulphate in acetone in the presence of an excess of anhydrous potassium carbonate. The subsequent condensation of the methoxy aldehyde (33) with diethyl succinate was effected by boiling in a solution of potassium t-butoxide in t-butyl alcohol to afford the acid (34). Without further purification the acid (34) was cyclised under reflux in acetic anhydride containing sodium acetate to furnish the naphthoate (35) in a two step yield of 35%, a yield typical for this type of reaction. That the desired Stobbe reaction was successful was borne out by the ^{1}H n.m.r. spectrum which showed inter alia the ortho coupled aromatic protons (J 8.1) as well as the required 1,3-disubstitution pattern (J1.8) as expected for the naphthoate (35). It was found that the condensation of the aldehyde (33) with dimethyl succinate proceeded in a similar yield with the advantage of simplification of the ^{1}H n.m.r. spectral analysis.

(30)



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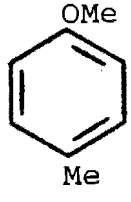

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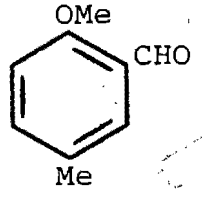
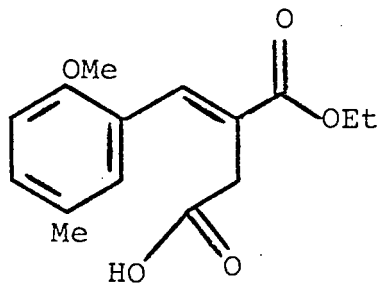


(33)

In order to obtain the desired ring methyl substituent on C-3 of structure (1), reduction of the ester (35) to the corresponding alcohol (36) and its subsequent hydrogenation was envisaged. However, upon treatment of the ester (35) with lithium aluminium hydride in anhydrous ether extensive decomposition of starting material was observed by t.l.c.



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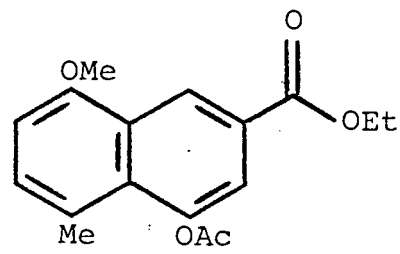

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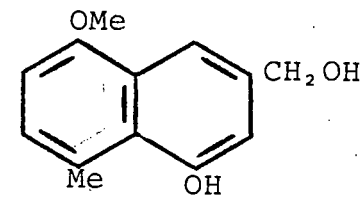
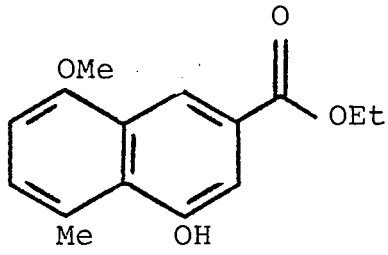


(36)

Treatment of the naphthoate (35) under mildly basic conditions (1% sodium hydroxide in methanol) resulted in hydrolysis of the acetoxy group yielding the naphthol (37) as witnessed by the disappearance of the ^{1}H n.m.r. acetyl signal (δ2.35). Owing to its instability, the naphthol (37) was neither isolated nor purified but directly isopropylated to the isopropyl ether (38) in a yield of 98% by heating the naphthol (37) at 60 °C in dimethylformamide in the presence of isopropyl bromide and potassium carbonate. It was also noted that hydrolysis under harsher conditions (10% sodium hydroxide solution in methanol, reflux) resulted in the hydrolysis of the ethyl ester group as well as shown by subsequent protection which gave the diisopropylated product

(39). This was evident from the mass spectrum which gave a molecular ion of *m/z* 316.



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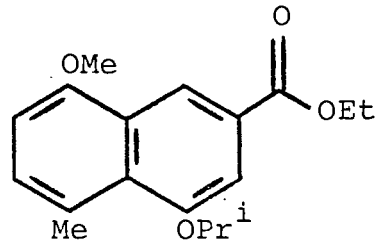

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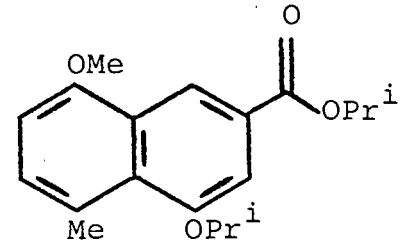
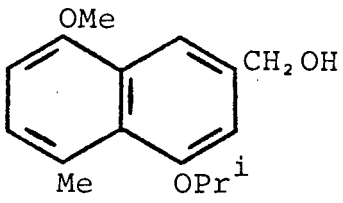


(39)

Reduction of the protected ester (38) was readily achieved by stirring in anhydrous ether in the presence of lithium aluminium hydride to afford the corresponding alcohol (40) in a yield of 85%. Subsequent hydrogenolysis of the alcohol (40), under optimised conditions using palladium on carbon as the catalyst, effected the conversion of the alcoholic function to the desired aromatic methyl substituent to afford compound (41) in a yield of 65%. This was clearly apparent by an inspection of the ^{1}H n.m.r. spectrum of compound (41) which showed inter alia the disappearance of the methylene doublet (δ4.73) and the hydroxy triplet signal (δ1.74) and the appearance of the methyl singlet (δ2.43) corresponding to the protons of the newly formed methyl substituent. It was found that a prolonged reaction time resulted in a lower yield due to over hydrogenation.

In order to oxidise compound (41) to the quinonoid level it was necessary to remove the protecting isopropyl group.

Deprotection was successfully achieved by stirring compound (41) in dry dichloromethane with an excess of the Lewis acid, boron trichloride, to afford the naphthol (42) in a 53% yield which, as expected, showed a much lower R_F than that of the starting material (41). The next aim was the synthesis of the juglone derivative (43), which it was intended to achieve by the oxidation of the naphthol (42) with Fremy's salt.



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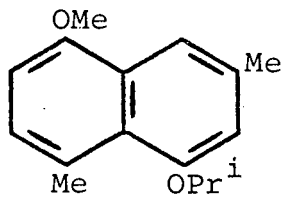

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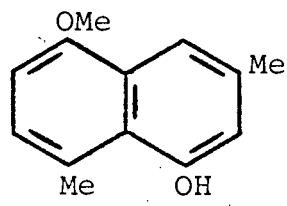

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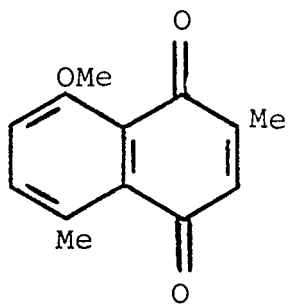
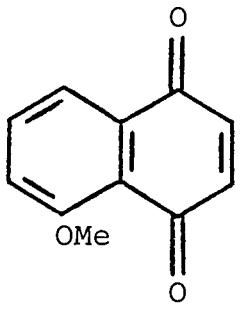
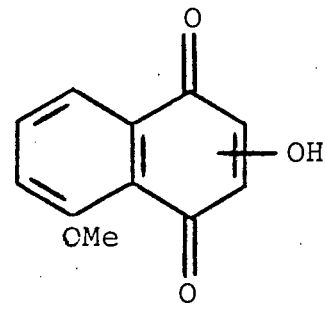


(43)

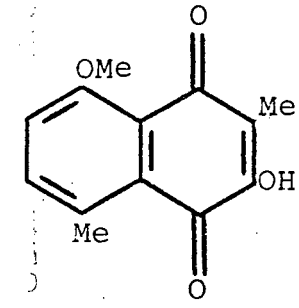
Rapoport [27] has shown that the naphthoquinone (44) underwent ready oxidation under basic conditions in the presence of hydrogen peroxide to give the hydroxynaphthoquinone (45) in 73% yield.



(44)

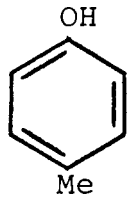


(45)



(46)

Accordingly we proposed that the juglone derivative (43) would afford the hydroxy quinone (46). Oxidation of the naphthol (42) by Fremy's salt, however, yielded the product that crystallized as bright red needles. Since the 1,4-naphthoquinone (43) would be expected to be yellow, as it lacks peri-hydrogen bonds and also additional auxochromic substituents on the quinone ring to markedly deepen the colour, it appeared much more likely that the product formed was in fact the 1,2-naphthoquinone (47) (Scheme 1, page 17). This was consistent not only with the fact that ortho-quinones are characteristically red in colour, but also with the ^{1}H n.m.r. and u.v. spectra of the new product. The former spectrum showed a significantly low field resonance for the quinonoid methyl protons (δ 2.05) typical of an ortho-quinone, and the u.v. spectrum, showed a band 3 absorption of a fairly long wavelength (471 nm in ethanol) in correspondence with ortho-quinones with similar substitution patterns. It was concluded that the ortho-quinone (47) (80%) had been synthesized.



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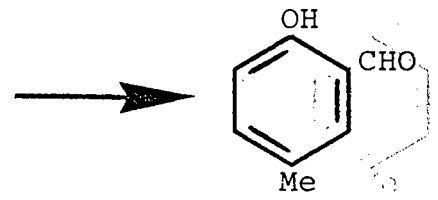

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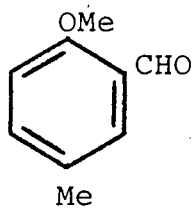

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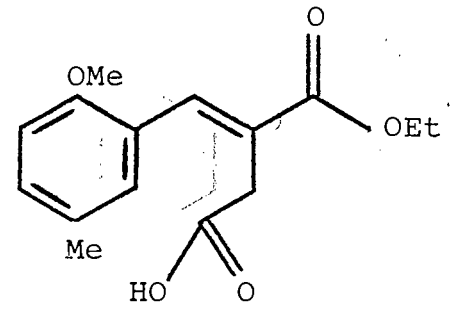

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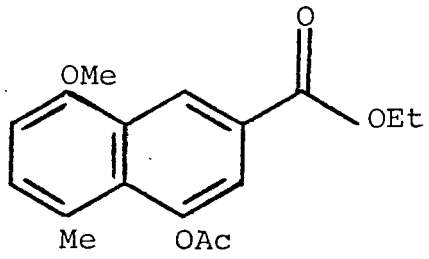

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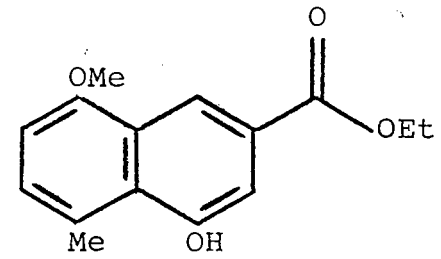

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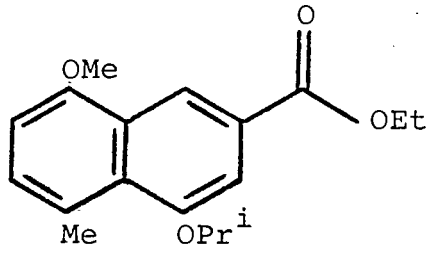

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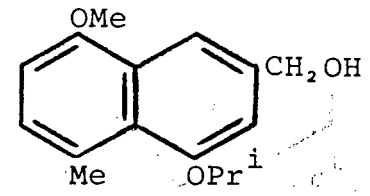

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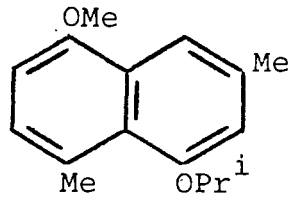

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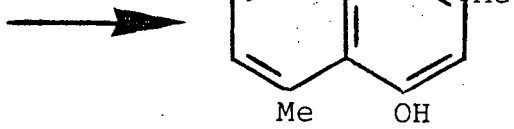

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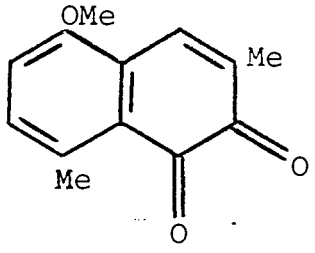
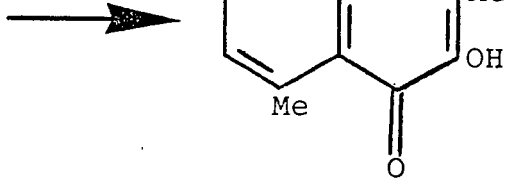
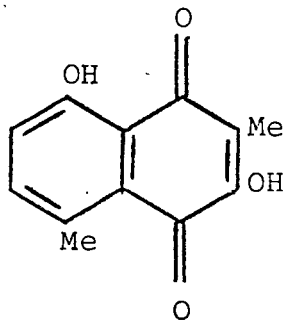


(47)



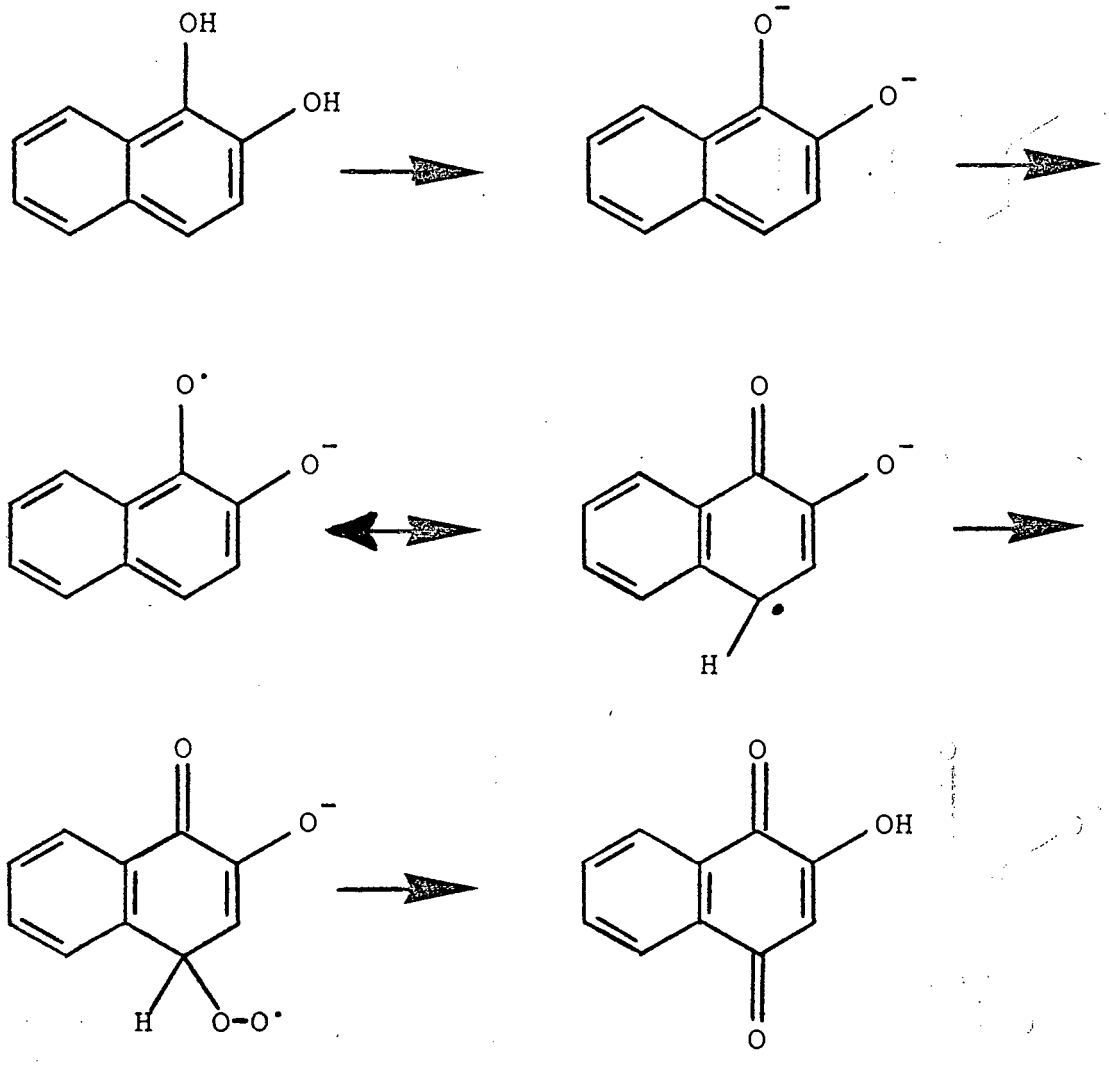
(46)



(1)

SCHEME 1

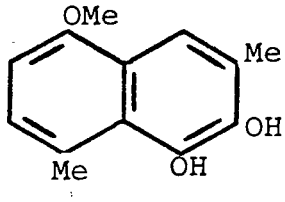
Thomson [29] has shown that 1,2-dihydroxy-naphthalenes rapidly autoxidise in the presence of potassium t-butoxide and oxygen to give 2-hydroxy-1,4-naphthoquinones and has accordingly proposed a mechanistic pathway which has been illustrated below (Scheme 2).



SCHEME 2

Evidently, the naphthalenediol would give the dianion in strongly basic solution which, in the presence of oxygen, would form the semiquinone anion. Further autoxidation may then proceed via the capture of a molecule of oxygen to give the hydroperoxy radical, and hence the quinone.

Reduction to the hydroquinone (48) was accomplished by shaking a solution of the ortho-quinone in benzene with a saturated aqueous sodium dithionite solution until the organic layer turned pale yellow. Due to the labile nature of the hydroquinone no isolation step was attempted and all further work was undertaken under a nitrogen atmosphere. The hydroquinone was then dissolved in t-butyl alcohol in the presence of potassium t-butoxide and oxygen bubbled through the solution for 5 min. After workup, however, a t.l.c. investigation revealed a complex reaction mixture from which no product could be characterised. The result was not disconcerting as McOmie et al.[30] showed that the orthoquinone (49) underwent Thiele acetylation using sulphuric acid as catalyst to give compound (50) in a 12% yield.



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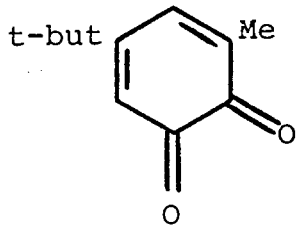
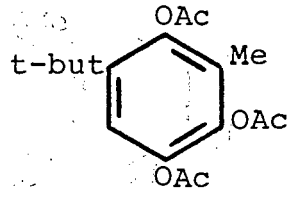
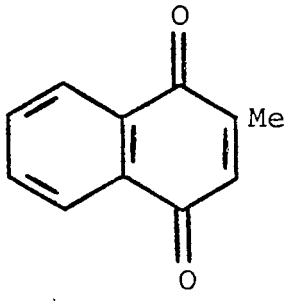


(49)

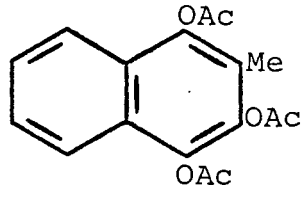


(50)

In a further literature search we found that Anderson and Newmann[31] had demonstrated that sulphuric acid was ineffective as a catalyst for the Thiele acetylation of 2-methyl-1,4-naphthoquinone (51). However, Burton and Prail[32] proved that in the same reaction perchloric acid successfully catalysed the acetylation of (51) affording the triacetate (52) in a yield of 43-54%. Alkaline hydrolysis of (52) with ready access to air was shown to be conducive to its concomitant oxidation to the hydroxy-1,4-naphthoquinone (53) in a high yield.



(51)



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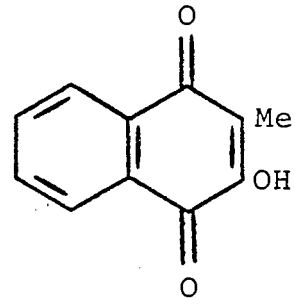
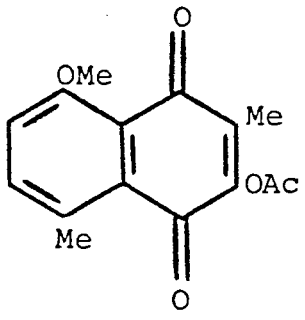


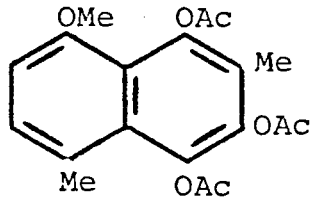
(53)

On this foundation it was proposed that our desired quinonoid system (46) could be established through a congruous reaction mode. In order to oxygenate the C-4 position the ortho-quinone (47) was stirred in acetic anhydride in the presence of a catalytic quantity of sulphuric acid. On workup under mildly basic conditions (dilute aqueous sodium hydrogen carbonate), the acetoxy quinone (54) was isolated albeit in a low yield of 24%. It was suspected that this poor yield was due to some material remaining at the triacetate level (55) and a further amount

being lost into the aqueous phase as the anion of the hydroxy quinone (46). In order to improve the yield the crude reaction product was worked up with a 3% sodium hydroxide solution. This resulted in effective cleavage of the acetoxy groups and after acidification gave the hydroxy quinone (46) in a much improved yield of 55%. It was also found that treatment of the acetoxyquinone (54) with an aqueous sodium hydroxide solution (5%) resulted in cleavage of the acetyl group to afford the hydroxyquinone (46) in a 75% yield.



(54)



(55)

The final synthetic step in this reaction sequence involved the hydrolysis of the remaining methoxy group. Demethylation of both (54) and (46) were found to proceed smoothly in the presence of an excess of boron trichloride in anhydrous dichloromethane at -10°C to afford the desired product, aristolindiquinone (1) (85%), which was found to be identical (t.l.c., n.m.r., i.r., u.v., mass spectrum and m.p.) with a naturally occurring sample[6].

Now that there was no doubt over the regiochemistry of aristolindiquinone (1) its synthesis via the two more elegant methods was embarked upon, of which the electrophilic substitution route will first be discussed (Chapter 3, Scheme 3, page 34).

CHAPTER 2

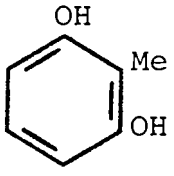
AN INVESTIGATION INTO THE SYNTHESIS OF ARISTOLINDIQUINONE VIA ELECTROPHILIC SUBSTITUTION METHODOLOGY

The readily available 2,6-dihydroxytoluene (56) was quantitatively methylated to the dimethyl ether (57) using dimethyl sulphate and potassium carbonate.

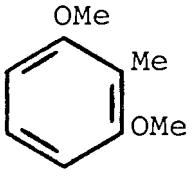
Sargent[26] has reported the preparation of methoxy aldehydes, in particular compound (58), using a modified Vilsmeier-Haack[33] procedure. He also reported the synthesis of their corresponding formate esters, obtained by the Baeyer-Villiger oxidation of the aldehyde with meta-chloroperbenzoic acid in refluxing dichloromethane. Accordingly the aldehyde (58) was synthesised in 81% yield and oxidised to the ester (59) in 94% yield.

Tedder[15] has shown that treatment of anisole with a mixture of trifluoroacetic anhydride and acetic acid gives good yields of para-acetyl anisole. In the present synthesis it was desirable for acylation of the ester (59) to occur ortho to the methoxy group. It was anticipated that of the two aromatic positions available for electrophilic substitution in compound (59), the site ortho and para to the two methoxy substituents would undergo reaction in preference to the alternative position which was activated by the addition

effects of formate and methyl, which would be weaker than two methoxy groups. The ester (59) was therefore used as a model to investigate the ease and position of acylation when treated with the mixed anhydride formed from the reaction between trifluoroacetic anhydride and acetic acid. It was found that acetylation proceeded cleanly to afford a mixture of the phenol (60) and the acetate (61).



(56)



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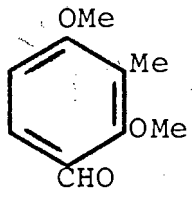
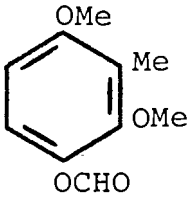
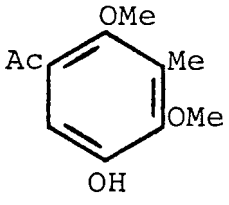


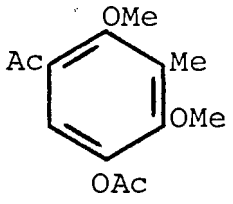
(58)



(59)



(60)



(61)

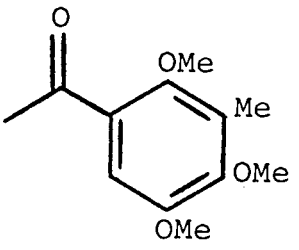
That this mixture was obtained was shown by t.l.c. and borne out by the ^{1}H n.m.r. spectrum of (60) which showed a singlet (δ2.59) corresponding to the three acetyl protons as well as a hydroxy proton signal (δ5.93) which disappeared after a deuterium oxide wash. The ^{1}H n.m.r. spectrum of compound (61) showed two signals (δ2.29) and (δ2.58) corresponding to the two acetyl substituents. As column chromatography was

not a viable means of separation of these two compounds due to the similarity in R_F values, the mixture was treated with pyridine in acetic anhydride to afford the oily acetate (61) in 60% yield as the sole product. Alternatively, hydrolysis of the mixture under basic conditions yielded the phenol (60) in 66% yield. Its ^1H n.m.r. spectrum indicated that the hydroxy and acetyl groups were meta to each other as shown by the chemical shift (δ 5.93) of the non hydrogen-bonded hydroxy singlet. No further purification was attempted due to its significant decomposition when column chromatography was employed as a purification technique. Treatment of the phenol (60) with dimethyl sulphate and potassium carbonate gave the corresponding methyl ether (62) in quantitative yield.

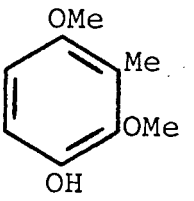
As neither compound (62) nor its isomer (66) had been reported in the literature before and as spectroscopic evidence alone could not give the correct assignment with a satisfactory degree of confidence, an unambiguous route to compound (66) was devised to allow decisive structures to be assigned to compounds (60) and (61).

The following experiments explicitly showed that acylation had indeed occurred at the proposed site. The formate ester (59) was quantitatively hydrolysed under mildly basic conditions in methanol to yield the labile phenol (63). Acetylation of the crude phenol (63) to the corresponding

acetate (64) was achieved in a 90% yield by treatment with a solution of acetic anhydride in pyridine.

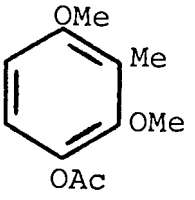


(62)

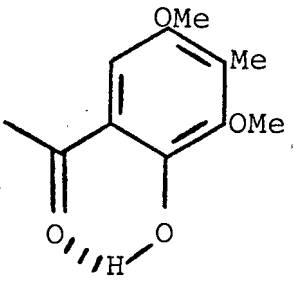


(63)

In the literature[34] Fries rearrangements have been successfully employed using boron trifluoride etherate to acetylate the position ortho to an acetoxy group thereby forming the corresponding C-acetyl phenol in a high yield. The application of freshly distilled boron trifluoride etherate (2 mol equiv.) to the acetate (64) in anhydrous dichloromethane at 0°C gave predominantly the Fries rearrangement product (65), which had the same R_F as the starting material (64). That ortho migration of the acetyl group had occurred was obvious from the ^1H n.m.r. spectrum which revealed inter alia, a highly deshielded singlet (δ12.22) characteristic of a hydroxyl proton ortho to a carbonyl group. The spectrum also showed the presence of unreacted starting material (64). Purification of the mixture was achieved by chromatography, after mild basic hydrolysis which converted the acetate (64) to the phenol (63) which had a markedly lower R_F, to give the pure product (65) in 63% yield.

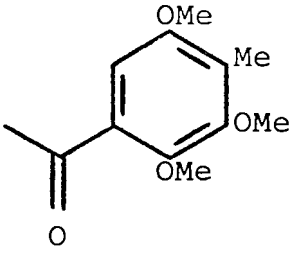


(64)

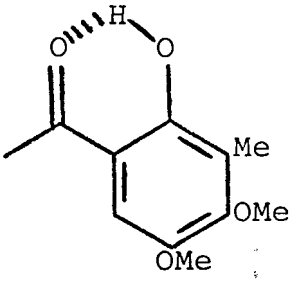


(65)

Methylation of the Fries product (65) with dimethyl sulphate quantitatively gave the desired methyl ether (66), which eventually crystallized as yellow needles. The differences in the ^{1}H n.m.r. and i.r. spectra of compounds (62) and (66) testified to their having different structures and thereby confirmed the proposed structures (60) and (61). Further evidence for the assignments was sought. As the methyl ether (62) could not be crystallized a comparison was made of the melting points of the phenolic isomers (65) and (67).



(66)



(67)

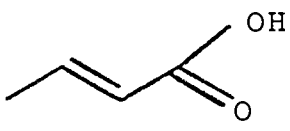
Selective ortho demethylation of the methyl ether (62) was accomplished using boron trichloride in anhydrous dichloromethane to give the crystalline product (67) in 38% yield after chromatography. The mixed melting point of

compounds (65) and (67) showed a significant depression and the corresponding spectroscopic data showed significant dissimilarity which substantiated their differences in structure.

As shown previously in the acetylation of compound (59), two products were isolated. The mixture was undesirable and complicated the product analysis, especially as the phenol formed was particularly unstable and as trans-esterification of the formate ester function resulted in further complexity of the ^{1}H n.m.r. spectrum. We envisaged that trimethoxytoluene (68) (Scheme 3, page 34), possessing the required substitution pattern, would constitute a valid synthetic precursor to the naphthalene (83) with the advantage of eliminating the two above mentioned problems. To this end, the phenol (63) was methylated using dimethyl sulphate to afford the trimethoxy compound (68) in a yield of 98%. Aromatic acylation of this compound was expected to occur meta to the methyl group due to the synergic accumulative ortho and para directing influence of two of the methoxy groups. This postulate was proved correct as the trimethyl ether (68) furnished the C-acetylated compound (62) as the sole product in a yield of 70% upon treatment with a premixed solution of acetic acid and trifluoroacetic anhydride as shown by the correlation of the spectroscopic data of compound (62) obtained via the two independent routes.

A series of preliminary acylation reactions was attempted in the hope that,in so doing, greater insight into the scope and limitations of this technique could be obtained. When the methyl ether (68) was treated with the mixed anhydrides formed from trifluoroacetic anhydride and crotonic acid (69), vinylacetic acid (70) and tiglic acid (71), the desired reactions products (72), (73) and (74) were not isolated and extensive decomposition of starting material was noted. The failure of these analogues to undergo the requisite acylation was in sharp contrast to the smooth acylation in the case of acetic acid.

An interesting anomaly was found in the case of the tiglic acid reaction and has been discussed at the end of this section (page 37).



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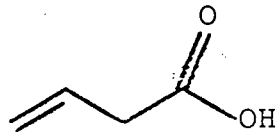

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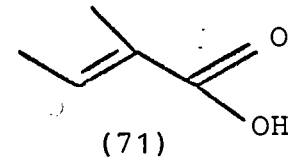

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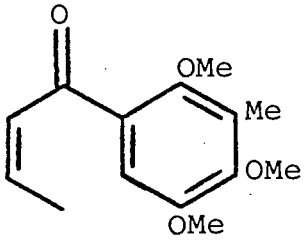

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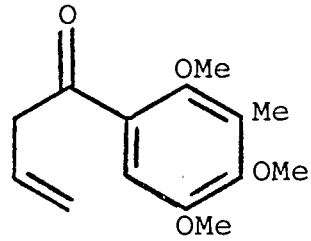

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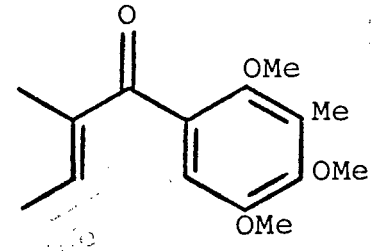
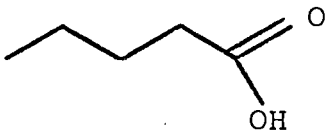


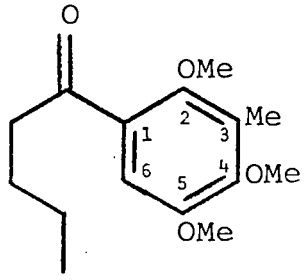
(74)

In contrast with the mixed anhydride acetylation reaction previously discussed, addition of a premixed solution of valeric acid (75) and trifluoroacetic anhydride to compound (68) not only gave compound (76) as the major product (40%) but also its regioisomer (77) (20%). These two isomers were effectively separated by column chromatography; the product of higher R_F being tentatively assigned structure (76) as this was the major product.

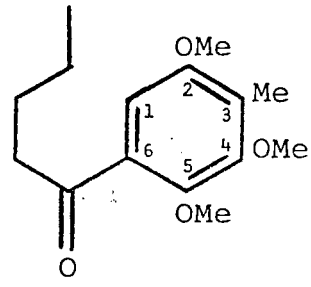
This assignment was later proved correct by an alternative unambiguous synthesis of compound (76). The formation of the two isomers could possibly be ascribed to C-6 having an environment sterically favourable to attack by a bulky electrophile due to out-of-plane bending of the vicinal methoxy substituent, but this would be highly speculative.



(75)



(76)

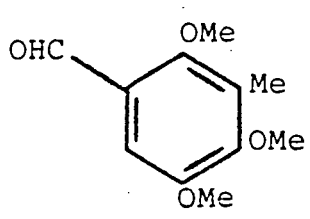


(77)

It was initially envisaged that acylation of compound (68) with the mixed anhydride formed from the reaction between 4-pentenoic acid and trifluoroacetic anhydride would afford compound (82). From this strategic position the success of the synthetic scheme would be contingent on the feasibility

of the oxidation (Scheme 4) of the acyl substituent and its subsequent aromatization to form the naphthalene (83). However, as 4-pentenoic acid was unavailable and, due to the unreactivity of the mixed anhydrides of its analogues with the desired substrate (68) and the fact that two regioisomers were formed in the case of the valeric acid acylation reaction, the more direct synthesis of compound (82) was rejected in favour of an alternative synthesis which involved the use of a Grignard reagent.

The trimethyl ether (68) (page 34) was formylated using dimethylformamide in the presence of phosphorus oxychloride (Sargent's[26] method, see page 24) to yield the aldehyde (78) (54%), which was conceived as being a plausible point of entry for obtaining the acyl analogues, and a quantity of starting material (21%). To confirm the position of formylation the aldehyde (78) was reacted with the Grignard reagent, methyl magnesium iodide, in anhydrous ether to give the crude alcohol (79) in a 95% yield. The alcohol (79) was not purified but was immediately oxidised using Jones' reagent[35]. The product obtained was shown to be identical with compound (62) obtained earlier, not only by spectroscopic comparison, but also by melting point, the latter being undepressed on admixture with authentic (62). Thus the position of formylation of compound (68) and therefore the proposed structure of the aldehyde (78) were proved correct.



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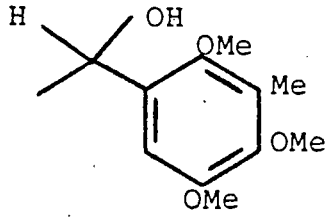
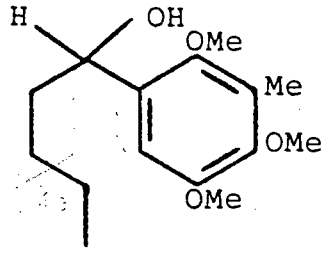


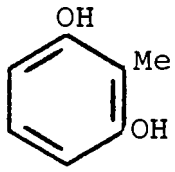
(79)



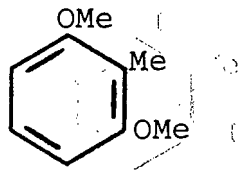
(80)

Butyl magnesium bromide underwent a similar Grignard reaction with compound (78) which gave the crude alcohol (80) in 64% yield. Jones' oxidation of the unpurified alcohol (80) afforded the ketone (76) in a yield of 84%.

The inclusion of the aldehyde (78) in the synthetic plan proved highly attractive as it made provision for acyl analogues of compound (62) to be prepared that were not feasible using the alternative mixed anhydride acylation technique. It was therefore proposed that the key intermediate (82) be synthesised. Thus, the aldehyde (78) was added to the Grignard reagent but-3-enyl-1-magnesium bromide, prepared in situ, to quantitatively give the alcohol (81). Upon Jones' oxidation, the unpurified alcohol (81) afforded the desired ketone (82) in two steps of 92% yield. It was anticipated that the ketone (82) would undergo acid catalysed cyclisation according to the mechanism illustrated in Scheme 4. However, the acyl derivative (82) failed to undergo the requisite ring closure using trifluoroacetic acid, trifluoroacetic acid in



(56)



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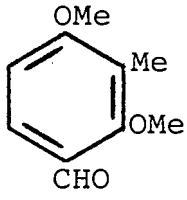

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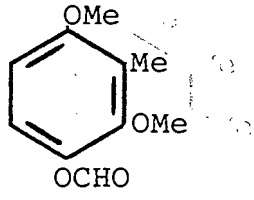

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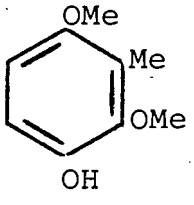
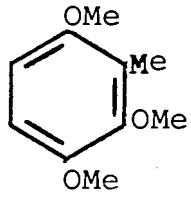
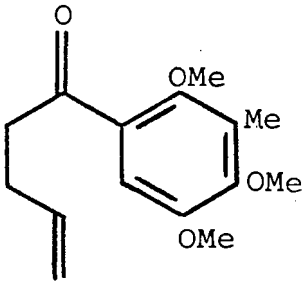


(63)



(68)



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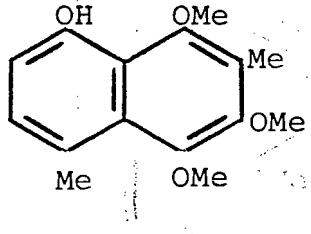

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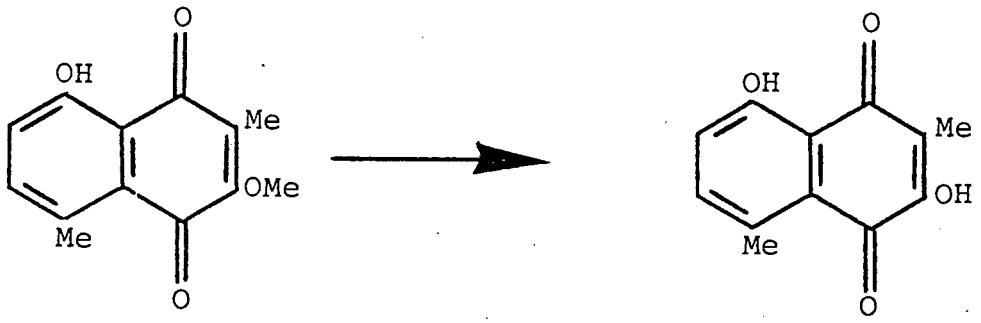
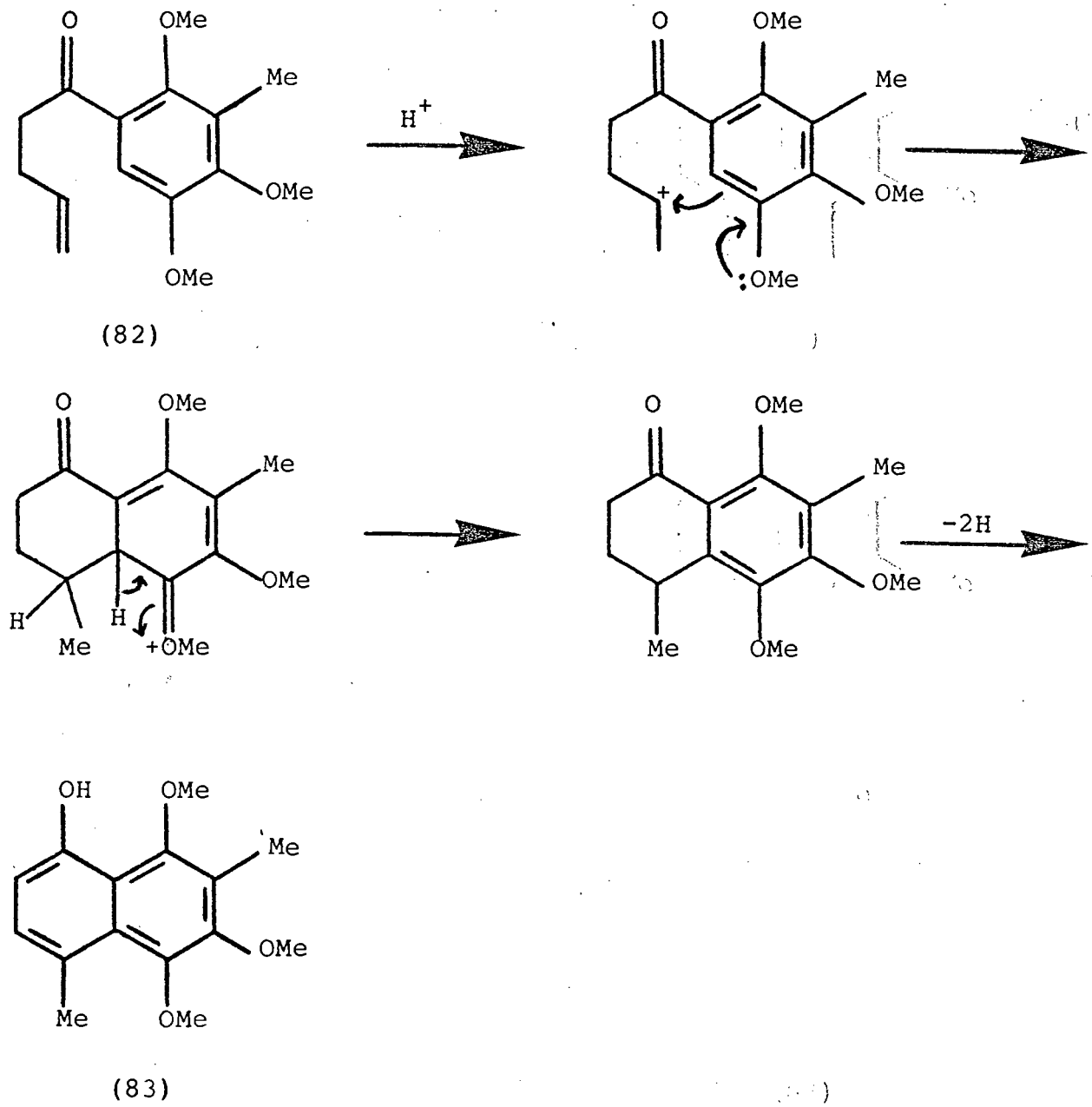


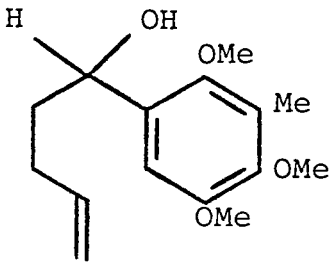
(110) (1)

SCHEME 3

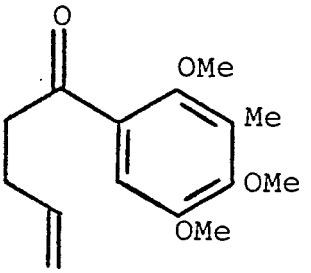


SCHEME 4: Proposed mechanism for acid catalysed cyclisation

dichloromethane and hydrochloric acid and sulphuric acid in methanol. Furthermore, in view of the fact that the alternative Diels-Alder synthesis was proving highly successful, work was discontinued on this route.



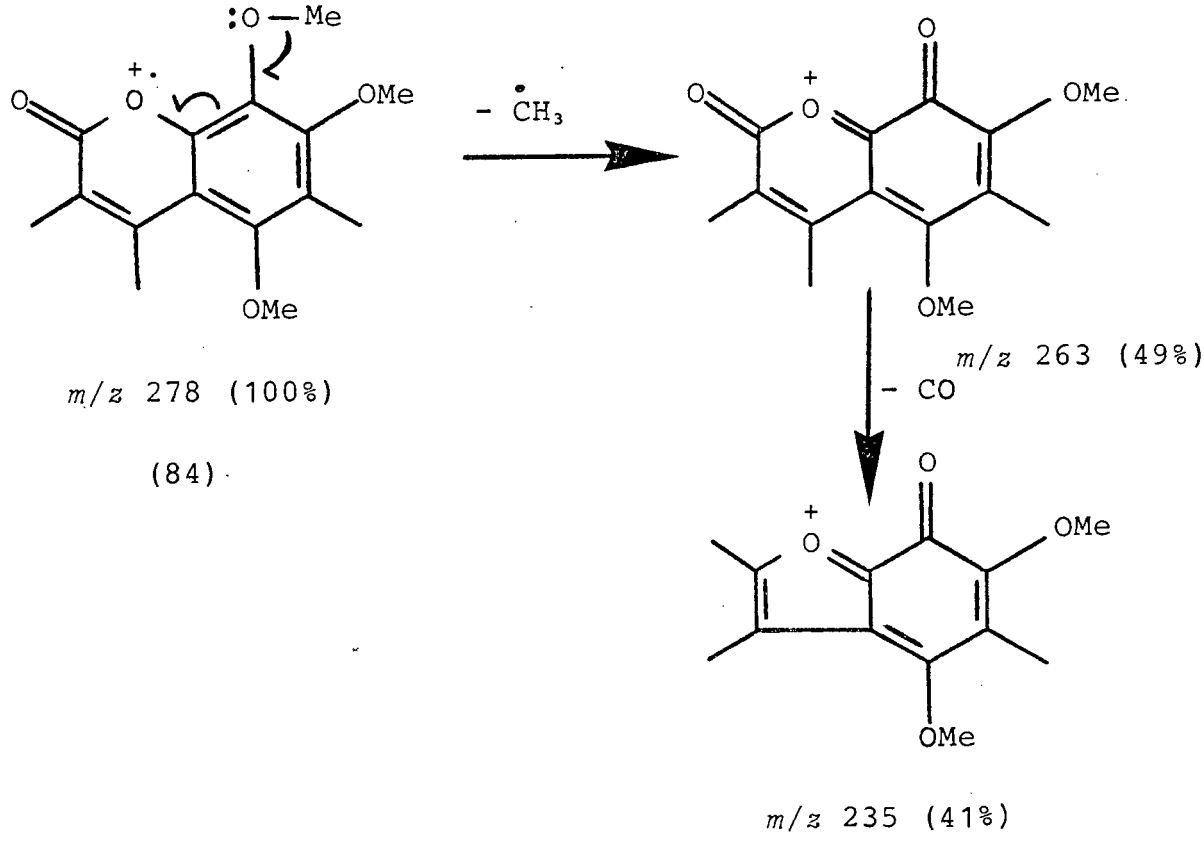
(81)



(82)

Returning to the reaction of compound (68) with premixed tiglic acid and trifluoroacetic anhydride it will be recalled that the desired product (74) was not obtained. However, it was interesting to note that the only characterisable product that was isolated from the reaction mixture was thought to be the coumarin derivative (84) obtained in 22% yield. Spectroscopic evidence that permitted the assignment of structure (84) to this compound included the mass, infra-red and ^{1}H n.m.r. spectrum. To account for the *m/z* values of the mass spectrum a fragmentation pattern is proposed and is illustrated in Scheme (5). According to this rationale the molecular ion of *m/z* 278 undergoes loss of a methyl radical to give the radical of *m/z* 263. Initial loss of a methyl radical prior to loss of CO is probably a result of the ability to stabilise itself as a quinonoid structure. An isocoumarin

would not show this ability and would more than likely lose CO initially. Subsequent loss of CO results in the species of *m/z* 235. This proposed fragmentation pattern was found to be consistent with the fragmentation patterns of similar methoxy coumarins as reported by Drewes [36]. The fragment with *m/z* 247 (61%) could conceivably be due to the loss of a methoxy radical from the molecular ion.



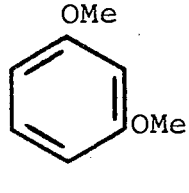
SCHEME 5: Proposed fragmentation pattern of the coumarin derivative (84)

The infra-red spectrum of compound (84) shows a carbonyl absorption at 1723 and two absorptions at 1641 and

1571 cm^{-1}. These absorptions are characteristic of an α-pyrone system.[37] The ^1H n.m.r. spectrum showed inter alia two singlets (δ2.23 and δ2.29) integrating for 6 protons, corresponding to the coumarin methyl substituents. A tentative mechanism to rationalise the formation of this unexpected product is set out in Scheme (6) (page 40). In terms of this proposal not all the acid is converted into the mixed anhydride. The free acid undergoes nucleophilic attack and concomitant protonation to form the dihydroxy intermediate which immediately undergoes cyclisation by nucleophilic attack of the hydroxy oxygen at the electrophilic carbon centre and subsequent aromatization to afford the coumarin (84). A mechanistic pathway for the formation of the expected yet not obtained product (74) has been proposed and is illustrated in Scheme (7) (page 41), as well as a possible indanone.

When congruous reaction conditions were employed using the analogous substrates (85), (86), (87) and (88) complex reaction mixtures resulted and no characterisable product was isolated.

Whether other substrates will lend themselves to coumarin formation under similar conditions and in the desired sense remains to be seen.



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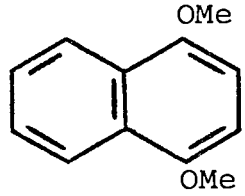
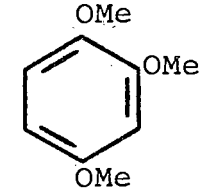


(86)

(87)



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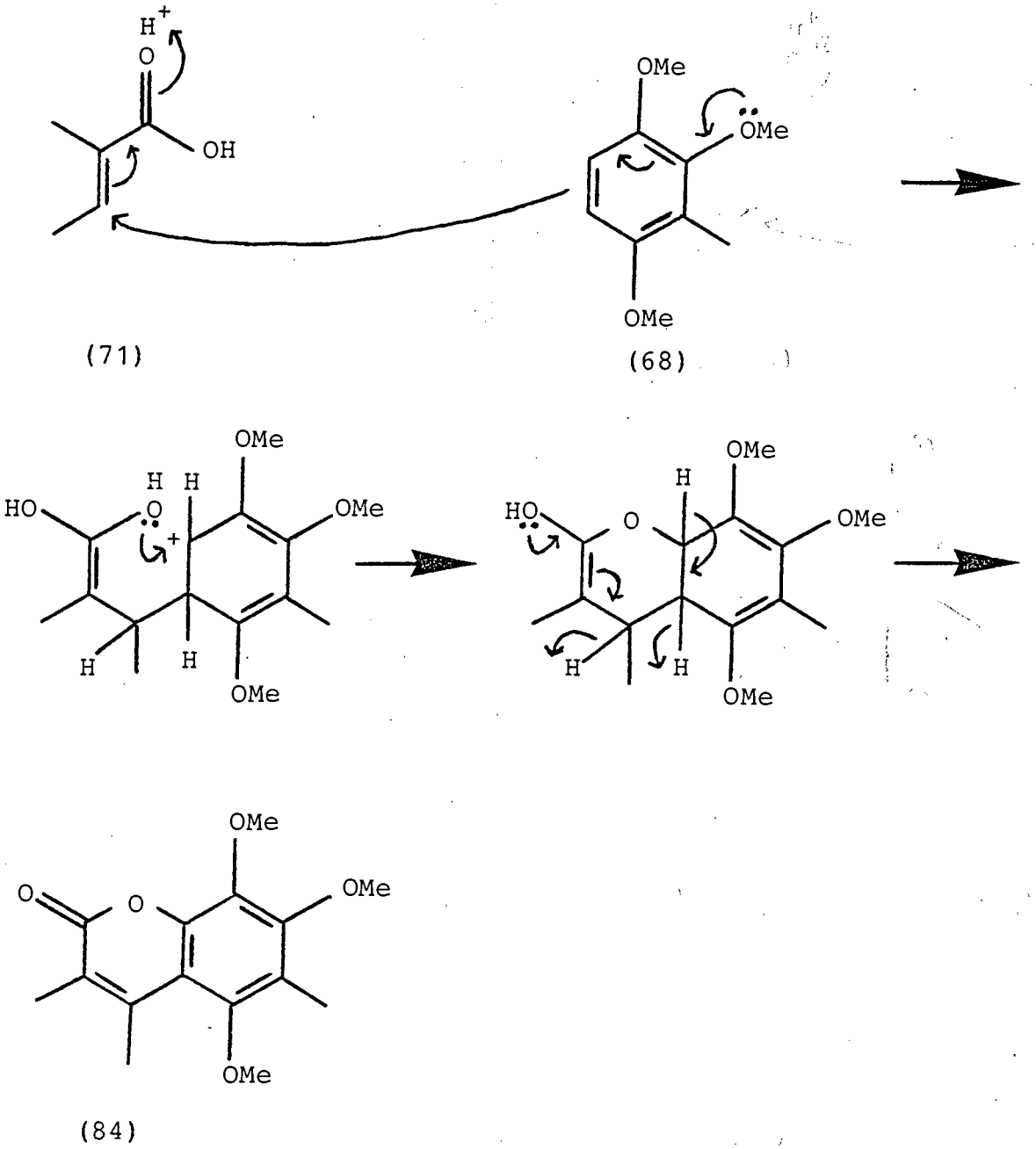
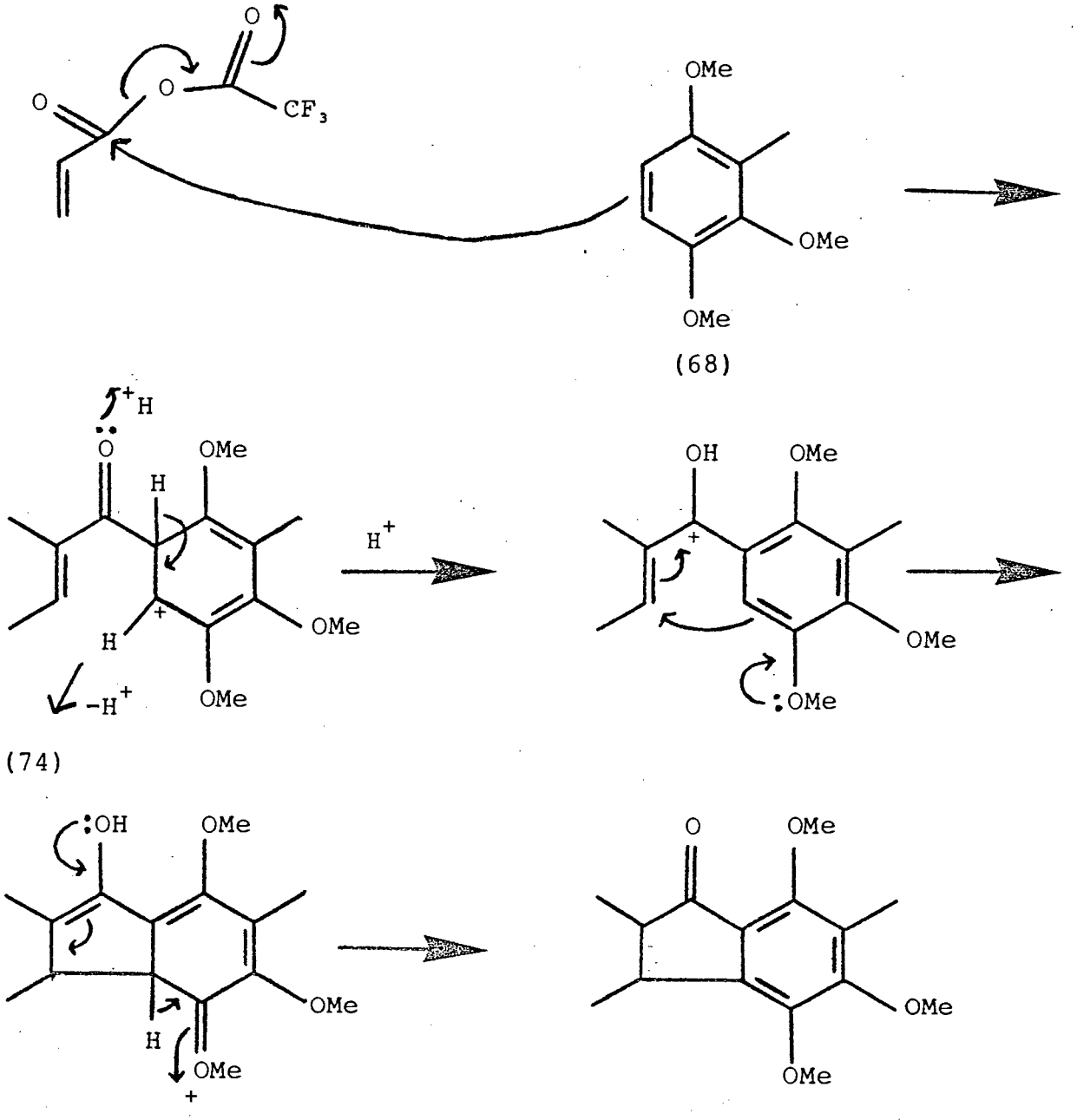


SCHEME 6: Proposed mechanism for coumarin formation



SCHEME 7: Proposed mechanism for expected reaction between compound (68) and tiglic acid

CHAPTER 3

THE SYNTHESIS OF ARISTOLINDIQUINONE VIA THE DIELS-ALDER REACTION

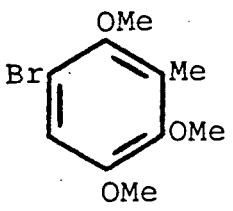
Another solution to the problem posed by the synthesis of aristolindiquinone (1) was realised via the Diels-Alder reaction of the quinonoid dienophile (90) with the syloxy diene (109). This synthesis (Scheme 8, page 53) was found to be advantageous in comparison to the Stobbe condensation reaction route (Scheme 1, page 17) for three reasons. First, it is a convergent synthesis involving far fewer reaction steps; secondly, the reactions undertaken, in general, are simpler; and thirdly, there is a decrease in the total reaction time and an increase in the overall yield. The synthesis herein described underlines the synthetic utility of the regiospecific Diels-Alder reaction technique.

We envisaged that compounds (90) and (97) constituted feasible dienophiles for the desired Diels-Alder reaction with diene (109). To this end synthetic routes to dienophiles (90) and (97) were investigated. A route was finally devised which gave a satisfactory yield of compound (90); however, attempts to synthesize the dienophile (97) proved unsuccessful.

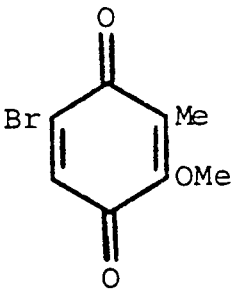
The initial aim was to synthesise bromoquinone (90) via bromination of the trimethyl ether (68) to give compound (89) and its subsequent oxidation to the quinonoid level. Bromination of compound (68) proceeded easily in a solution of acetic acid containing sodium acetate to give the bromo derivative (89) in a 75% yield. Rapoport[38] showed that hydroquinone dimethyl ethers were efficiently oxidised with silver(II) oxide in dioxan containing nitric acid to yield the corresponding ortho and para quinones. However, the oxidation of compound (89) with argentic oxide in dioxan and nitric acid showed extensive decomposition of starting material when monitored by t.l.c.. This was in contrast to its expected stability towards silica gel and consequently we assumed that compound (89) would not oxidize in the required mode. As an alternative oxidant, cerium (IV) ammonium nitrate afforded the desired product (90) albeit in a low yield of 20%, as well as two other major components, one of which was red on t.l.c. and ran at a lower R_F than the starting material (89). This was assumed to be the corresponding ortho quinone but it was not isolated due to its susceptibility to decomposition during chromatography.

We anticipated that oxidation of the phenol (92) would proceed more readily than oxidation of the methyl ether (89). Hence, according to the procedure adopted earlier for compound (68), the formate ester (59) was brominated to

yield a clean mixture of compounds (91) and (92). The crude reaction mixture was directly hydrolysed with dilute sodium hydroxide which gave solely the labile bromo phenol (92) in a crude yield of 83%. Oxidation of the crude phenol (92) with cerium (IV) ammonium nitrate gave the required bromoquinone (90) in a yield of 45%. The present synthetic route to the target bromoquinone (90) was unattractive due to its length and impracticability and thus new routes to compound (90) were explored.



(89)



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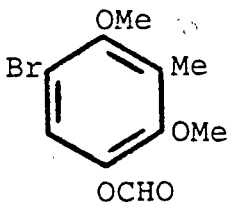
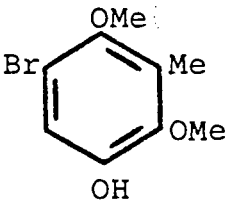
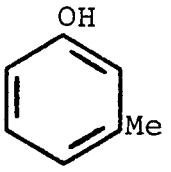


(91)



(92)

In general the presence of a halogen <u>para</u> to a phenolic group facilitates and improves yields of oxidation reactions[2,39]. Trost[40] has shown the twofold purpose for the bromination of <u>meta</u>-cresol (93) to give the bromo derivative (94) in a yield of 83%. First, the bromine <u>para</u> to the phenolic function facilitates oxidation to the <u>para</u>- quinone (95) in a yield of 84% using chromium trioxide in acetic acid, and secondly, the bromine <u>para</u> to the methyl group controls the orientation of the reaction of the two Diels-Alder partners.



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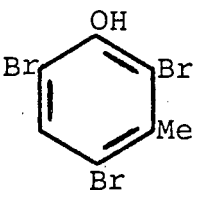

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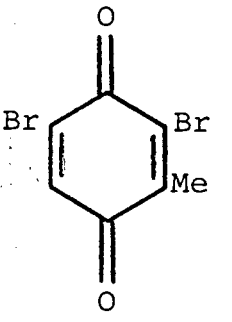
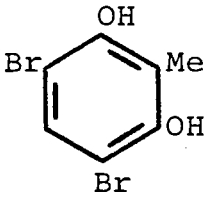
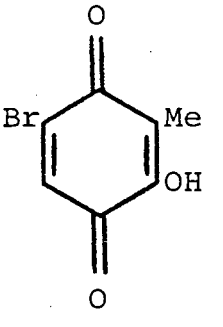


(95)

Thus, an alternative route was devised which embraced the above idea. It was envisaged that the bromoquinone (97), possessing the required substitution pattern, represented a plausible dienophile in the Diels-Alder reaction with diene (109) to give aristolindiquinone (1) and could conceivably be obtained by bromination of the diol (56) and its subsequent oxidation to the quinonoid level. According to the previously mentioned bromination procedure, dihydroxytoluene (56) afforded the dibromo-compound (96) in 84% yield. The subsequent oxidation procedure with chromium trioxide and acetic acid, however, resulted in total decomposition of starting material as witnessed by a t.l.c. investigation of the reaction product.



(96)

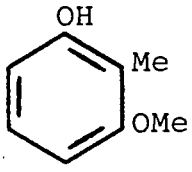


(97)

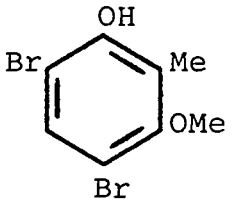
This result can be understood in terms of the lesser stability of hydroxy-quinones in comparison with their corresponding methoxy compounds. Hence we returned to our original aim of obtaining a more efficient synthesis of the dienophile (90).

Giles[41] showed that the mono demethylation of the dimethoxy compound (57) using sodium thioethoxide gave the phenol (98) in a yield of 70%. Owing to the large quantity of the phenol (98) required and due to the unpleasant nature of ethane thiol, an alternative synthesis was investigated. Instead, the phenol (56) was methylated with 1.1 mol equiv. of dimethyl sulphate which gave a mixture of monomethyl ether (98), dimethyl ether (57) and starting material (56). The dimethyl ether (57) (35%) was easily separated from the starting material (56) and product (98) by extraction of the latter two compounds, from an ether solution of the mixture, with aqueous sodium hydroxide. The product (98) (35%) was then readily separated from the starting material (56) (25%) by column chromatography.

Bromination of the mono methyl ether (98) proceeded easily to give the crystalline dibromo compound (99) in a 98% yield. Subsequent chromium trioxide oxidation of compound (99) in an aqueous solution of acetic acid gave the required bromoquinone (90) in a yield of 83%.



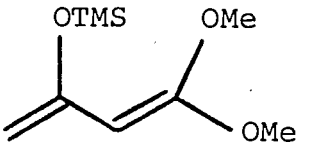
(98)



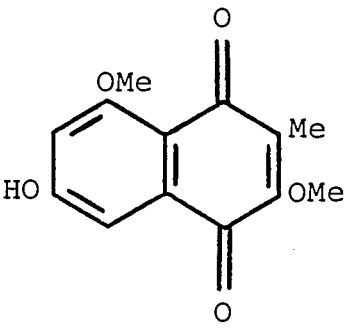
(99)

This synthesis is far superior to the route previously described as it involves far fewer and comparatively simpler reaction steps which result in a decrease in the total reaction time and an increase in the overall yield. Having achieved a preparative synthesis of the dienophile (90) its reactivity and selectivity was investigated using a well-established diene as a model.

Brassard[42] has synthesized and shown the usefulness of diene (100) in Diels-Alder reactions. Thus this diene was reacted with the dienophile (90) in anhydrous tetrahydrofuran at room temperature. Aromatization of the corresponding Diels-Alder adduct was achieved by the addition of a solution of aqueous sodium hydrogen carbonate (1%) with stirring in the presence of air. The expected phenolic naphthoquinone (101) was neither isolated nor purified due to its susceptibility to decomposition on silica. Instead, it was directly converted to its methyl ether (102) in a yield of 91% by methylation with methyl iodide in the presence of silver(I) oxide.

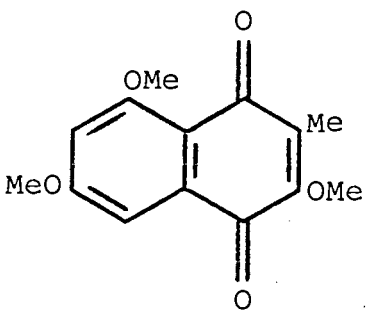


(100)

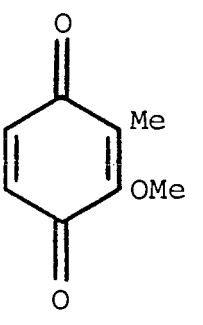


(101)

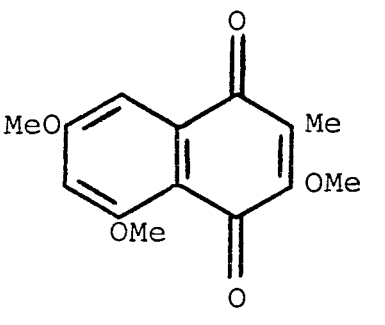
It was considered pertinent to investigate the selectivity induced by the bromine substituent in order to obtain an overview of the regiospecific reactivity of the bromoquinone (90). It was envisaged that the debromo analogue (103), readily prepared in a yield of 94% by cerium (IV) ammonium nitrate oxidation of the phenol (63), would concede the alternative isomer (104) when treated with diene (100) under the above mentioned conditions.[41] In practice this was found to be coincident with expectations, the alternative regioisomer (104) being produced in a yield of 89%. This conclusively showed the effectiveness of bromine as a directing group and also opens a synthetic route to the regiochemical isomer of aristolindiquinone (1), viz. compound (2).



(102)

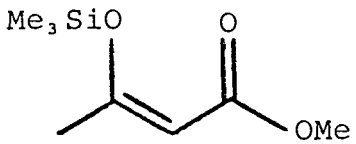


(103)

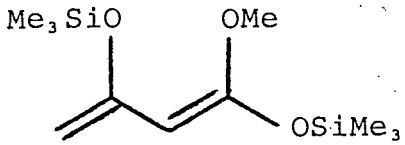


(104)

The synthesis of the required diene (109) was next investigated. Chan[43] reported the synthesis of diene (106), assigned the E-isomer, in a yield of 93% by deprotonation of the ester (105) with lithium diisopropylamide in tetrahydrofuran at 0° C followed by quenching with trimethylchlorosilane at -78°C.

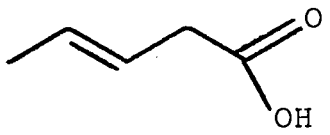


(105)

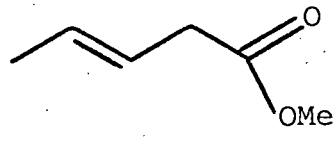


(106)

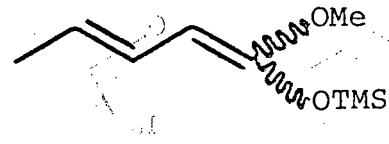
Preparation of the diene (109) commenced with the condensation of malonic acid and propionaldehyde according to a literature procedure[44,45] to give the β,γ-pentenoic acid (107) in a yield of 35%. Subsequent conversion to the methyl ester (108) was effected in a near quantitative yield by refluxing the acid (107) in methanol containing a catalytic quantity of sulphuric acid. Application of the same strategy to the ester (108) as that employed by Chan[43] proceeded uneventfully to give the diene (109) in a nearly quantitative yield. It was found that the diene (109) slowly hydrolyses to (108) on standing exposed to air but can be kept stoppered for up to two weeks at -10° C without any significant decomposition occurring.



(107)



(108)



(109)

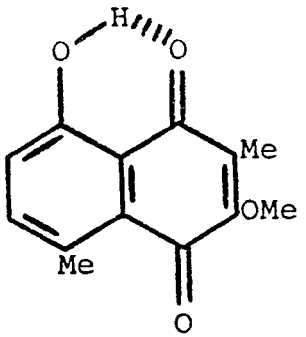
The Diels Alder reaction between dienophile (90) and diene (109) (1.5 mol equiv.) was found to proceed in best yields when reacted in a large volume of benzene at 60 ° C for 4 hours under a nitrogen atmosphere. A t.l.c. investigation of the reaction product showed an intermediate being formed having a lower R_F than that of starting material (90), which was not isolated due to its instability towards silica gel. Subsequent pyrolysis of the reaction mixture at 60°C for 30 min in air solely afforded the desired naphthoquinone (110) in a yield of 60%.

Demethylation of the methyl ether (110) was initially achieved by heating it at 60° C in a 3% sodium hydroxide solution to give aristolindiquinone (1) in a poor yield of 50%. This low yield was ascribed to the difficulty in forming the required dianion brought about by the presence of the existing hydroxy group as well as the viable decomposition pathways of the anionic intermediates. In an attempt to improve the yield, demethylation was attempted using concentrated sulphuric acid (98%), however, at room

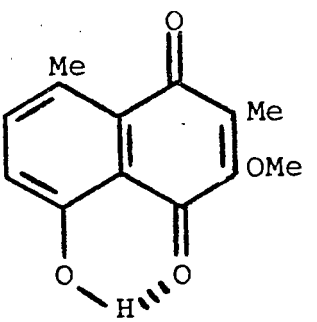
temperature no reaction took place and at 60°C total decomposition of starting material occurred. Best results were finally achieved by boron trichloride (4 mol equiv.) mediated demethylation of compound (110) in anhydrous dichloromethane at 0°C which afforded aristolindiquinone (1) in a yield of 85%. The quinone's chemical and physical properties corresponded to those of a naturally occurring sample of aristolindiquinone (1), kindly provided by Professor C. Cordell.[6]

As a spectroscopic, physical and biological comparison, the regiochemical isomer of aristolindiquinone, viz. compound (2), was synthesized. The diene (109) was reacted with the dienophile (103) under the conditions prescribed and gave the expected isomer (111) in 58% yield and a small quantity of the regioisomer (110) in 8% yield. The product (111) was purified by recrystallization from hexane. As an alternative purification method, the mixture was dissolved in dichloromethane and treated with a solution of boron trichloride in dichloromethane at 0°C for 20 min. This resulted in selective demethylation of isomer (110) to give aristolindiquinone (1) which has a significantly lower R_F than compound (111). Subsequent chromatography resulted in easy separation of the mixture to give compound (111) and aristolindiquinone (1) respectively.

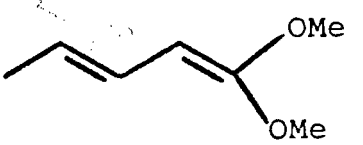
It was interesting to note that isomer (110) was more stable towards chromatography than isomer (111). Demethylation of compound (111) proved ineffectual using a large excess of boron trichloride or aluminium trichloride in dichloromethane; presumably due to the fact that complex formation preferentially occurs with only the hydroxy oxygen in the peri position. Demethylation was finally accomplished by heating compound (111) in a 3% aqueous sodium hydroxide solution to give compound (2) in a yield of 38%. That the regioisomer (2) was obtained manifested itself in the ^{1}H n.m.r. spectrum which showed inter alia an upfield shift of the proton ortho to the hydroxyl group (δ7.08) relative to the chemical shift (δ 7.62) for the corresponding proton in aristolindiquinone (1). This observation is accordant with the anticipated decrease in the hydrogen bonding suffered as a result of the competitive hydrogen bonding of the ortho-hydroxyl hydrogen.



(110)



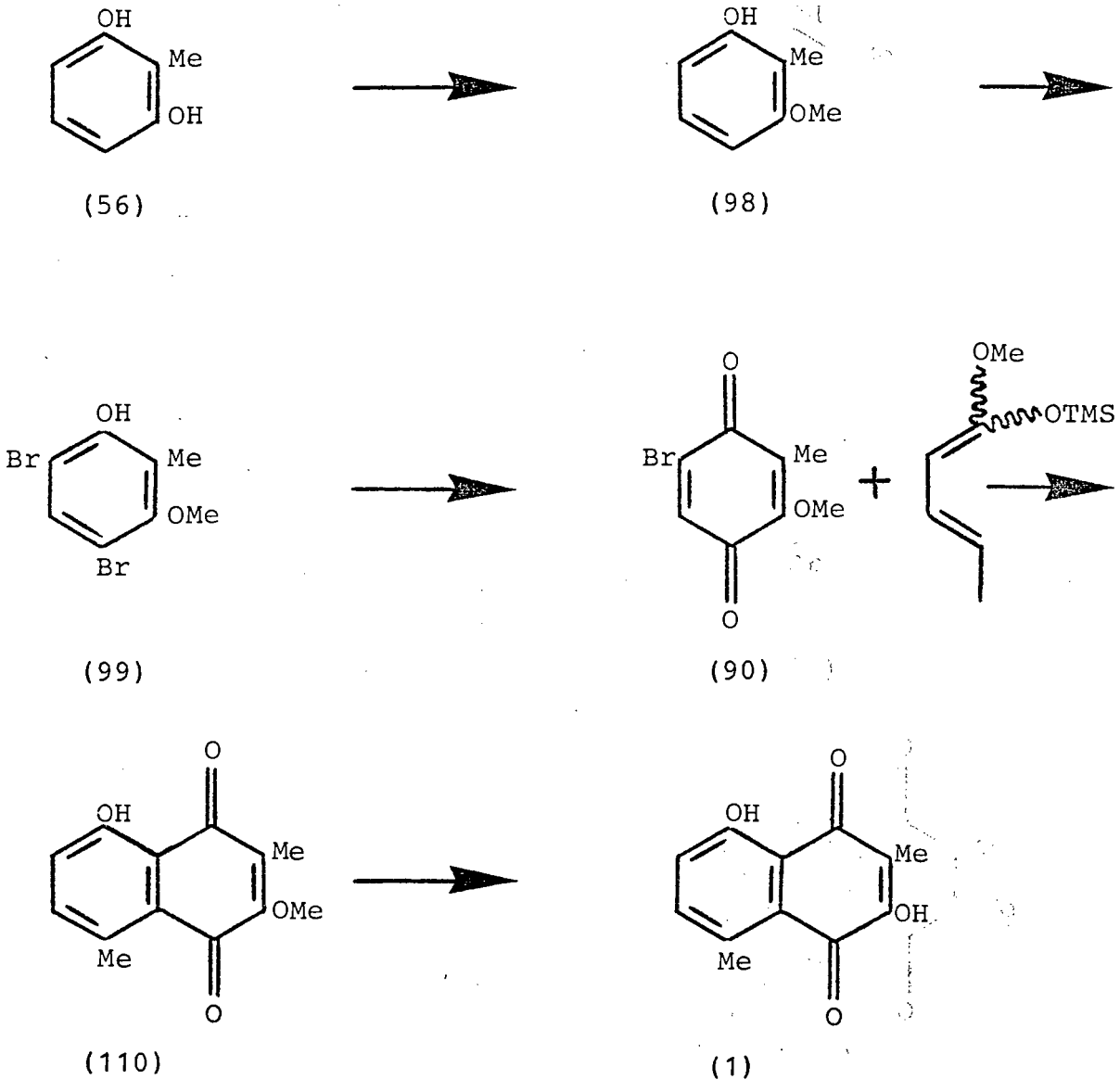
(111)



(112)

The relatively low yields for the latter two Diels-Alder reactions, to form the naphthoquinone (110) and (111) in 60

and 58% respectively, were considered due to the unreactivity of the diene (109), as the reactivity of the quinone (90) has already been shown. It seemed advisable at this point to convert the diene into a more reactive form. A promising alternative could possibly be the use of the alternative diene (112), as yet not synthesized. Whether this would lend itself to addition to bromoquinone (90) in the desired sense and in higher yield remains to be seen.



SCHEME 8

CONCLUSION

In this project we have successfully synthesized aristolindiquinone (1) via two independent routes. The synthesis via the Stobbe route (Scheme 1) entails 10 steps and results in an overall yield of 1%. The Diels-Alder route (Scheme 8) was found to be far superior than the above route with aristolindiquinone (1) being synthesized in an overall yield of 22% in only 5 reaction steps. This route compares favourably with the synthesis of aristolindiquinone by Pakrashi[23]; (overall yield (7%), steps (7)).

EXPERIMENTAL

GENERAL

1. ^{1}H n.m.r. spectra were recorded on a 100 MHz Varian XL-100 and a 90 MHz Bruker WH-90. All ^{1}H n.m.r. spectra were recorded at ambient temperature in deuterochloroform using tetramethylsilane as an internal standard.

2. Mass spectra were recorded on a VG Micromass 16 F mass spectrometer at 70 eV and an ion source temperature between 180 and 220°C.

3. Infra-red spectra were measured for Nujol mulls unless otherwise stated using a Perkin-Elmer 983 spectrophotometer.

4. Elemental analyses were performed on a Heraeus CHN-RAPID analyser.

5. Melting points were determined on a Fisher-John melting point apparatus and are quoted uncorrected.

6. Column chromatography was performed on dry columns using Merck Kieselgel 60 (70-230 mesh), the material to be separated being preadsorbed onto Merck Kieselgel 60 (35-70 mesh). Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while thin layer chromatography (t.l.c.) was

carried out on aluminium plates coated with the same material.

7. Light petroleum refers to the fraction of boiling point 60-80°C, and ether to diethyl ether.

8. Anhydrous magnesium sulphate was used to dry the organic solvents after extraction procedures, and most organic solvents and liquid reagents were distilled immediately before use.

2-hydroxy-5-methyl benzaldehyde (31)

A solution of sodium hydroxide (84.0 g) in water (150 ml) was added to a stirred solution of the phenol (30) (30.0 g, 277.8 mmol) in water (60 ml). Chloroform (69.5 g, 581.6 mmol) was introduced in three portions, at intervals of 15 min, with the reaction mixture being maintained at 60-65°C by immersing the flask in an ice bath. The solution was then heated at 100°C for 1 hour after which the excess chloroform was removed by distillation, the solution was acidified with dilute hydrochloric acid and extracted with ether. The organic layer was dried over magnesium sulphate, filtered, and the solvent removed to yield a residue which was chromatographed (eluant 2% ethyl acetate - light petroleum). Early fractions afforded the aldehyde (31) (14.4 g, 38%) as colourless needles, m.p. 54-57°C (ethanol-water) (Lit.,[46] 56°C).

2-methoxy-5-methyl benzaldehyde (33)

The phenol (31) (3.22 g, 23.7 mmol) was dissolved in anhydrous acetone (250ml). Thereafter potassium carbonate (3 mol equiv.) and dimethyl sulphate (3 mol equiv.) were added and the mixture allowed to stir for 24 hours at room temperature. The excess potassium carbonate was removed by filtration and the acetone was evaporated to yield a residue which was taken up in ether and washed successively with aqueous ammonia (25%) (twice), water, dilute hydrochloric acid and then more water. After separation the ether layer was

dried over magnesium sulphate, filtered and the ether removed to give a residue which was chromatographed (eluant 10% ethyl acetate - light petroleum) to yield the product (33) (3.34 g, 94%) as a clear oil, $\nu_{max.}$ 1671 cm^{-1} (C = O); δ2.28 (3H, s, $ArCH_3$), 3.82 (3H, s, OCH_3), 6.87 (1H, d, *J* 9 Hz, 3-H), 7.35 (1H, dd, *J* 9. and 2 Hz, 4-H) and 7.62 (1H, d, *J* 2 Hz, 6-H).

Attempted formylation of para-methyl anisole (32)

Para-methyl anisole (32) (400 mg, 3.28 mmol) was reacted under the same conditions as compound (57) in the preparation of compound (58) (page 68). Upon workup significant decomposition of starting material was noted but no product could be characterised.

Ethyl 4-acetoxy-5-methyl-8-methoxy-2-naphthoate (35)

The aldehyde (33) (5.54 g, 36.9 mmol) and diethyl succinate (8.7 g, 49.9 mmol) in sodium-dried t-butyl alcohol (66 ml) were added to a solution of potassium t-butoxide (50 mmol) [from potassium (1.99 g) and t-butyl alcohol (51 ml)]. The resultant solution was boiled under reflux for 1 hour then thrown into water, acidified, and extracted with ether. After separation, the acid product was extracted (3 times) from the organic phase with aqueous sodium hydrogen carbonate. The aqueous fractions were combined, acidified, and the organic material extracted with ether, which was then dried over magnesium sulphate, filtered, and evaporated to give the

crude benzylidenesuccinic half ester (34) (6.52 g) as an oil. Without further purification this was boiled under reflux with anhydrous sodium acetate (4.26 g) in acetic anhydride (47 ml) for 5.5 hours and then poured into water (300 ml). The organic material was extracted with ether (4 x 75 ml), combined, and backwashed with water before being dried over magnesium sulphate, filtered and the ether evaporated to yield a residue which after chromatography (eluant 10% ethyl acetate - light petroleum) afforded the napthoate (35) (3.90 g, 35%) as transparent cubes, m.p. 156-157°C (dichloromethane-light petroleum) (Found: C,67.7; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.6; H, 5.9%); $\nu_{max.}$ 1758 and 1705 cm^{-1} (C = O); δ1.39 (3H, t, 7 Hz, $CH_2\underline{CH_3}$), 2.35 (3H, s, $OCOCH_3$), 2.63 (3H, s, $ArCH_3$), 3.91 (3H, s, OCH_3), 4.38 (2H, q, *J* 7 Hz, CH_2), 6.67 (1H, d, *J* 8 Hz, 7-H), 7.17 (1H, bd d, *J* 8 Hz, 6-H), 7.66 (1H, d, *J* 2 Hz, 1-H) 7.89 (1H, d, *J* 2 Hz, 3-H); *m/z* 302(M^+,16%), 261(17), 260(100), 246(10), 245(15), 232(9), and 231(6).

Attempted reduction of ethyl 4-acetoxy-5-methyl-8-methoxy-3-naphthoate (35)

The same procedure was adopted for compound (35) (250 mg, 3.3 mmol) as for the reduction of the naphthoate (38) in the preparation of the alcohol (40) (page 61). After workup, however, a t.l.c. investigation showed total decomposition of starting material and no characterisable product.

Ethyl 4-(2-propyloxy)-5-methyl-8-methoxy-2-naphthoate (38)

The naphthoate (35) (450.0 mg, 1.49 mmol) was dissolved in a sodium hydroxide solution (1%) in methanol (100 ml) and stirred at room temperature for 20 min before the solution was diluted with water (300 ml), acidified with dilute hydrochloric acid and extracted with ether. After separation the ether layer was dried over magnesium sulphate, filtered, and evaporated to give the crude naphthol (37) (334.0 mg). This was dissolved in dry dimethylformamide (36 ml), thereafter isopropyl bromide (0.68 ml) and potassium carbonate (1.5 g) were added and the solution heated at 60°C under nitrogen overnight. After the solution had cooled, it was filtered, diluted with water (300 ml) and exhaustively extracted with ethyl acetate. Magnesium sulphate was then added to the separated ethyl acetate layer; this was filtered and evaporated to give a residue which was chromatographed (p.l.c. eluant 30% ethyl acetate-light petroleum) to yield the product (38) (420.0 mg, 93%) as a pale yellow oil (Found: C, 71.2; H, 7.1. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%); $\nu_{max.}$ 1710 cm^{-1} (C = O); δ1.41 (3H, t, *J* 7 Hz, $CH_2\underline{CH_3}$), 1.42 (6H, d, *J* 6 Hz, $C(CH_3)_2$), 2.78 (3H, s, $ArCH_3$), 3.91 (3H, s, OCH_3), 4.39 (2H, q, *J* 7 Hz, CH_2), 4.78 (1H, septet, *J* 6 Hz, $(CH_3)_2\underline{CH}$), 6.66 (1H, d, *J* 8 Hz, 7-H), 7.12 (1H, d, *J* 8 Hz, 6-H), 7.38 (1H, d, *J* 2Hz, 1-H), and 8.55 (1H, d, *J* 2 Hz, 3-H); *m/z* 302(M^+, 54%), 288(21), 261 (17), 260(100), 246(38), 245(17), 232(17), 231(21), and 217(9).

2-propyl 5-methyl-8-methoxy-4-(2-propyloxy)-2-naphthoate (39)

The naphthoate (35) (300 mg, 0.99 mmol) was refluxed in a sodium hydroxide solution (10%) in methanol (50 ml) for 30 min. The same isopropylation procedure was then applied as previously described in the preparation of compound (38) and the product (39) (282 mg, 90%) was obtained as a pale yellow oil; $\nu_{max.}$ (neat) 1700 cm^{-1} (C = O); δ1.44 (6H, d, *J* 6 Hz, $C(CH_3)_2$), 1.47 (6H, d, *J* 6 Hz, $C(CH_3)_2$), 2.86 (3H, s, $ArCH_3$), 3.98 (3H, s, OCH_3), 4.83 (1H, Septet, *J* 6 Hz, $(CH_3)_2$ CH), 5.33 (1H, Septet, *J* 6 Hz, $(CH_3)_2$CH), 6.70 (1H, d, *J* 8 Hz, 7-H), 7.17 (1H, d, *J* 8 Hz, 6-H), 7.47 (1H, bd s, 1-H), and 8.62 (1H, d, *J* 1.4 Hz, 3-H); *m/z* 316(M^+, 51%), 274(70), 232(100) and 217(28).

7-methylalcohol-1-methoxy-4-methyl-5-(2-propyloxy) naphthalene (40)

The naphthoate (38) (420.0 mg, 1.39 mmol) was dissolved in anhydrous ether (10 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (55 mg, 1.44 mmol) in dry ether (10 ml) over 5 min at room temperature. After allowing the solution to stir for a further 10 min, sufficient saturated ammonium chloride was added to destroy the excess of lithium aluminium hydride and magnesium sulphate was then added. The mixture was then dried over magnesium sulphate, filtered and the ether removed under reduced pressure to give the product (40) (307.8 mg, 85%) as white needles, m.p. 96.0-96.5°C (light petroleum-dichloromethane) (Found: C, 73.8; H, 7.7. $C_{16}H_{20}O_3$

requires C, 73.8; H, 7.7%); $\nu_{max.}$ 3292 (OH) and 1276 cm^{-1} (O-$CH(CH_3)_2$); δ1.40 (6H, d, *J* 6 Hz, $C(CH_3)_2$), 1.74 (1H, t, *J* 6 Hz, OH, D_2O exchangeable), 2.77 (3H, s, 4-CH_3), 3.89 (3H, s, OCH_3), 4.71 (1H, septet, *J* 6 Hz, $CH_3\underline{CH}CH_3$), 4.73 (2H, d, *J* 6 Hz, CH_2), 6.63 (1H, d, *J* 8 Hz, 2-H), 6.82 (1H, bd s, 8-H), 6.99 (1H, d, *J* 8 Hz, 3-H), and 7.71 (1H, bd s, 6-H); *m/z* 260(M^+, 40%), 219(21), 218(100), 217(16), 203(39), 126(10), and 115(10).

1-methoxy-4,7-dimethyl-5-(2-propyloxy) naphthalene (41)

The alcohol (40) (307.0 mg, 1.18 mmol) was added to a suspension of ethyl acetate (160 ml), concentrated hydrochloric acid (3 drops) and 10% palladium on carbon (1.004g) and stirred for 35 min at room temperature under a hydrogen atmosphere. The solution was then filtered, evaporated and the crude solid chromatographed (eluant 10% ethyl acetate - light petroleum) to afford the product (41) (162 mg, 56%) as transparent cubes, m.p. 93-94°C (light petroleum-dichloromethane) (Found: C, 78.5; H, 8.2. $C_{16}H_{20}O_2$ requires C, 78.7; H, 8.2%); $\nu_{max.}$ 1272 cm^{-1} (O-$CH(CH_3)_2$); δ1.39 (6H, d, *J* 6 Hz, $CH(\underline{CH_3})_2$), 2.43 (3H, d, *J* 0.5 Hz, 7-CH_3), 2.77 (3H, d, *J* 0.5 Hz, 4-CH_3), 3.89 (3H, S, OCH_3), 4.68 (1H, Septet, *J* 6 Hz, $\underline{CH}(CH_3)_2$), 6.60 (1H, d, *J* 7.5 Hz, 2-H), 6.64 (1H, d, *J* 0.5 Hz 8-H), 6.94 (1H, d, *J* 7.5 Hz, 3-H), and 7.58 (1H, d, *J* 0.5 Hz, 6-H); *m/z* 244(M^+, 72%), 202(100), 201(26), 167(65), 159(11), 158(10), 141(16), 120(18), and 115(28).

3,8-dimethyl-5-methoxy-1-naphthol (42)

The napthalene (41) (50.0 mg, 0.205 mmol) was dissolved in dry dichloromethane (5 ml) and a solution of boron trichloride (55 mg, 0.47 mmol) in dry dichloromethane (5 ml) was added. The mixture was stirred for 30 min at 0°C; the reaction being terminated by the addition of water and the extraction of the product into dichloromethane. After separation the organic phase was dried over magnesium sulphate, filtered and evaporated to give a residue which was chromatographed (p.l.c. 20% ethyl acetate - light petroleum, showed significant decomposition). The front band yielded the product (42) (21.8 mg, 53%) as white needles, m.p. 128.5°C (light petroleum), $\nu_{max.}$ 3501 cm^{-1} (OH); δ2.36 (3H, s, $ArCH_3$), 2.79 (3H, s, $ArCH_3$), 3.88 (3H, s, OCH_3), 5.24 (1H, s, OH, D_2O exchangeable), 6.52 (1H, d, *J* 1.5 Hz, 4-H), 6.59 (1H, d, *J* 7.5 Hz, 5-H), 6.95 (1H, d, *J* 7.5 Hz, 7-H), and 7.60 (1H, d, *J* 1.5 Hz, 2-H); *m/z* 202(M^+, 100%), 187(76), 159(14), 141(11), 115(13), and 101(8).

2-hydroxy-5-methoxy-3,8-dimethyl-1,4-naphthoquinone (46)

METHOD 1

The acetate (54) (45.0 mg, 0.164 mmol) was dissolved in ether (30 ml) and then washed with an aqueous sodium hydroxide (5%) solution until the yellow ether layer turned colourless. The aqueous phase was then separated, acidified with dilute hydrochloric acid and extracted with ether

(twice). The organic fractions were combined and dried over magnesium sulphate, filtered and evaporated to give a yellow solid which was chromatographed (p.l.c. eluant 30% ethyl acetate - light petroleum) to yield the product (46) (28.1 mg, 75%) as yellow crystals, m.p. 131-132°C (methanol) (Found: C, 67.3; H, 5.2. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); $\nu_{max.}$ 3321 (OH), 1650 and 1629 cm^{-1} (C = O); δ2.04 (3H, s, CCH_3), 2.66 (3H, s, CCH_3), 3.95 (3H, s, OCH_3), 7.19 (1H, d, *J* 9 Hz, 6-H), 7.28 (1H, s, OH), and 7.39 (1H, d, *J* 9 Hz, 7-H); *m/z* 232(M^+, 100), 217(18), 215(11), 203(38), 193(17), 189(26), 175(23), 158(10), and 131(16).

METHOD 2

The orthoquinone (47) (35.0 mg, 0.162 mmol) was dissolved in acetic anhydride (10 ml) and concentrated sulphuric acid (2 drops) was added and the mixture stirred. After 45 min the reaction mixture was thrown onto ice and basified with aqueous sodium hydroxide (5%). The solution was then acidified with dilute hydrochloric acid, extracted with ether and dried over magnesium sulphate. The organic solvent was filtered and evaporated to give a residue which after chromatography (10% ethyl acetate - light petroleum) afforded the product (46) (20.7 mg, 55%) as yellow needles, m.p. 130-132°C (light petroleum) (Lit.,[23] 130°C). On admixture with (46) obtained via Method 1 (page 63) the melting point showed no depression and all the spectroscopic data were found to be identical.

3,8-dimethyl-5-methoxy-1,2-naphthoquinone (47)

The naphthol (42) (150.0 mg, 0.743 mmol) was dissolved in methanol (10 ml). To this was added a solution of Fremy's salt[28] (0.4 g) in water (20 ml) and sodium acetate (0.05 g) in water (5 ml) and the mixture stirred for 30 min at room temperature. The organic material was extracted with ether, washed with water, dried over magnesium sulphate, filtered and evaporated to yield a crude red solid which was chromatographed (eluant 10% ethyl acetate - light petroleum) to yield the product (47) (128.3 mg, 80%) as fine red needles, m.p. 188-190°C (chloroform - light petroleum), volatization 190-195°C and charring 195-198°C (Lit.,[23] m.p. 108-110°C) (Found: C, 72.1; H, 5.5. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.5%); $\nu_{max.}$ 1654 and 1630 cm^{-1} (C = O); δ2.05 (3H, s, 3-CH_3), 2.58 (3H, s, 8-CH_3), 3.90 (3H, s, OCH_3), 7.02 (1H, d, *J* 8 Hz, 6-H), 7.18 (1H, d, *J* 8 Hz, 7-H), and 7.79 (1H, bd s, 4-H); *m/z* 216(M^+, 6%), 189(10), 188(100), 187(12), 173(35), 171(14), 145(23), 115(28), and 91(12); u.v. (EtOH) $\nu_{max.}$ 192(log ε 5.01), 215(5.02), 255(5.13), 387(5.18, sh) and 471(3.84) nm.

2-acetoxy-3,8-dimethyl-5-methoxy-1,4-naphthoquinone (54)

The orthoquinone (47) (40.0 mg, 0.185 mmol) was dissolved in acetic anhydride (3.5 ml) and concentrated sulphuric acid (1 drop) was added with stirring. After 50 min the reaction mixture was diluted with water and extracted with ether. The organic layer was then washed with dilute sodium

hydrogen carbonate, dried over magnesium sulphate, filtered and evaporated to yield a residue which was chromatographed (p.l.c. 30% ethyl acetate - light petroleum) to yield the product (54) (12.2 mg, 24%) as yellow needles, m.p 131-133°C (light petroleum), $\nu_{max.}$ 1768, 1662 and 1626 cm^{-1} (sh)(C = O); δ2.05 (3H, s, 3-CH_3), 2.39 (3H, s, $OCOCH_3$), 2.65 (3H, s, 8-CH_3), 3.98 (3H, s, OCH_3), 7.21 (1H, d, *J* 8 Hz, 6-H), and 7.47 (1H, d, *J* 8 Hz, 7-H); *m/z* 274 (M^+, 94%), 232(100), 217(26), 203(65), 189(19), 175(17), 131(11), and 115(19); UV (EtOH) $\nu_{max.}$ 309 (log ε 5.00) and 405 (4.74) nm.

2,5-dihydroxy-3,8-dimethyl-1,4-naphthoquinone (1)

METHOD 1

The naphthoquinone (54) (70.0 mg, 0.255 mmol) was dissolved in dry dichloromethane (10 ml) and boron trichloride (119 mg, 1.02 mmol) in anhydrous dichloromethane (2 ml) was added and the mixture was stirred for 20 min at -10°C. The reaction mixture was then thrown into water and extracted with dichloromethane which, after separation from the aqueous layer, was dried over magnesium sulphate, filtered and the solvent removed to afford a red solid which was chromatographed (p.l.c. 30% ethyl acetate - light petroleum) to afford the product (1) (47.3 mg, 85%) as red needles, m.p. 191°C (Methanol) (Lit.,[6,23] 176-178°C, 190°C) (Found: C, 65.9; H, 4.9. $C_{12}H_{10}O_4$ requires C, 66.0; H, 4.6%); $\nu_{max.}$

3322 (OH), 1641 and 1615 cm^{-1}(C = O); δ2.03 (3H, s, 3-CH_3), 2.62 (3H, bd s, 8-CH_3), 7.12 (1H, d, *J* 8 Hz, 6-H), 7.32 (1H, d, *J* 8 Hz, 7-H), 7.62 (1H, s, 2-OH), and 10.76 (1H, s, 5-OH); *m/z* 218(M^+, 100%), 190(21), 175(13), 172(14), 161(17), 147(22), 135(13) and 115(25).

METHOD 2

As an alternative route to compound (1) the naphthoquinone (46) (101 mg, 0.435 mmol) was dissolved in dry dichloromethane (10 ml) and boron trichloride (203 mg, 1.74 mmol) in dry dichloromethane (4 ml) was added and the mixture stirred for 15 min at -10°C. The reaction mixture was then thrown into ice-water and extracted with dichloromethane which, after separation from the aqueous phase, was dried over magnesium sulphate, filtered and the solvent removed to afford (1) (81 mg, 85%) as a red solid which was identical in physical and chemical properties to that of Aristolindiquinone obtained by the above method.

2,6-dimethoxy toluene (57)

2,6-Dihydroxytoluene (56) (10.0 g, 80.6 mmol), potassium carbonate (55.6 g, 402 mmol) and dimethyl sulphate (50.6 g, 402 mmol) were refluxed in anhydrous acetone (400 ml) for four hours. The reaction mixture was cooled, filtered and the solvent removed. The residue was taken up in ether and washed successively with an aqueous ammonia solution (to decompose the excess dimethyl sulphate), water, dilute

aqueous hydrochloric acid and water and dried over magnesium sulphate. The solution was filtered and the solvent removed to yield the product (57) (11.9 g, 97%) as colourless needles, m.p. 36-39°C (light petroleum) (Lit.,[47] 37.5-40°C).

2,4-dimethoxy-3-methyl benzaldehyde (58)

The Vilsmeier complex was prepared by the dropwise addition of freshly distilled phosphoryl chloride (28 ml) to dry NN-dimethylformamide (50 ml) during 30 min with stirring and cooling in ice. The complex was then allowed to warm to room temperature and was then added during 1.5-2 hours to a stirred solution of 2,6-dimethoxy toluene (57) (33.0 g, 0.22 mol) in dry NN-dimethyl formamide (50 ml) at 100-110°C (bath). Heating and stirring was continued for 4 hours. The mixture was poured onto ice-water, made just basic by the addition of aqueous sodium carbonate, and exhaustively extracted with ethyl acetate. The combined extracts were washed successively with dilute hydrochloric acid, water, and saturated brine, and finally dried over magnesium sulphate. The crude product was chromatographed (eluant 30% ethyl acetate - light petroleum) to yield the product (58) (32.1 g, 81%) as glistening needles, m.p. 54-55 °C (light petroleum) (Lit.,[26,48] 52-53°C and 54-55°C).

2,6-dimethoxy-3-formyloxytoluene (59)

The benzaldehyde (58) (2.52 g, 14.0 mmol) and meta-chloro-perbenzoic acid (3.58 g, 19.2 mmol) were heated under reflux

in anhydrous dichloromethane (56 ml) for 24 hours. Most of the dichloromethane was then removed by distillation and the residue was dissolved in ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate until effervescence ceased, and then with saturated brine, and dried over magnesium sulphate. Removal of the solvent left the crude ester which was chromatographed (eluant 10% ethyl acetate - light petroleum) to yield the product (59) (2.58 g, 94%) as a pale yellow oil, δ2.17 (3H, s, $ArCH_3$), 3.74 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.59 (1H, d, *J* 9 Hz, 4-H), 6.94 (1H, d, *J* 9 Hz, 5-H), and 8.27 (1H, s, OCHO) (Lit.,[27] δ($CDCl_3$) 8.12 (1H, s, OCHO)).

2,4-dimethoxy-3-methyl-5-acetylphenol (60)

Compound (61) (510 mg, 2.02 mmol) was dissolved in a sodium hydroxide solution (3%) in methanol (50 ml) and stirred at room temperature for 20 min before the solution was acidified with dilute hydrochloric acid. The solution was then diluted with water (200 ml) and exhaustively extracted with ethyl acetate which, after being dried over magnesium sulphate, was filtered and evaporated to give a residue which was chromatographed (p.l.c. 25% ethyl acetate - light petroleum) to afford the product (60) (360 mg, 85%) as an unstable pale yellow oil, $\nu_{max.}$ (neat) 3385 (OH) and 1669 cm^{-1} (C = O); δ2.23 (3H, s, $ArCH_3$), 2.59 (3H, s, $COCH_3$), 3.69 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.93

(1H, br s, OH, disappears on D_2O wash), and 7.1 (1H, s, ArH); *m/z* 210(M^+, 54%) and 195(100).

3-acetoxy-5-acetyl-2,6-dimethoxytoluene (61)

The formate ester (59) (290 mg, 1.48 mmol) was added to a mixture of trifluoroacetic anhydride (622 mg, 2.96 mmol) and acetic acid (71 mg, 2.22 mmol) and the mixture was kept at 60°C for 15 hours. The solution was neutralised with aqueous sodium hydrogen carbonate and exhaustively extracted with dichloromethane. The extracts were dried over magnesium sulphate, filtered and evaporated to yield a crude mixture of compound (60) and (61). The mixture was treated with acetic anhydride (2 ml) and pyridine (0.5 ml) and heated at 100°C (bath) for 3 hours. The resulting oily mixture was dissolved in ethyl acetate (50 ml) and shaken with methanol (50 ml). The solution was successively washed with dilute sodium hydrogen carbonate, water, dilute hydrochloric acid and then more water. The organic layer was dried over magnesium sulphate, filtered and evaporated to give an oil which was chromatographed (30% ethyl acetate - light petroleum) to afford the product (61) (224 mg, 60%) as a clear oil (Found: C, 61.6; H, 6.5. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.3%); δ2.22 (3H, s, $ArCH_3$), 2.29 (3H, s, $OCOCH_3$), 2.58 (3H, s, $ArCOCH_3$), 3.79 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 7.23 (1H, s, ArH); $\nu_{max.}$ (neat) 1768 and 1676 cm^{-1} (C = O); *m/z* 252(M^+, 20%), 210(90), 195(100), 184(13), and 169(9).

5-acetyl-2,3,6-trimethoxytoluene (62)

METHOD 1

The crude phenol (60) (422 mg, 2.01 mmol), prepared according to the method described in the synthesis of compound (60) (page 69), was dissolved in anhydrous acetone (250 ml), whereafter potassium carbonate (3 mol equiv.) and dimethyl sulphate (3 mol equiv.) were added and the mixture stirred overnight at room temperature. The excess potassium carbonate was removed by filtration and the acetone evaporated to yield a residue which was taken up in ether and washed successively with ammonia (25%) (twice), water, dilute hydrochloric acid and then more water. After separation, the ether layer was dried over magnesium sulphate, filtered and the ether removed to give a residue which was chromatographed (eluant 5% ethyl acetate - light petroleum) to afford the product (62) (360 mg, 80%) as a pale yellow oil (Found: C, 64.2; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%); $\nu_{max.}$ (neat) 1671 cm^{-1} (C = O); δ2.25 (3H, s, $ArCH_3$), 2.64 (3H, s, $COCH_3$), 3.72 (3H, s, OCH_3), 3.86 (6H, s, 2 x OCH_3), and 7.14 (1H, s, ArH); *m/z* 224(M^+, 62%), 209(100), and 181(12).

METHOD 2

Compound (68) (90 mg, 0.49 mmol) was added to a mixture of acetic acid (44 mg, 0.74 mmol) and trifluoroacetic anhydride (206 mg, 0.98 mmol) and the mixture stirred for 24 hours at 25°C. The solution was neutralised with aqueous sodium

hydrogen carbonate and exhaustively extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered and evaporated to yield a residue which was chromatographed (p.l.c. 5% ethyl acetate - light petroleum) to afford the product (62) (76,8 mg, 70%) with identical spectroscopic data to compound (62) obtained via Method 1.

METHOD 3

The Grignard reagent, methyl magnesium iodide, was prepared by adding magnesium pellets (150 mg, 6.1 mmol) to a solution of methyl iodide (436 mg, 3.07 mmol) in anhydrous ether (3 ml) with constant stirring until effervescence ceased and the solution turned milky. The aldehyde (78) (129 mg, 0.614 mmol) in anhydrous ether (3 ml) was introduced into the solution and allowed to stir for 20 min. Saturated aqueous ammonium chloride was then added and stirring continued for a further 20 min. The organic material was extracted with ether, washed with water, separated and the excess solvent evaporated. The residue was dissolved in acetone (0.2 ml) and Jones' reagent[35] was added. After constant stirring for 2 hours water (50 ml) was added and the organic material extracted with ether, dried over magnesium sulphate, filtered and the solvent evaporated to yield a residue which was chromatographed (p.l.c. 5% ethyl acetate - light petroleum) to afford the product (62) (80 mg, 58%) as an oil with identical spectroscopic data to compound (62) obtained via Method 1.

3-acetoxy-2,6-dimethoxytoluene (64)

The formate ester (59) (491.9 mg, 2.51 mmol) was dissolved in a 3% solution of sodium hydroxide in methanol (20 ml) and stirred at room temperature for 30 min before the solution was acidified with dilute hydrochloric acid. The methanol was then removed under reduced pressure and more water added to the residue. This was extracted repeatedly with ethyl acetate which, after being dried over magnesium sulphate, was filtered and evaporated to yield the crude phenol (63). This was dissolved in acetic anhydride (14 ml) whereafter dry pyridine (3.5 ml) was added and the reaction mixture allowed to stir for 3 hours at room temperature. Methanol was then added to quench the excess acetic anhydride and the mixture stirred for a further 20 min. The reaction solvents were removed under reduced pressure (0.1 mm) with heating at 40°C. The resulting residue was chromatographed (eluant 20% ethyl acetate - light petroleum) to give the product (64) (474.4 mg, 90%) as a clear oil, $\nu_{max.}$ 1767 cm^{-1}(C = O); δ2.15 (3H, s, $ArCH_3$), 2.29 (3H, s, $OCOCH_3$), 3.72 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.48 (1H, d, *J* 9 Hz, 5-H), and 6.79 (1H, d, *J* 9 Hz, 4-H); *m/z* 210(M^+, 15%), 168(100), and 153(40).

4-acetyl-3-hydroxy-2,6-dimethoxytoluene (65)

The acetate (64) (495 mg, 2.36 mmol) and freshly distilled boron trifluoride etherate (1.5 ml) were heated in an oil bath maintained at 95°C for 3 hours. The reaction mixture

was then thrown onto ice (20 ml), extracted with dichloromethane, separated and the organic solvent evaporated. The residue was dissolved in a sodium hydroxide solution (3%) in methanol (25 ml) and stirred at room temperature to hydrolyse any existing starting material. The solution was then diluted with water (200 ml) and repeatedly (3 times) extracted with dichloromethane. Thereafter, the organic phase was separated, dried over magnesium sulphate, filtered and evaporated, to yield a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum). Early fractions gave the product (65) (312 mg, 63%) as white crystals, m.p. 73.5-75.0°C (isopropyl alcohol) (Found: C, 62.8; H, 6.6. $C_{11}H_{14}O_4$ requires C, 62.8; H, 6.7%); $\nu_{max.}$ 1635 and 1614 cm^{-1} (C = O); δ2.16 (3H, s, $ArCH_3$), 2.57 (3H, s, $COCH_3$), 3.77 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.77 (1H, s, ArH), and 12.22 (1H, s, OH, disappears on D_2O wash); *m/z* 210(M^+, 100%), 196(20), 195(86), 181(15), 167(43), 149(27), and 121(19). Latter fractions gave hydrolysed starting material (63) (36 mg, 9%).

4-acetyl-2,3,6-trimethoxytoluene (66)

The phenol (65) (191.1 mg, 0.91 mmol) was dissolved in dry acetone (5 ml) and dimethyl sulphate (286 mg, 2.27 mmol) and potassium carbonate (32 mg, 2.4 mmol) were added. The mixture was stirred for 24 hours after which the solvent was filtered and evaporated under reduced pressure. The residue

was partitioned between water and ether and washed successively with ammonia (25%), water, dilute hydrochloric acid, then water again before the ether layer was separated and dried over magnesium sulphate. Filtration and removal of the ether under reduced pressure gave an oil which was chromatographed (eluant 10% ethyl acetate - light petroleum) to yield the methyl ether (66) (199.7 mg, 98%) as pale yellow needles, m.p. 28-30°C (light petroleum) (Found: C, 64.5; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%); $\nu_{max.}$ 1678 cm^{-1} (C = O); δ2.18 (3H, s, $ArCH_3$), 2.65 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), and 6.99 (1H, s, ArH); *m/z* 224(M^+, 88%), 209(100), 181(20), 166(12), and 149(25).

Attempted synthesis of 5-(1-oxo-but-2-enyl)-2,3,6-trimethoxy-toluene (72)

Compound (68) (200 mg, 1 mmol) was treated under the same conditions as described in the preparation of compound (62) (page 71, Method 2) with the exception that in this reaction crotonic acid was used instead of acetic acid. After workup the reaction mixture gave an intractable tar of which none of the products could be characterised.

Attempted synthesis of 5-(1-oxo-but-3-enyl)-2,3,6-trimethoxy-toluene (73)

Compound (68) (210 mg, 1.2 mmol), was treated under the same conditions as described in the preparation of compound (62) (page 71, Method 2) with the exception that in this reaction

vinylacetic acid was used instead of acetic acid. After workup a t.l.c. examination showed much degradation of starting material as well as the formation of many products, none of which were characterisable.

Attempted synthesis of 5-(1-oxo-2-methyl-but-2-enyl)-2,3,6-trimethoxytoluene (74)

The preparation of this compound was not successful. For the experimental details see the preparation of the coumarin derivative (84) (page 82).

2-methyl-3,4-dimethoxy-6-acetyl phenol (67)

Compound (66) (132.0 mg, 0.59 mmol) was dissolved in anhydrous dichloromethane (10 ml) and boron trichloride (0.271 g, 2.310 mmol) in anhydrous dichloromethane (2.5 ml) was added and the reaction mixture stirred for 80 min at 0°C. The resulting red complex was decomposed by the addition of water with stirring for 5 mins. The organic material was extracted with dichloromethane which, after separation from the aqueous layer, was dried over magnesium sulphate, filtered and the solvent removed to afford a pale yellow solid which was recrystallized to give the product (67), (105.3 mg, 85%) as colourless needles, m.p. 86-87°C (dichloromethane - light petroleum) (Found: C, 62.8; H, 6.7. $C_{11}H_{14}O_4$ requires, C, 62.8; H,6.7%); $\nu_{max.}$ 1619 cm^{-1} (C = O); δ2.17 (3H, s, $ArCH_3$), 2.58 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.99 (1H, s, ArH), and 12.59 (1H, s, OH, disappears on D_2O wash); *m/z* 210(M^+, 85%), 195(100), 167(11), 149(14), and 121(11).

2,3,6-trimethoxytoluene (68)

The formate ester (59) (1.51 g, 7.70 mmol) was dissolved in a sodium hydroxide solution (3%) in methanol (50 ml) and stirred at room temperature for 15 min before the solution was acidified with dilute hydrochloric acid. The solution was then diluted with water (300 ml) and exhaustively extracted with ethyl acetate which, after being dried over magnesium sulphate, was filtered and evaporated. The crude phenol (63) was dissolved in dry acetone (100 ml), whereafter dimethyl sulphate (0.97 g, 19.25 mmol) and anhydrous potassium carbonate (2.66 g, 19.25 mmol) were added. After heating the solution under reflux for 2 hours, the mixture was cooled, filtered to remove the excess potassium carbonate and the acetone removed under reduced pressure. The oily residue was partitioned between water and ether, and washed successively with ammonia (25%), water, hydrochloric acid (1 M), then water again before the ether layer was separated and dried over anhydrous magnesium sulphate. Filtration and removal of the ether under reduced pressure gave an oily material which was chromatographed (eluant 15% ethyl acetate - light petroleum) to give the product (68) (1.34 g, 96%) as white crystals, m.p. 29-30°C (Lit.,[49] 30-31°C); δ2.14 (3H, s, $ArCH_3$), 3.75 (3H, s, OCH_3), 3.79 (6H, s, 2 x OCH_3), 6.46 (1H, d, *J* 9.5 Hz, ArH), and 6.69 (1H, d, *J* 9.5 Hz, ArH).

2,3,6-trimethoxy-5-pentan-1-one toluene (76)

METHOD 1

Compound (68) (117.8 mg, 0.647 mmol) was treated with a mixture of trifluoroacetic anhydride (271.7 mg, 1.29 mmol) and valeric acid (98.99 mg, 0.97 mmol) with stirring at room temperature. After 24 hours the solution was neutralised with aqueous sodium hydrogen carbonate and exhaustively extracted with dichloromethane. The extracts were combined, dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a residue which was chromatographed (p.l.c. 5% ethyl acetate - light petroleum). Early fractions afforded the desired product (76) (68.8 mg, 40%) as a clear oil (Found: C, 67.7; H, 8.3. $C_{15}H_{22}O_4$ requires C, 68.0; H, 8.1%); $\nu_{max.}$ 1669 cm^{-1} (C = O); δ0.82-1.02 (3H, m, $CH_2\underline{CH_3}$), 1.16-1.88 (4H, m, CH_2CH_2), 2.21 (3H, s, $ArCH_3$), 2.86-3.08 (2H, m, $COCH_2$), 3.66 (3H, s, $ArOCH_3$), 3.80 (6H, s, $ArOCH_3$), and 6.96 (1H, s, ArH); *m/z* 266(M^+, 25%), and 209(100).

A second band at lower R_F afforded the regioisomer (77) (32.7 mg, 19%) as a clear oil; $\nu_{max.}$ 1675 cm^{-1} (C = O); δ0.81-1.05 (3H, m, $CH_2\underline{CH_3}$), 1.19-1.27 (2H, m, CH_2), 2.01 (3H, s, $ArCH_3$), 2.23-2.55 (2H, m, CH_2), 2.90-3.13 (2H, m, $COCH_2$), 3.73 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), and 7.08 (1H, s, ArH); *m/z* 266(M^+, 30%), 209(100).

METHOD 2

Compound (76) was prepared from the reaction between compound (78) and the Grignard reagent, butyl magnesium bromide, using the same molar ratios and identical reaction conditions as described in the preparation of compound (62) (Method 3, page 72). The product (76) was obtained in a yield of 54% as a pale yellow oil and its spectroscopic data were found to be identical to that of compound (76) obtained via Method 1.

2,4,5-trimethoxy-3-methyl benzaldehyde (78)

Freshly distilled phosphoryl chloride (4.3 ml) was added to NN-dimethyl formamide (7.5 ml) during 30 min with stirring and cooling in ice. The complex was allowed to warm to room temperature and was then added during 1.5-2 hours to a stirred solution of compound (68) (5.555 g, 30.5 mmol) in dry NN-dimethyl formamide (7.5 ml) at 105°C (bath). Heating and stirring was continued for 4 hours. The mixture was then poured onto ice-water, made just basic by the addition of aqueous sodium hydrogen carbonate, and exhaustively extracted with ethyl acetate. The combined extracts were washed successively with dilute hydrochloric acid, water, and saturated brine, and dried over magnesium sulphate. The solvent was filtered and removed under reduced pressure to give a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum). Early fractions afforded the starting material (68) (1.156 g) and latter fractions gave

the product (78)(3.478 g, 54%) (68% based on unrecovered starting material) as pale yellow needles, m.p. 51-52°C (light petroleum) (Lit.,[50] reported as an oil); $\nu_{max.}$ 1671 cm^{-1} (C = O) (Lit.,[50] (neat) 1680 cm^{-1} (C = O)); δ2.20 (3H, s, $ArCH_3$), 3.82 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 7.19 (1H, s, ArH), and 10.26 (1H, s, CHO); *m/z* 210(M^+, 100), 195(40), 164(20), 152(13), 139(13), 124(10), and 109(11).

5-(1-oxopent-4-enyl)-2,3,6-trimethoxytoluene (82)

The Grignard reagent, but-3-enyl-1-magnesium bromide was prepared by adding magnesium pellets (100 mg, 4.1 mmol) to a solution of but-3-enylbromide (0.2 ml, 1.9 mmol) in dry ether (2 ml) with constant stirring until the solution turned milky and effervescence ceased. The aldehyde (78) (110 mg, 0.524 mmol) in anhydrous ether (2 ml) was added and the reaction mixture stirred for 15 min. Saturated ammonium chloride was then added and the solution was stirred at room temperature for a further 15 min. This mixture was added to water, extracted with ether which, after separation from the aqueous layer, was dried over magnesium sulphate, filtered and the solvent removed to yield a residue (140.3 mg). The residue was dissolved in acetone (3 ml), Jones' reagent[35] (0.3 ml) was added and the solution stirred for 5 min. Water (50 ml) was added and the organic material was extracted with ethyl acetate which, after separation from

the aqueous layer, was dried over magnesium sulphate, filtered, the solvent removed and the resultant residue chromatographed (eluant 10% ethyl acetate – light petroleum) to afford the product (82) (128 mg, 92%) as a clear oil (Found: C, 68.2; H, 7.5. $C_{15}H_{20}O_4$ requires C, 68.4; H, 7.3%); $\nu_{max.}$ (neat) 1669 (C = O) and 1640 cm^{-1} (C = C); δ2.19 (3H, s, $ArCH_3$), 2.45 (2H, dt *J* 7 Hz, allyl), 3.08 (2H, distorted t, *J* 7 Hz, $COCH_2$), 3.66 (3H, s, OCH_3), 3.81 (6H, s, 2 x OCH_3), 4.84-5.14 (2H, m, C = CH_2), 5.62-6.08 (1H, m, C = CH), and 6.98 (1H, s, ArH); *m/z* 264(M^+, 33%), 210(13), and 209(100).

Attempted ring closure of compound (82)

METHOD 1

Compound (82) (5 mg, 0.02 mmol) was dissolved in chloroform (2 ml) and trifluoroacetic acid (15 drops) was added with constant stirring. After 20 min water was added and the organic material extracted with ether, separated, dried over magnesium sulphate and evaporated to quantitatively yield the unchanged starting material (82).

METHOD 2

This procedure and the quantities used were the same as described in Method 1, with the exception that in this reaction no chloroform was used as solvent. The results obtained were consistent with those found using Method 1.

METHOD 3

Compound (82) (5 mg, 0.02 mmol) was dissolved in methanol (2 ml) and concentrated hydrochloric acid (15 drops) was added and the solution allowed to stir for 30 min. After workup, as described in Method 1, the starting material (82) was recovered in quantitative yield.

METHOD 4

The same quantities and conditions were used as described in Method 3 with the exception that in this reaction sulphuric acid was used instead of hydrochloric acid. After workup the same results were obtained as in Method 3.

3,4,6-trimethyl-5,7,8-trimethoxy-2H-1-benzopyran-2-one (84)

Trimethoxy toluene (68) (125.4 mg, 0.689 mmol) was treated with a premixed solution of tiglic acid (275.6 mg, 2.753 mol) and trifluoroacetic anhydride (578.9 mg, 2.756 mmol) with stirring at room temperature. After 24 hours the solution was neutralised with aqueous sodium hydrogen carbonate and exhaustively extracted with dichloromethane. The extracts were combined, dried over magnesium sulphate, filtered and the solvent removed under vacuum to give a residue which upon chromatography (20% ethyl acetate - light petroleum) afforded the coumarin (84) (40.2 mg, 21%) as white needles, m.p. 103-105°C (light petroleum - chloroform). This was the only characterisable product (Found: C, 64.9; H, 6.6. $C_{15}H_{18}O_5$ requires C,

64.7; H, 6.5%); $\nu_{max.}$ 1723 (C = O), 1641 and 1571 cm^{-1} (C = C); δ2.23 (6H, s, $ArCH_3$ and pyrone ring CH_3), 2.29 (3H, s, pyrone ring CH_3), 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), and 3.89 (3H, s, OCH_3); *m/z* 278(M^+, 100%), 263(49), 247(61), 235(41), 221(14), 206(11), and 191(7).

Attempted synthesis of coumarin derivative using 1,3 dimethoxybenzene (85) as substrate

The same experimental conditions were applied as described in the synthesis of compound (84) with the exception that in this reaction the substrate 1,3-dimethoxybenzene (85) (120 mg, 0.9 mmol) was used instead of compound (68). After workup the ^1H n.m.r. spectrum of the reaction mixture showed the absence of starting material, however no characterisable product could be isolated.

Attempted synthesis of coumarin derivative using 1,4-dimethoxynaphthalene (86) as substrate

The same conditions were applied as described in the synthesis of compound (84) with the exception that in this reaction the substrate 1,4-dimethoxynaphthalene (86) (150 mg, 0.8 mmol) was used instead of compound (68). After workup a t.l.c. investigation showed many different products of lower R_F than starting material, however none of these compounds could be characterised.

Attempted synthesis of coumarin derivative using 1,4 dimethoxybenzene (87) as substrate

The same conditions were applied as described in the synthesis of compound (84) with the exception that in this reaction the substrate 1,4-dimethoxybenzene (87) (105 mg, 0.8 mmol) was used instead of compound (68). A t.l.c. investigation of the reaction mixture showed many different products, none of which were characterisable.

Attempted synthesis of coumarin derivative using 1,2,4-trimethoxybenzene (88) as substrate

The same conditions were applied as described in the synthesis of compound (84) with the exception that in this reaction the substrate 1,2,4-trimethoxybenzene (88) (100 mg, 0.6 mmol) was used instead of compound (68). A t.l.c. investigation showed the formation of many uncharacterisable products.

5-bromo-2,3,6-trimethoxytoluene (89)

The trimethyl ether (68) (300 mg, 1.65 mmol), glacial acetic acid (10 ml) and anhydrous sodium acetate (189 mg, 2.31 mmol) were heated and stirred until all the sodium acetate had dissolved. After the mixture was allowed to cool to room temperature bromine (316 mg, 1.9 mmol) in glacial acetic acid (8 ml) was added over 10 min and the solution allowed to stir for a further 6 min. The reaction mixture was then diluted with water (60 ml) and repeatedly extracted with ether. The combined organic fractions were washed with

saturated aqueous sodium hydrogen carbonate (twice), dried over magnesium sulphate, filtered and evaporated to give a residue which was chromatographed (10% ethyl acetate - light petroleum) to afford the product (89) (323 mg, 75%) as a pale yellow oil (Found: C, 46.4; H, 5.1. $C_{10}H_{13}BrO_3$ requires C, 46.0; H, 5.0%); $\nu_{max.}$ (film) 1592 (Aryl), 1261, 1237 and 1219 cm^{-1} (COMe); δ2.21 (3H, s, $ArCH_3$), 3.71 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), and 6.88 (1H, s, ArH); *m/z* 262 and 260, (M^+ 262, 97%), (M^+ 260, 100%), 248(25), 247(32), 245(34), 218(19), 204(12), and 202(13).

2-bromo-5-methoxy-6-methyl-1,4-benzoquinone (90)

METHOD 1

The formate ester (59) (300 mg, 1.53 mmol) and sodium acetate (149 mg, 1.82 mmol) were heated and stirred in glacial acetic acid (7 ml) until dissolution. After cooling to 10°C, bromine (320 mg, 2 mmol) in glacial acetic acid (5 ml) was added and the mixture stirred for 5 min. This mixture was then added to water and exhaustively extracted with ether. The ether phase was separated and evaporated to yield a crude mixture of the bromoformyloxy compound (91) and the bromophenol (92). This was dissolved in a sodium hydroxide solution (2%) in methanol and allowed to stir for 30 min. The solution was then diluted with water, acidified (dilute hydrochloric acid) and extracted with ether (twice). The organic layer was dried over

magnesium sulphate, filtered and evaporated to give solely the crude bromophenol (92) (210 mg, 82%). This was dissolved in acetonitrile (30 ml) and water (16 ml), cerium (IV) ammonium nitrate (2.5 g, 4 mmol) in water (3.3 ml) was added and the solution stirred for a further 5 min. The reaction mixture was then extracted with dichloromethane, dried over magnesium sulphate, filtered and evaporated. The residue was chromatographed (flash column, eluant 10% ethyl acetate - light petroleum) to afford the quinonoid product (90) (131 mg, 37%) as dark yellow needles, m.p. 70-70.5°C (isopropanol) (Found: C, 41.6; H, 3.0. $C_8H_7BrO_3$ requires C, 41.6; H, 3.0%); $\nu_{max.}$ 1654, 1625 (C = O) and 1590 cm^{-1} (C = C); δ1.99 (3H, s, CCH_3), 4.02 (3H, s, OCH_3), and 7.08 (1H, s, ArH); *m/z* 232 and 230, (M^+ 232, 52%), 231(17), (M^+ 230, 55%), 229(12), 202(35), 200(24), 189(13), 187(15), 133(20), 131(19), 123(23), 121(13), 93(69), 83(57), and 53(100).

METHOD 2

The phenol (99) (3.54 g, 11.97 mmol) was dissolved in a solution of acetic acid (70 ml) and water (30 ml). Chromium trioxide (3.50 g, 35 mmol) was added over 10 min with the reaction temperature being maintained below 35°C. After stirring for a further 45 min the reaction mixture was thrown into water and extracted with dichloromethane. The organic phase was separated, backwashed with water, dried over magnesium sulphate, filtered, and evaporated to give an

oily solid which was chromatographed (flash column, eluant 10% ethyl acetate - light petroleum) to afford the product (90) (2.29 g, 83%) as dark yellow needles. The mixed melting point with compound (90) obtained via the previous route showed no depression and the spectroscopic data of compound (90) obtained via the two different routes were found to be identical.

3,5-dibromo-2,6-dihydroxytoluene (96)

Dihydroxytoluene (56) (3.15 g, 25.4 mmol) was subjected to the same bromination conditions as in the preparation of (89) (page 84). However, on the addition of the second equivalent of bromine a white precipitate formed. The precipitate was filtered off and washed with water (to remove any residual acetic acid) and dried. Water was added to the filtrate which was then repeatedly extracted with dichloromethane (3 times) and backwashed with water to remove the last traces of acetic acid. The dichloromethane layer was dried over magnesium sulphate, filtered and evaporated to give a residue which was chromatographed (eluant 15% ethyl acetate - light petroleum) to yield a white solid. This was combined with the precipitate to give the product (96) (6.01 g, 84%) as white needles, m.p. 98-99°C (dichloromethane-light petroleum), $\nu_{max.}$ 3506, 3420 br cm^{-1} (OH); δ2.22 (3H, s, CH_3), 5.50 (2H, s, OH) and 7.38 (1H, s, ArH); *m/z* 284, 282 and 280, (M^+284, 49%), (M^+282, 100%), (M^+280, 51%), 203(25), 201(29).

Attempted synthesis of 5-bromo-2-hydroxy-3-methyl 1,4-benzoquinone (97)

The same conditions and mole ratios were applied to the bromo-derivative (96) (1.01 g, 3.58 mmol) as were applied to compound (99) in the preparation of the quinone (90) (page 86). After workup a t.l.c. investigation showed total decomposition of starting material with no characterisable product.

2-hydroxy-6-methoxytoluene (98)

Dihydroxytoluene (56) (20.0 g, 161 mmol) was dissolved in anhydrous acetone (500 ml), whereafter dimethyl sulphate (23.3 g, 185 mmol) and anhydrous potassium carbonate (33.1 g, 240 mmol) were added, and the mixture stirred overnight. The solution was then filtered and the acetone removed under reduced pressure. The residual material was taken up into ether and exhaustively extracted with aqueous sodium hydroxide (2%). The ether layer was dried over magnesium sulphate, filtered and evaporated to yield pure dimethoxytoluene (57) (8.68 g, 35%). The aqueous phases were combined, acidified with dilute hydrochloric acid and extracted with ether (twice). Magnesium sulphate was then added to the separated ether layer; this was filtered and the ether evaporated to give a residue which was chromatographed (eluant 15% ethyl acetate - light

petroleum). Initial fractions afforded the product (98) (8.74 g, 39%, 52% based on unrecovered starting material) as pale yellow needles, m.p. 44-46°C (light petroleum) (Lit.,[51] 47°C) and latter fractions afforded the starting material (38) (5.0 g, 25%).

2-hydroxy-3,5-dibromo-6-methoxytoluene (99)

The monomethyl ether (98) (5.0 g, 36.2 mmol), glacial acetic acid (50 ml) and anhydrous sodium acetate (6.5 g, 79.6 mmol) were heated and stirred until dissolution. The solution was cooled to 10°C (bath) and bromine (11.6 g, 72.4 mmol) in glacial acetic acid (50 ml) was added over 10 min. The reaction mixture was stirred for a further 5 min before being thrown into water and repeatedly extracted with dichloromethane. The organic phase was then backwashed with water, dried over magnesium sulphate, filtered, and evaporated to give an oily solid which, on standing overnight, crystallized totally to give the product (99) (10.4 g, 98%) as pale yellow needles, m.p. 73°C (hexane) (Found: C, 32.4; H, 2.7. $C_8H_8Br_2O_2$ requires C, 32.5; H, 2.7%); $\nu_{max.}$ 3407 cm^{-1} (v.br. OH); δ2.23 (3H, s, $ArCH_3$), 3.74 (3H, s, OCH_3), 5.53 (1H, s, OH, D_2O exchangeable) and 7.45 (1H, s, ArH); *m/z* 298, 296 and 294, (M^+298, 50%), (M^+296, 100%), (M^+ 294, 50%), 283(23), 281(47), 279(25), 255(12), 253(23), 251(23), 174(19), and 172(20).

2-methoxy-3-methyl-1,4-benzoquinone (103)

The formate ester (59) (1.20 g, 6.12 mmol) was dissolved in a sodium hydroxide solution (3%) in methanol (50 ml) and stirred at room temperature for 15 min before the solution was acidified with dilute hydrochloric acid. The solution was then diluted with water (300 ml) and exhaustively extracted with ethyl acetate which, after being dried over magnesium sulphate, was filtered and evaporated. The residue was dissolved in a solution of acetonitrile (56 ml) and water (28 ml) and a solution of cerium (IV) ammonium nitrate (10.0 g, 18.09 mmol) in water (26 ml) was added with constant stirring at room temperature. After 10 min a further quantity of water was added and the organic material was extracted (twice) with dichloromethane. After drying over magnesium sulphate, the organic solvent was filtered and evaporated to yield a residue which was flash chromatographed (eluant 15% ethyl acetate - light petroleum) to afford the product (103) (0.81 g, 87%) as a yellow solid, m.p. 19-21°C (Lit.,[52] m.p. 20-21°C); $\nu_{max.}$ 1648 cm^{-1}(C = O); δ1.94 (3H, s, CCH_3), 4.01 (3H, s, OCH_3), 6.75 (1H, d, *J* 10.0 Hzm quinone-H), and 6.71 (1H,d, *J* 10.0 Hz, ArH); *m/z* 152(M^+, 100%), 151(13), 139(13), 122(50), and 109(15).

2,5,7-trimethoxy-3-methyl-1,4-naphthoquinone (102)

The bromoquinone (90) (100 mg, 0.433 mmol) was dissolved in dry dichloromethane (8 ml) and the reaction system thoroughly flushed with nitrogen. The diene (100) (200 mg,

0.989 mmol) was added and the reaction stirred at room temperature for 24 hours after which aqueous sodium hydrogen carbonate (1%, 2 ml) was added and the reaction stirred in air for a further 10 min. After acidification with dilute hydrochloric acid the organic layer was separated, dried over magnesium sulphate, filtered and evaporated to yield a dark brown oily residue. This was taken up in chloroform (10 ml) whereafter methyl iodide (709 mg, 5 mmol) and silver (I) oxide (1.09 g, 4.3 mmol) were added and the solution stirred under a nitrogen atmosphere overnight. The mixture was then filtered, evaporated and chromatographed (15% ethyl acetate - light petroleum) to afford the product (102) (103 mg, 91%) as yellow needles, m.p. 151-152°C (dichloromethane - isopropanol) (Found: C, 64.0; H, 5.3. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); $\nu_{max.}$ 1664 and 1641 cm^{-1} (C = O); δ2.02 (3H, s, CCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.65 (1H, d, *J* 3 Hz, ArH), and 7.18 (1H, d, *J* 3 Hz, ArH); *m/z* 262(M^+, 100%), 247(50), 233(12), 219(35), 201(14), 190(20), 163(12), and 106(13).

2,6,8- trimethoxy-3-methyl-1,4-naphthoquinone (104)

Compound (104) was prepared using the same mole ratios and reaction conditions as described in the preparation of compound (102) (page 90), with the exception that in this reaction dienophile (103) was used instead of dienophile (90). Yield 89%, m.p. 141-142°C (dichloromethane -isopropanol) (Found: C, 63.7; H, 5.4. $C_{14}H_{14}O_5$ requires

C, 64.1; H, 5.4%); $\nu_{max.}$ 1660 cm^{-1}(C = O); δ1.99 (3H, s, $ArCH_3$), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 6.64 (1H, d, *J* 2 Hz, ArH), and 7.21 (1H, d, *J* 2 Hz, ArH); *m/z* 262(M^+, 100%), 247(32), 244(11), 239(12), 219(19), 203(11), 191(16), and 169(11).

β,γ-pentenoic acid (107)

Compound (107) was prepared according to the method of Linstead [44] (the condensation of malonic acid and propionaldehyde). Yield 35%, b.p. 85-90°C/10 mm (Lit.,[44] 90°C/10 mm).

Methyl-3-pentenoate (108)

Compound (108) was prepared according to the method of Buchta and Burger[53] which entailed refluxing the acid (107) in methanol in the presence of concentrated sulphuric acid. Yield 90%, b.p. 45-50°C/20 mm (Lit.,[53] 42.7°C/14 mm).

(E) and (Z)-1-methoxy-1-trimethysilyloxpenta-1,3-diene (109)

Dry diisopropylamine (7 ml, 53 mmol) in dry tetrahydrofuran (100 ml) was cooled to 0°C under a nitrogen atmosphere and a solution of butyl lithium in hexane (35 ml, 1.6 M, 56 mmol) was added. The solution was then cooled to -78°C using a dry-ice/acetone bath. The methyl ester (108) (5 g, 43.86 mmol) was added and the mixture stirred for 2 min. The reaction was quenched with trimethylchlorosilane (9 ml, 71.0 mmol) and the solution stirred for a further 10 min. The solvent was then removed under vacuum (25 mm) and the

white solid byproduct filtered off and washed with dry hexane. Finally the hexane was removed under vacuum (25 mm) leaving a pale yellow liquid which, after distillation, gave the pure product (109) (7.9 g, 97%) as a colourless liquid, b.p. 81° C/1 mm, 52-58°C/0.55 mm, 41-44°C/0.3 mm (Found: C, 58.1; H, 9.5. $C_9H_{18}SiO_2$ requires C, 58.0; H, 9.7%) $\nu_{max.}$ 1664, 1627 (C = C), 1277, 1253 (COMe), and 845 cm^{-1} (Si - C); δ0.21 and 0.24 (9H, s, E- and Z- CH_3Si), 1.69 (3H, dd, *J* 7.0 and 1.5 Hz, CCH_3), 3.51 and 3.53 (3H, s, E- and Z- OCH_3), 4.41 (1H, dd, *J* 10.1 and 3.6 Hz, H-2), 5.95-6.33 (1H, m, H-4), 6.14 (1H, ddq, *J* 10.1, 12 and 3.6 Hz, H-3); *m/z* 186(M^+, 17%), 89(14), 82(100), 75(10), 73(32), 59(11), and 54(11).

2-methoxy-3,8-dimethyl-5-hydroxy-1,4-naphthoquinone (110)

The bromoquinone (90) (1.00 g, 4.33 mmol) was dissolved in dry benzene (250 ml) and the system thoroughly flushed with nitrogen. The diene (1.0 g, 5.36 mmol) was then added and the solution stirred at 60°C for 4 hours. The benzene was then removed under vacuum, the residue taken up in a small amount of ether and thoroughly shaken with water. The organic layer was then separated, dried over magnesium sulphate, filtered and evaporated to give the crude adduct. This was pyrolysed at 70°C for 30 min and subsequently chromatographed (eluant 10% ethyl acetate - light petroleum) to give the product (110) (0.60 g, 60%) as orange needles, m.p. 124-125 °C (hexane) (Found: C, 67.3; H, 5.3. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); $\nu_{max.}$ 1657 and 1624 cm^{-1} (C = O);

δ2.02 (3H, s, quinone-CH_3), 2.58 (3H, s, ArCH_3), 4.07 (3H, s, OCH_3), 7.07 (1H, d, *J* 8.6 Hz, ArH), 7.32 (1H, d, *J* 8.8 Hz, ArH), and 12.8 (1H, s, OH, D_2O exchangeable); *m/z* 232(M^+, 100%), 217(23), 214(15), 202(12), 189(30), 115(16), and 105(10).

2-methoxy-3,5-dimethyl-8-hydroxy-1,4-naphthoquinone (111)

Compound (111) was prepared according to the synthesis of compound (110) (page 93) with the exception that in this reaction dienophile (103) was used instead of dienophile (90). Yield 65% after flash chromatography (eluant 15% ethyl acetate - light petroleum); however, the ^1H n.m.r. spectrum of the combined fractions showed the presence of ±8% of isomer (110). Compound (111) was obtained pure by two recrystallizations from isopropanol to give orange needles, m.p. 144 °C (sublimes 135°C) (Found: C, 67.0; H, 5.1. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); $\nu_{max.}$ 1615 cm^{-1} (C = O); δ2.65 (3H, s, ArCH_3), 2.58 (3H, s, ArCH_3), 4.02 (3H, s, OCH_3), 7.06 (1H, d, *J* 8.5 Hz, ArH), 7.36 (1H, d, *J* 8.5 Hz, ArH), and 12.41 (1H, s, OH, D_2O exchangeable); *m/z* 232(M^+, 100%), 217(29), 202(17), 189(48), 187(14), 161(12), and 143(10).

As the isomer (110) was difficult to remove by recrystallization an alternative purification technique for compound (111) was undertaken. According to the above reaction conditions, the dienophile (103) (900 mg,

5.92 mmol) was reacted with the diene (109) (1.36 g, 7.33 mmol). After pyrolysis the residue was flash chromatographed to once again yield a mixture of compound (110) (137 mg, 10%) and the product (111) (824 mg, 60%) as shown by the ^1H n.m.r. spectrum. The isomeric mixture was dissolved in dry dichloromethane (20 ml) and a solution of boron trichloride (2.7 g, 23.35 mmol) in dry dichloromethane was added and the reaction mixture allowed to stir for 30 min at 0°C. Ice-water was then added and the organic material extracted with dichloromethane. After separation from the aqueous layer, the organic phase was dried over magnesium sulphate, filtered and the solvent removed to yield a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum). Early fractions afforded the product (111) (755 mg, 55%) as orange needles and latter fractions gave Aristolindiquinone (1) (103 mg, 8%).

2,5-dihydroxy-3,8-dimethyl-1,4-naphthoquinone (1)

Compound (110) (500 mg, 2.16 mmol) was dissolved in dry dichloromethane (10 ml) and boron trichloride (1.0 g, 8.52 mmol) in dichloromethane (20 ml) was added and the reaction mixture stirred for 1 hour at 0°C. The resulting dark purple complex was decomposed by the addition of ice-water and the organic material extracted with dichloromethane. After separation from the aqueous layer, the organic phase was dried over magnesium sulphate, filtered and the solvent removed to yield an orange solid

which was flash chromatographed (eluant 30% ethyl acetate - light petroleum, 60% ethyl acetate -light petroleum) to give the product (1) (400 mg, 85%) as orange needles, m.p. 191°C (methanol). The spectroscopic data were found to be identical to that of compound (1) prepared by the previous method (page 66) and the mixed melting point of the two compounds was not depressed.

2,8-dihydroxy-3,5-dimethyl-1,4-napththoquinone (2)

Compound (111) (500 mg, 2.15 mmol) was added to an aqueous solution of sodium hyroxide (3%, 300 ml) and heated to 60°C with constant stirring. After 30 min the solution was acidified with dilute hydrochloric acid and extracted with ether. The organic phase was dried over magnesium sulphate, filtered, evaporated and chromatographed (eluant 20% ethyl acetate - light petroleum, 30% ethyl acetate - light petroleum). Early fractions gave the starting material (111) (79 mg, 0.34 mmol) and latter fractions afforded the product (2) (178 mg, 38%) as orange needles, m.p. 134-136°C (methanol) (Found: C, 65.8; H, 4.7. $C_{12}H_{10}O_4$ requires C, 66.0; H, 4.7%); $\nu_{max.}$ 3443 (br OH) and 1616 cm^{-1}(C = O); δ2.08 (3H, s, CH_3), 2.63 (3H, s, CH_3), 7.08 (1H, d, *J* 8.5 Hz, ArH), 7.12 (1H, s, 2-OH, D_2O exchangeable), 7.45 (1H, d, *J* 8.5 Hz, ArH), and 11.75 (1H, s, 8-OH, D_2O exchangeable); *m/z* 218(M^+, 100), 190(13), 173(11), 172(12), 147(10), 115(10) and 77(10).

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