SYNTHESES RELATED TO SOME NATURALLY OCCURRING NAPHTHOPYRANQUINONES

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by

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"SYNTHESES RELATED TO SOME NATURALLY OCCURRING NAPHTHOPYRANQUINONES"

ABSTRACT

The naphtho[2,3-*c*]pyran ring system occurs not infrequently in Nature as derivatives of the 5,10-quinone. Examples include the eleutherins, the nanaomycins and the protoaphins - some of which have been shown to possess antibiotic activity. The synthesis of these natural products requires appropriate regiospecific aromatic oxygenation of 2-acetylnaphthoquinone. Syntheses of 3-acetyl-5-methoxy-1,4-naphthoquinone and the corresponding 5,7-dimethoxy analogue are described and the use of these in the syntheses of several naturally occurring pyranquinones or their derivatives, has been investigated. In the course of this work, an unusual Fries rearrangement and a novel base-induced cyclisation were discovered - the latter affording several naphtho[2,3-*c*]pyrans in high yield.

Previous routes to (±)-isoeleutherin and (±)-deoxyquinone A dimethyl ether have been recorded, but they give rise to a mixture of eleutherin and isoeleutherin in the first case, and a mixture of deoxyquinone A dimethyl ether and its *cis*-dimethyl isomer. The synthetic routes to isoeleutherin and deoxyquinone A dimethyl ether developed during this investigation are highly stereoselective. The formation of the dimethyl ethers of quinones A and A', which is also highly stereoselective represents the first reported synthesis of the degradation products of the aphid pigments, protoaphin-*fb* and protoaphin-*sl*. The synthesis of 7-methoxyeleutherin is also described.

The reaction of trifluoroacetic anhydride with various naphthalene derivatives is described and the potential of some of these acylated naphthalenes to be employed in the syntheses of naphtho[2,3-*c*]pyrans and naturally occurring quinones has been investigated.

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August 1986

to my parents

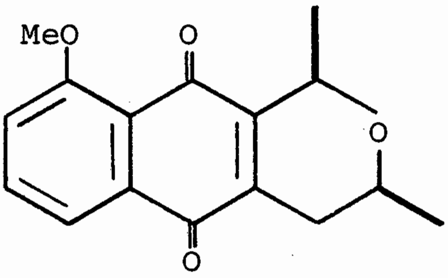
their love and inspiration afforded me the opportunity

for academic advancement

GENERAL INTRODUCTION

Several naturally occurring quinones contain the naphtho [2,3-*c*]pyran ring system. These pyranquinones are widely distributed in nature and are found in certain insects, higher plants and microorganisms.

The epimeric naphtho[2,3-*c*]pyran -5,10-quinones eleutherin (1) and isoeleutherin (2) were isolated from the tubers of *Eleutherine bulbosa* by Schmid and co-workers[1-3]



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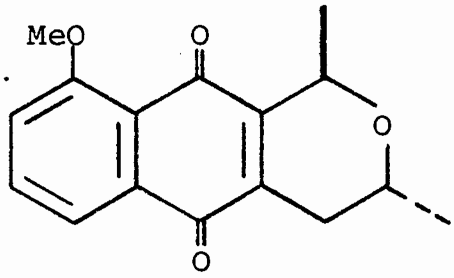

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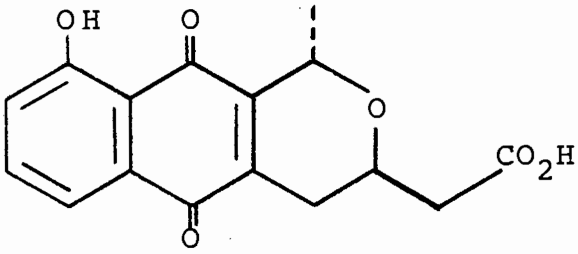
Nanaomycins A(3), B(4), C(5) and D(6) are examples of antifungal antibiotics from *Streptomyces rosa* var. *notensis*.[4]

Nanaomycin D(6) has been shown to be the enantiomer of kalafungin (7)[5] isolated from *Streptomyces tanashiensis*[6]



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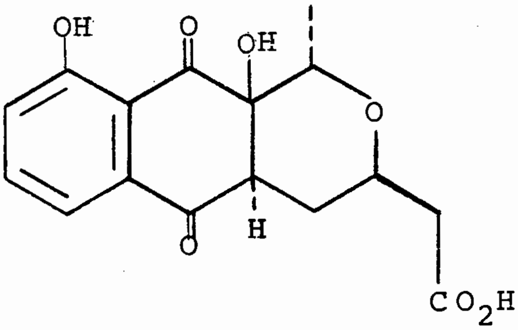

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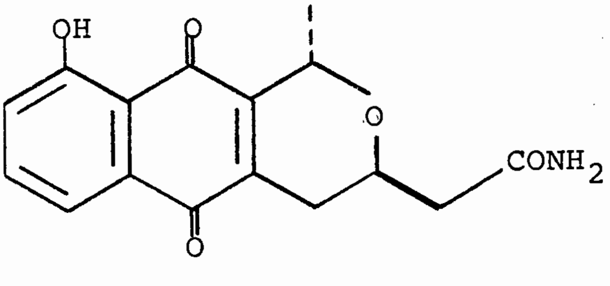

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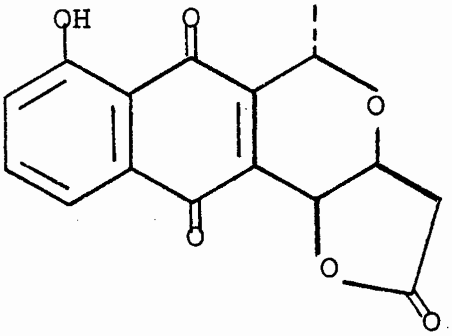

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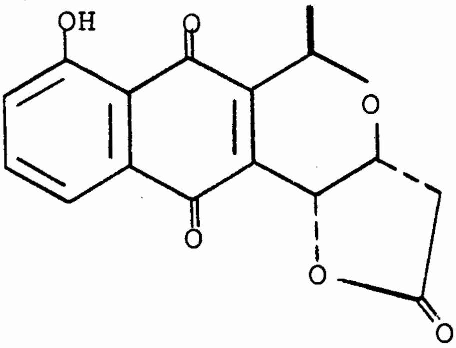

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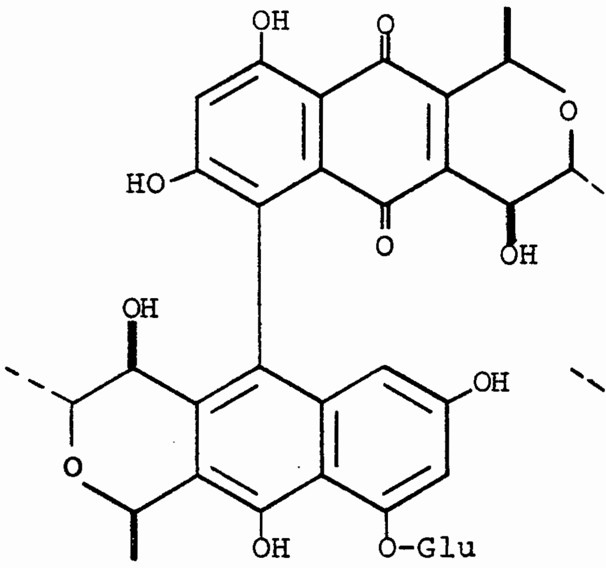
Protoaphin-*fb* (8) was isolated from the haemolymph of the bean aphid, *Aphis fabae* Scop. and the isomeric protoaphin-*sl* (9) was isolated from the willow aphid, *Tuberlachnus salignus*[7].



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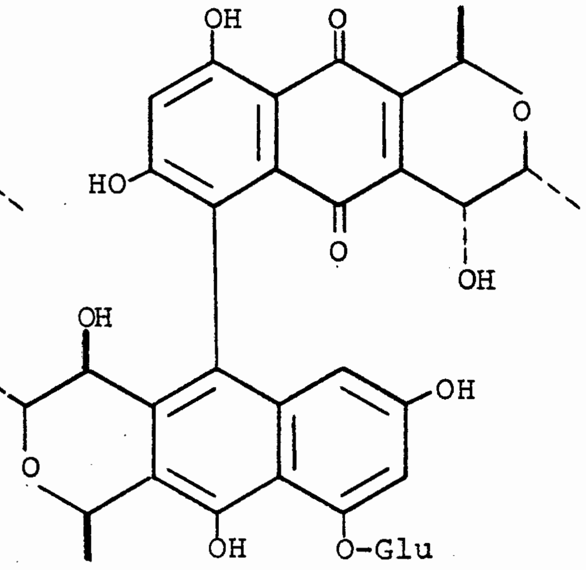

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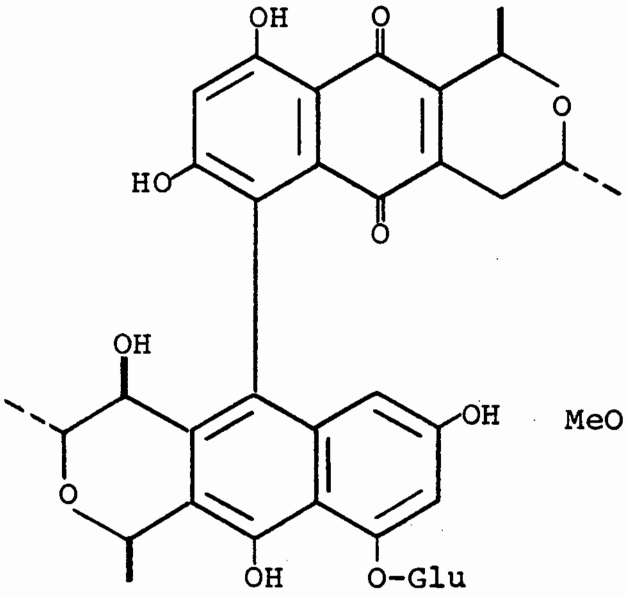
The protoaphins (8) and (9) are brownish-yellow, hygroscopic and acidic pigments that are essentially binaphthyl derivatives containing two such ring systems - the one as a 5,10-quinone and the other as a naphthyl glucoside.

Cameron and Banks[8] isolated deoxyprotoaphin (10) from *Dactynotus* aphid species and Daves *et al.* isolated 7-

methoxyeleutherin and the pyran (11) from the neurotoxic seeds of *Karwinskia humoldtiana*[9] (Rhamnaceae)



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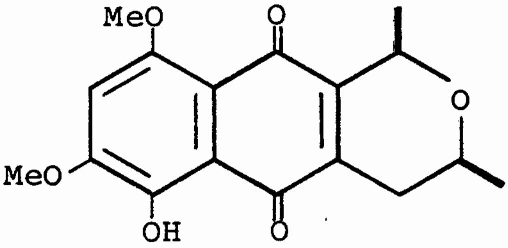

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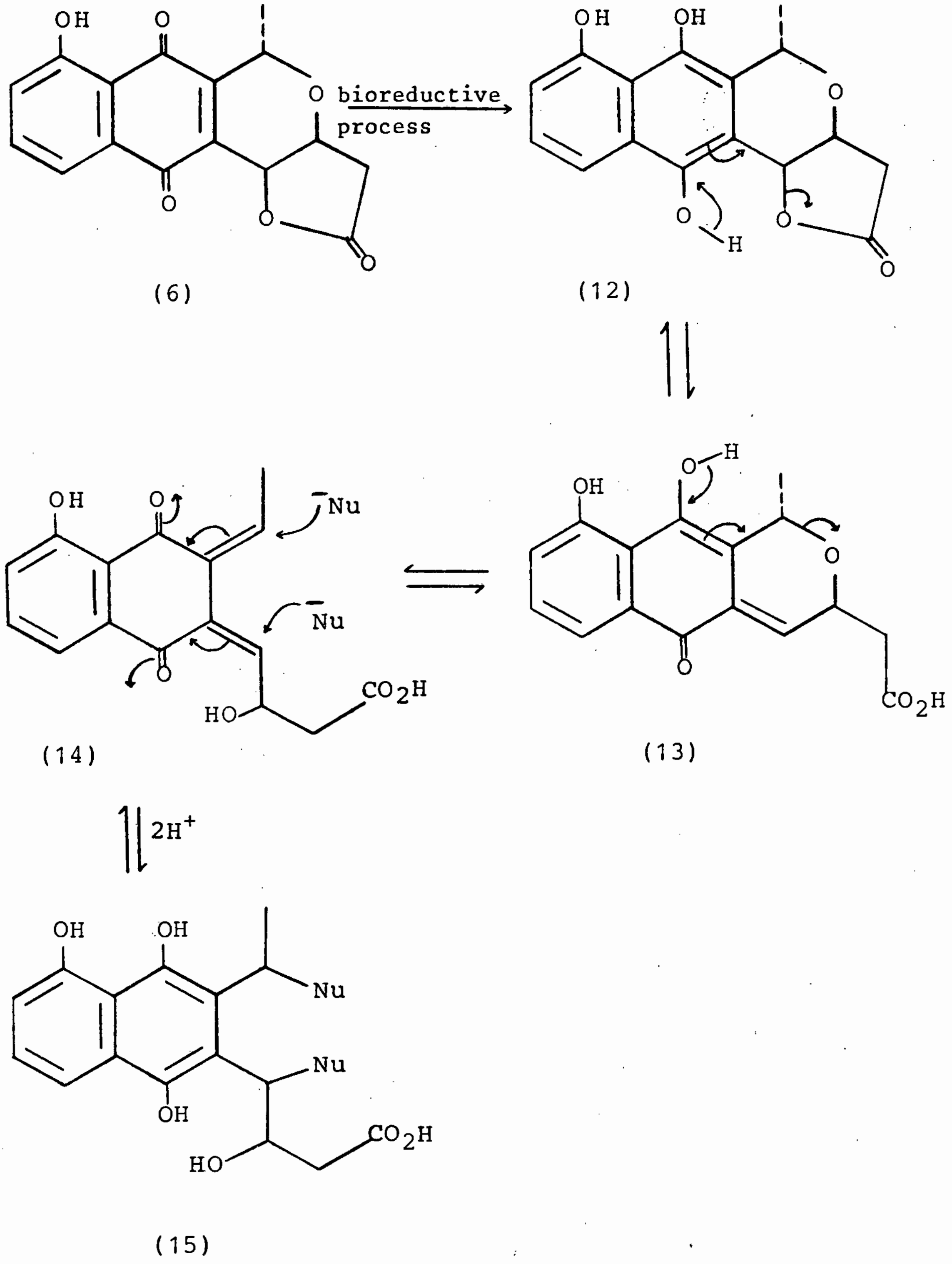
In the past decade several pyranquinones, for example the nanaomycins, have been shown to possess antimicrobial activity and thus their laboratory synthesis became a particular challenge to several medicinal and synthetic organic chemists.

It is believed that the benzoisochromanquinone skeleton of these compounds plays an important role in the appearance of biological activity. Moore[10] reviewed several compounds which show or may show antineoplastic activity by functioning as alkylating agents *via* quinone methide formation after they undergo an *in vivo* reduction to an active hydroquinone which functions as a bis-alkylating agent.

Nanoamycin D(6) and related compounds may function as alkylating agents after an *in vivo* reduction as in Scheme A.



Scheme A

The hydroquinone (12) derived from quinone (6) by a bioreductive process, may undergo ring opening of the γ-lactone moiety with the formation of the intermediate quinone methide (13) which may give rise to (14) through opening of its heterocyclic ring.

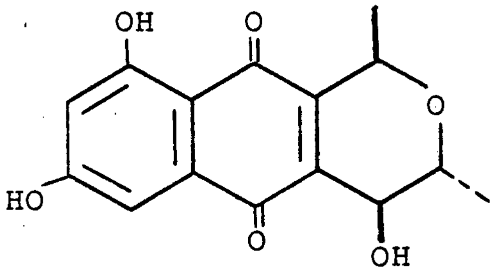
The quinone methide (14) could act as a Michael-type acceptor to nucleophiles (Nu^-) which may be certain nucleophilic centres in the D.N.A. molecule, thereby binding the nucleic acid, as in (15), and preventing it from further replication.

It thus seems possible that several compounds containing the naphtho[2,3-*c*]pyran ring system could well be biologically active as a result of bioreductive alkylation.

In view of the above our research team under the guidance of Professor R.G.F. Giles at the University of Cape Town started a programme directed towards the synthesis of compounds which contain the naphtho[2,3-*c*]pyran ring system.

This study investigated potential routes to pyranquinones based on the 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone and 5,7-dihydroxy-1,4-naphthoquinone skeletons.

Of particular interest to us were the syntheses of the eleutherins (1) and (2) as racemates, (±)-quinone A (16), derived from protoaphin-*fb* (8), (±)-quinone A' (17), derived from protoaphin-*sl* (9), (±)-deoxyquinone A (18), derived from deoxyprotoaphin (10), (±)-7-methoxyeleutherin (19), and the isomeric demethoxyeleutherins (20) and (21) as their racemates. In the first instance it was decided to attempt the syntheses of the dimethyl ethers of the derivatives of the aphid pigments (16), (17), and (18) to see if these naphthopyranquinones could be constructed with the correct relative stereochemistry of the substituents about the pyran ring while at the same time carrying oxygenation in the form of methoxy groups at C-7 and C-9 of the ring system. The synthesis of the methyl ethers of the quinones would be particularly convenient since these had been obtained (as single enantiomers) from the natural compounds by Todd and Cameron,[7] and a comparison could then be made between synthetic and naturally derived material. If this work proceed successfully, a synthesis would then be investigated at a later stage using protecting groups other than methyl on oxygen which might readily be removed in the ultimate step of the final synthesis.



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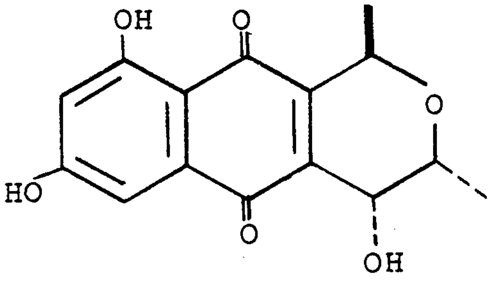

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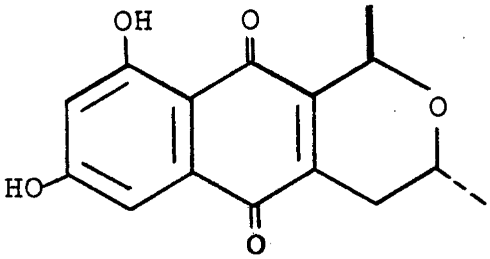

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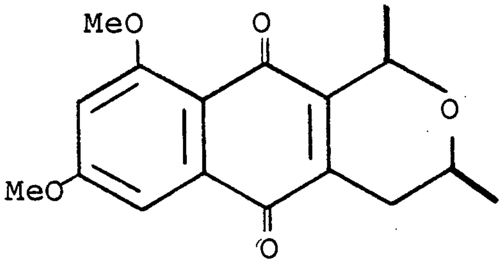

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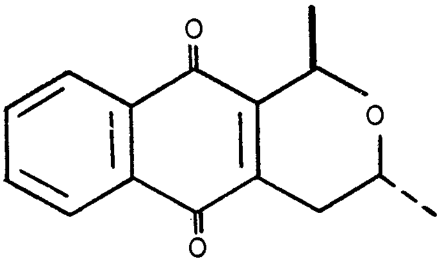

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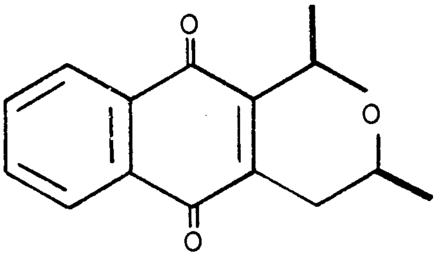

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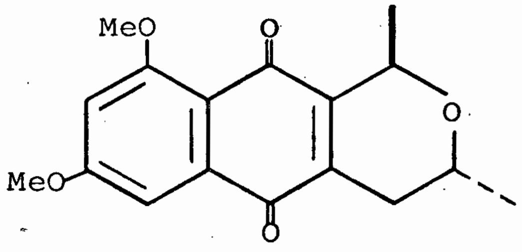
In considering syntheses for these naphthopyrans, routes that give rise to products with the same relative stereochemistry[11] of the substituents as that found for the natural products themselves would, of course, be obligatory.

Such routes with a high degree of stereospecificity were developed during this investigation and several pyranquinones, some of which are natural products or their derivatives, were synthesised as their racemates from the corresponding acetyl-1,4-naphthoquinones (28) - (30).

These pyranquinones include (±)-isoeleutherin (2), (±)-7-methoxyeleutherin (19), (±)-deoxyquinone A dimethyl ether (22), (±)-quinone A' dimethyl ether (23), (±)-quinone A dimethyl ether (24), the (±)-4-hydroxy-isoeleutherin isomers (25) and (26), and compound (27) derived from the alcohol (31).

The pyran ring system of these compounds has been synthesised by a novel base-induced cyclisation reaction discovered during this investigation.



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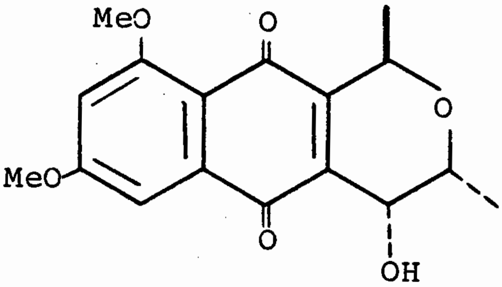

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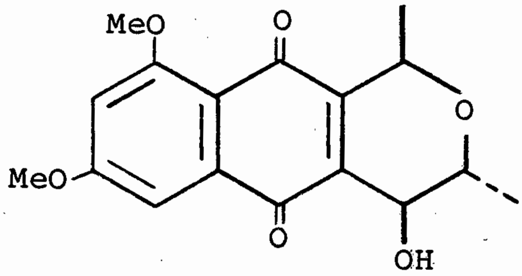

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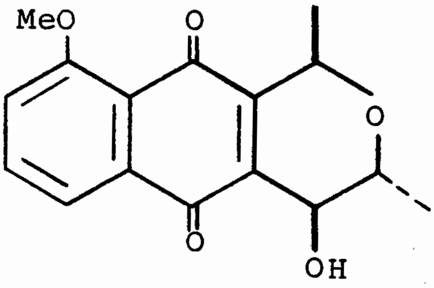

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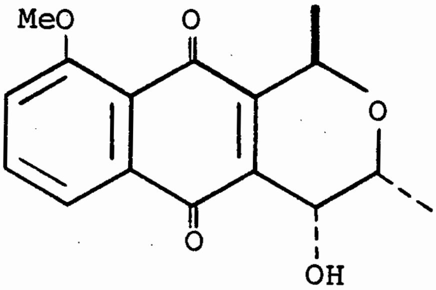

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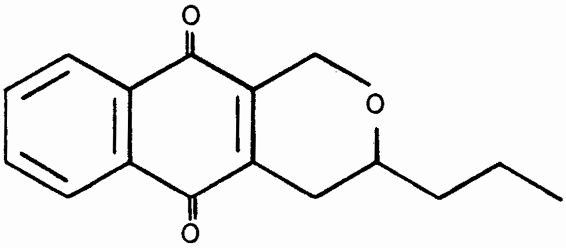

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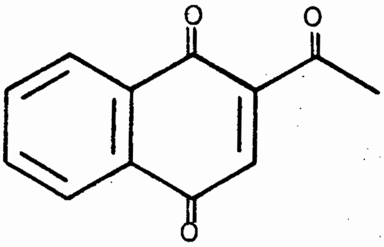

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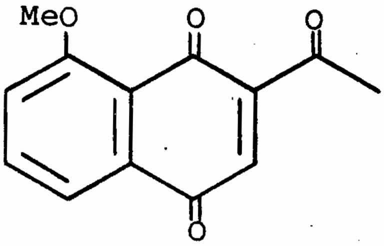

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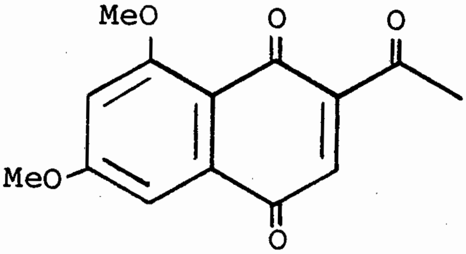

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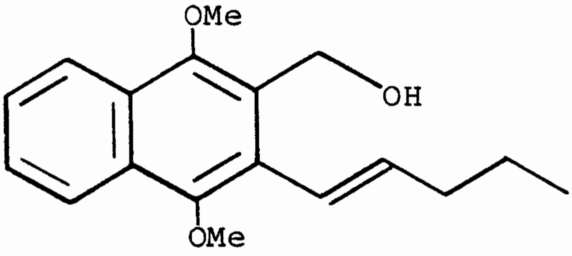

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In chapter I the synthesis of 3-acetyl-5-methoxy-1,4-naphthoquinone (29)[12,13] and its 7-methoxy analogue (30)[13] from juglone (35) and 5,7-dimethoxy-1,4-naphthoquinone (51) respectively, is described. The crucial regiospecific C-acetylation was effected using the Fries rearrangement.

While investigating routes to the isomeric 2-acetyl derivatives, an uncommon *meta* Fries rearrangement was observed.[13] This is also discussed in chapter I.

In chapter II our methodology for the synthesis of the naphtho[2,3-*c*]pyran ring system is described with emphasis on the base-induced cyclisation reaction developed during this investigation which eventually afforded syntheses of naturally occurring or naturally derived pyranquinones as their racemates.

The routes described here for isoeleutherin (2) and deoxyquinone A dimethyl ether (22) are highly stereoselective. The formation of the dimethyl ethers of quinones A and A', which is also highly stereoselective, represents the first reported synthesis of degradation products of the aphid pigments, protoaphin-*fb* (8) and protoaphin-*sl* (9).

Possible factors influencing the base-induced cyclisation reaction are also considered in terms of electronic and steric factors.

Chapter III deals with the regiospecific reaction of trifluoroacetic anhydride with various naphthalene methyl ethers and also with a number of naphthols. In all cases (except that of 1-naphthol itself) the oxygenation pattern chosen for the naphthalene substrates was that commonly found amongst naturally occurring naphthoquinones.

Trifluoroacetic anhydride is shown to acylate 1,4,5-tri- and 1,4,5,7-tetramethoxynaphthalenes, the former at C-3 or C-8, and the latter at C-8 exclusively. The reagent is also shown to acylate 1-naphthol and its 4,8-dialkoxy- and 4,6,8-trialkoxy derivatives to afford (almost exclusively) *ortho*-trifluoroacetylnaphthols in high yield. It is further shown that cerium(IV) ammonium nitrate (C.A.N.) oxidation of the ortho-trifluoroacetylalkoxynaphthols yields the corresponding (1,1-dihydroxy- 2,2,2- trifluoroethyl) - 1,4-naphthoquinones which undergo hydroxypentylation of the quinonoid nucleus with 3-hydroxyhexanoic acid to give naphtho[2,3-*c*]pyran - 5,10-quinones.

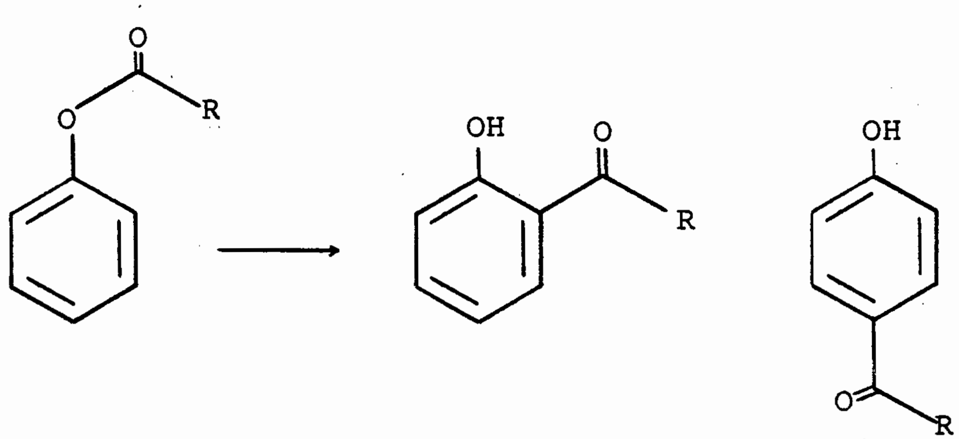
The potential of these acylation reactions in the synthesis of naturally occurring naphthoquinones is investigated and referred to.

CHAPTER I

THE SYNTHESIS OF 3-ACETYL-5-METHOXY-1,4-NAPHTHOQUINONE AND ITS 7-METHOXY ANALOGUE EMPLOYING A FRIES REARRANGEMENT

1.1 A general review of the Fries rearrangement

The classical Fries rearrangement of phenolic esters of the type (32) involves the migration of an acyl group to an *ortho* or *para* position in the presence of a Lewis acid with the formation of *ortho*-(33) and *para*-(34) hydroxyphenyl ketones.[14]



(32) (33) (34)

Another method available for the synthesis of similar compounds is the well-known Friedel-Crafts reaction in which a phenol or phenolic ether is treated with an acid chloride or acid anhydride in the presence of a Lewis acid. The Fries method usually is to be preferred for the preparation of phenolic ketones as better yields are normally obtained.

The mechanism involved in the Fries rearrangement has received considerable attention.[14-18] There seems to be no decisive evidence as to whether the migration of the acyl group is intermolecular or intramolecular or both, although there is some evidence suggesting that it is at least partly intermolecular, in certain cases.

Ogata and Tabuchi[15] studied the aluminium chloride-catalysed rearrangement of phenyl acetate to *ortho* and *para*-hydroxyacetophenones in the presence of acetic anhydride-1^{14}C as the tracer in various solvents. They found evidence for a mechanism involving a comparatively fast ester exchange followed by an intramolecular acetyl migration probably *via* a π-complex.

Cullinane *et al.*[16,17] postulated a mechanism involving both inter- and intramolecular migrations whereas Hauser and Man[18] suggested that the rearrangement of phenolic esters involves an intermolecular mechanism, especially for those carried out at relatively low temperatures (60° - 84°C)

It was earlier shown that use of low temperatures favours the formation of the *para* product; higher temperatures favour the formation of the *ortho* product in the rearrangement of phenolic esters.[14] This has also been observed in the rearrangement of 1-naphthyl esters.[19]

The photo-Fries rearrangement has also received considerable attention since its discovery in 1960. Kobsa[20] found that several substituted phenolic esters were converted to *ortho*-hydroxybenzophenones by irradiation with ultraviolet light (245 - 330 nm) in benzene or ethanol solutions. He proposed a free radical mechanism. Finnegan and Mattice[21] extended this photo-Fries rearrangement of phenolic esters to a number of substituted phenyl benzoate derivatives and found that when the phenol moiety was unsubstituted a mixture of *ortho*- and *para*-hydroxyphenyl ketones was obtained.

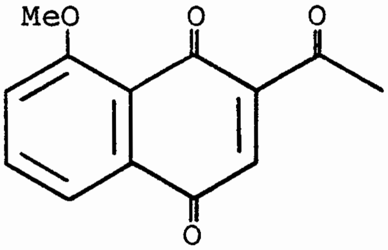
Wheeler *et al.*[22] also used this photo-Fries rearrangement to convert esters of 1-naphthol and 5-methoxy-1-naphthol to the corresponding 2-acyl-1-hydroxynaphthalenes in solvents such as methanol, benzene, dimethylformamide, and ethyl acetate. This is a convenient regioselective route to some 2-acylnaphthoquinones since they were able to oxidise the 2-acylnaphthols to the corresponding 2-acyl-1,4-naphthoquinones with thallium trinitrate.

Syntheses of natural products which use a photo-Fries rearrangement include griseofulvin[23] and an early synthesis of daunomycinone.[24]

It is evident from the foregoing that the Fries rearrangement is a useful tool in organic synthesis and it was employed in this investigation into potential regioselective routes to naturally occurring quinones, or their derivatives, which contain the naphtho[2,3-*c*]pyran ring system.

1.2 The synthesis of the 3-acetyl-1,4-naphthoquinones (29) and (30) *via* an *ortho*-Fries rearrangement[13]

The quinones (29)[12,13] and (30)[13] are potentially useful precursors to some naturally occurring quinones which contain the naphtho[2,3-*c*]pyran ring system. A convenient laboratory synthesis of (29) and (30) would thus constitute an important part in the total synthesis of some of these natural products or their derivatives.



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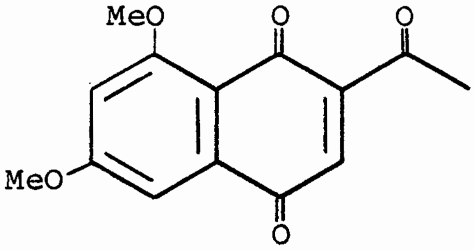
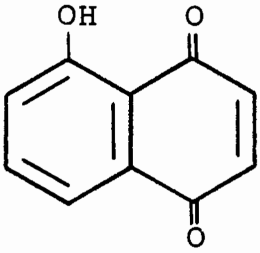


(30)

The naphthoquinone (29) has previously been synthesised[12] but the low yield (34%) in the final step made an alternative route to (29) desirable.

Giles *et al.*[13] and Maruyama *et al.*[25] independently developed a new route to (29) from the natural product juglone (35) and 1,5-dimethoxy-4-naphthol (38)[26] respectively.

The former route involved the methylation of juglone (35) using iodomethane and silver (I) oxide in chloroform at room temperature to afford juglone methyl ether (36) which was reductively monomethylated at the less hindered oxygen to give the naphthol (38)[26] from the intermediate diol (37) in high yield.



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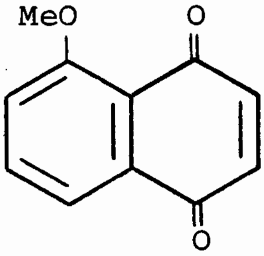

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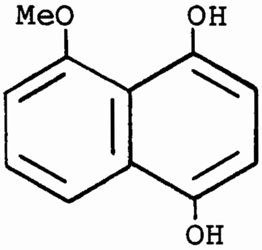

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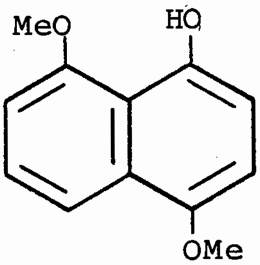

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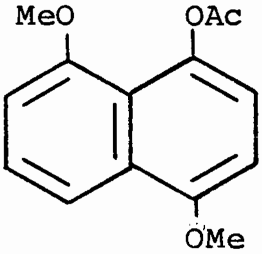
The acetate (39) was readily available from the naphthol (38) by reaction with acetic anhydride in pyridine. Treatment of acetate (39) with boron-trifluoride-diethyl ether gave the product (40) of Fries rearrangement, together with deacylated material (38) which could be recycled, thereby increasing the overall yield of compound (40).



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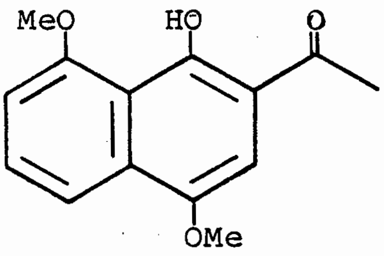
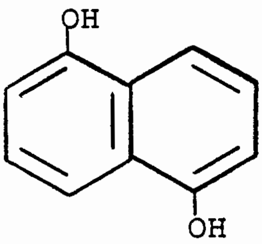


(40)

A sharp lowfield singlet at δ 13.46 in the ^{1}H n.m.r. spectrum due to the strongly hydrogen-bonded hydroxy group, supported the assignment of structure (40) to the product of Fries rearrangement.

The acetylquinone (29) was readily available in high yield from compound (40) by oxidative demethylation with cerium(IV) ammonium nitrate (CAN).

The naphthol (38) has also been prepared in a four-step synthesis by Rapoport *et al.*[26] from 1,5-dihydroxynaphthalene (41).



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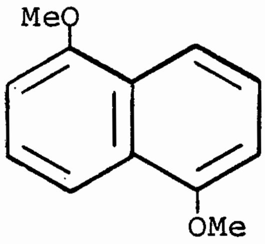
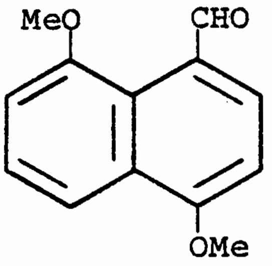
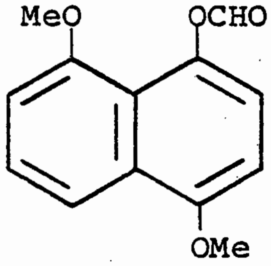


(42)

The naphthalene dimethyl ether (42), available from (41) by methylation with dimethyl sulphate, was treated with dimethylformamide and $POCl_3$ in toluene to afford the naphthaldehyde (43). Baeyer-Villager oxidation of the aldehyde (43) gave the formate (44) from which the naphthol (38) was prepared by alkaline hydrolysis.



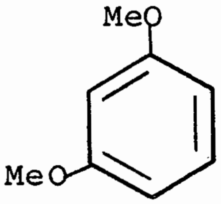
(43)



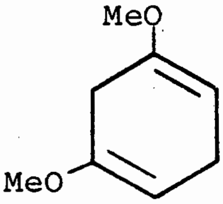
(44)

Quinone (30) was synthesised from 5,7-dimethoxy-1,4-naphthoquinone (51) for which several methods of synthesis have been reported.[27-29] The method mainly employed in this work was that of Birch[29,30a] with some modifications.

Recorcinol dimethyl ether (45) was reduced with sodium metal and absolute ethanol as the proton source in liquid ammonia to the non-conjugated diene (46).[30a]

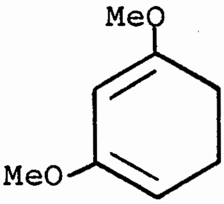


(45)



(46)

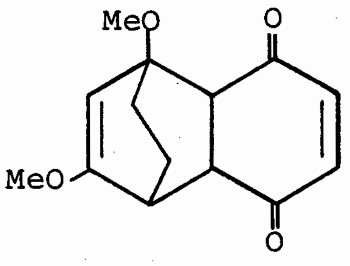
This product was treated with potassium amide[31,32] to afford the conjugated diene (47). On several occasions compound (45) was converted directly into the conjugated diene (47) in a one-pot reaction.



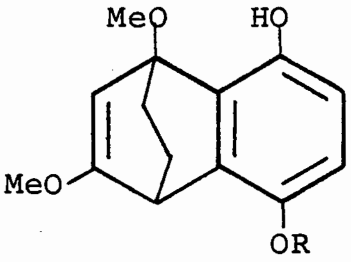
(47)

The Diels-Alder adduct (48) was obtained in good yield by the addition of portions of recrystallised 1,4-benzoquinone to the diene (47) in hot benzene. It was found that the portionwise addition of benzoquinone to the diene solution minimised the formation of quinhydrone which may interfere during work-up and contaminate the adduct.

Compound (48), which contains the labile enol-ether function, was immediately converted by enolisation with a 10% aqueous ammonia solution to the diol (49 a).

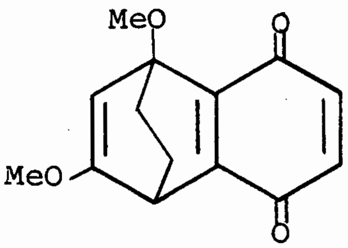


(48)

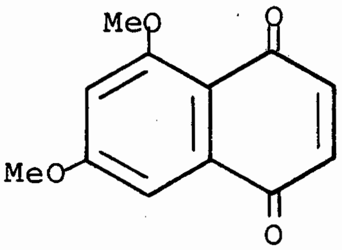


(49 a), R = H
(49 b), R = Me

This diol was smoothly oxidised by silver(1) oxide to the bridged-quinone (50) from which the ethano-bridge was thermally eliminated under reduced pressure (80°C - 160°C at 0,5 mm Hg) to yield the target quinone (51).

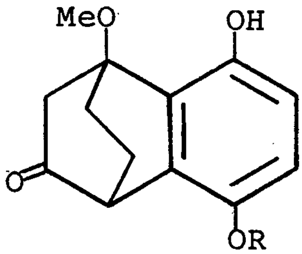


(50)



(51)

The enol-ether (49 a) is apparently sufficiently acidic to catalyse its own hydrolysis to the ketone (52 a). Thus great care must be taken during its work-up.[29,33]

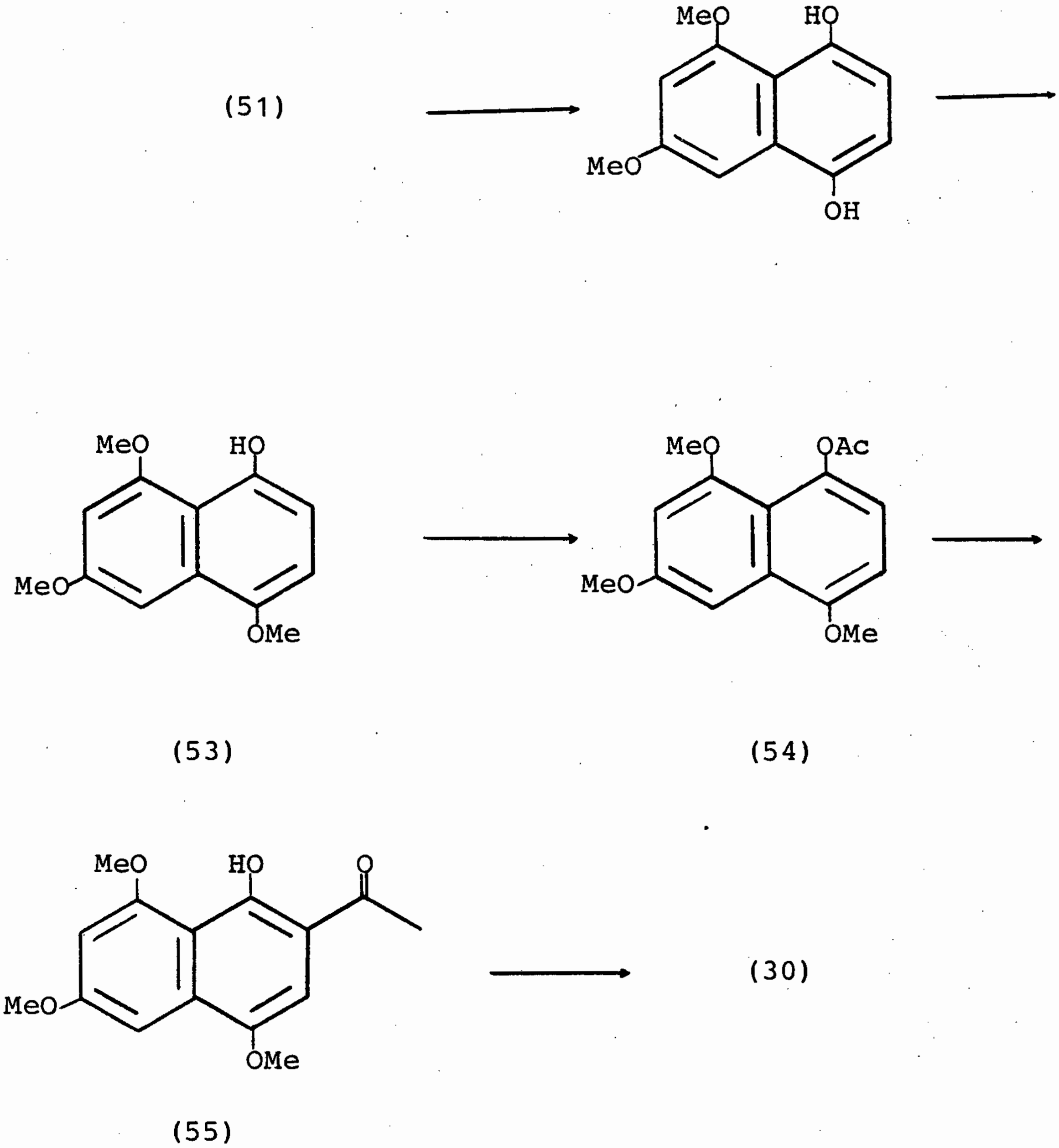


(52 a), R = H

(52 b), R = Me

Enolisation of adducts of the type (48) can also be achieved by treatment with potassium hydrogen carbonate in hot methanol followed by the addition of water, sodium acetate and Fremy's salt (potassium nitrosodisulphonate).[33,34] A disadvantage of this method is the relative instability of Fremy's salt, thus requiring its preparation immediately prior to use.

The synthesis of quinone (30) was accomplished by a regiospecific route, as in Scheme B similar to that described earlier for the synthesis of the analogue (29)[13]



(51) (53) (54) (55) (30)

Scheme B

Quinone (51) was reduced to the corresponding quinol with aqueous sodium dithionite which in turn was treated with dimethyl sulphate and anhydrous potassium carbonate in boiling acetone under nitrogen to afford the naphthol (53) in good yield (81%).

Due to the cryptophenolic nature of the *peri*-hydroxyl group in the quinol, monomethylation was readily achieved at the less hindered oxygen under the chosen reaction conditions. This is supported by the lowfield singlet at δ 8.72 in the ^{1}H n.m.r. spectrum of (53) due to the hydrogen bonded hydroxy group. As expected, the position of this signal was unaltered by dilution and disappeared upon addition of deuterium oxide. A relatively sharp absorption band was also observed at 3390 cm^{-1} in the infrared spectrum of (53). The sharpness of this absorption band is undoubtedly indicative of intramolecular hydrogen bonding.

An alternative method for the synthesis of naphthol (53) was also attempted. The Diels-Alder adduct (48) was treated with anhydrous potassium carbonate in boiling acetone under nitrogen for 1 hour. Dimethyl sulphate was then added to the mixture which was heated under reflux for an additional 3 hours. Work-up followed by chromatography afforded two compounds which were identified as the enol-ether (49 b), the major product, and the bridged-ketone (52 b).

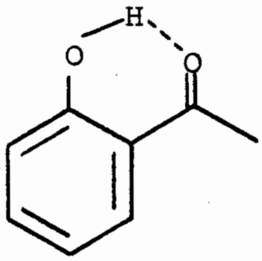
An attempt to thermally eliminate the ethano-bridge in (49 b) under reduced pressure failed. Under these conditions compound (49 b) sublimed and was almost quantitatively recovered. Elimination of the bridge was readily achieved to afford naphthol (53) in a yield of 65%, when compound (49 b) was heated at 160°C under nitrogen at atmospheric pressure.

When compound (53) was heated under reflux with an excess of acetic anhydride in pyridine, the acetate (54) was obtained in a 85% yield. Under these conditions the cryptophenolic hydroxyl could be readily acetylated.

Treatment of the acetate (54) with boron trifluoride etherate afforded mainly the product (55) of *ortho* rearrangement, together with deacetylated material (53) which were separated by chromatography. Naphthol (53) could be reacetylated and recycled, thereby increasing the overall yield of the Fries rearrangement.

That rearrangement to the *ortho*-position had occurred was supported by the lowfield singlet at δ14.0 in the ^{1}H n.m.r. spectrum of compound (55) corresponding to the naphthalenic hydroxyl group hydrogen-bonded to the carbonyl-oxygen of the acetyl group at C-3.

Of particular interest is the absence of a strong hydroxy absorption band in the region 4000-3000 cm^{-1} in the infrared spectrum of compound (55). This phenomenon was also observed in the infrared spectrum of 2-hydroxyacetophenone (56)



(56)

The optimum reaction conditions for the above Fries rearrangement were determined by comparing the amounts of compounds (53), (54) and (55) isolated at a specific and constant reaction temperature under nitrogen, by varying the reaction time. Freshly distilled boron trifluoride etherate [1 ml/100 mg acetate (54)] was always used.

For example, treatment of acetate (54) (100 mg) with the Lewis acid at room temperature for 30 minutes, resulted in the recovery of starting material (80 mg), together with deacylated material (53) (15 mg) and 60°C for 15 minutes gave compound (55), (56 mg), together with (53), (28 mg), and starting material (6 mg).

The acetate (54) and the product (55) of Fries rearrangement could not be separated by the chromatographic system employed. By comparing the relative intensities of the signals at $\delta 2.32$ and 2.62 in the ^{1}H n.m.r. spectrum of the mixture obtained after chromatography, (which correspond to the methyl protons of the acetoxy group and the acetyl group respectively) their relative abundance could be determined and expressed in terms of percentages.

The optimum reaction conditions on this scale were found to be a reaction temperature of 60°C and a reaction time of 20 minutes under nitrogen, using freshly distilled boron trifluoride etherate. In this manner 58 mg of (55) and 28 mg of (53) were isolated from 100 mg (54).

The conditions and results for this Fries rearrangement reaction are summarised in Table 1. [100 mg of acetate (54) was used in each determination]

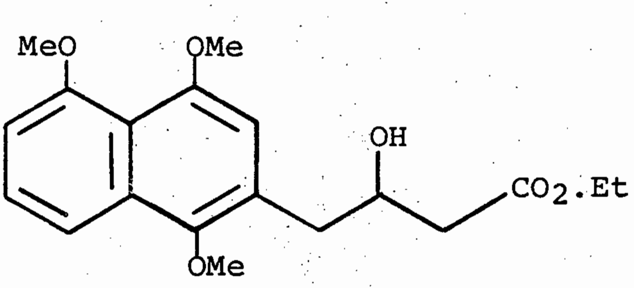
Temp. °C	Time (min.)	Amount isolated (mg)		
		55	53	54
20	30	-	15	80
50	30	-	20	69
60	15	56	28	6
60	20	56	28	-
60	30	54	28	-
70	10	41	33	-
70	20	32	31	-

Table 1

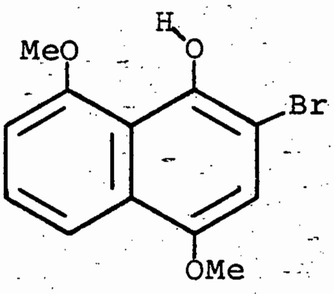
Oxidative demethylation[35] of compound (55) employing C.A.N. in acetonitrile gave the target quinone (30) in good yield (86%). Purification of this quinone was accomplished by recrystallisation from a dichloromethane-petroleum ether solution as the compound was found to be unstable upon chromatography.

C.A.N. has recently been used fairly frequently for the oxidative demethylation of hydroquinone dimethyl ethers to afford quinonoid systems. Two interesting examples of such use are the oxidation of ester (57)[36] and the bromonaphthalene (58)[26] to the quinones (59) and (60) respectively. The selectivity and mildness of these oxidation reactions are illustrated by the fact that a variety of functional groups are tolerated.

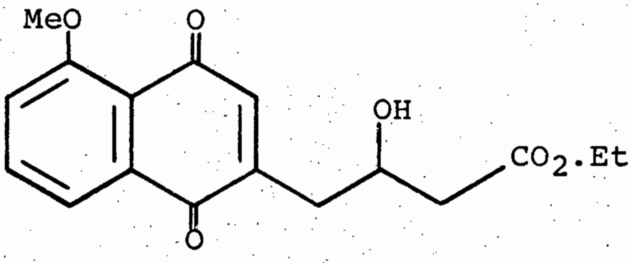
The mechanism[35] of the oxidative demethylation process was shown to involve aryl-oxygen bond cleavage rather than alkyl-oxygen bond cleavage[37].



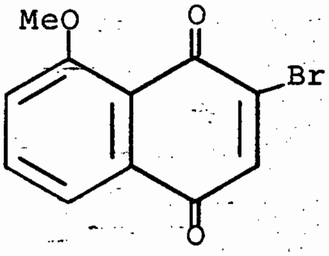
(57)



(58)



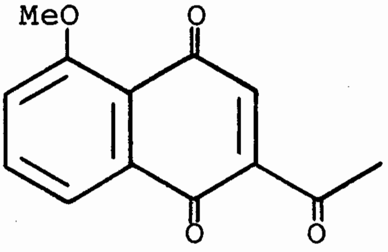
(59)



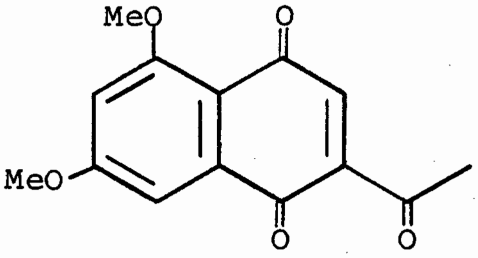
(60)

1.3 An alternative route to quinones (29) and (30) *via* an uncommon *meta*-Fries rearrangement[13]

While investigating routes to the isomeric 2-acetyl derivatives (61) and (62), an uncommon *meta*-Fries rearrangement was observed.

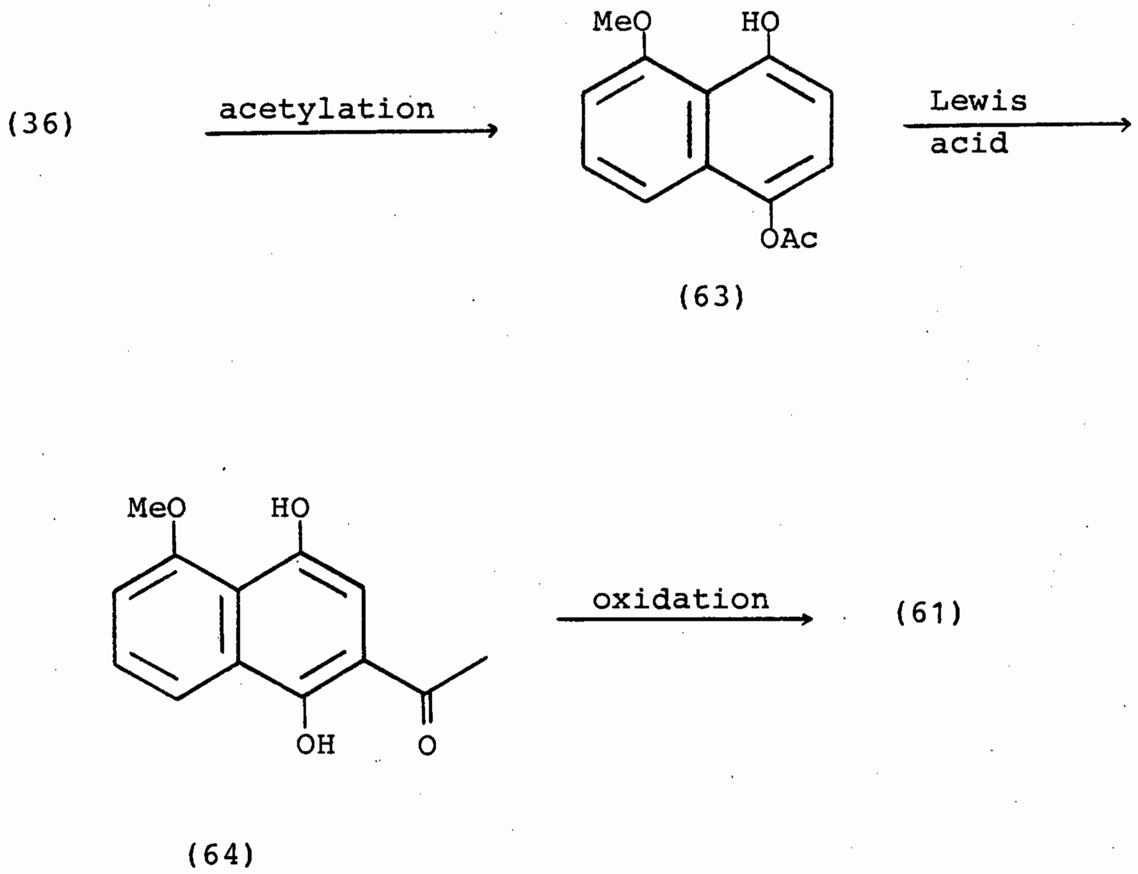


(61)



(62)

It was envisaged that, for example, 2-acetyl-5-methoxy-1,4-naphthoquinone (61) could be synthesised from juglone methyl ether (36) *via* the acetate (63), employing a Fries rearrangement reaction. Oxidation of the quinol (64), the product of *ortho*-Fries rearrangement, would lead to the 2-acetyl derivative (61).

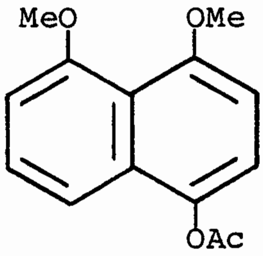


Scheme C

The acetate (63) was readily available, in good yield (72%), from juglone methyl ether (36) by reductive monoacetylation employing acetic anhydride, pyridine and zinc dust in boiling chloroform under nitrogen.

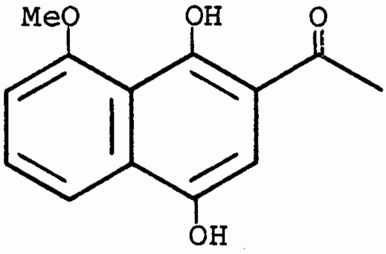
The assignment of structure (63) to the product was supported *inter alia* by a sharp lowfield singlet at δ9.25 in its ^{1}H n.m.r. spectrum due to the intramolecularly hydrogen bonded *peri*-hydroxy group.

Further support for structure (63) was obtained by methylation of acetate (63) to afford compound (65), which proved to be isomeric with compound (39).



(65)

Treatment of acetate (63) with boron trifluoride etherate at 60°C resulted in the formation of the unstable naphthoquinol (66) in which the acetyl had undergone *meta* migration, together with deacetylated material.



(66)

Acetylation of this deacetylated material afforded acetate (63) which could be recycled.

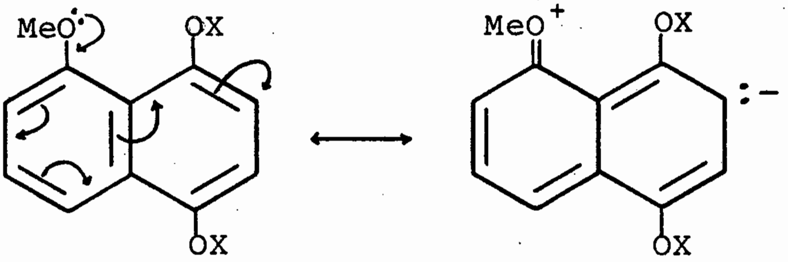
The quinol (66) was found to be almost insoluble in chloroform and thus its ^{1}H n.m.r. spectrum was recorded in deuterated acetone as the solvent.

An important feature of this spectrum is the lowfield singlet at δ13.4 due to strong intramolecular hydrogen bonding, presumably between the hydroxyl at C-4 and the carbonyl oxygen of the acetyl group at C-3, and a broad signal at δ5.7 whose chemical shift was solvent dependent. Both signals disappeared upon addition of deuterium oxide. The latter signal is therefore due to the hydroxyl at C-1. Had the product been the isomeric 2-acetyl-5-methoxynaphtho-1,4-hydroquinone, one would have expected two hydrogen-bonded hydroxyl groups, the one to acetyl at about δ13-14, while that to the *peri* methoxy group would have been anticipated in the region δ8-10.

Treatment of this quinol with silver(I) oxide afforded quinone (29) adding further support to the correctness of the assigned structure (66).

It is therefore clear that the acetyl group migrated to C-3, or to a *meta* position relative to the acetoxy group of compound (63). Since there is evidence that Fries rearrangements can be either intra or intermolecular, it is assumed that since a *meta* migration is occurring, the process is entirely intermolecular.

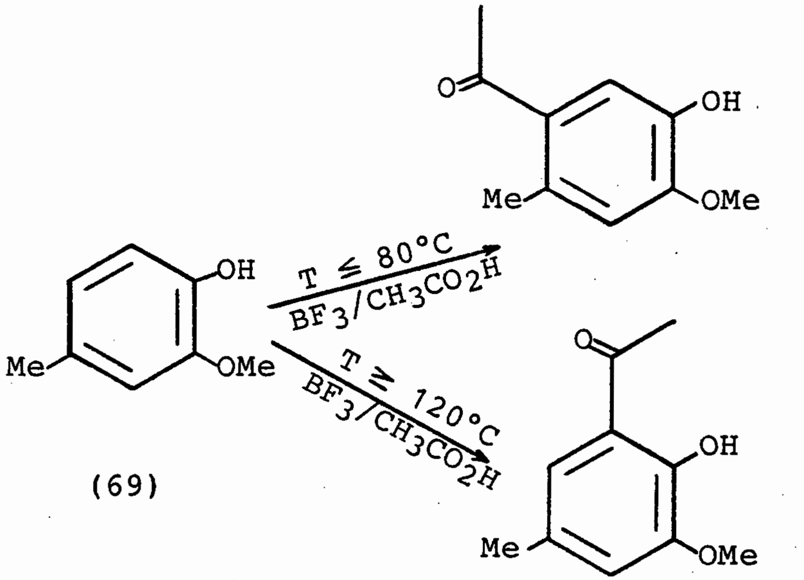
This being the case, one can explain the acetylation at C-3 rather than at C-2 on the basis that the former is activated to attack by electrophiles by the methoxy group at C-5 as in (67) and (68).



(67) X = H or BF_3^- (68)

Meta migration during Fries rearrangement appears to be unknown for naphthalenes although for certain phenolic esters the phenomenon has previously been observed.

Da Re and Cimatoribus[38] observed that in the acylation of the cresol (69) by the boron trifluoride-carboxylic acid method involving a Fries rearrangement, it was possible to obtain selectively, by variation of the reaction temperature, a predominance of either *meta* or *para* migration of the acetyl group as in the products (70) and (71) respectively.



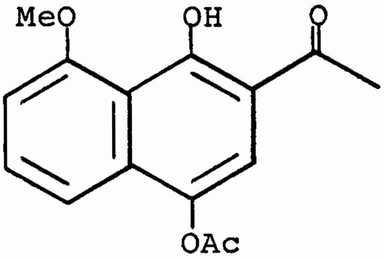
(70)

(69)

(71)

The activating effect of the methoxy group is presumably also here a prominent factor.

Due to the instability of quinol (66) it was converted to the monoacetate (72) by acetylation of the crude reaction mixture with acetic anhydride and pyridine in chloroform containing zinc dust - the function of the latter being to convert any of quinone (36), which may arise by aerial oxidation of compound (37), a byproduct of the Fries rearrangement, to the acetate (63) by reductive monoacetylation. At the same time, any of the quinone (29) which may similarly be obtained by oxidation of hydroquinone (66), would be converted to (72). This procedure simplified the isolation of products from the reaction mixture by reducing their number. The acetate (63) was then recycled thereby increasing the overall yield of the Fries reaction.



(72)

Since Da Re and Cimatoribus[38] obtained the product of *ortho* rearrangement, at relatively high reaction temperatures ($\geq$ 120°C), it was decided to treat the acetate (63) with boiling boron trifluoride etherate under nitrogen. Once again no product of *ortho* rearrangement was identified and (66) was isolated, in low yield, as its monoacetate (72) after intermediate acetylation.

The reaction of compound (65) with boron trifluoride etherate and with titanium tetrachloride was also investigated. In both cases a complex mixture was obtained which was not further investigated.

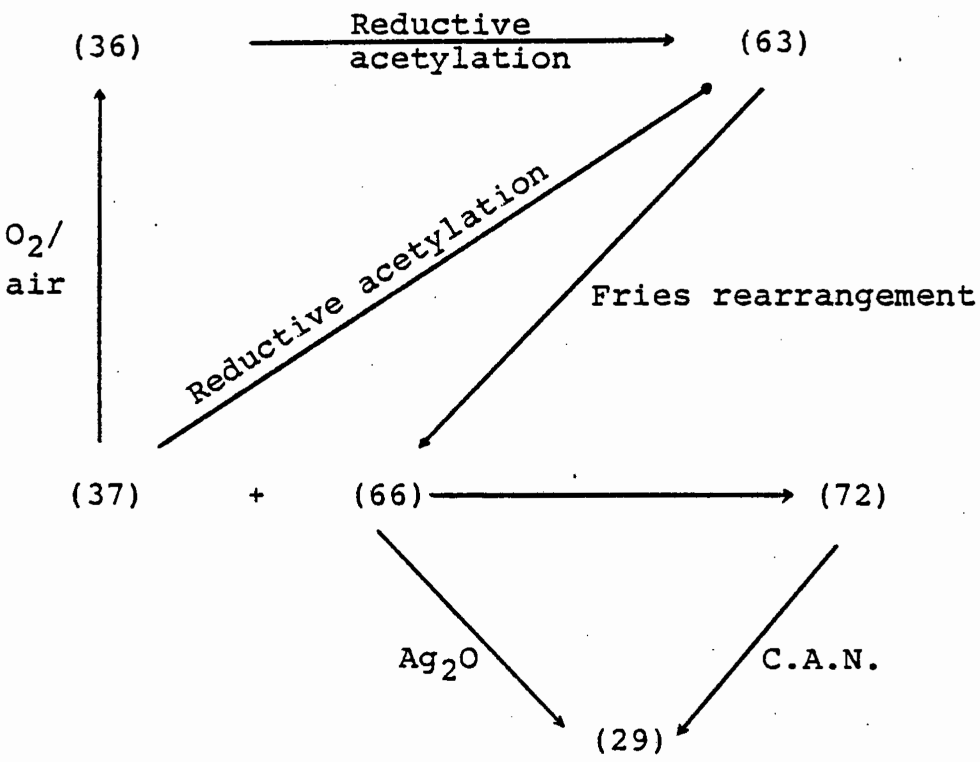
Table 2 summarises the results obtained of the Fries rearrangement reaction of acetate (63) under different reaction conditions [100 mg of acetate (63) was used in each determination].

Temp °C	Time min.	(72) mg	(63) mg	Total amount (72) + (63) recovered (mg)
60	20	29	42	71
60	30	27	39	66
65	30	43	35	78
60	40	44	30	74
65	40	42	22	64
70	30	40	22	62

Table 2

Oxidation of the monoacetate (72) employing aqueous C.A.N.[35] gave 3-acetyl-5-methoxy-1,4-naphthoquinone (29) in excellent yield (91%).

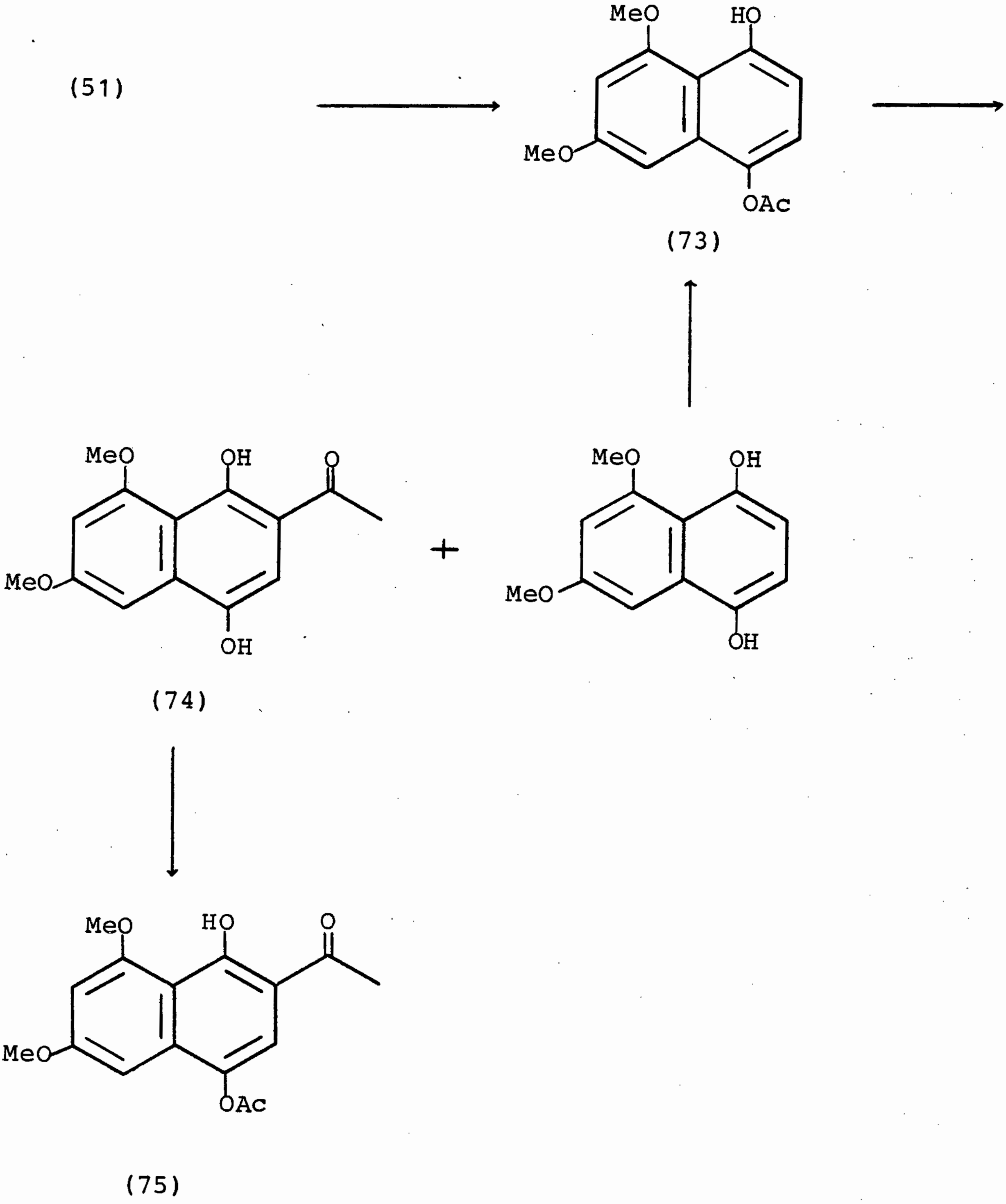
Scheme D summarises the route to quinone (29) *via* the *meta* Fries rearrangement.



<u>Scheme D</u>

Final evidence for the *meta* Fries rearrangement was obtained by reductive acetylation of quinone (29), obtained *via* the route (36) → (38) → (39) → (40) → (29) described earlier, to the monoacetate (72).

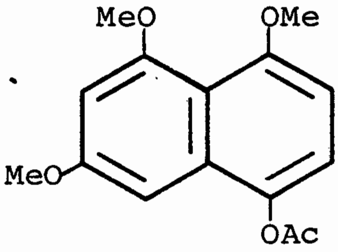
3-Acetyl-5,7-dimethoxy-1,4-naphthoquinone (30) was also available from quinone (51) *via* a *meta* Fries rearrangement. This route is shown in Scheme E.


(51)
MeO
HO
MeO
OAc
(73)
MeO
OH
O
MeO
OH
(74)
+
MeO
OH
MeO
OH
MeO
HO
O
MeO
OAc
(75)

Scheme E

1-Acetoxy-5,7-dimethoxy-4-naphthol (73) was available from quinone (51) by reductive monoacetylation using the reaction conditions mentioned above for the conversion of quinone (36) to the monoacetate (63). As was expected, acetylation occurred only at the less hindered oxygen. The sharp downfield signal at $\delta 9.07$ in the ^1H n.m.r. spectrum of the product due to the hydroxyl at C-4 which is hydrogen bonded to the *peri*-methoxy group, supported the assignment of structure (73).

Of further support is the fact that the monoacetate (73) could be methylated to yield compound (76) which is isomeric with the acetate (54).



(76)

Treatment of compound (73) with boron trifluoride etherate, followed by similar treatment as for quinol (66) described earlier, converted the intermediate quinol

(74) to the monoacetate (75). At the same time the deacetylated material could be converted to the acetate (73), which was recycled.

The electronic activation at C-3 is presumably even more pronounced in (73) as compared to the activation at C-3 of acetate (63), since both methoxyls tend to increase the electron density at that position through the mesomeric effect and thus the *meta* migration of the acetyl group was in this case not unexpected.

Apart from spectroscopic evidence supporting the assignment of structure (75) to the product of Fries rearrangement, is the fact that quinone (30), available *via* the route shown in scheme B on page 27, afforded the monacetate (75) upon reductive acetylation.

A summary of the results obtained for the Fries rearrangement of compound (73) under different reaction conditions, is shown in Table 3. [100 mg of acetate (73) was used in each determination].

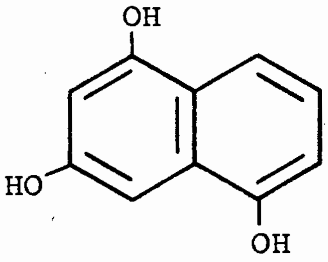
Temp. °C	Time min.	(75) mg	(73) mg	Total amount (73) + (75) recovered (mg)
60	30	50	34	84
65	30	59	31	90
60	40	52	28	80
60	45	51	28	79
65	40	38	31	69

Table 3

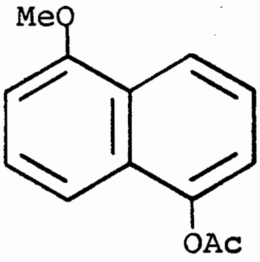
Acetate (75) was smoothly oxidatively deacetylated to the quinone (30) with aqueous C.A.N.[35]

As mentioned earlier, Wheeler *et al*[22] prepared several 2-acyl-5-methoxy-1,4-naphthoquinones by a photo-Fries rearrangement of the corresponding 5-methoxy-1-naphthol esters to the 2-acyl-5-methoxy-1-naphthols. The latter were oxidised to the corresponding 2-acylquinones by thallium (111) nitrate.

Unfortunately, the Wheeler method cannot be readily generalised for many other unsymmetrically substituted naphthols such as, for example, compound (77), due to the high degree of regiospecificity required in methylation and acetylation reactions which gave rise to his compound (78).



(77)



(78)

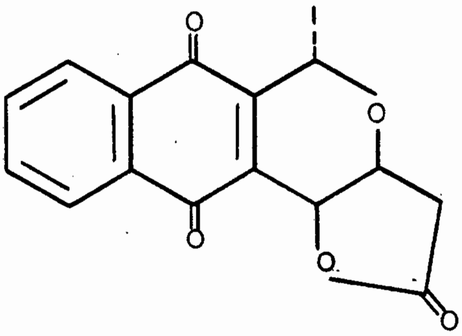
CHAPTER II

SYNTHESES OF RACEMIC NATURALLY OCCURRING NAPTHO [2,3-*c*] PYRANQUINONES, OR THEIR DERIVATIVES, BY A NOVEL BASE-INDUCED CYCLISATION

2.1 Introduction:

In considering syntheses for quinones A (16) and A' (17), the isomeric eleutherins (1) and (2), 7-methoxyeleutherin (19) and deoxyquinone A dimethyl ether (22), appropriate aromatic oxygenation of 2-acetyl-1,4-naphthoquinone (28) is required.

Certain analogues lacking oxygen(s) in the aromatic ring have been synthesised employing the quinone (28) as starting material. These include 9-deoxykalafungin (79)[39] and 7,9-dideoxyquinones A (80) and A' (81)[40] as their racemates.



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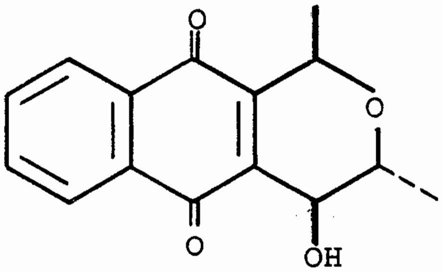

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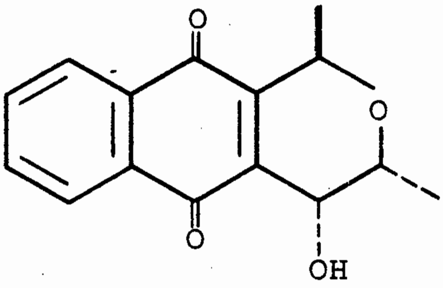
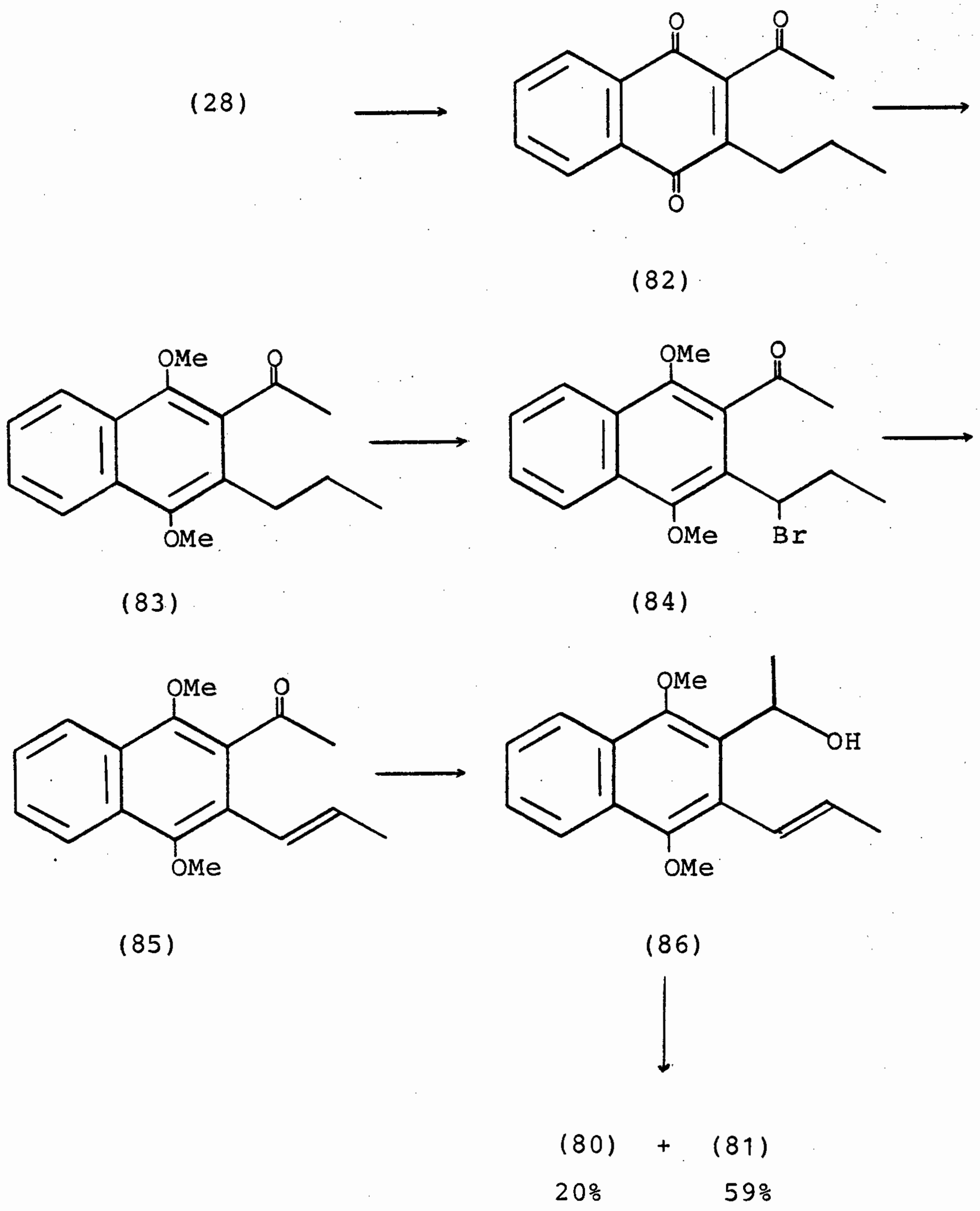


(81)

Compounds (80) and (81) were prepared by Giles *et al.*[40] from quinone (28) by a route which involved a novel oxidative cyclisation reaction employing C.A.N. This route is shown in Scheme F.



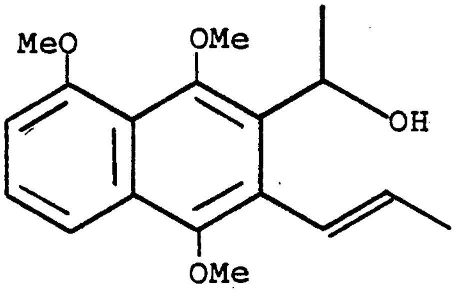
Scheme F

Quinone (28) was propylated with butanoic acid in the presence of silver nitrate and potassium persulphate to afford quinone (82) which was reductively methylated to the dimethyl ether (83).

Compound (83) was brominated with *N*-bromosuccinimide to afford the benzylic bromide (84). Dehydrobromination of this bromide was achieved in 65% yield employing the base 1,5-diazabicyclo[4.3.0]non-5-ene in dimethylformamide, to give the *trans*-olefin (85). The alcohol (86) was readily available from compound (85) by reduction with lithium aluminium hydride.

Oxidation of compound (86) with four molar equivalents of C.A.N. gave two products with markedly different R_F values. The product of higher R_F was assigned structure (80) in which the hydroxyl at C-4 occupies a *pseudo*-equatorial position and the product of lower R_F, the major product, was assigned structure (81) in which the hydroxyl occupies the *pseudo*-axial position.

The synthesis of aromatic oxygenated naphthalenic olefins, for example compounds (87) and (88) was envisaged to be possible, from the quinones (29) and (30) respectively, *via* synthetic routes similar to the route shown in Scheme F.



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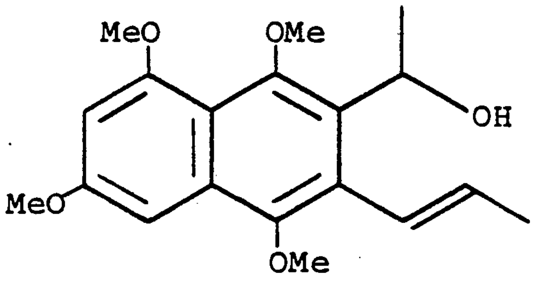
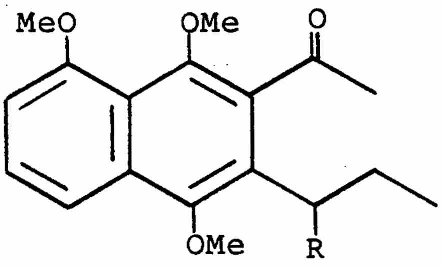


(88)

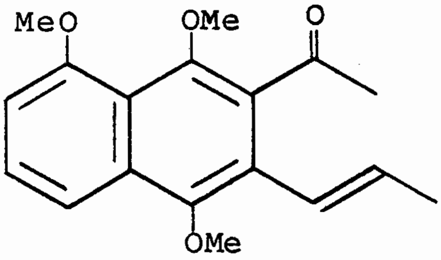
It was anticipated that treatment of compounds (87) and (88) with C.A.N. would result in oxidative cyclisation [as experienced with compound (86)[40]] of (87) and (88) to yield the dimethyl ethers of the isomeric quinones A (24) and A'(23) from (88) and compounds (25) and (26) from (87).

It was also envisaged that removal of the hydroxyls at C-4 in the isomeric pyrans (25) and (26) with sodium stannite[41] would afford isoeleutherin (2) as its racemate.

However, the *trans*-olefin (90) was obtained in moderate yield (46%) upon treatment of the benzylic bromide (89 b) with the bicyclic amidine 1,5-diazabicyclo [4.3.0] non-5-ene.



(89 a, R = H)
(89 b, R = Br)

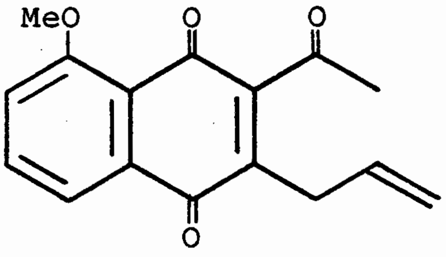


(90)

The low yield in this dehydrobromination step prompted us to investigate alternative routes to olefins of the type (90). Our synthetic strategy involved allylation of the quinonoid nucleus of quinones (28)-(30) employing the Jacobsen-Torssell reaction conditions.[42] It was expected that compounds of the type (90) would be available *via* conjugation of the allyl group.

2.2 The synthesis of allylated naphthalenes from the quinones (28)-(30)[43,47]

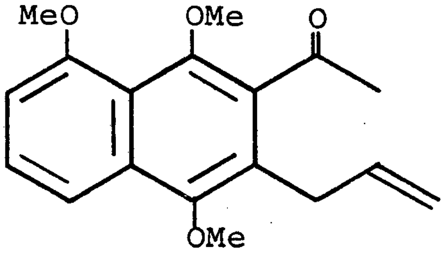
The first method employed was the allylation of quinone (29) with vinyl acetic acid in the presence of silver nitrate and potassium persulphate. This Jacobsen-Torssell-type reaction[42] gave the quinone (91) in a yield of 50%.



(91)

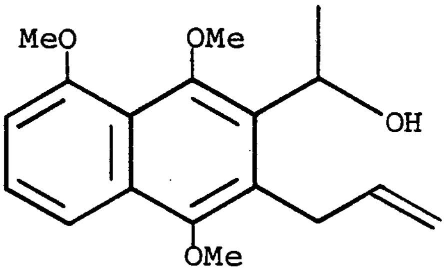
The ^{1}H n.m.r. spectrum of this product showed *inter alia* a doublet of doublets (J 1 and 6 Hz) at δ3.32 due to the methylene protons of the propenyl chain at C-2 which are coupled to the olefinic protons. The terminal olefinic protons resonated as a two-proton multiplet centred at δ5.12, whereas the C-2 vinylic proton resonated as a one-proton multiplet at δ5.6-6.1

Reductive methylation of quinone (91), with aqueous sodium dithionite followed by treatment with an excess of potassium carbonate and dimethyl sulphate, gave the trimethoxy-naphthalene (92)[44] in good yield.



(92)

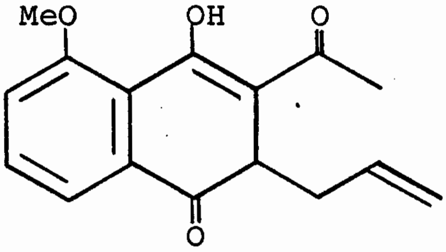
The non-conjugated naphthyl alcohol (93) was available by reduction of the ketone (92). The reaction of compound (92) with sodium borohydride in dry ethanol at room temperature proceeded extremely slowly. In contrast, the reaction of (92) with lithium aluminium hydride in dry ether at room temperature proceeded rapidly to afford the corresponding alcohol (93) in high yield.



(93)

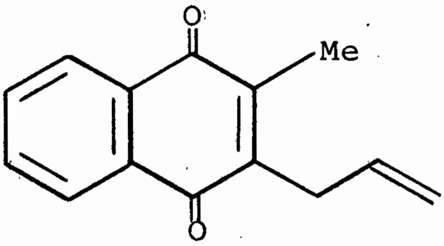
The ^1H n.m.r. spectral characteristics of the non-conjugated alcohol (93) prepared by our route, corresponded entirely to those reported by Kometani *et al*[45].

After the completion of this work an alternative method for the synthesis of compound (92) was reported.[25,44] This method employs allyltrimethylstannane and boron trifluoride etherate to allylate quinone (29). The intermediate (94) afforded (92) after methylation.



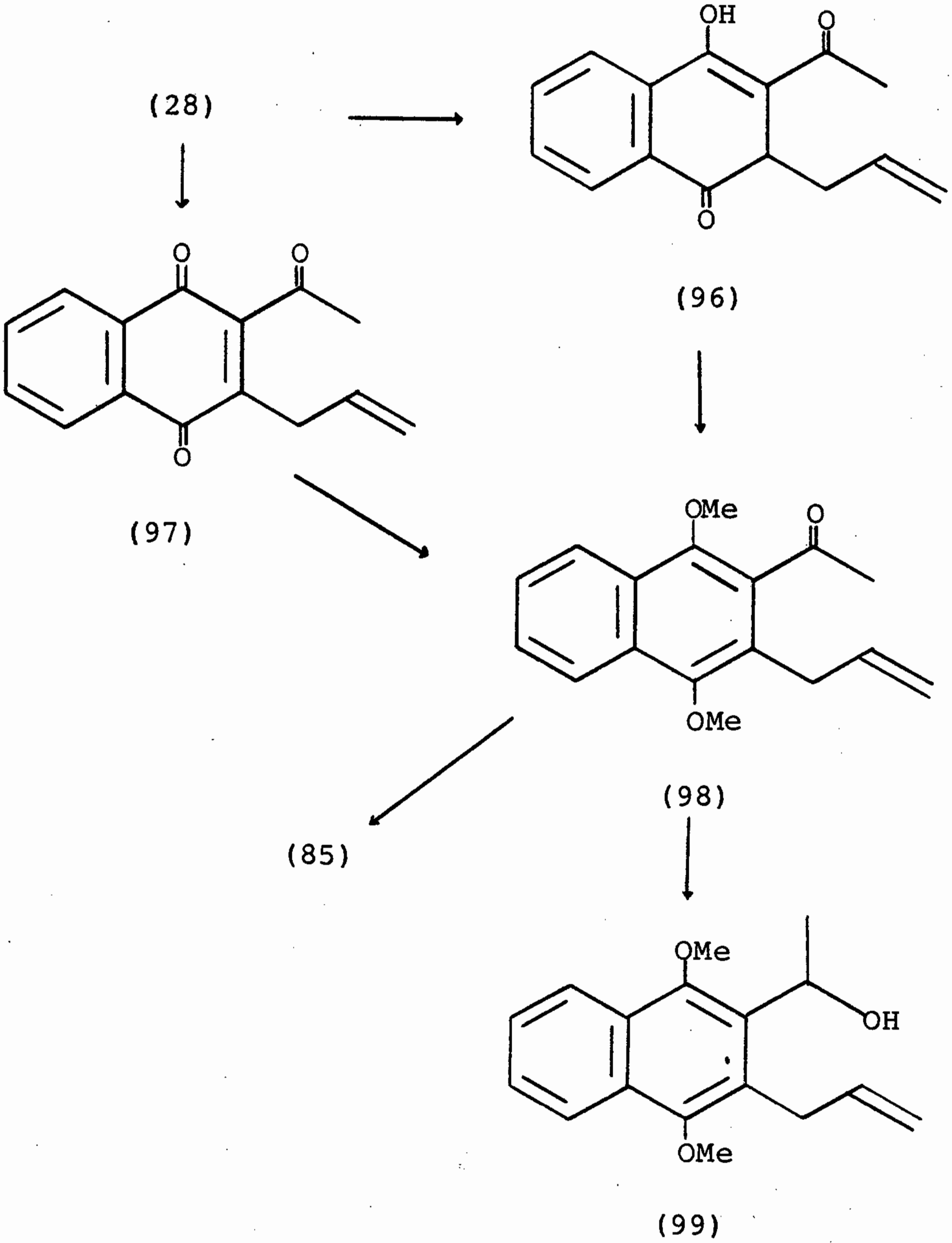
(94)

Recently, electrophilic allylation at C-3 of 2-methyl-1,4-dihydroxynaphthalene was achieved by an enzymatic method[46] employing allyl bromide in the presence of β-cyclodextrin, which afforded the vitamin K analogue (95) in a one-step preparation.



(95)

It was decided at this stage to prepare the analogues (98) and (99), as in Scheme G, from the more readily available quinone (28), and to employ this non-conjugated naphthyl ketone or the corresponding alcohol (99) in our studies to optimise the reaction conditions for the conjugation of the allyl group.[43,47]

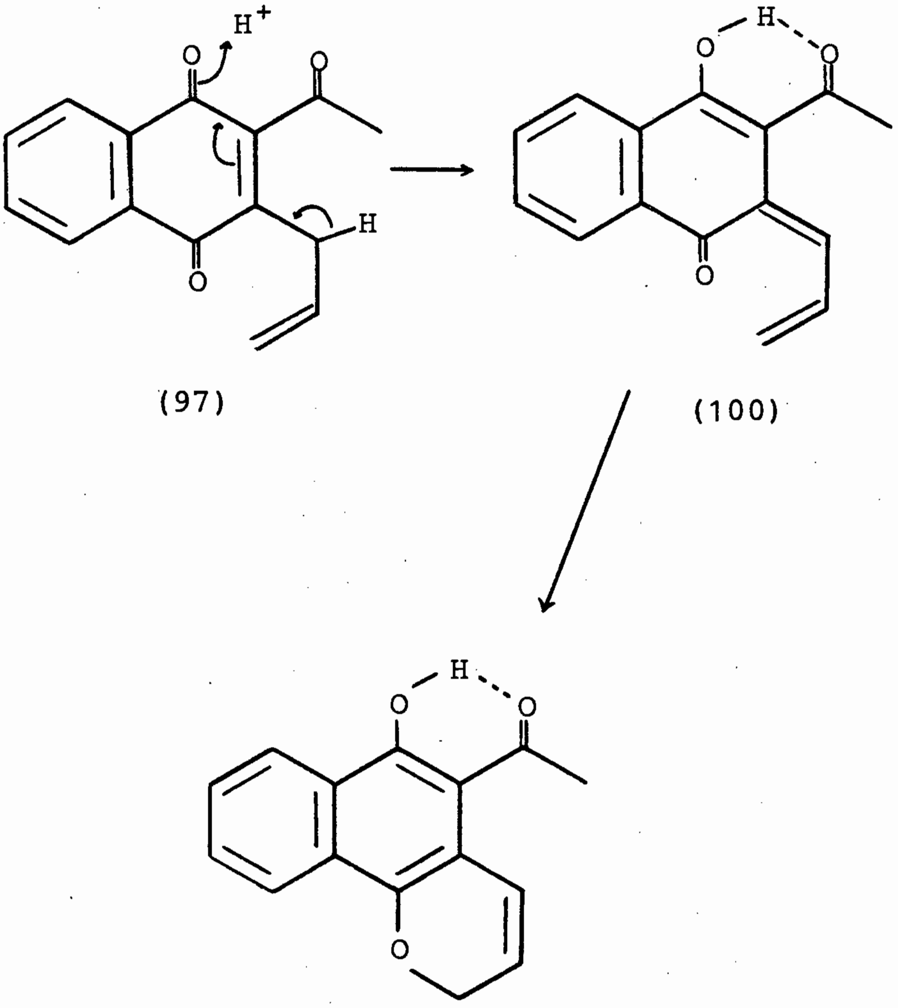


Scheme G

The first route involved the allylation of quinone (28) using vinyl acetic acid in the presence of silver nitrate and potassium persulphate, to give the quinone (97) in a yield of 43%. In this step, small quantities of a second yellow product, isomeric with quinone (97) and difficult to separate from it, were observed.

The ^{1}H n.m.r. spectrum of this contaminant showed, *inter alia*, a two-proton doublet of doublets (J 1 and 4 Hz) at δ4.8, a one-proton doublet of triplets at δ5.91 (J 4 and 10 Hz), a one-proton doublet of doublets (J 1 and 10 Hz) at δ6.78 and a lowfield one-proton singlet at δ13.86

This spectroscopic data enabled the assignment of structure (101) to this compound which presumably arises through acid-catalysed enolisation of quinone (97) to give compound (100), followed by cyclisation.

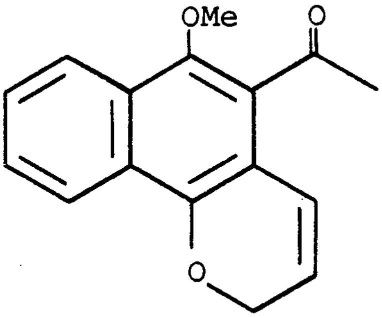


(97)

(100)

(101)

Compound (101) was characterised as its methyl ether (102) after being carried through to the next step of the reaction sequence where the naphthalene dimethyl ether (98) and compound (102) were more readily separated by chromatography.



(102)

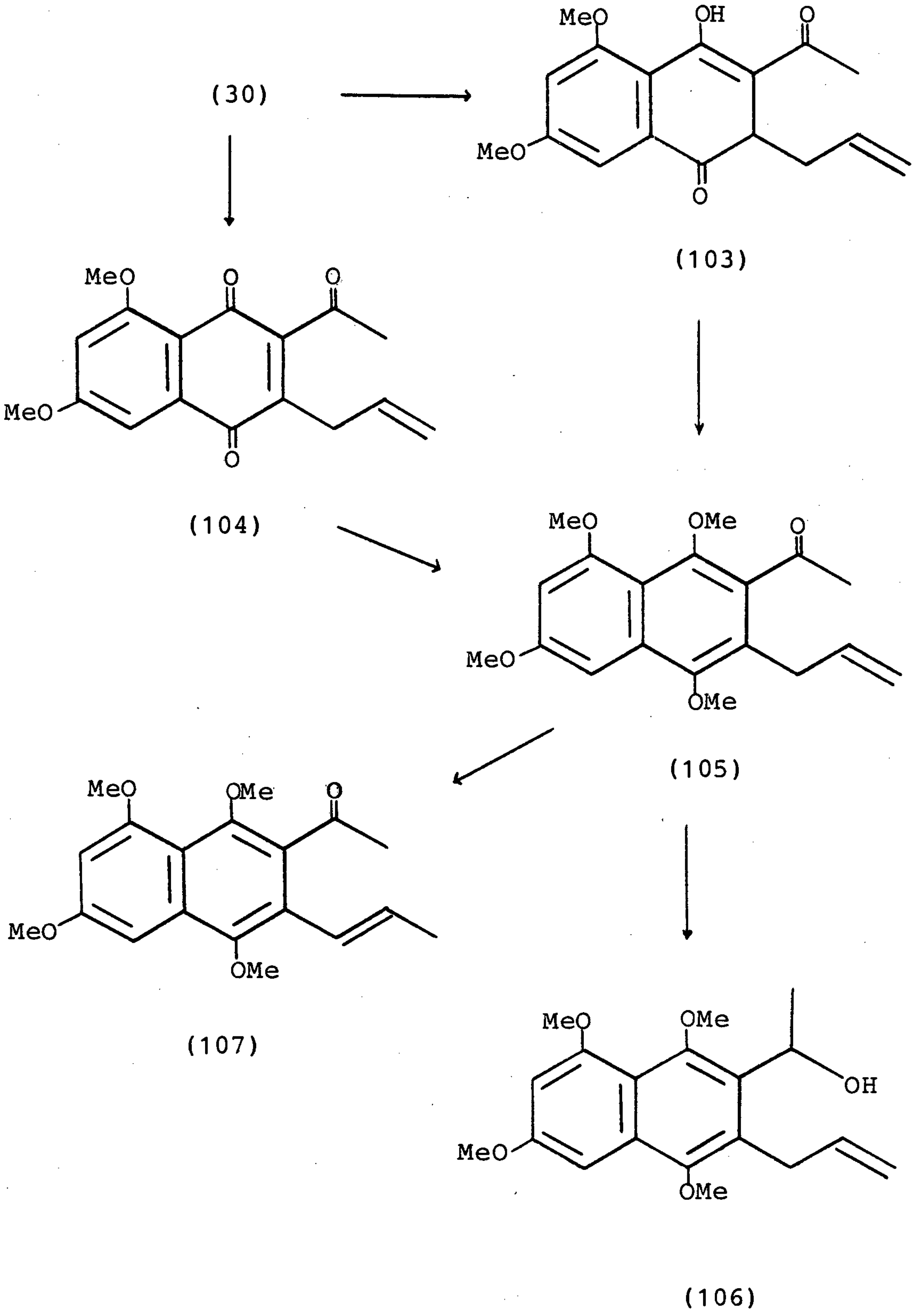
The allyl quinone (97), contaminated with a small amount of (101), was reductively methylated with aqueous sodium dithionite followed by dimethyl sulphate and potassium carbonate in dry acetone. Purification of this mixture by chromatography afforded compounds (98) and (102).

The second route to the ketonic naphthalene (98) was effected in these laboratories by the alternative allylation of quinone (28) using allyltrimethylstannane and boron trifluoride etherate,[25,44] followed by methylation of the crude product obtained. This method gave considerably improved yields of compound (98).

The allylic double bond of compound (98) was readily conjugated with potassium *t*-butoxide (4 equiv.) in tetrahydrofuran to afford the ketone (85) as the sole product in high yield. The stereochemistry of the olefinic bond was solely *trans*, as indicated by the large coupling constant (16 Hz) of the olefinic protons. The spectral characteristics of this ketone corresponded entirely with that of authentic material prepared by Giles *et al*[40] described earlier.

The non-conjugated alcohol (99) was readily available by lithium aluminium hydride reduction of compound (98).

The ketonic naphthalene (105) was synthesised from quinone (30) by the two routes as in Scheme H on page 64.


(30)
MeO
OH
O
MeO
O
(103)
MeO
O
O
MeO
O
(104)
MeO
OMe
O
MeO
OMe
(105)
MeO
OMe
O
MeO
OMe
(107)
MeO
OMe
OH
MeO
OMe
(106)

Scheme H

The first route involved allylation of quinone (30) with vinyl acetic acid to afford the allyl quinone (104). However, the yield was low, being 44% overall in the two steps from the naphthol (55)[13]

Reductive methylation of quinone (104) gave the tetramethyl ether (105) in fair yield.

The second route to the product (105) involved the allylation of quinone (30) using allyltrimethylstannane in the presence of boron trifluoride etherate. This step afforded the adduct (103), which was methylated without purification to yield the ketone (105) in an overall yield of 64% from the naphthol (55).

Ketone (105) was smoothly reduced with lithium aluminium hydride in dry ether to the corresponding non-conjugated alcohol (106) in excellent yield (91%).

The conjugated ketone (107) in which the double bond is also solely *trans* was readily available from the olefin (105) by treatment with potassium *t*-butoxide, as for compound (98).

The corresponding alcohol (88) was available from (107) in good yield by reduction with lithium aluminium hydride.

Conjugation of the allylic double bond of ketone (92) was also effected in high yield (81%) by treatment with potassium-*t*-butoxide in tetrahydrofuran, to afford the conjugated ketone (90) as the sole product. Its ^{1}H n.m.r. spectrum showed, *inter alia*, a doublet (J 6 Hz) at δ1.92, due to the methyl of the 1-propenyl chain. The signal for the C-2 olefinic proton resonated as a doublet of quartets (J 6 and 16 Hz) at δ6.20 while the C-1 olefinic proton resonated as a doublet (J 16 Hz) at δ6.54. The relatively large coupling constant (16 Hz) between the olefinic protons was again indicative of the (E)-geometry at the double bond of compound (90).

This ketone was reduced with lithium aluminium hydride to the corresponding naphthyl alcohol (87) in excellent yield (87%).

2.3 Naphtho[2,3-*c*]pyrans by cyclisation of substituted naphthalenes using potassium *t*-butoxide in dimethylformamide[43,47]

2.3.1 The synthesis of some 7,9-dideoxynaphtho[2,3-*c*]pyrans

The possibility of conjugation of the allylic double bond of the alcohol (99) to give the isomeric alcohol (86) was also investigated.

Treatment of the non-conjugated alcohol (99) with 2 equivalents of potassium *t*-butoxide in dimethylformamide under nitrogen at 60°C for 2 hours, afforded a mixture which by ^{1}H n.m.r. contained, *inter alia*, some conjugated alcohol (86) as well as starting material (99).

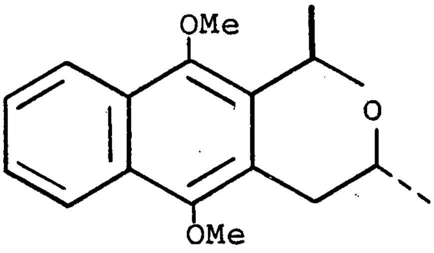
Since compounds (86) and (99) have similar R_F values it was difficult to follow the progress of the conjugation reaction by thin layer chromatography (t.l.c.). However, t.l.c. of the reaction mixture revealed the presence of traces of products with higher R_F's than starting material.

When alcohol (99) was treated as above, but with four equivalents of the base, starting material was rapidly consumed. The progress of the reaction was followed by t.l.c. which showed that after two minutes a new product with a higher R_F than alcohol (99) had formed.

After five minutes of reaction, t.l.c. of the reaction mixture showed all starting material had been consumed, but traces of a product of slightly higher R_F than the first product started to appear.

The ^{1}H n.m.r. spectrum of the first product, which was obtained in almost quantitative yield showed, *inter alia*, a three-proton doublet (J 6 Hz) at δ1.39; another three-proton doublet (J 6 Hz) at δ1.63; a one-proton doublet of doublets (J 11 and 16 Hz) at δ2.59; another one-proton doublet of doublets (J 3.5 and 16 Hz) at δ3.11; a one-proton multiplet at δ3.9-4.3, and a one-proton quartet (J 6 Hz) centred at δ5.35.

The above spectroscopic data supported the assignment of structure (108) to the product in which the partially unsaturated pyran ring may be represented as in Figure 1.[48]



(108)

The shape of the pyran ring is distorted from that of the normal chair geometry in order to accommodate the trigonal carbon atoms of the aromatic ring

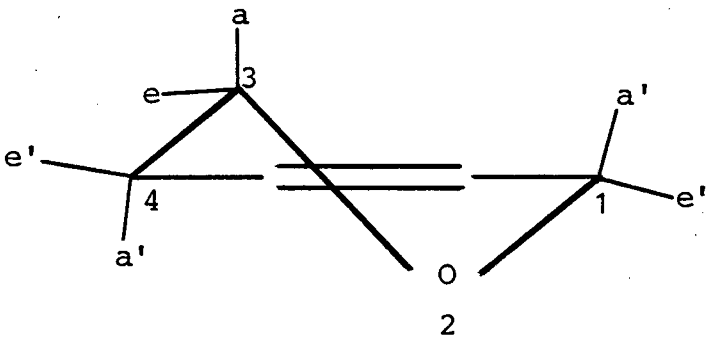


Fig.1

The substituents attached to C-3 occupy normal equatorial (e) and axial positions (a), but those attached to C-1 and C-4 are imperfectly staggered and are said to occupy *pseudo*-equatorial (e') and *pseudo*-axial (a') positions.

The doublet at δ1.39 is due to the methyl group at C-3, which adopts the less crowded equatorial position, coupled to 3-H. The doublet at δ1.63 is due to the C-1 *pseudo*-axial methyl coupled to the adjacent hydrogen at C-1 of the pyran ring.

The doublet of doublets which resonate at δ2.59 represent the *pseudo*-axial 4-H which is not only geminally coupled to the *pseudo*-equatorial 4-H, but also vicinally coupled to the axial 3-H. The coupling constant of 11 Hz (J vic) between 3-H and 4-H confirmed that the former is axial since the relatively large coupling constant implies a large dihedral angle between the axial 3-H and one of the hydrogens at C-4. The coupling constant of 16 Hz represent the geminal coupling between the two hydrogens at C-4. The doublet of doublets at δ3.11 is due to the *pseudo*-equatorial 4-H which again is geminally coupled to the *pseudo*-axial 4-H and vicinally coupled to the axial 3-H. The relatively smaller coupling constant (J vic) of 3.5 Hz indicates a smaller dihedral angle between the one 4-H and 3-H.

The multiplet at δ3.9-4.3 is due to the *pseudo*-axial 3-H, whereas the quartet at δ5.35 is due to the 1-H coupled to the *pseudo*-axial methyl group.

It is apparent from the foregoing that J vic is a function of the dihedral angle, Ø, between 3-H and 4-H of the pyran ring and its magnitude is given by the Karplus equations,[49,50] which frequently agree with the observed values.

Figure 2 summarises in a qualitative manner the dependence of J vic on the dihedral angle Ø

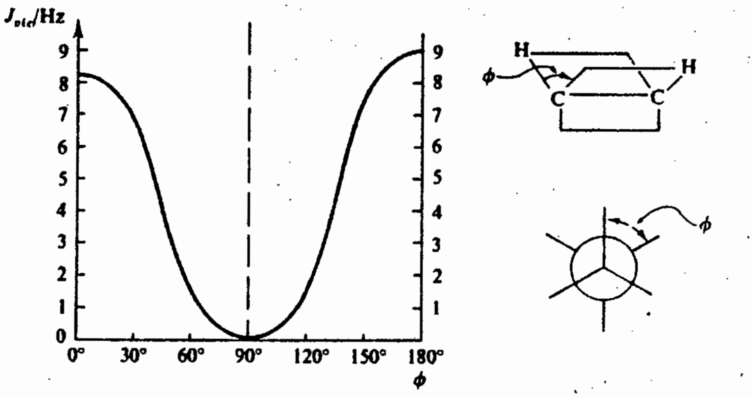
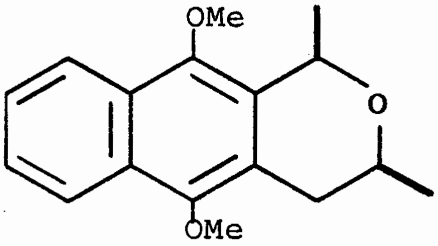


Fig. 2

The largest vicinal couplings arise with protons in the *trans* co-planar position (Ø = 180°), while vicinal coupling for *cis* co-planar protons are almost as large (Ø = 0°). In contrast very small couplings arise between protons at 90° to each other.

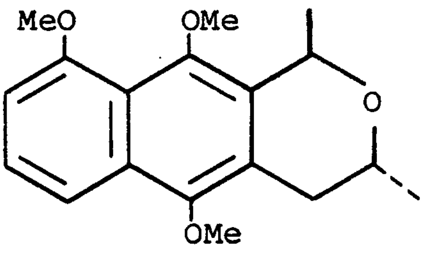
A repeat of the above base-induced cyclisation reaction, but for 1.25 hours, resulted in an overall recovered yield of 93% with the individual yields of the *trans*-pyran (108) and the new product being 53% and 40% respectively.

The ^{1}H n.m.r. spectrum of the new product showed it to be the *cis*-dimethylnaphthopyran (109)[44]



(109)

The ^{1}H n.m.r. spectra of compounds (108) and (109) do not appear to be published as yet, but a comparison with those reported[45] for the trimethoxy analogues (110) and (111) enabled a distinction to be made between compounds (108) and (109).



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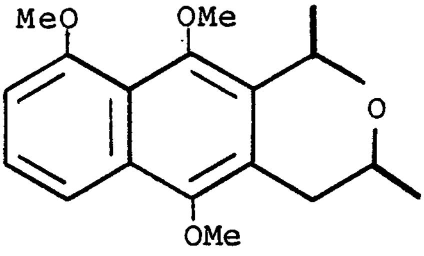


(111)

The 3-H multiplets differ substantially in chemical shift; those for the *trans* isomer (110) fall in the range δ3.9–4.3, while those for the *cis* isomer (111) resonate at δ3.5–3.8. In addition, the chemical shifts of the 1-H quartets also differ; those for the *trans*-pyran appear at about 5.3 while the quartet of the *cis* compound occur at δ *ca.* 5.2.

The cyclisation of the non-conjugated alcohol (99) to afford the *trans*-pyran (108)[44] was also effected at room temperature under anaerobic conditions for 10 minutes. In this case, no *cis*-pyran (109) was detected by t.l.c.

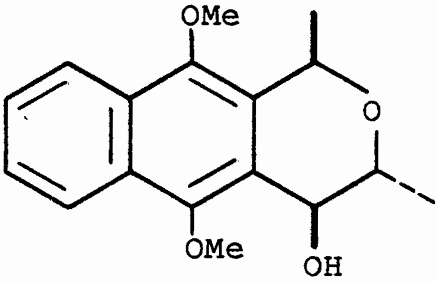
It is also noteworthy that when the *cis*-pyran (109) was treated at 65°C for several hours with butoxide, none of the *trans* isomer (108) was detected by either t.l.c. or ^{1}H n.m.r. spectroscopy.

Under the reaction conditions so far described, the product of kinetic control is presumably the *trans*-pyran, while the *cis*-pyran seems to be the thermodynamically favoured isomer. This is derived from the observation that the *cis*-pyran (109) became the major product when the alcohol (99) was treated with a twenty-fold excess of the base at 60°C for several hours.

When the conjugated alcohol (86)[40] was treated with butoxide under anaerobic conditions, it also afforded the *trans*-pyran (108) exclusively in high yield, with the formation of the *cis* isomer (109) again being observed for longer reaction times.

The cyclisation reactions so far described have all been effected under anaerobic conditions. A comparison as to the effectiveness of the butoxide reaction, under aerobic conditions, was also made.

Reaction of alcohol (99) with butoxide without the exclusion of air, afforded in addition to the pyrans (108) and (109), two minor products with significantly lower R_F's than the isomeric pyrans. The ^{1}H n.m.r. spectra of the two new products supported the assignment of structures (112) and (113) and agreed entirely with the spectroscopic data reported for the compounds isolated by Giles *et al.*[40] as intermediates in the oxidative cyclisation of the conjugated alcohol (86) to the isomeric quinones (80) and (81).



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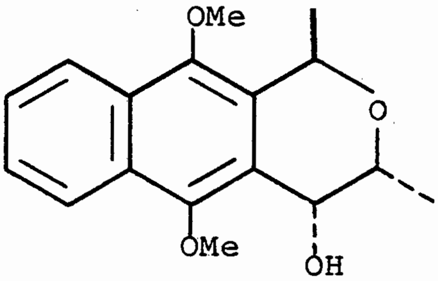


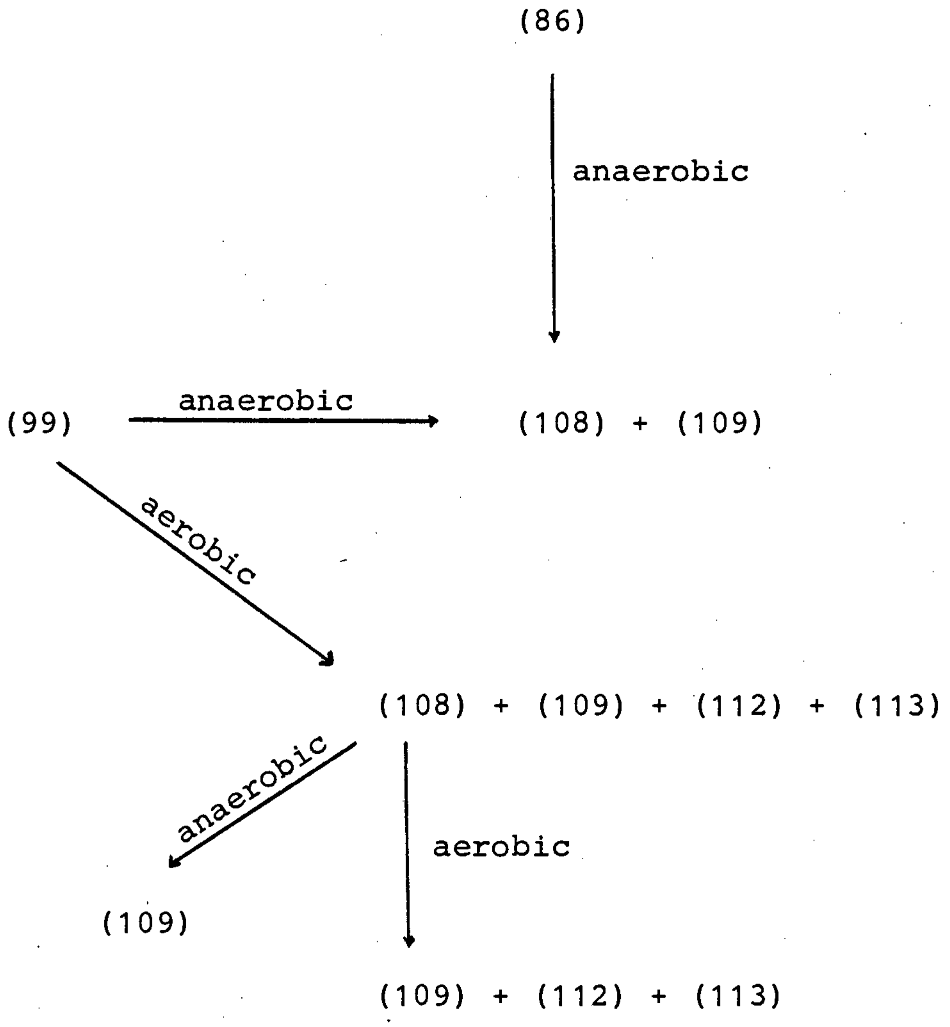
(113)

The aerobic base-induced cyclisation reaction afforded the pyrans (108) and (109) in considerable lower yield and the diastereomeric 4-hydroxypyrans (112) and (113) were isolated in a relatively moderate combined yield of 35% in the ratio 4:1.

Under these conditions compound (112), in which the hydroxyl occupies the *pseudo*-equatorial position (e'), was more abundant than (113) in which the hydroxyl is *pseudo*-axial (a'), while in the oxidative cyclisation reaction[40] the latter product predominated.

Compounds (112) and (113) were also prepared in these laboratories by treatment of the *trans*-pyran (108) in air with the same base for 2 hours. Under these conditions compound (109) (12%), the 4-hydroxypyrans (112) (28%) and (113) (7%) as well as the unreacted *trans*-pyran (108) (23%) were isolated.

Scheme I summarises the base-induced cyclisation reactions and interconversions so far described.



Scheme I

The stereochemistry at the chiral centres of the isomeric compounds (112) and (113) was also established by (i) the reasonable assumption that the C-3 methyl adopts the less crowded equatorial position in each case and (ii) the magnitude of vicinal coupling (J vic) between 3-H and 4-H as observed in their individual ^{1}H n.m.r. spectra.

In the case of compound (112) the vicinal coupling constant of 8 Hz between 3-H and 4-H confirmed the latter as *pseudo*-axial. The hydroxy group thus occupies the *pseudo*-equatorial position at C-4.

For the isomeric (113), the smaller vicinal coupling constant of 2 Hz indicated a smaller dihedral angle between 3-H and 4-H, which with 3-H again axial, required 4-H *pseudo*-equatorial and thus the hydroxyl *pseudo*-axial.

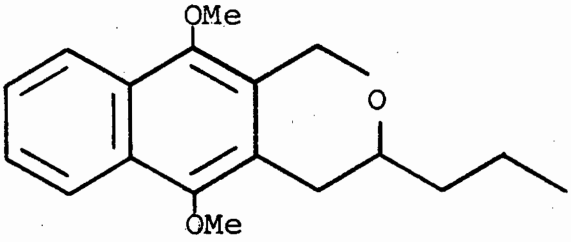
Since long-range coupling between 1-H and 4-H is too small to be measured, it was more difficult to assign configuration at C-1. However, the stereochemistry at C-1 was readily established after oxidation of compounds (112) and (113) to the corresponding quinones (80) and (81).[40]

It is known that measurable long-range coupling of the type (*H*-C-C=C-C-*H*), occurs by the operation of a mechanism involving presumably hyperconjugation and σ - π electron interaction[11]. In compounds (80) and (81) the C-H bonds at C-1 and C-4 assume different conformations with respect to the plane of C = C of the quinone ring. Karplus[49] has shown that long-range couplings of this type will be a maximum between C-H bonds which are perpendicular to the plane defined by the double bond and almost zero between C-H bonds in the plane of the double bond.

For compound (80), the doublet of doublets due to 4-H at δ4.47 showed coupling constants of magnitude 8 and 2 Hz, while the doublet of quartets due to 1-H centred at δ4.92, showed coupling constants of magnitude 7 and 2 Hz. The smaller coupling constant in each case is undoubtedly due to the long-range coupling discussed above between 1-H and 4-H. In the case of compound (81) no such long-range coupling was observed.

The stereochemistry at C-1 of compound (113) was established by melting point and mixed-melting point comparison with authentic (113)[40].

Another example of the base-induced cyclisation reaction was obtained when the alcohol (31) afforded the pyran (114) (83%) when treated with butoxide under anaerobic conditions.



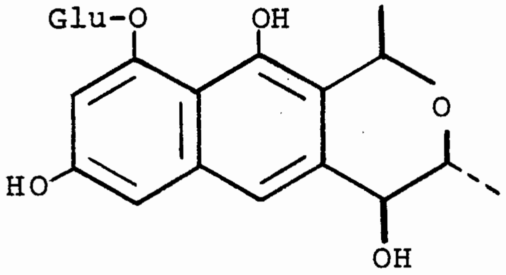
(114)

Oxidative demethylation of (114) with C.A.N. gave the quinone (27) in high yield (90%).

The heterocyclic ring protons of quinone (27) gave the following signals: a doublet of doublets (J 3 and 19 Hz) at δ4.88 due to the *pseudo*-equatorial 1-H. The smaller coupling is due to long-range coupling to the *pseudo*-axial 4-H, but not to the *pseudo*-equatorial 4-H. The *pseudo*-axial 1-H resonated as a doublet of triplets (J 19 and 3.5Hz) at δ4.46. This proton is almost equally coupled to both 4-H protons. The axial 3-H appeared as a multiplet at δ3.3-3.7. The *pseudo*-

equatorial 4-H resonated as a doublet of triplets centred at δ2.76 with coupling constants 3.5 and 19 Hz, the latter being due to geminal coupling to the *pseudo*-axial 4-H and the former due to approximately equal coupling to the *pseudo*-axial 1-H and to 3-H. The sixteen-line signal centred at δ2.28 was due to the *pseudo*-axial 4-H as a result of geminal coupling (J 19 Hz) to the *pseudo*-equatorial 4-H, vicinal coupling (J 10 Hz) to 3-H, and long range couplings (J 3 and 3.5 Hz) to the *pseudo*-equatorial and *pseudo*-axial protons at C-1 respectively.

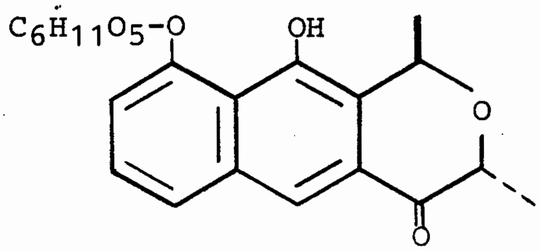
The aphid pigments protoaphin-*fb* (8), protoaphin-*sl* (9)[7] and deoxyprotoaphin (10)[8], undergo reductive cleavage to afford three closely related naphthopyranquinones i.e. quinone A(16), quinone A'(17)[51] and deoxyquinone A(18)[8] respectively, together with, in case, the same naphthalenic glycoside, glucoside B(115)[51] in which the sugar moiety is bonded to the genin *via* a β-glycosidic linkage.



(115)

Evidence for the β-glycosidic linkage was obtained by Cameron and Craik[52] from the observation that hydrolysis was almost complete on treatment with almond emulsin, whereas α-glycosidases had no effect.

Glucoside B(115) has also been found in the aphid, *Aphis nerii* (and other species) along with related compounds, for example, the pigment neriaphin (116).[53]



(116)

The base-induced cyclisation reaction, discussed above, might be applied in the synthesis of glucoside B(115).

It remains to be seen whether or not the hydroxylation of naphthopyrans without oxygen at C-5 takes place.

The aphin-derived quinones (16), (17) and (18) have been subjected to methylation of the phenolic hydroxy groups to afford the respective dimethyl ethers (24),[11,51] (23),[11,51] and (22),[8,54] since the greater solubility of these dimethyl ethers in chloroform enabled the study of their ^{1}H n.m.r. spectral characteristics.

The synthesis of (±)-isoeleutherin (2) has been achieved by several groups,[44,45,55] but a mixture of racemic eleutherin (1) and isoeleutherin (2) has been obtained in all of these syntheses. Cameron and co-workers[54] also obtained a mixture of the dimethyl ether of racemic deoxyquinone A (22) and 7-methoxyeleutherin (19) in their route to compound (22).

Our routes to racemic isoeleutherin (2) and deoxyquinone A dimethyl ether (22) described in this work, are highly stereoselective and high yielding. The syntheses of 7-methoxyeleutherin (19), quinones A' dimethyl ether (23), and A dimethyl ether (24) as their racemates, have also been achieved by our anaerobic or aerobic base-induced cyclisation reactions.

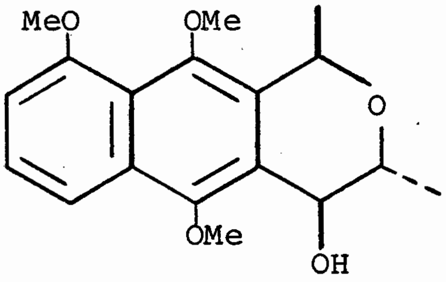
2.3.2 The synthesis of compounds (2), (25) and (26)

The non-conjugated alcohol (93) was readily available by lithium aluminium hydride reduction of the ketone (92). Treatment of compound (93) with potassium *t*-butoxide in dimethylformamide under nitrogen gave the *trans*-dimethylnaphthopyran (110)[45,55] in high yield (87%). The ^1H n.m.r. spectral characteristics of this pyran were identical to those reported for it by Eisenhuth and Schmid.[55]

Oxidative demethylation of (110) with C.A.N. afforded (±)-isoeleutherin (2).

The allylic double bond of the ketone (92) was also readily conjugated with butoxide in dry tetrahydrofuran to afford ketone (90) in which the stereochemistry of the resulting olefinic bond was solely *trans*, as shown by the coupling constant (16 Hz) of the olefinic protons. Treatment of this ketone with lithium aluminium hydride afforded the conjugated alcohol (87) in high yield.

Treatment of alcohol (87) with butoxide as for compound (93), but in air, gave the pyran (110) and its *pseudo*-equatorial hydroxy derivative (117).



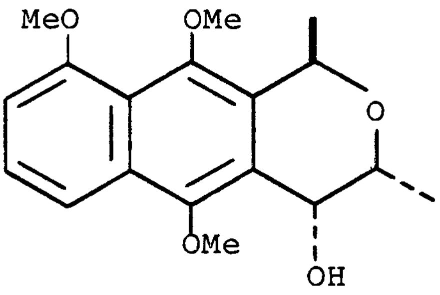
(117)

Assignment of structure (117) to the minor product was supported by its ^{1}H n.m.r. spectrum which showed, *inter alia*, a broad singlet at δ4.2 (which disappeared on addition of deuterium oxide) due to the C-4 hydroxy group, and a one-proton doublet (J 8.5 Hz) at δ4.76 due to the *pseudo*-axial 4-H which is vicinally coupled to the axial 3-H. The resonance of the latter appeared at *ca.* δ3.97 as a doublet of quartets (J 6.5 and 8.5 Hz).

C.A.N. oxidation of compound (117) gave the corresponding quinone (25). The stereochemistry at C-1 of compound (25) was confirmed by its ^{1}H n.m.r. spectrum which clearly showed the long-range coupling[49] (1.5 Hz) between the *pseudo*-axial 4-H and the *pseudo*-equatorial 1-H.

When the conjugated alcohol (87) was treated with four equivalents of C.A.N., all starting material was consumed. However, a complex mixture of products was obtained which was not further investigated. This is in contrast to the finding of Giles *et al.*[40] where oxidation of alcohol (86) with the same oxidant, under identical conditions, afforded the aphin-related pyranquinones (80) and (81). The former result may be ascribed to a higher electron-rich system in which several oxidation pathways may be possible.

Treatment of (87) with two equivalents of C.A.N. afforded the 4-hydroxypyran (118) in poor yield (14%).

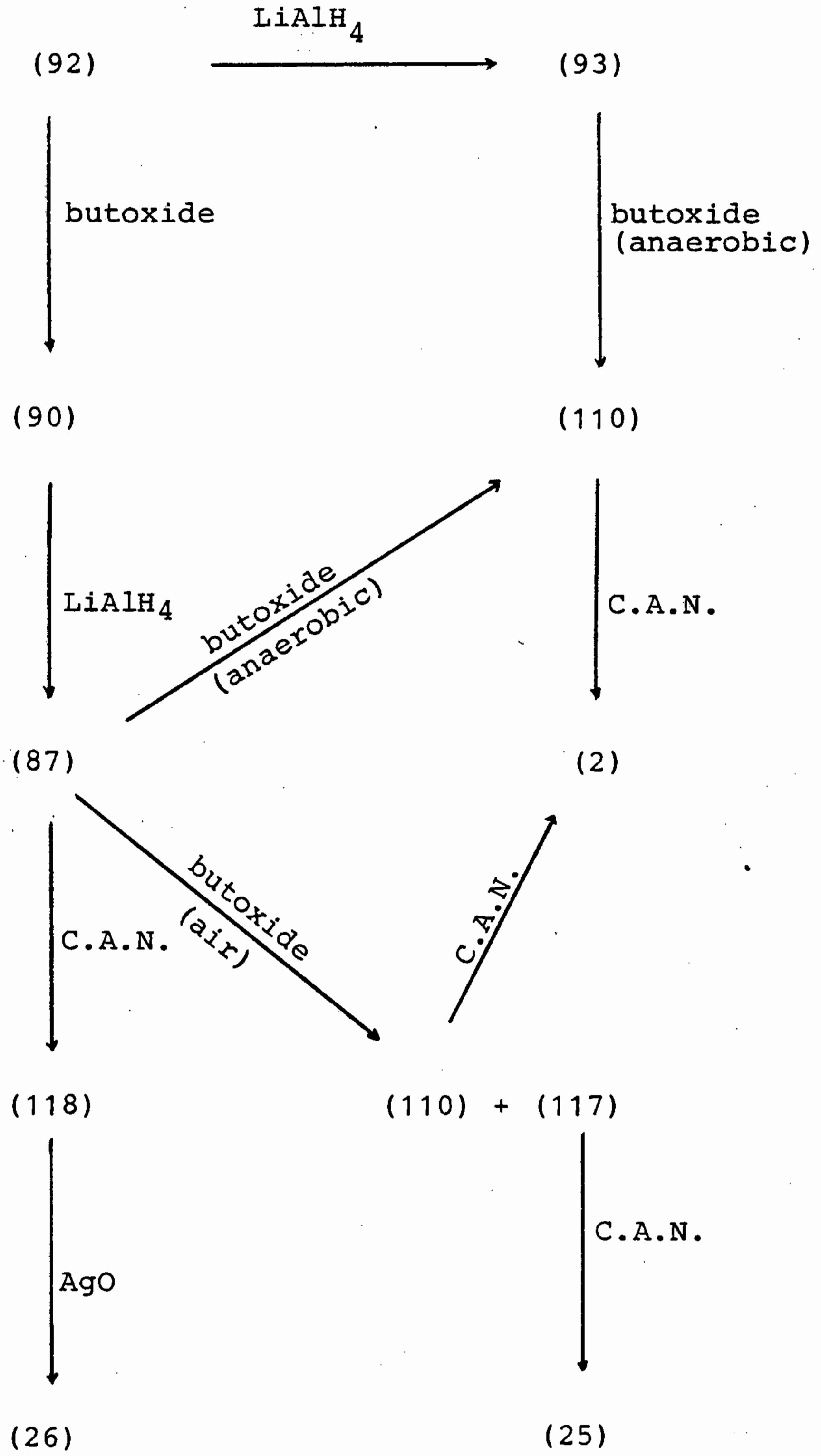


(118)

The ^{1}H n.m.r. spectrum of this product showed, *inter alia*, a one-proton doublet (J 8 Hz) at δ2.2 due to the C-4 hydroxyl, a doublet of quartets (J 2 and 6 Hz) at δ4.14 due to the axial 3-H, a doublet of doublets (J 2 and 8 Hz) at δ6.76, due to the *pseudo*-equatorial 4-H, which collapsed to a doublet (J 2 Hz) on addition of deuterium oxide, and a one-proton quartet (J 7 Hz) at δ5.34 due to 1-H coupled to the methyl group at C-1.

Pyran (118) was smoothly oxidised to the corresponding quinone (26) with silver(11) oxide[56] in a yield of 88%. Conclusive evidence for the stereochemistry at C-1 was once again derived from the ^{1}H n.m.r. spectrum of quinone (26) in which no measureable long-range coupling[49] between 1-H and 4-H and could be detected.

Scheme J on page 88 summarises the routes described to compounds (2), (25) and (26).

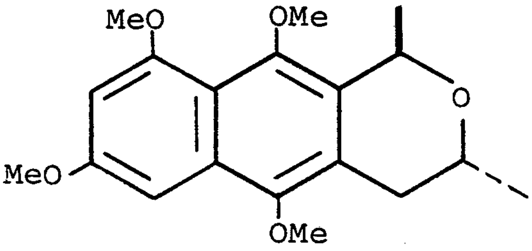

(92)
LiAlH$_4$
(93)
butoxide
butoxide (anaerobic)
(90)
(110)
LiAlH$_4$
butoxide (anaerobic)
C.A.N.
(87)
(2)
C.A.N.
butoxide (air)
C.A.N.
(118)
(110) + (117)
AgO
C.A.N.
(26)
(25)

Scheme J

2.3.3 The synthesis of compounds (19), (22), (23) and (24).

In the light of the success achieved in the synthesis of isoeleutherin (2) and other related naphthopyrans by the novel anaerobic or aerobic base-induced cyclisation reactions discussed earlier, the conjugated alcohol (88) and the non-conjugated alcohol (106) seemed to be plausible precursors for deoxyquinone A dimethyl ether (22), quinone A' dimethyl ether (23), quinone A dimethyl ether (24) and 7-methoxyeleutherin (19). Indeed this proved to be the case.

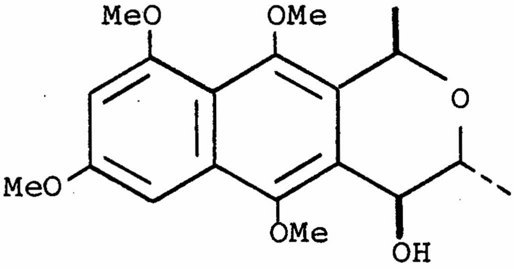
Treatment of the conjugated alcohol (88) with butoxide in dry dimethylformamide under nitrogen for fifteen minutes at 60°C, afforded the *trans*-pyran (119) in excellent yield (92%).



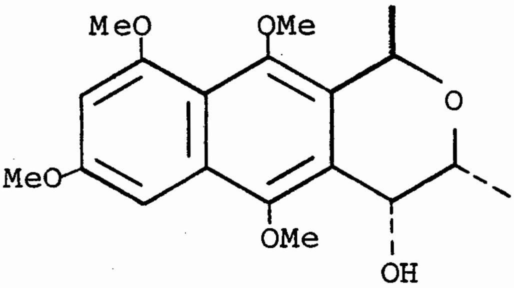
(119)

A second product was also isolated under these conditions. It was identified as the C-4 hydroxylated pyran (120) which formed in a yield of only 2%. It is noteworthy that none of the pyrans (121) and (122) were observed under these conditions.

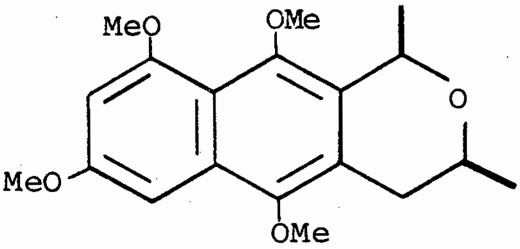
Similar treatment of the non-conjugated alcohol (106) with butoxide afforded, as expected the *trans*-pyran (119) in excellent yield (86%), together with compound (120) (5%).



(120)



(121)



(122)

The ^{1}H n.m.r. spectrum of the *trans*-pyran (119) showed the following: a three-proton doublet (J 6 Hz) at δ1.39 due to the C-3 methyl coupled to 3-H; another three-proton doublet (J 7 Hz) at δ1.63 due to the C-1 methyl coupled to 1-H; a one-proton doublet of doublets (J 10 and 17 Hz) at δ2.56 due to the *pseudo*-axial 4-H which is vicinally coupled to the axial 3-H and geminally coupled to the *pseudo*-equatorial 4-H; a one-proton doublet of doublets (J 3.5 and 17 Hz) at δ3.06 due to the *pseudo*-equatorial 4-H coupled to 3-H and the *pseudo*-axial 4-H.

Assignment of structure (120) to the minor product was also supported by its ^{1}H n.m.r. spectrum which showed, *inter alia*, a three-proton doublet (J 6.5 Hz) at δ1.42 due to methyl at C-3 coupled to the axial 3-H; another three-proton doublet (J 7.5 Hz) at δ1.68 due to the C-1 methyl coupled to 1-H; a broad deuterium oxide exhangeable singlet at δ3.85 due to the C-4 hydroxy group, and a one-proton doublet (J 9 Hz) due to the *pseudo*-axial 4-H which is vicinally coupled to the axial 3-H. The signals due to the resonance of 3-H appeared at δ3.97 as a doublet of quartets (J 6.5 and 9 Hz), while the *pseudo*-axial 4-H resonated as a doublet (J 9 Hz) at δ4.74.

Oxidation of the naphthopyran (119) with two molar equivalents of C.A.N. did not afford deoxyquinone A dimethyl ether (22). Instead, starting material was destroyed and no product was identified in the complex mixture.

Alternative oxidation of compound (119) with silver (11) oxide[56] afforded the target quinone (22) in good yield (82%). The ^{1}H n.m.r. spectrum of our synthetic racemic deoxyquinone A dimethyl ether (22) is shown in Figure 3.

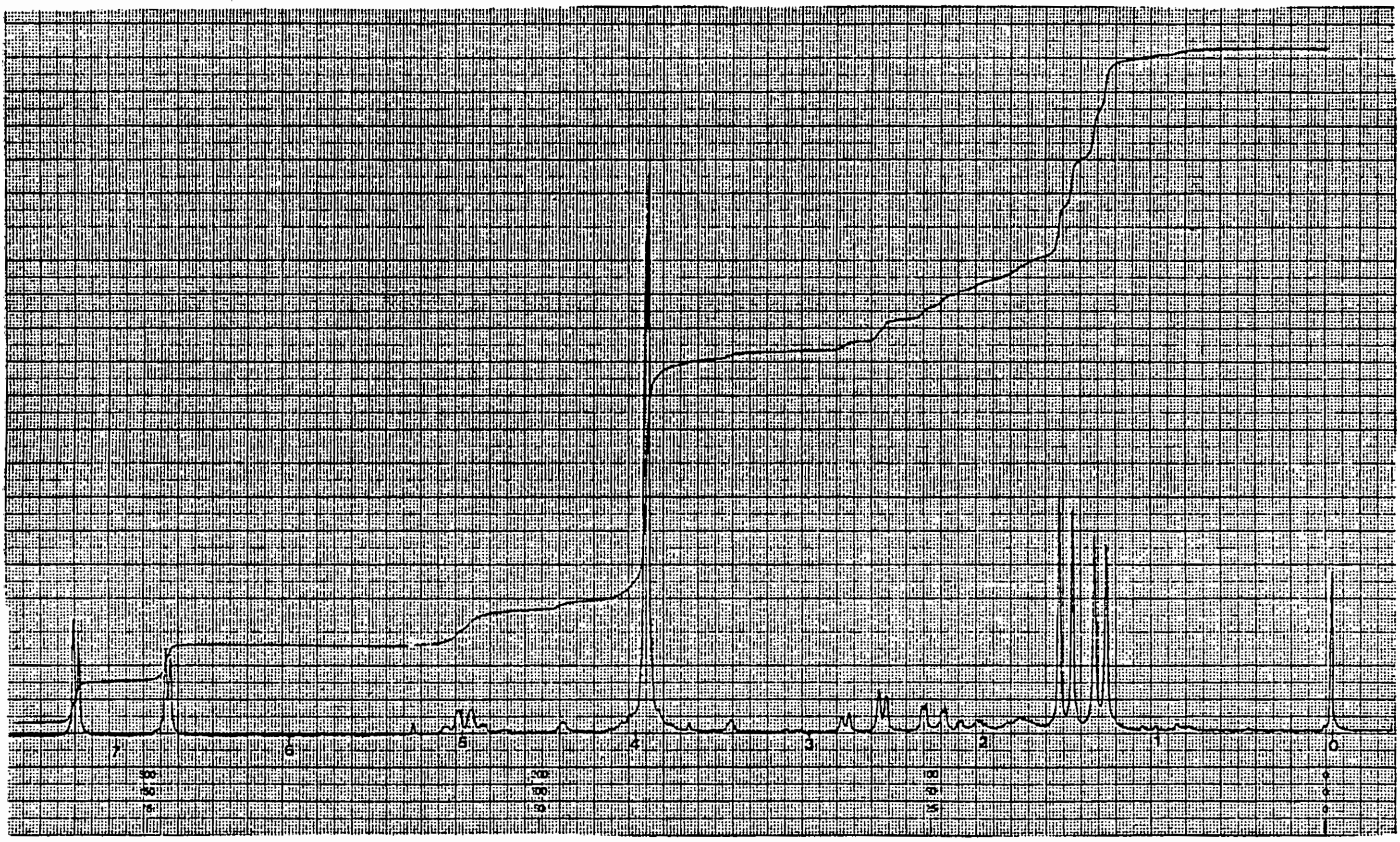


Fig. 3

C.A.N. has been shown[40] to oxidise the naphthyl alcohol (86) to a mixture of racemic 7,9-dideoxyquinones A (80) and A' (81), the latter predominating. However, when the tetramethoxynaphthyl alcohol (88) was treated with four molar equivalents of this oxidant, all starting material was consumed but no product corresponding to either (23) or (24), the dimethyl ethers of quinones A' and A respectively, could be identified.

Treatment of (88) with two molar equivalents of the same oxidant also provided neither cyclised naphthalene (120) nor (121), although the naphthyl alcohol (86) afforded the naphthopyrans (112) and (113) under similar conditions.[40]

However, when the non-conjugated alcohol (106) was briefly treated with butoxide in dimethylformamide but in the presence of air, a higher proportion (21%) of the hydroxylated pyran (120) was obtained. Under these conditions, the pyran (119) was isolated in a yield of 44%.

When the pyran (119) was treated with butoxide in dimethylformamide for several hours in the presence of air, three new products were isolated. The compound with R_F just greater than (119) was identified as the *cis*-pyran (122) (8%), epimeric with (119) at C-1.[47] The major product (35%), of lower R_F than starting material, was the leucotetramethyl ether (120) of quinone A. The third product (7%) was identified as the leucotetramethyl ether of quinone A' (121).

The heterocyclic ring protons of pyran (121) gave the following ^1H n.m.r. spectral absorptions: a one-proton doublet of quartets (J 2 and 6.5 Hz) at *ca.* δ4.13 due to 3-H; a one-proton doublet (J 2 Hz) at δ4.72 due to 4-H. The relatively small coupling constant (2 Hz) indicated a smaller dihedral angle between 3-H and 4-H, and with 3-H again axial, required 4-H *pseudo*-equatorial. A broad singlet centred at δ2.22 and found to be exchangeable with deuterium oxide, was assigned to the hydroxy group at C-4. In addition, the proton at C-1 resonated as a quartet (J 7 Hz) at δ5.31.

The ^1H n.m.r. spectrum of compound (122) showed, *inter alia*, two doublets (J 6.5 Hz each) at δ1.40 and 1.54 which were assigned to the C-3 methyl and C-1 methyl respectively; a one-proton doublet of doublets (J 11 and 16 Hz) at δ2.54 assigned to the *pseudo*-axial 4-H; another one-proton doublet of doublets (J 2.5 and 16 Hz) at δ3.04 due to the resonance of the *pseudo*-equatorial 4-H; a multiplet at δ3.5-3.9 integrating for one proton and partially obscured by the singlets of the methoxy groups, due to 3-H. The C-1 proton resonated as a quartet (J 6.5 Hz) at δ5.21.

Silver(11) oxide[56] oxidation of the *cis*-pyran (122) afforded 7-methoxyeleutherin (19) in good yield (75%). The ^{1}H n.m.r. spectrum of our synthetic natural product (19) (see Figure 4) agreed entirely with the spectra of the natural product kindly supplied by Dr. G.D. Daves of the Department of Chemistry at Oregon Graduate Center, Beaverton.

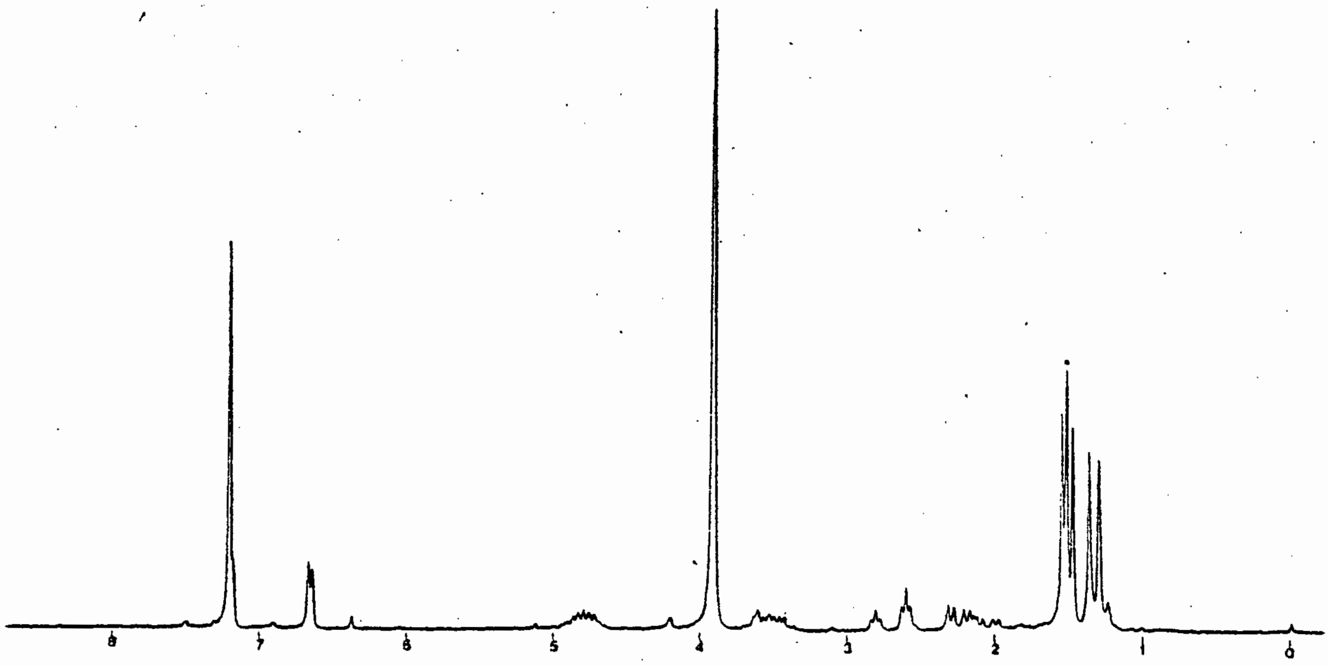


Fig. 4

Similar oxidation of the tetramethyl ethers (120) and (121) with silver(11) oxide gave the dimethyl ethers of quinones A (24) (90%) and A' (23) (88%) respectively.

The three heterocyclic ring protons of the quinone (24) gave the following signals: a one-proton doublet of quartets (J 6 and 8 Hz) at *ca.* δ3.81 due to the axial 3-H; a broad one-proton doublet (J 8 Hz) at δ4.44 due to the *pseudo*-axial 4-H. This signal collapsed to a sharpened doublet of doublets (J 1.5 and 8 Hz) on addition of deuterium oxide.

The former value (1.5 Hz) indicated long-range coupling between the *pseudo*-axial 4-H and 1-H, thus requiring the C-1 proton *pseudo*-equatorial.[47,49]

The signal assigned to 1-H appeared as a doublet of quartets (J 1.5 and 7 Hz), the smaller coupling constant confirming long-range coupling between 1-H and 4-H.

The ^{1}H n.m.r. spectrum of our synthetic quinone A dimethyl ether (24) is shown in figure 5 below. Figure

6 illustrates the ^1H n.m.r. spectrum of (24) on addition of deuterium oxide.

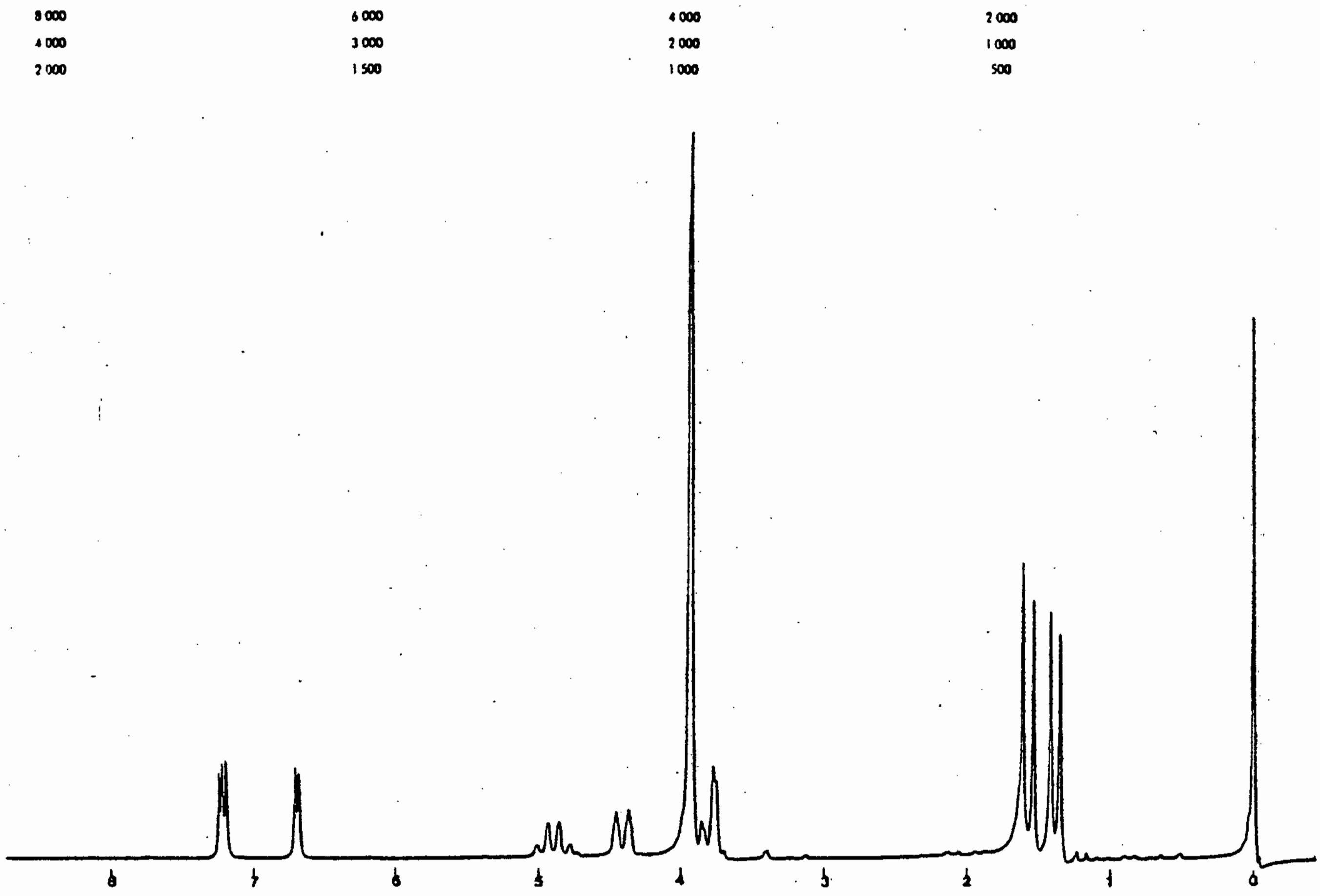


Fig. 5

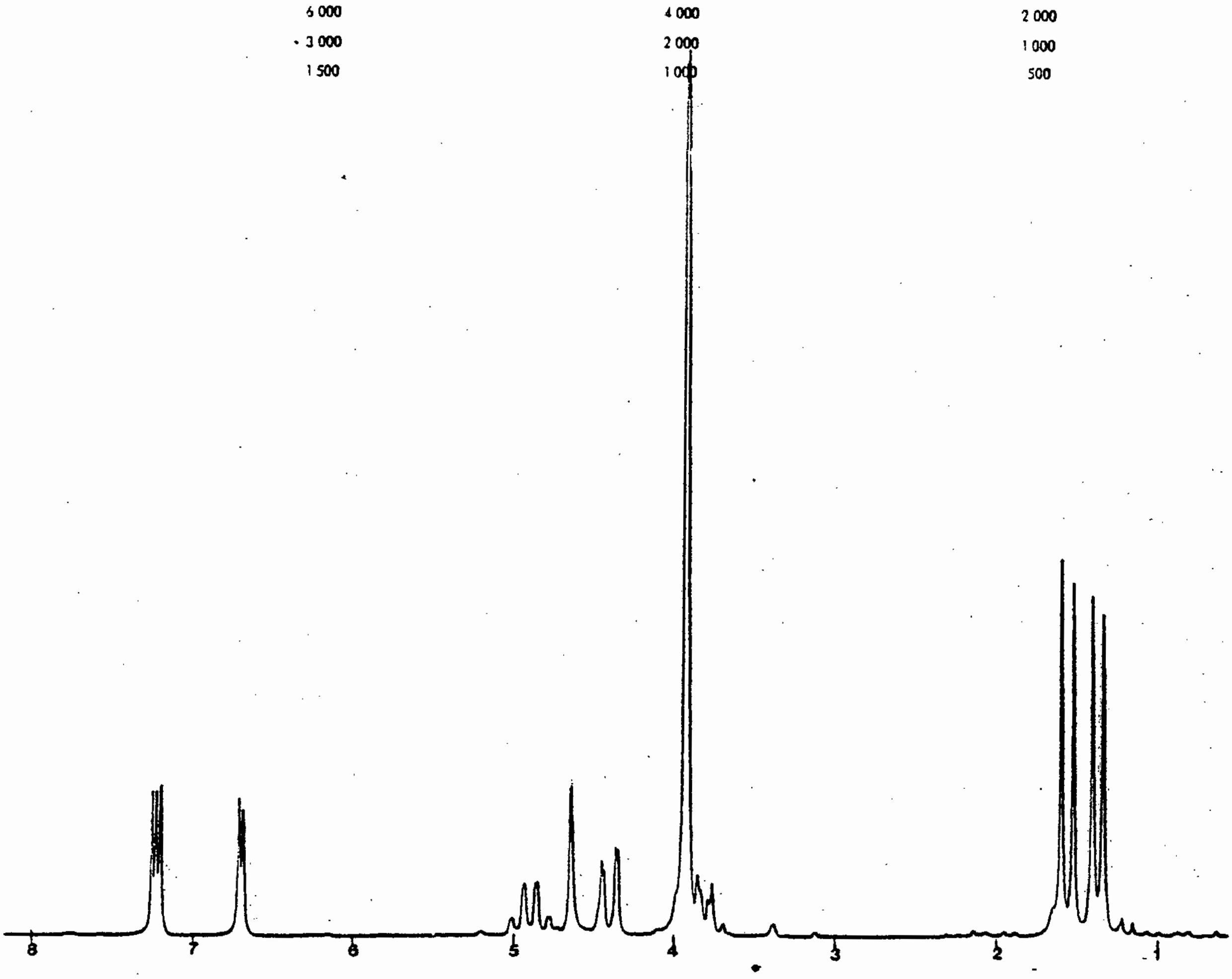


Fig. 6

The ^{1}H n.m.r. spectrum of quinone A' dimethyl ether (23) was also very clear (see figure 7) and showed the heterocyclic ring protons as follows: a one-proton doublet of quartets (J 2.5 and 6 Hz) due to 3-H at *ca.* δ3.95; a broad singlet integrating for one proton at δ4.44, which collapsed to a doublet (J 2.5 Hz) on addition of deuterium oxide, (Figure 8) assigned to the *pseudo*-equatorial 4-H, and a one-proton quartet (J 7 Hz) at δ4.99 due to 1-H. The absence of long-range coupling between 1-H and the *pseudo*-equatorial 4-H essentially requires the former to be pseudo-equatorial.

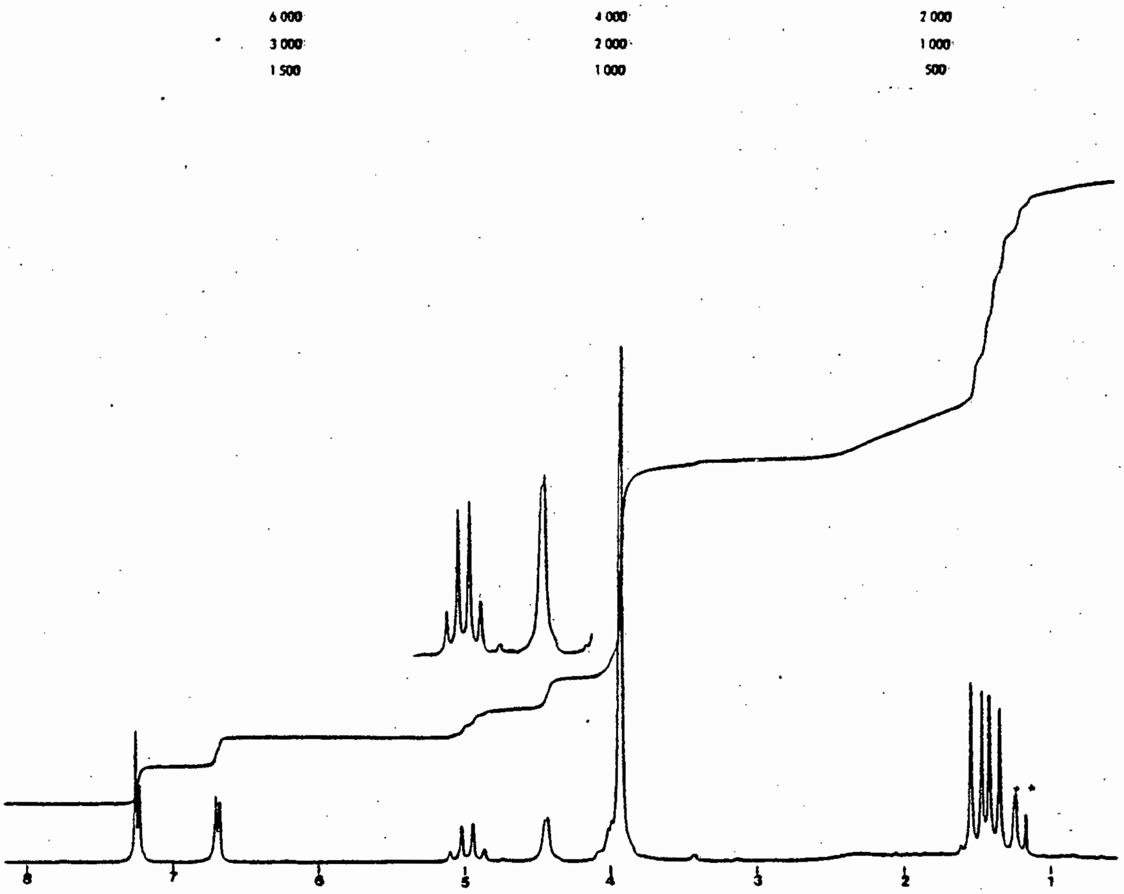


Fig. 7

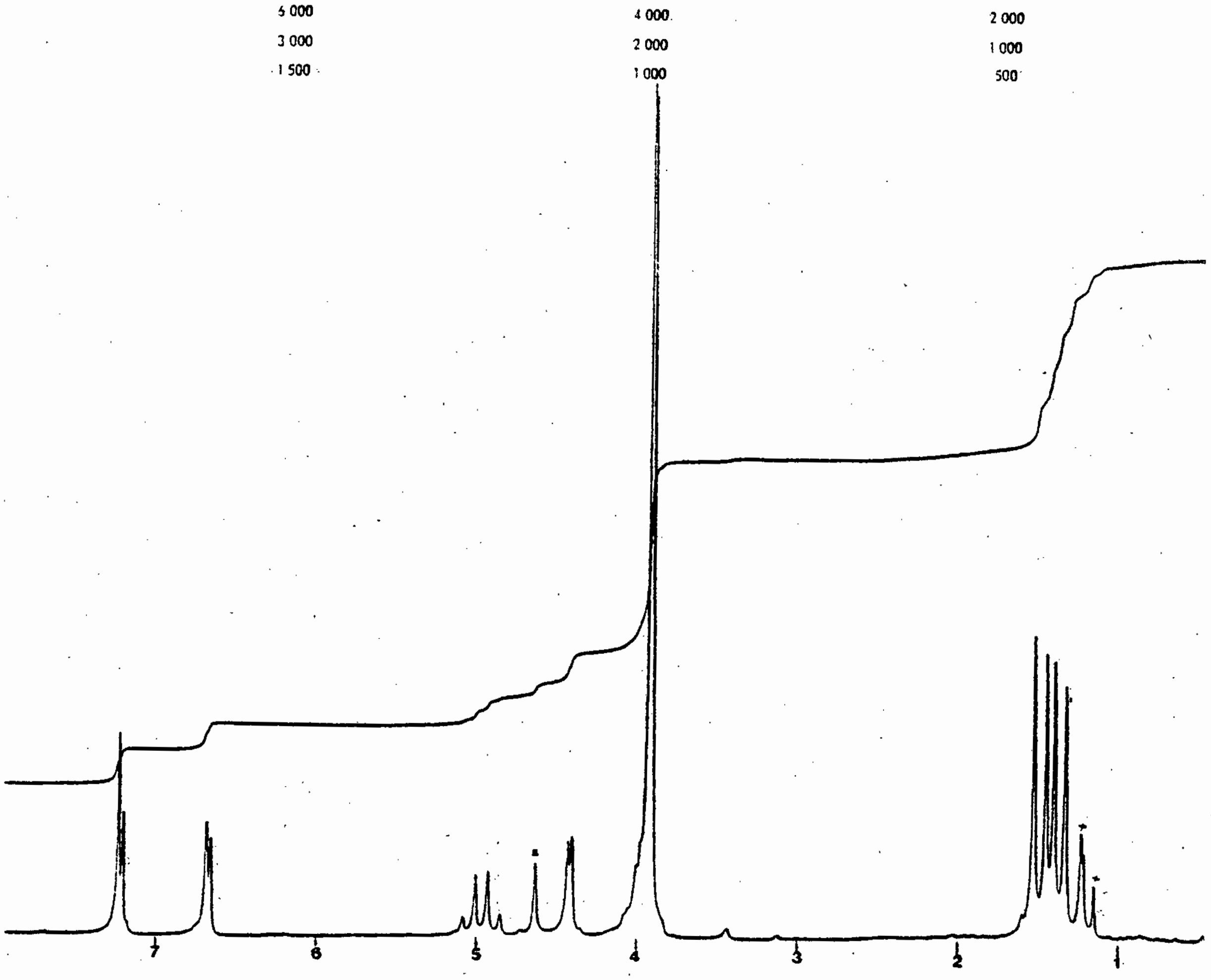


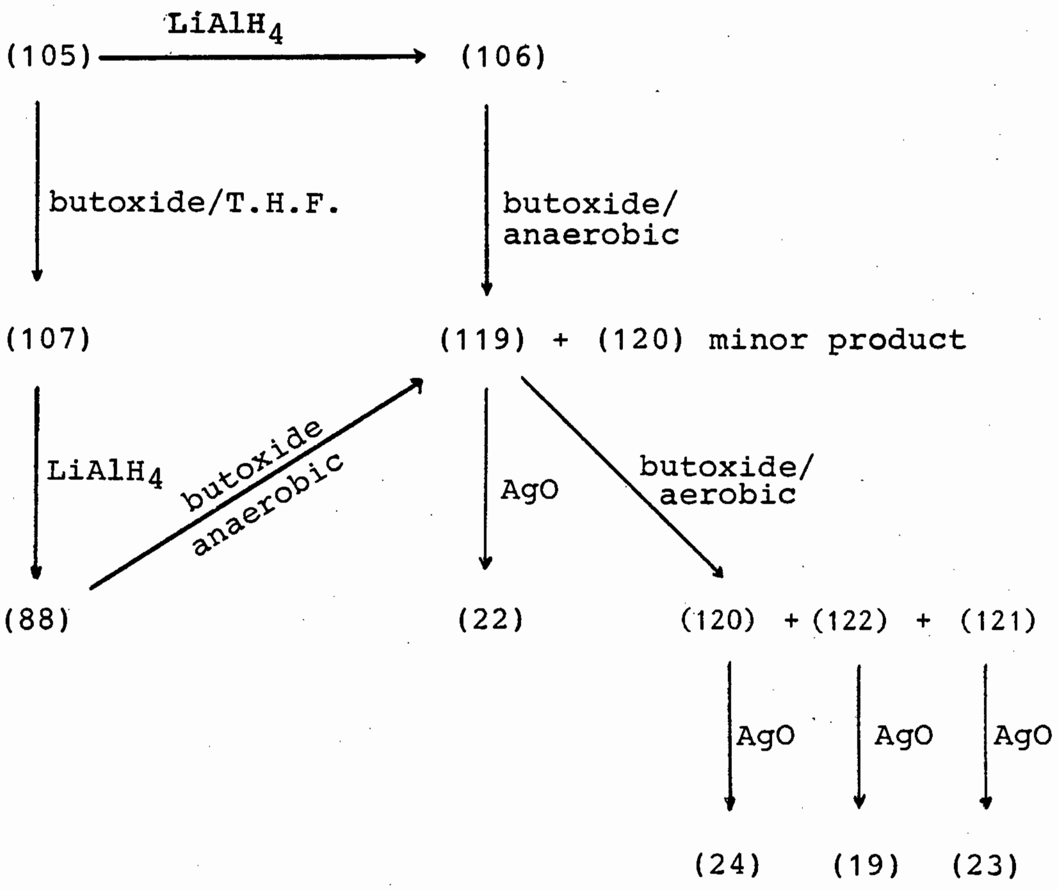
Fig. 8

The ^{1}H n.m.r. spectral characteristics of quinones (23) and (24) verified the tentative stereochemical assignments made above for the two tetramethyl ethers (120) and (121), particularly at C-1 in each case.

A comparison was also made between our synthetic samples of the racemic dimethyl ethers of deoxyquinone

A (22), quinones A (24) and A' (23), and the naturally derived materials which were kindly made available by Professor D.W. Cameron of the University of Melbourne. The natural and synthetic materials were found to be indentical by t.l.c., infrared and ^{1}H n.m.r. spectroscopy.

Our routes to compounds (19), (22), (23) and (24) are summarised in Scheme K below.

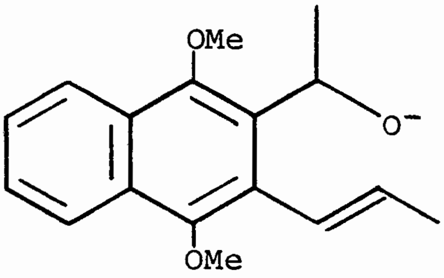


Scheme K

2.3.4 Proposed mechanisms for the base-induced cyclisation reaction under anaerobic and aerobic conditions

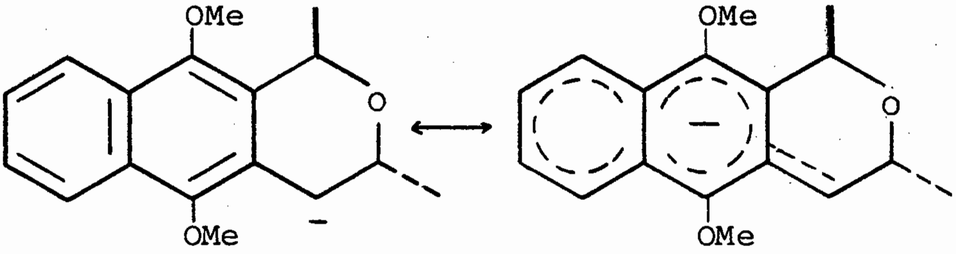
The following proposed mechanisms for the cyclisation of the conjugated alcohols (86), (87) and (88), as well as the non-conjugated alcohols (93), (99) and (106) to afford the corresponding naphtho[2,3-*c*]pyrans under anaerobic conditions, and the hydroxylation of these pyrans under aerobic conditions, are only tentative and speculative at this stage.

In the case of a conjugated alcohol, the alkoxide anion for example, (123) is formed under the strongly basic conditions generated by butoxide in the dipolar aprotic solvent, dimethylformamide.



(123)

In the case of a non-conjugated alcohol, conjugation of the olefinic bond occurs prior to cyclisation. This is supported by the observation of the presence of signals indicating *trans*-coupling of the olefinic protons in the ^{1}H n.m.r. spectrum of the crude product when the non-conjugated alcohol (99) was treated with 1.5-2 equivalents of butoxide. With a larger excess (e.g. four equivalents) of base the anion (123) is ultimately produced which then undergoes cyclisation to afford the *trans*-dimethyl pyran anion (124). This anion is of lower energy than anion (123) since the negative charge in (124) may be delocalised over the aromatic system as in (125), and is favoured kinetically because the C-3 methyl prefers the less crowded equatorial position. The methyl at C-1 however, adopts the *pseudo*-axial position to reduce *peri* interactions.

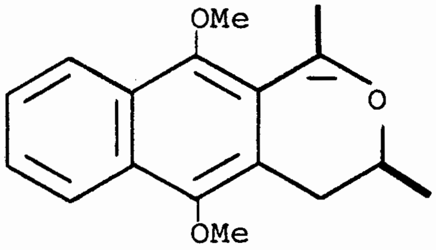


(124) (125)

The anion (124 ⟷ 125) then undergoes rapid protonation to afford the product (108). It is noteworthy that no incorporation of deuterium in (108) took place when the reaction was quenched with deuterium oxide during work-up.

Prolonged treatment with base converts the *trans*-pyran (108) into the *cis*-pyran (109). This conversion may occur by one of several routes. The *trans*-pyran (108) may be deprotonated at C-4 to afford the anion (124 ⟷ 125) again, which reverts to anion (123) before reclosing to yield the thermodynamically favoured *cis* compound (109).

Alternatively, deprotonation of (108) takes place at C-1 to afford the anion (126), thermodynamically preferred under the reaction conditions.



(126)

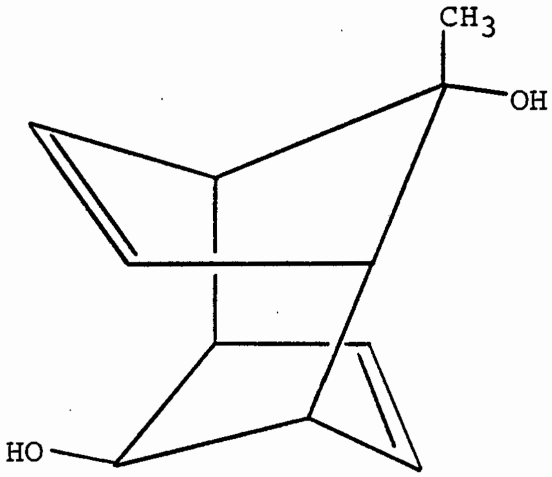
However, the former suggestion, giving rise to the anion (124 ⟷ 125) seems more likely, particularly in view of the hydroxylation of pyran (108) at C-4.

In the case of the hydroxylation reaction, the anion (124 ⟷ 125) regenerated from (108) may undergo oxidation, either to the corresponding carbonium ion followed by reaction with moisture to form the products, or to the corresponding radical which reacts with molecular oxygen to afford the products, or the anion (124 ⟷ 125) may react with molecular oxygen directly.

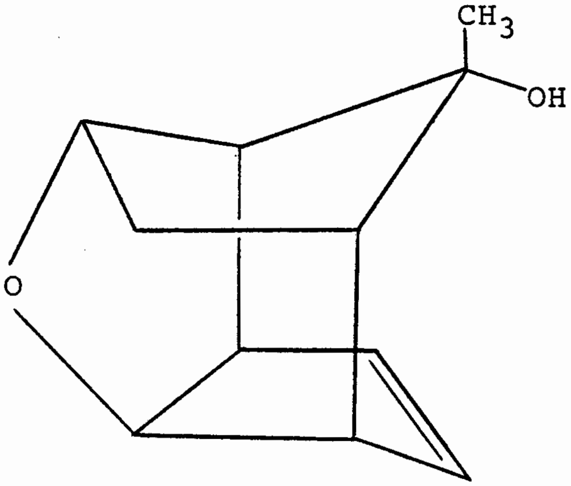
In order to determine which structural features present in the alcohols, for example, (86) or (99), are required for these unusual base-induced cyclisations, J.A.X. Pestana[57] synthesised in these laboratories a series of *ortho*-alkenylbenzyl- and *ortho*-alkenylhydroxyalkyl naphthalenes carrying methoxy, ethyl or hydrogen substituents at appropriate positions on the aromatic rings.

It was observed that although no conclusive general mechanism has yet been inferred from the results obtained by Pestana, the explanation for this cyclisation reaction may involve steric factors. It was only those alcohols in which both the hydroxyalkyl and alkenyl side chains were flanked by bulky substituents forcing the reacting centres into close proximity, which cyclised in high yield.

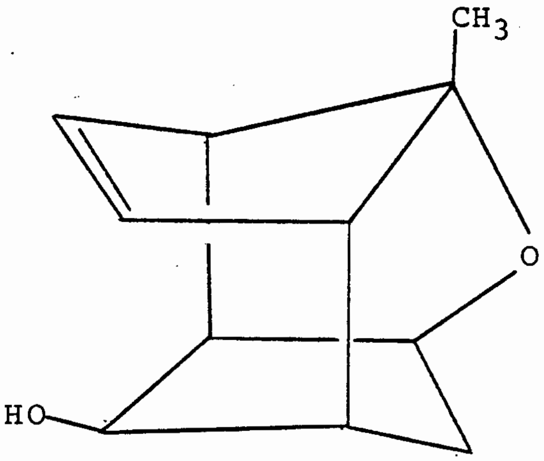
Recently, another group[58] reported the formation of a cyclic ether from the reaction of an alcohol function with an unactivated double bond. They observed that the diol (127), when treated with a 50% aqueous sodium hydroxide-methanol solution, afforded the cyclic ether (128) in high yield with none of the isomeric (129) identified.



(127)



(129)



(128)

This regioselectivity clearly indicates that the side with higher steric compression undergoes cyclisation.

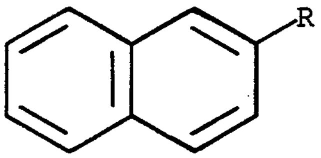
However, the involvement of electronic factors and electronic 'assistance' of the bulky substituents (particularly in our examples) to the cyclisation reaction, cannot be excluded.

CHAPTER III

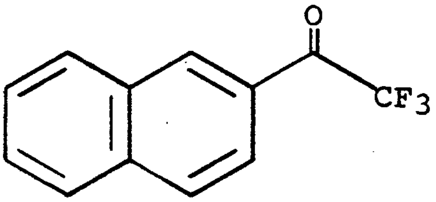
THE ACYLATION OF OXYGENATED NAPHTHALENES: SYNTHESES OF SOME NAPHTHOPYRANS AND POTENTIAL SYNTHETIC ROUTES TO SOME NAPHTHOPYRANONES

3.1 Introduction

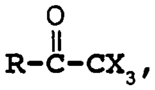
An acetylated naphthalene, for example (130a), is a useful precursor for the synthesis of the naphthalenic carboxylic acid (130b). Conversions of this type are usually readily accomplished by employing the well-known haloform reaction.



(130a) R = $COCH_3$
(130b) R = CO_2H

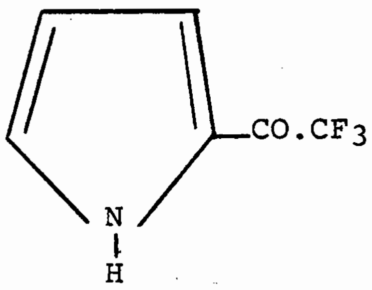


(131)

Since intermediates of the type,  $R-\overset{\overset{O}{\|}}{C}-CX_3$, where R = alkyl or aryl, and X = Cl, Br or I, are formed in the haloform reaction, it was envisaged that trifluoroacetylnaphthalenes of the type (131) may be useful as precursors to naphthalenic carboxylic acids and in particular, to naturally occurring lactones (isocoumarins or 3,4-dihydroisocoumarins) or their derivatives, and naphtho[2,3-*c*]pyrans.

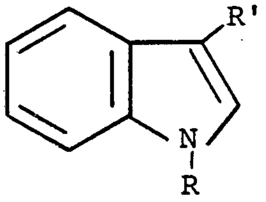
The trifluoracetylation of several electron-rich aromatic systems employing trifluoroacetic anhydride (T.F.A.A.) has been reported.[59-63] Marino *et al.*[59] described the relative rates of electrophilic substitution of furan, thiophen, pyrrole and several of their derivatives with T.F.A.A. in 1,2-dichloroethane.

W.D. Cooper[60] treated pyrrole in benzene to obtain 2-trifluoroacetylpyrrole (132) in a yield of 66%.



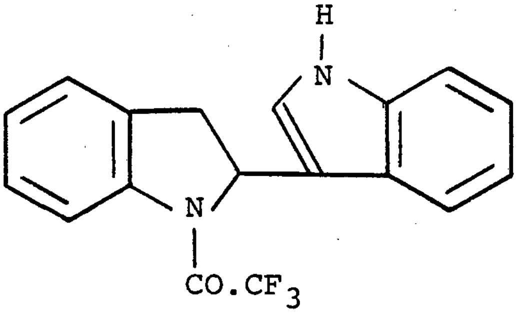
(132)

Linda and co-workers[61] found that the trifluoroacetylation of indole with T.F.A.A. in 1,2-dichloroethane at 0°C afforded a mixture of N- and C-trifluoroacetyl derivatives. For example, the reaction mixture consisted of 3-trifluoroacetylindole (133) (20%), N-trifluoroacetylindole (134) (50%), N-trifluoroacetyl-2-(3-indolyl) indoline (135) (15%) and unreacted starting material (15%).



(133) R = H; R' = CO.CF$_3$

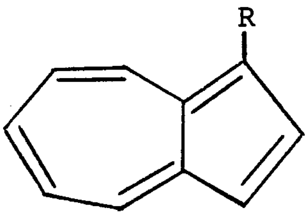
(134) R = COCF$_3$; R' = H



(135)

However, when the reaction was carried out in dimethylformamide, 3-trifluoroacetylindole (133) was obtained as the sole product.

A.G. Anderson and R.G. Anderson[62] investigated the reaction of azulene (136) with trifluoro- and trichloroacetic anhydrides and obtained good to high yields of the corresponding 1-trihaloacetylazulenes. It was also found that the acylation of azulene (136) with acetic anhydride required a catalyst,[63] whereas the reaction with T.F.A.A. proceeded smoothly without any catalyst and afforded 1-trifluoroacetylazulene (137) in a yield of 91%.



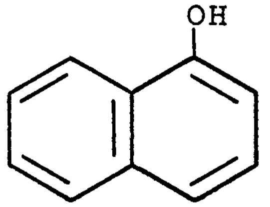
(136) R = H
(137) R = CO.CF$_3$

Trichloroacetic anhydride was also found[62] to react with azulene although the rate of reaction was appreciably slower than in the case of T.F.A.A. The yield of 1-trichloroacetylazulene (48%) was also inferior to that obtained with T.F.A.A. However, the rate of hydrolysis of the trichloroacetyl analogue was much faster than that of the trifluoroacetyl derivative. This is in agreement with the observation of Hine *et al*.[64] that α-halogen substituents facilitate carbanion formation in the order Cl > F.

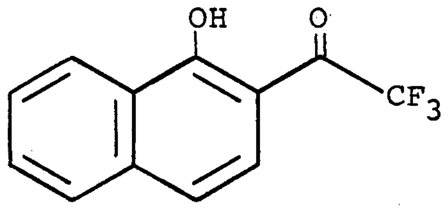
3.2 Trifluoroacetylation of naphthols and the formation of some naphtho[2,3-*c*]pyrans[65]

1-Naphthol (138) in dry dichloromethane reacted slowly with T.F.A.A. at room temperature to afford a mixture, which by t.l.c., consisted of a yellow product with a higher R_F than starting material and another product with a slightly lower R_F than starting material.

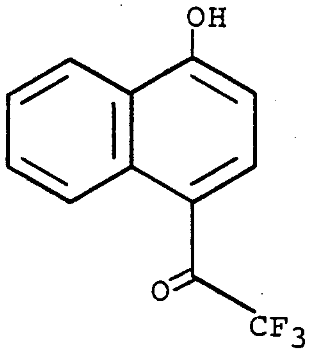
The ^1H n.m.r. spectrum of the yellow component showed, a one-proton doublet (J 9 Hz) at δ7.28, a multiplet integrating for four protons between δ7.4 and 7.85, another one-proton doublet (J 9 Hz) at δ8.45, and a low-field singlet at δ12,85 which disappeared on addition of deuterium oxide. This ^1H n.m.r. spectral data and the mass spectrum of the product supported the assignment of structure (139), the product of *ortho* substitution. The other product was identified as the 4-trifluoroacetylnaphthol (140).



(138)

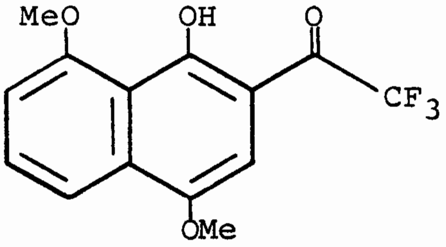


(139)



(140)

1,5-Dimethoxy-4-naphthol (38) reacted readily with T.F.A.A. to afford the *ortho*-trifluoroacetylnaphthol (141) as the sole product (84%). Again, the low-field signal in the ^{1}H n.m.r. spectrum of this product at δ12.85 due to the hydrogen-bonded hydroxy-group, confirmed *ortho*-trifluoroacetylation.

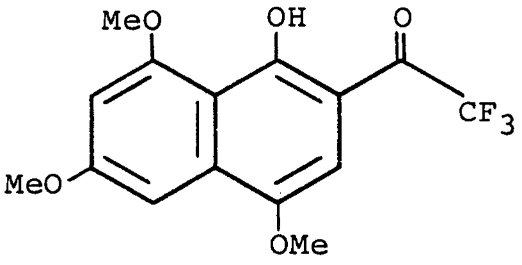


(141)

Another interesting ^1H n.m.r. spectral characteristic of naphthol (141) is the apparent multiplicity [quartet (J 2 Hz)] of the signal due to 2-H at δ6.91. This same phenomenon was observed in the ^1H n.m.r. spectra of several other *ortho*-trifluoroacetylated naphthols (see below). The broadening or multiplicity of the 2-H signal may be attributed to the presence of the trifluoromethyl in which the fluorines are presumably long-range coupled to 2-H, thus giving rise to the multiplicity of the expected singlet.

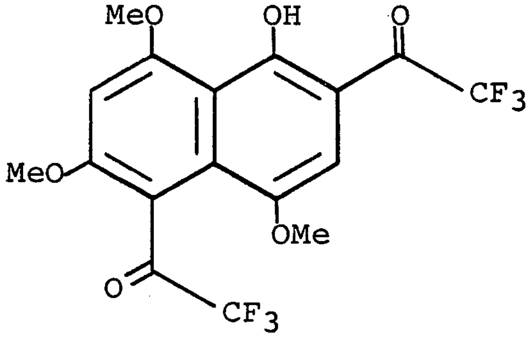
Of further note is (i) the observation that no multiplicity or broadening of the signal of 2-H occurred in the corresponding products derived from the *ortho*-trifluoroacetylated products by methylation of the hydrogen-bonded hydroxy group. It thus appears as if the hydrogen bonding between the hydroxyl and the carbonyl oxygen of the trifluoroacetyl group is essential for the opperation of long-range coupling between 2-H and the trifluoromethyl group (ii) no such multiplicity is observed for the signal of 2-H in the ^{1}H n.m.r. spectra of the naphthols (40) and (55).

1,5,7-Trimethoxy-4-naphthol (53) reacted much more rapidly with T.F.A.A. than did naphthol (38). Within four hours, all starting material was consumed and t.l.c. of the reaction mixture showed the presence of two yellow products which could be readily separated from one another by column chromatography. The ^{1}H n.m.r. spectrum of the component with higher R_F showed, *inter alia*, two meta-coupled one-proton doublets (J 2.5 Hz) at δ6.58 and 7.16, and a low-field deuterium oxide exchangeable singlet at δ13.33. As in the case of compound (141), a broadened signal [quartet (J 2 Hz)] integrating for one proton was observed at δ6.86. This enabled the assignment of structure (142) to the major product (89%).



(142)

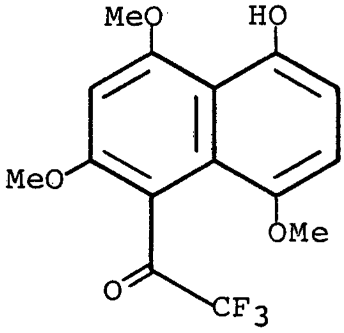
The ^{1}H n.m.r. and mass spectra of the minor component enabled the assignment of structure (143) to the second product.



(143)

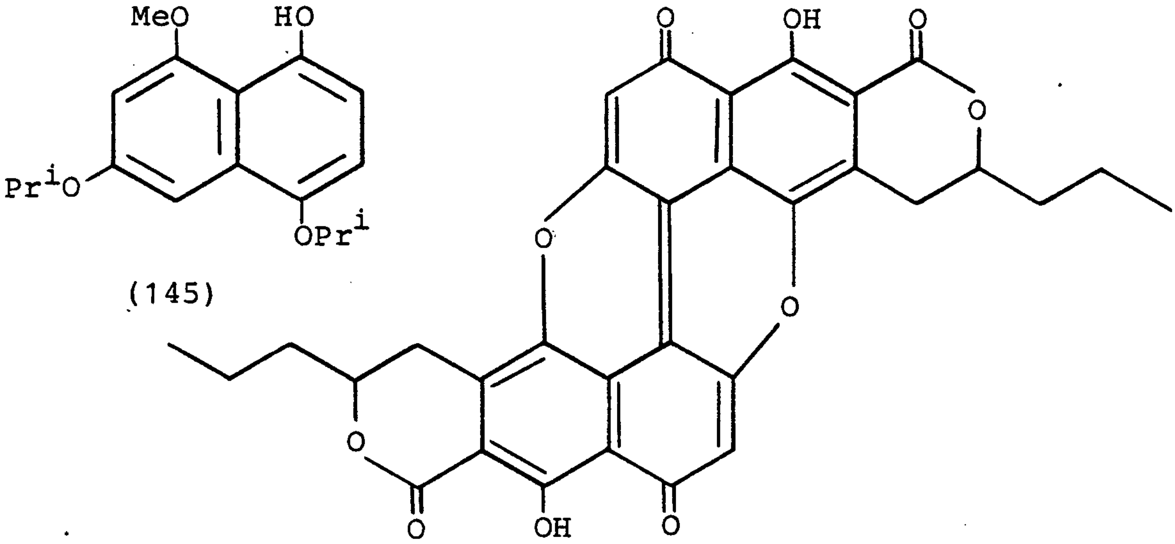
In the case of compound (143), obtained in a yield of 6%, the signal due to 7-H resonated as a singlet at δ6.28 while the signal due to 3-H appeared as a quartet (J 2 Hz) at δ6.52.

Compound (143) presumably arises by trifluoroacetylation of the electron-rich aromatic system of (142) since (144), isomeric with (142), was not observed under these conditions.



(144)

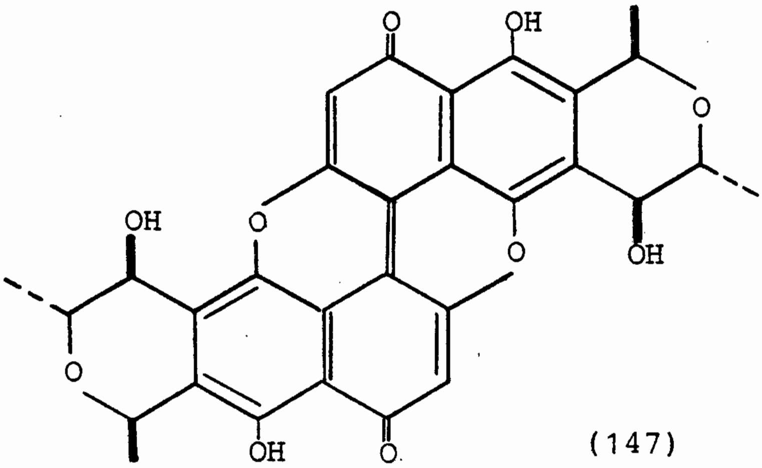
It was decided at this stage to investigate the synthesis of naphthols which have readily removable protection at O-6. It was envisaged that such compounds, for example (145), may be useful synthetic precursors to a variety of naturally occurring naphthoquinones of polyketide origin[52b] such as the aphid pigments, protoaphin-*fb* (8) and *-sl* (9), the quinonoid pigment xylindein (146),[66], or the aphin derived quinones A (16) and A' (17).



(145)

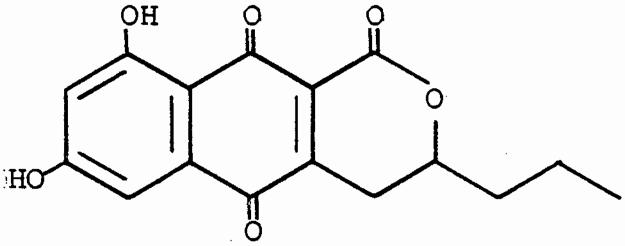
(146)

Cameron *et al.*[67] effected the anaerobic coupling of the aphid degradation product, quinone A (16), to afford xylaphin (147) which differs from xylindein only in the construction of the two heterocyclic rings.



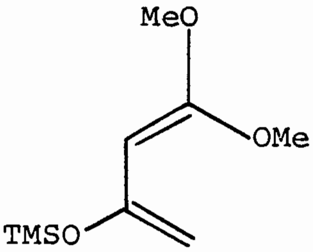
(147)

In the light of this successful coupling, Giles *et al.*[68] proposed the lactone (148) as a likely synthetic precursor to xylindein (146).

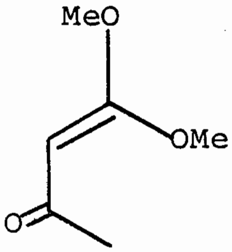


(148)

Naphthol (145) was synthesised by employing Brassard's diene (149).[69] This diene was available from the acylketen acetal (150) obtained by Friedel-Crafts reaction of acetyl chloride with 1,1-dichloroethene, followed by methoxydehalogenation.[70]

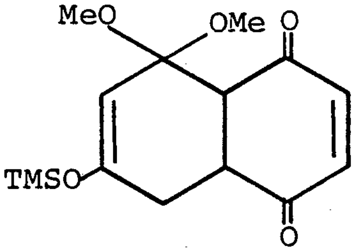


(149)



(150)

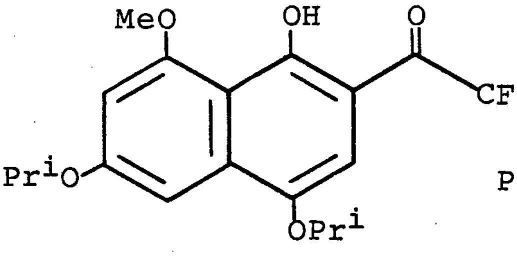
Diels-Alder addition of diene (149) to 1,4-benzoquinone, followed by alkylation of the intermediate crude adduct (151) with 2-bromopropane and potassium carbonate in dry dimethylformamide, afforded the naphthol (145) in fair yield (64% after chromatography).



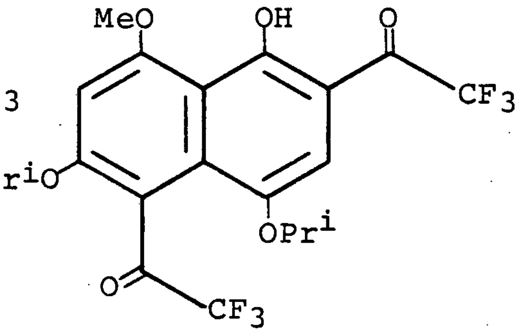
(151)

The ^{1}H n.m.r. spectrum of naphthol (145) showed, *inter alia*, two six-proton doublets (each J 6.5 Hz) at δ1.36 and 1.40 due to the methyls of the isopropoxy groups at C-4 and C-6. The protons of the methoxy group resonated at δ3.98, while the signal of the methine protons appeared as a broad multiplet centred at δ4.6. The hydroxy group which remained unprotected under these conditions and which is intramolecularly hydrogen-bonded to the *peri*-methoxyl, gave rise to the deuterium oxide exchangeable singlet at δ8.77.

Naphthol (145) also reacted smoothly with T.F.A.A. to afford the *ortho*-trifluoroacetylnaphthol (152) (85%), and the 2,5-disubstituted derivative (153) (4%).



(152)



(153)

As in the cases of the ^{1}H n.m.r. spectra of naphthols (141), (142) and (143) discussed earlier, the signals due to the proton *ortho* to the trifluoroacetyl group of (152) and (153) also showed multiplicity. A portion of the ^{1}H n.m.r. spectrum of compound (152), which clearly shows this multiplicity, is depicted in Figure 9.

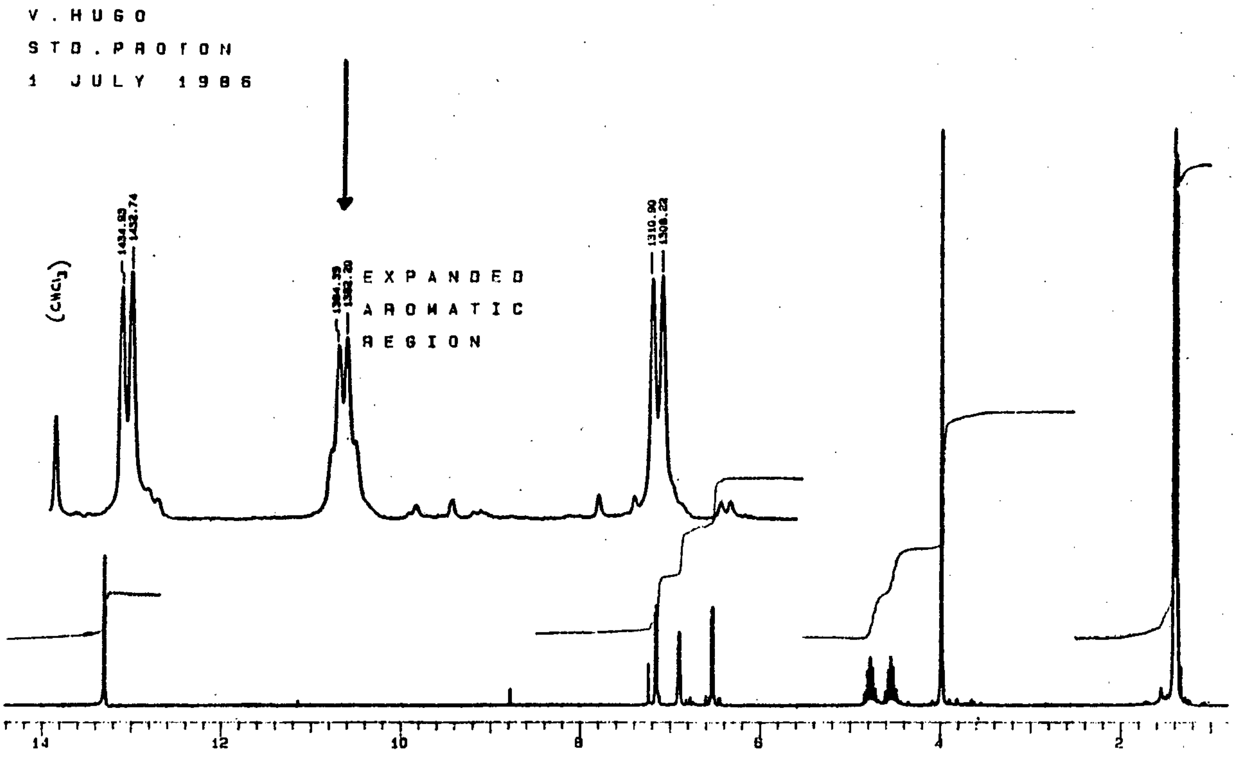
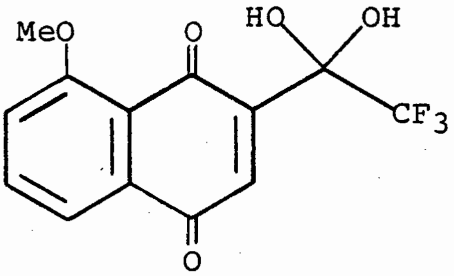


Fig. 9

In view of the oxidation of the 3-acetylnaphthols (40) and (55) to afford the acetyl quinones (29) and (30) respectively, the possible oxidation of the *ortho*-trifluoroacetylnaphthols (141) and (152) was investigated.

Treatment of naphthol (141) with two molar equivalents of C.A.N. gave the dihydroxyethylquinone (154) in a yield of 86%. The hydration of the trifluoroacetyl carbonyl group is reminiscent of the formation of chloral hydrate and of hexafluoroacetone hydrate.



(154)

The ^{1}H n.m.r. spectrum of compound (154) in deuterated acetone showed, *inter alia*, a three-proton singlet at δ7.27 which diminished on treatment with deuterium oxide, leaving a singlet which integrated for one proton. This signal was assigned to the quinonoid proton.

As the molecule possesses two other carbonyl groups, either of which could be alternative (but not likely) sites of hydration, a crystal structure determination was kindly performed by Dr. Margaret Niven of the Department of Physical Chemistry at this university which confirmed the structure of the quinone as (154).

A perspective drawing of the molecule, with atomic nomenclature is shown in Figure 10. All bond lengths and angles were the expected order of magnitude and the planarity of the quinonoid moiety is observed.

The molecular packing is shown in Figure 11 which reveals an interesting network of inter- and intra-molecular hydrogen bonding, in which the water of crystallisation (presumably derived from adventitious moisture in the solvent employed for recrystallisation) is intimately involved.

For the sake of completeness, the final fractional atomic coordinates and temperature factors for all the non-hydrogen atoms are listed in Table 4.

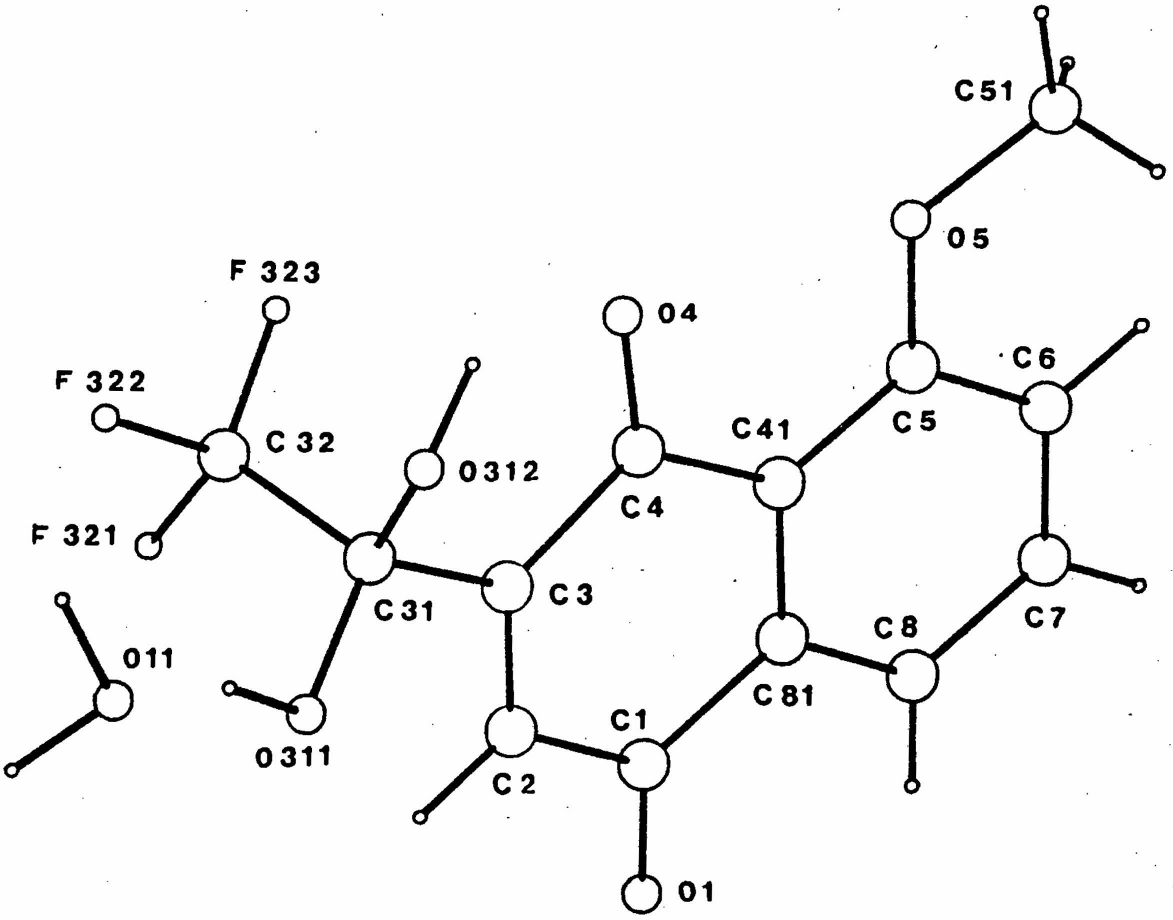

C51
05
F 323
04
F 322
C6
C5
C41
C 32
0312
C4
F 321
C31
C3
C7
C8
011
C81
C1
0311
C2
01

Fig. 10

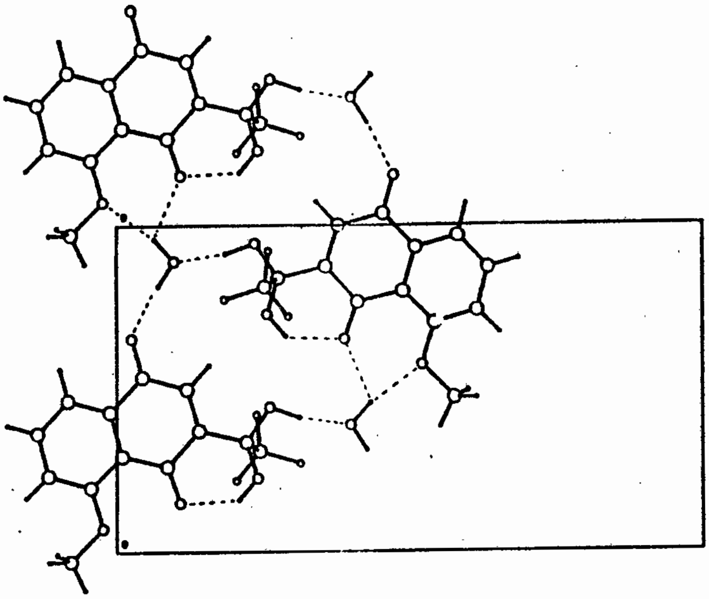


Fig. 11

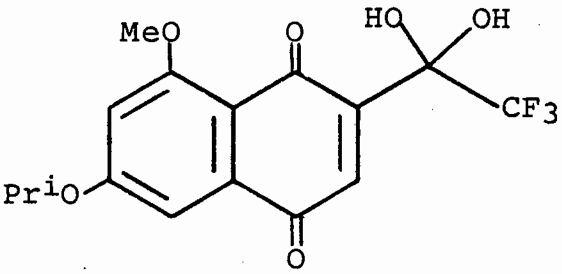
Fractional atomic coordinates (x 10^4) and thermal parameters ($\mathring{A}^2$ x 10^3) for the non-hydrogen atoms

	x/a	y/b	z/c	U(equiv)*
C(1)	4558(2)	10371(3)	8607(3)	48(2)
C(2)	3791(2)	10003(3)	8268(3)	48(2)
C(3)	3576(2)	8746(3)	8150(3)	43(2)
C(31)	2767(2)	8396(3)	7761(3)	45(2)
C(32)	2536(2)	8126(4)	8666(3)	58(2)
C(4)	4125(2)	7653(3)	8393(3)	46(2)
C(41)	4900(2)	7980(3)	8687(3)	44(2)
C(5)	5438(2)	7012(4)	8857(3)	48(2)
C(51)	5779(3)	4737(4)	8851(5)	80(3)
C(6)	6164(2)	7396(4)	9114(3)	62(2)
C(7)	6352(2)	8702(4)	9208(3)	64(2)
C(8)	5834(2)	9680(4)	9053(3)	56(2)
C(81)	5114(2)	9321(3)	8788(3)	46(2)
O(1)	4740(2)	11540(3)	8729(3)	76(2)
O(4)	3902(2)	6518(3)	8340(3)	79(2)
O(5)	5229(1)	5729(2)	8741(2)	62(2)
O(311)	2367(1)	9453(2)	7228(2)	61(2)
O(312)	2577(1)	7285(2)	7127(2)	53(2)
F(321)	2599(2)	9220(3)	9215(2)	93(2)
F(322)	1847(1)	7740(3)	8367(2)	75(2)
F(323)	2941(2)	7211(3)	9283(2)	95(2)
O(11)	988(2)	8909(3)	6163(3)	70(2)

*U(equiv) = $\frac{1}{3}$ (trace of orthogonalized Uij matrix)

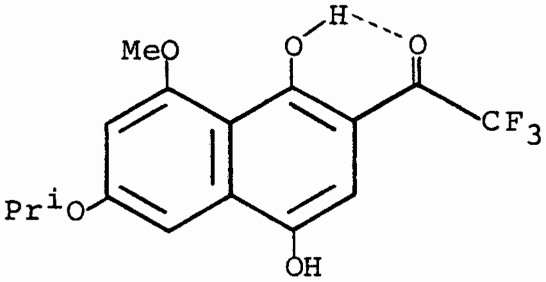
Table 4

Similar oxidation of the naphthol (152) afforded the quinone (155) in excellent yield (92%).



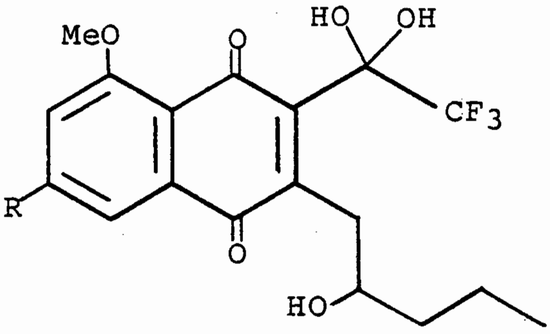
(155)

The *gem*-diol configuration is undoubtedly stabilised by hydrogen bonding between the quinonoid carbonyl-oxygen and the hydroxyl groups since reduction of compound (155) with an aqueous sodium dithionite solution resulted in the loss of water from the molecule to afford the hydroquinone (156) in good yield (72%).



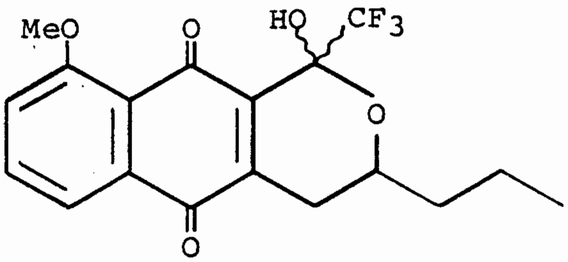
(156)

The next aim was to employ the quinones (154) and (155) as starting materials for the synthesis of naphtho [2,3-*c*] pyrans. It was envisaged that by treating these quinones with 3-hydroxyhexanoic acid[71] (prepared from methylbromoacetate and butanal) and using the method of Jacobsen and Torssell[42] as an initial step, cyclisation of the intermediates (157a) derived from (154), and (157b) derived from (155) would afford the corresponding naphtho[2,3-*c*]pyrans.



(157a) R = H
(157b) R = Pr^iO

This aim was in fact achieved in high yield (80%) with the formation of the naphthopyran (158) from quinone (154), with compound (157a) not being observed.

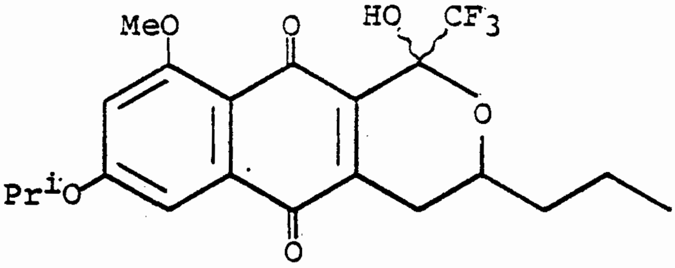


(158)

The ^1H n.m.r. spectrum of this product showed *inter alia* a one-proton singlet at δ6.23, which underwent exchange with deuterium oxide, due to the hydroxy group, a one-proton doublet of doublets (J 2.5 and 18 Hz) at δ2.93 due to the *pseudo*-equatorial 4-H, and a one-proton doublet of doublets (J 11 and 18 Hz) at δ2.13 due to the *pseudo*-axial 4-H. The signal for the axial 3-H appeared as a multiplet at δ3.8, partly obscured by the signal of the methoxy protons.

The stereochemistry at C-1 has not been determined with certainty. It is assumed that the more bulky trifluoromethyl group occupies the *pseudo*-axial position, where it would suffer less from *peri*-interaction with the neighbouring carbonyl group than if it were *pseudo*-equatorial, while the hydroxy group is *pseudo*-equatorial where it would enjoy stronger intramolecular hydrogen-bonding to the carbonyl group than if it were *pseudo*-axial.

The quinone (155) similarly afforded the pyran (159). The ^{1}H n.m.r. spectrum of this compound is shown in Figure 12.



(159)

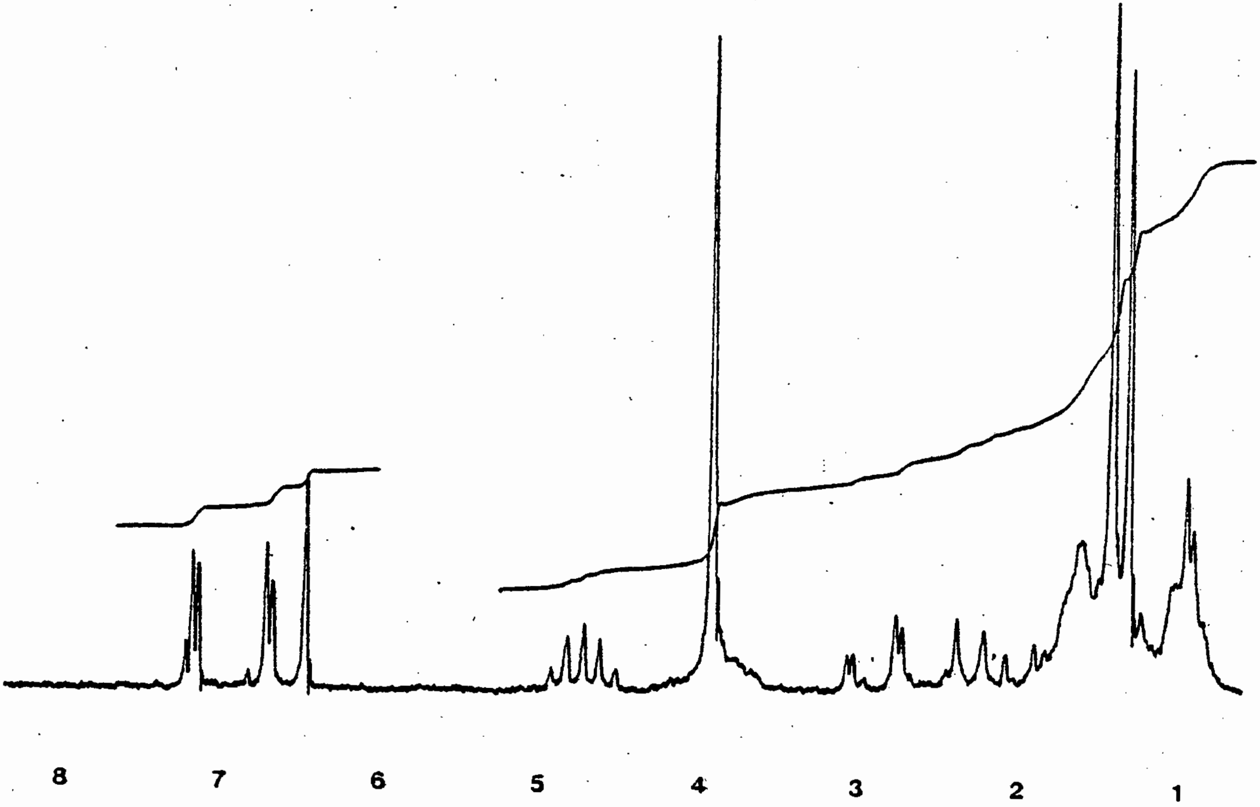
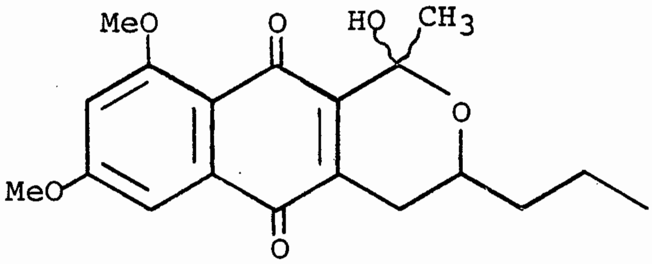


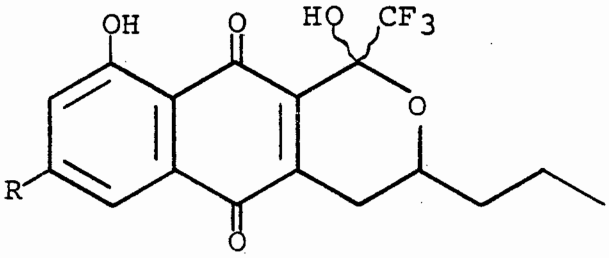
Fig. 12

An analogous cyclisation was also observed when the acetyl quinone (30) was treated as for compounds (154) and (155), to afford the pyran (160)



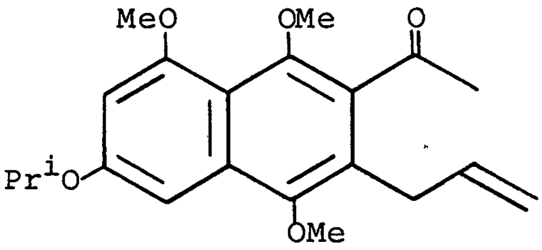
(160)

The deprotection of the C-9 oxygen in the case of pyran (158) and the C-7 and C-9 oxygens in the case of pyran (159) to afford the phenolic pyrans (161a) and (161b) respectively, was also attempted. The reagent of choice in these cases was boron trichloride since it was shown in these laboratories that this reagent cleaved the ether functions at C-4 and C-7 of the naphthalene (162) to afford compound (163), and it also deprotected the C-7 and C-9 oxygens of quinone (164) to afford quinone A (16).

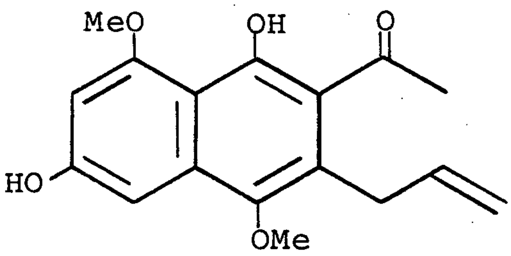


(161a) R = H

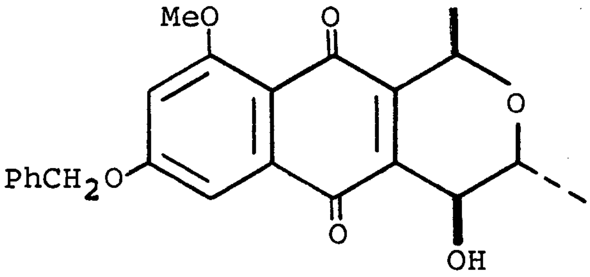
(161b) R = OH



(162)

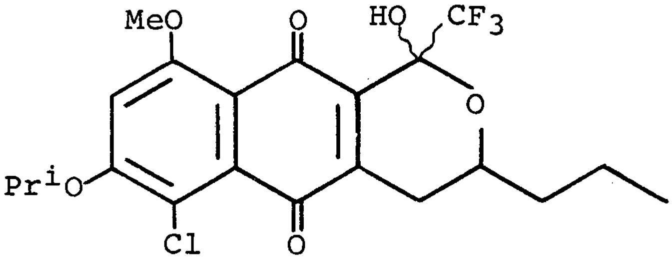


(163)



(164)

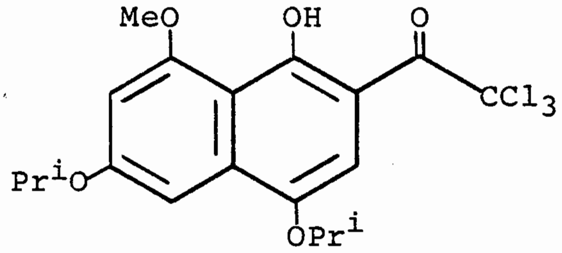
However, treatment of pyran (158) with boron trichloride in dichloromethane at -78° and 0°C afforded a multicomponent mixture in which only starting material (63%) was readily identified. In the case of the pyran (159), the only readily identifiable product, apart from starting material (23%), was the chloro-derivative (165) (37%)



(165)

The position of chlorination was inferred from a comparison of the chemical shifts of 8-H in pyran (159) and the product (165). In the former case, 8-H resonated as a doublet (J 2.5 Hz) at δ6.68 and 6-H appeared as a doublet (J 2.5 Hz) at δ7.17, whereas in pyran (165) the resonance of H-8 appeared as a singlet at δ6.83.

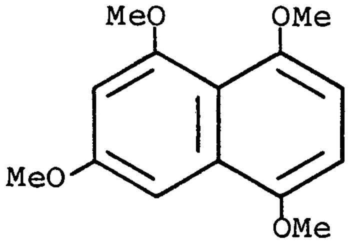
The reaction of the naphthol (145) and trichloroacetic anhydride was also investigated. In contrast with T.F.A.A., this anhydride reacted markedly more slowly (*circa* sixty times) with (145) at room temperature to afford the trichloroacetyl derivative (166) in moderate yield (38%)



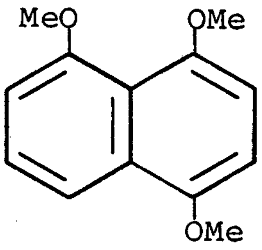
(166)

3.3 Trifluoroacetylation of some naphthalene methyl ethers[65]

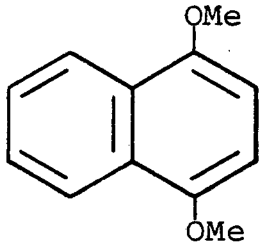
The reaction of the naphthalene methyl ethers (167)-(169) in dichloromethane with T.F.A.A. at room temperature was also investigated. The oxygenation pattern chosen for these naphthalene substrates was that commonly found amongst naturally occurring naphthoquinones.



(167)

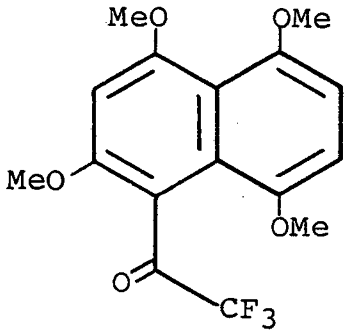


(168)



(169)

Compound (167), available by methylation of the naphthol (53), reacted smoothly with T.F.A.A. and after 2.5 hours all starting material was consumed to give the 8-trifluoroacetylnaphthalene (170) as the sole product in a yield of 69%.

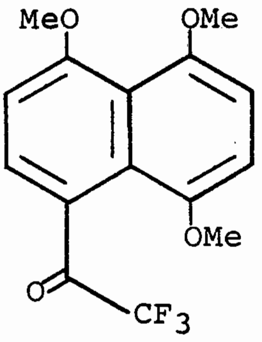


(170)

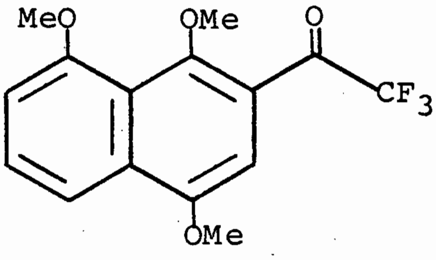
The assignment of structure (170) to the product was supported by its ^1H n.m.r. spectrum which showed *inter alia* two *ortho*-coupled protons (J 9 Hz) at δ6.64 and 6.78 due to 2-H and 3-H. In the case of the starting material (167) these protons resonated as two ortho-coupled protons at δ6.63 and 6.74. H-6 resonated as a singlet at δ6.64 in product (170), which compared well with the chemical shift of δ6.56 for 6-H in (167), where it resonated as a *meta*-coupled doublet (J 2.5 Hz).

The α-position of electrophilic attack on the naphthalene nucleus was in accord with the preferred orientation of electrophilic substitution of naphthalene itself, and no doubt the positive mesomeric effect of the methoxy groups would enhance this orientation of substitution.

The trimethoxynaphthalene (168), available from the naphthol (38) by methylation of the hydroxy group, also reacted with T.F.A.A. but much more slowly (10 days) than the tetramethoxy analogue (167), to afford two products in moderate yield. These products were identified on the basis of their ^1H n.m.r. spectral characteristics as the isomeric 8- and 3-trifluoroacetylated naphthalenes (171) and (172) respectively - the former being the major product. (28% based on unrecovered starting material). The latter compound was obtained in a yield of only 14%, based on unrecovered starting material.



(171)



(172)

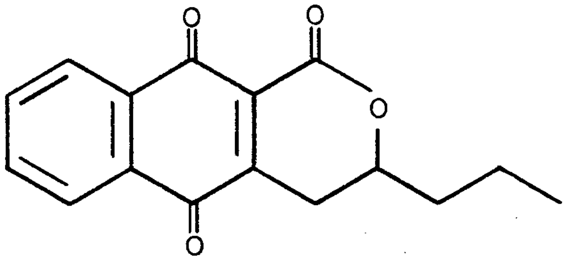
The ^1H n.m.r. spectrum of compound (171) showed two *ortho*-coupled doublets (both J 9 Hz) due to 6-H and 7-H which required acylation at C-6 or C-8. The latter was preferred by comparison with the acylation of the tetramethoxynaphthalene (167) and also the known preference for naphthalenes to undergo electrophilic attack at the α-positions. Further support for structure (171) was derived from the observation that the lowest-field doublet, assignable to 8-H in the trimethyl ether (168), had disappeared in the ^1H n.m.r. spectrum of the product (171).

Support for structure (172) assigned to the minor product, was obtained by methylation of the *ortho*-trifluoroacetyl naphthol (141) which afforded compound (172), identical by t.l.c., ^1H n.m.r. and infrared spectroscopy to the material obtained in this case.

1,4-Dimethoxynaphthalene (169) did not react with T.F.A.A., even after prolonged treatment (5 days at room temperature) nor on addition of trifluoroacetic acid to the mixture.

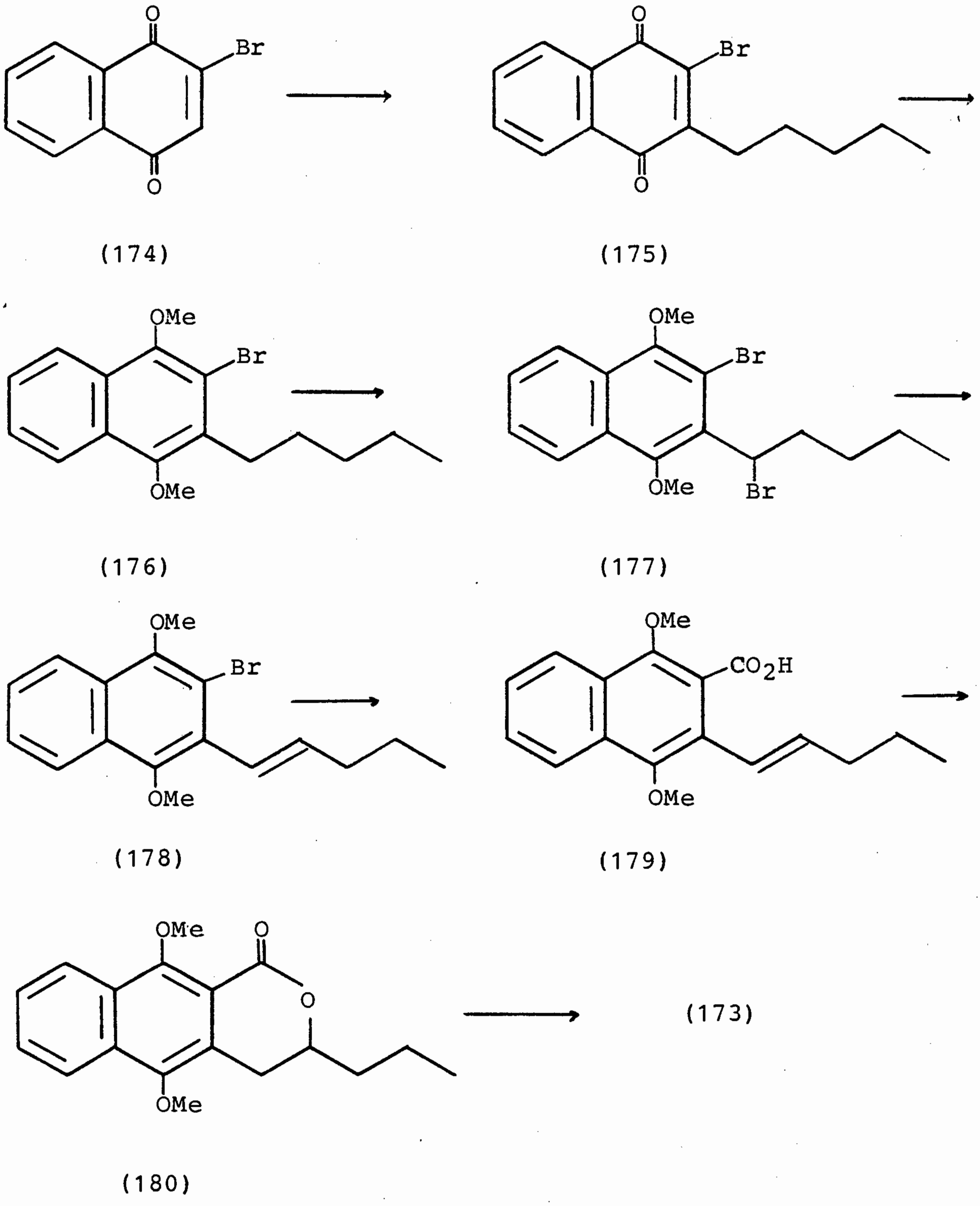
3.4 Potential synthetic routes to naphtho[2,3-*c*]pyranones

Recently, Giles and co-workers [68] synthesised the quinonoid naphthopyranone (173) (as in Scheme L) with a view to determining a pathway to its 7,9-dihydroxy-analogue (148).



(173)

It is envisaged that lactone (148) may give rise to the quinonoid pigment xylindein (146) by anaerobic coupling[67] of (148).


O
Br
O
(174)
O
Br
O
(175)
OMe
Br
OMe
(176)
OMe
Br
OMe
Br
(177)
OMe
Br
OMe
(178)
OMe
CO_2H
OMe
(179)
OMe
O
O
OMe
(180)
(173)

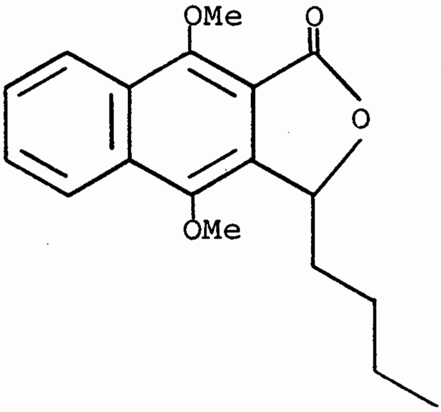
Scheme L

Their first step involved the alkylation of the bromoquinone (174)[72] with hexanoic acid employing the experimental conditions of Jacobsen and Torssell,[42] to obtain the quinone (175) in excellent yield (90%). This compound was converted to the dimethyl ether (176) by reductive methylation with aqueous sodium dithionite, followed by treatment with dimethyl sulphate.

Bromination of (176) with *N*-bromosuccinimide in the presence of di-*t*-butyl peroxide afforded the benzylic bromide (177) which could be dehydrobrominated by boiling in lutidine to yield the *trans*-olefin (178) in good yield. [88% from (176)]. Treatment of the olefin (178) with butyl-lithium in dry ether followed by carbon dioxide, afforded the acid (179).

The formation of the lactone ring system from the olefinic acid (179) was accomplished by a novel photochemical ring closure. The acid (179) was irradiated in solution in cyclohexane through quartz and a Vycor filter to afford the lactone (180) in a yield of 40%.

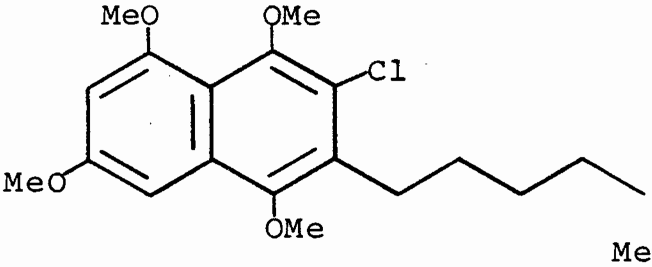
Further support for the assignment of structure (180) to their product was obtained by the synthesis of the alternative γ-lactone (181), and comparison of the ^{1}H n.m.r. spectral characteristics of (180) and (181).



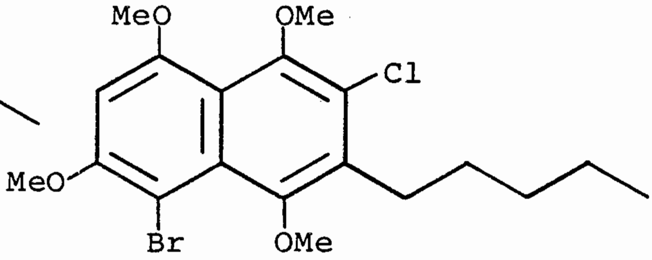
(181)

Oxidative demethylation of (180) with silver(II) oxide gave the quinonoid pyranone (173) in good yield (80%).

It was later shown in these laboratories[73] that higher oxygenated naphthalenes, for example (182), underwent bromination of the naphthalene nucleus under a variety of conditions with *N*-bromosuccinimide, to afford mainly (183).



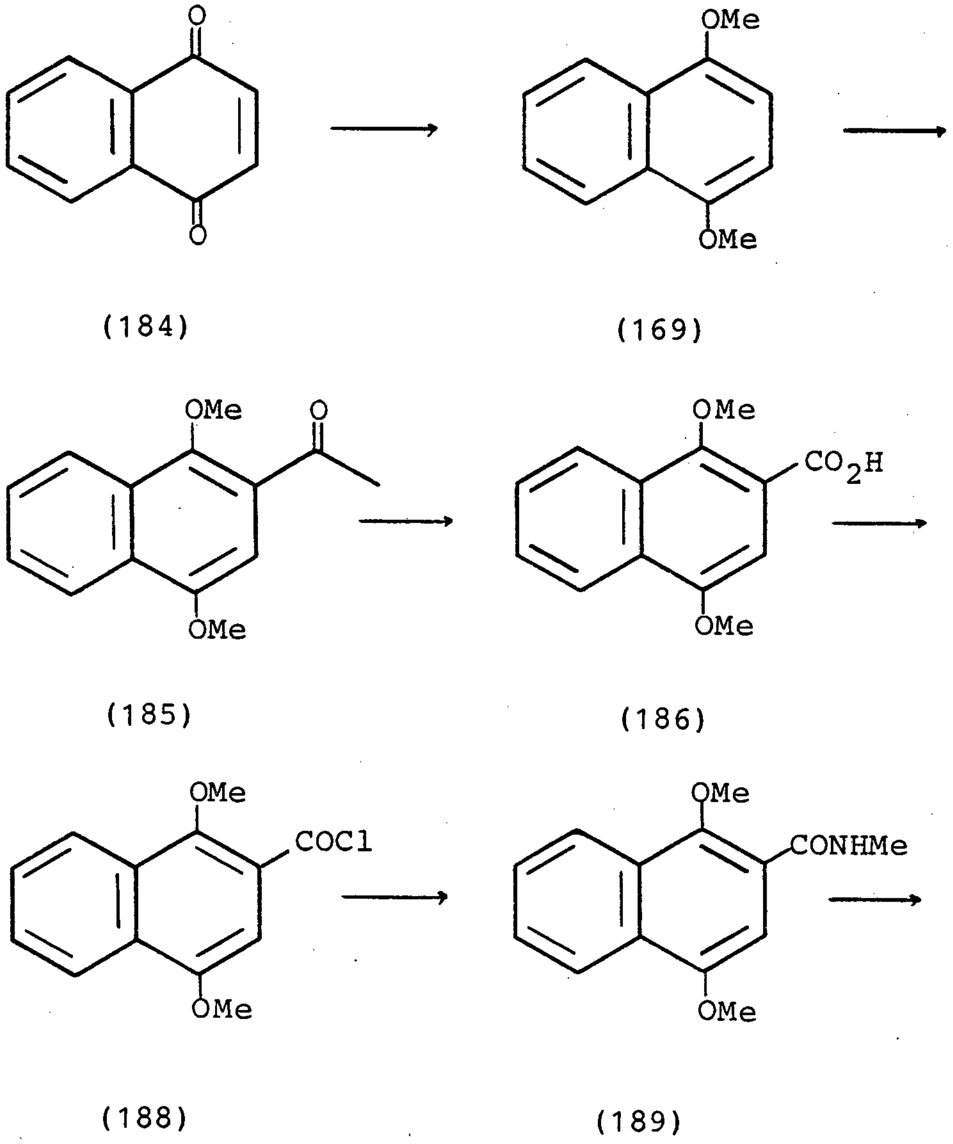
(182)



(183)

In the light of these findings it was decided to develop an alternative model route to the lactone (180) by means of which other aromatic oxygenated naphthopyranones may be available.

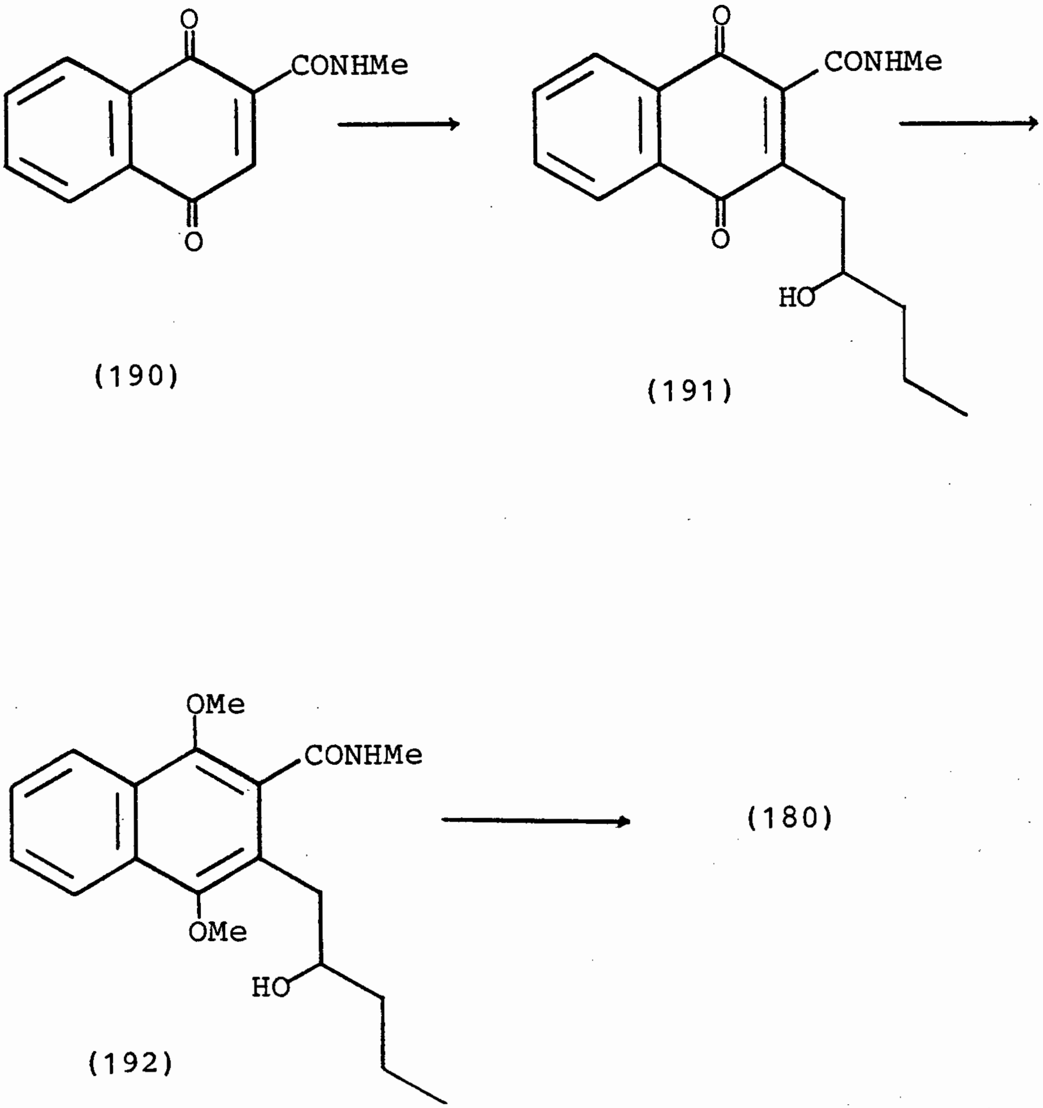
The new route to lactone (180) as in Scheme M, employs the readily available 1,4-naphthoquinone (184) as starting material.



(184) (169)

(185) (186)

(188) (189)



(190)

(191)

(192)

(180)

Scheme M

The quinone (184) was reductively methylated by employing the usual conditions to give the naphthalene dimethyl ether (169) in a yield of 75% after chromatography. As the naphthalene derivative (169) was found not to react with T.F.A.A. it was decided to synthesise the 2-acetyl derivative (185). This was achieved in excellent yield (95%) by treatment of (169) with premixed T.F.A.A. and glacial acetic acid.[74]

Compound (185) afforded the acid (186) in good yield on treatment with aqueous sodium hypochlorite. This acid gave the amide (189) on treatment with thionyl chloride followed by ammonolysis of the intermediate acyl chloride (188) with an aqueous methylamine solution.

Oxidative demethylation of amide (189) using silver(II) oxide, gave the corresponding quinone (190) in good yield after chromatography.

The next step in the synthetic sequence involved the hydroxypentylation of the quinonoid moiety of (190) using 3-hydroxyhexanoic acid to afford quinone (191). The ^{1}H n.m.r. spectrum of this product showed, *inter alia*, a distorted triplet (J 6 Hz) at δ0.9 due to the methyl of the hydroxypentyl side-chain, and a broad one-proton signal at δ5.2 which disappeared on addition of deuterium oxide, due to the hydroxy group. The amido-nitrogen proton resonated as a broad singlet at δ7.01.

The direct conversion of quinone (191) to the lactone (173) by pyrolysis was next attempted. Heat treatment of (191) under nitrogen gave a mixture of compounds in which the lactone (173) was not identified.

It was thus decided to convert quinone (191) to the corresponding dimethyl ether (192). This was achieved by reductive methylation, employing the usual reagents, in a yield of 55% after chromatography.

Pyrolysis of compound (192) under nitrogen afforded the naphthopyranone (180) (37%), identical to the material obtained by Giles *et al*.[68] The ^{1}H n.m.r. spectrum of this lactone (Figure 13) showed the characteristic doublet of doublets (J 11 and 16 Hz) due to the *pseudo*-axial 4-H at δ2.81, while the *pseudo*-equatorial 4-H appeared as a doublet of doublets (J 2.5 and 16 Hz) at δ3.37. The axial 3-H resonated as a multiplet at δ4.42. The 1'- and 2'-methylene groups of the C-3 propyl side-chain resonated as a multiplet at δ1.4-1.95 while the methyl group appeared as a deformed triplet (J 7 Hz) at δ0.96.

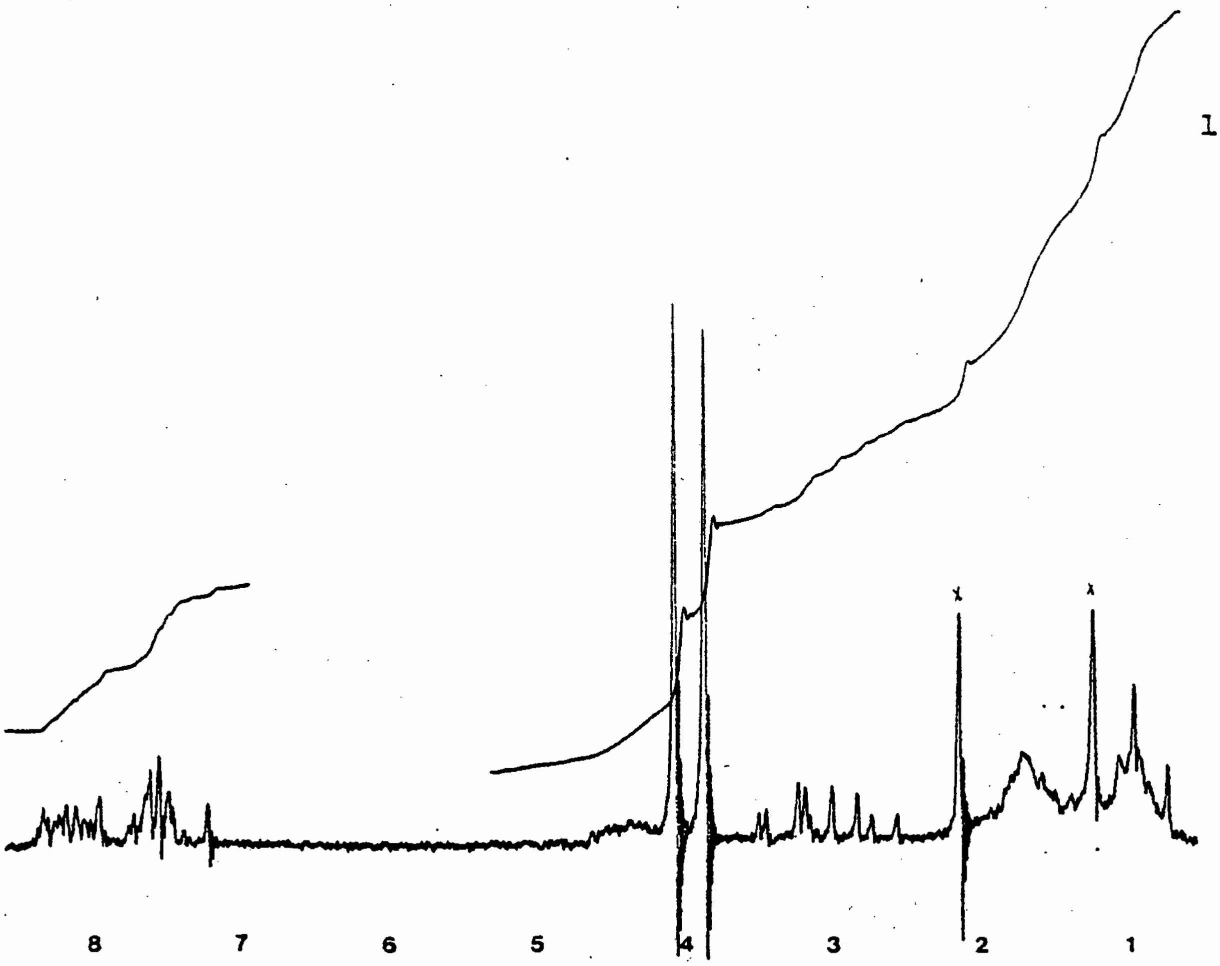
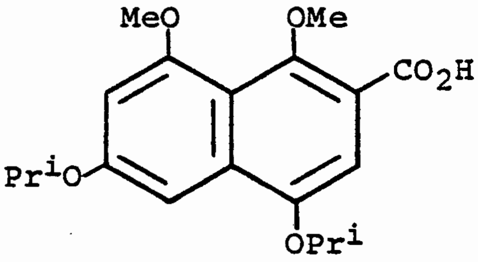
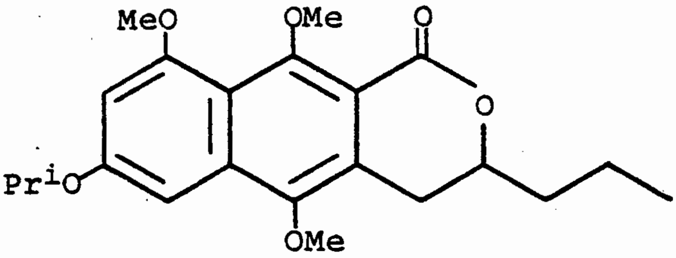


Fig. 13

In the light of the success achieved in synthesising the lactone (180) *via* the route as in Scheme M above, the acid (193) seemed to be a suitable synthetic precursor to the lactone (194) which has readily removeable protection at 0-7.

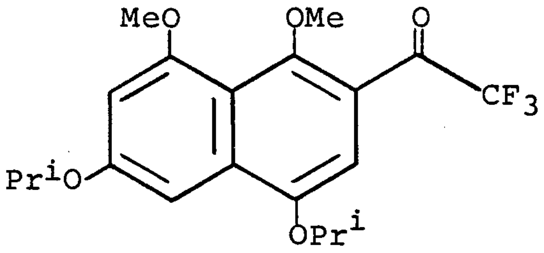


(193)



(194)

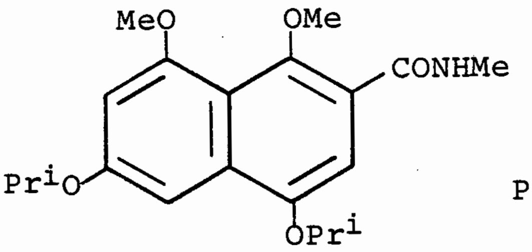
The synthesis of acid (193) involved firstly, the methylation of the hydroxy group of the trifluoroacetylnaphthol (152), to afford the derivative (195), followed by alkaline hydrolysis of its trifluoroacetyl group.



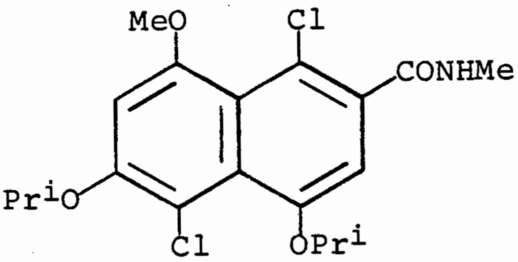
(195)

Treatment of the acid (193) with hot thionyl chloride followed by methylamine as for the acid (186), afforded a single compound of slightly higher R_F than starting material. The ^1H n.m.r. spectrum of the product showed, *inter alia*, a three-proton doublet (J 5 Hz) at δ3.04, another three-proton singlet at δ3.37, two sharp one-proton singlets at δ7.33 and 7.53, and a broad one-proton singlet centred at δ7.9.

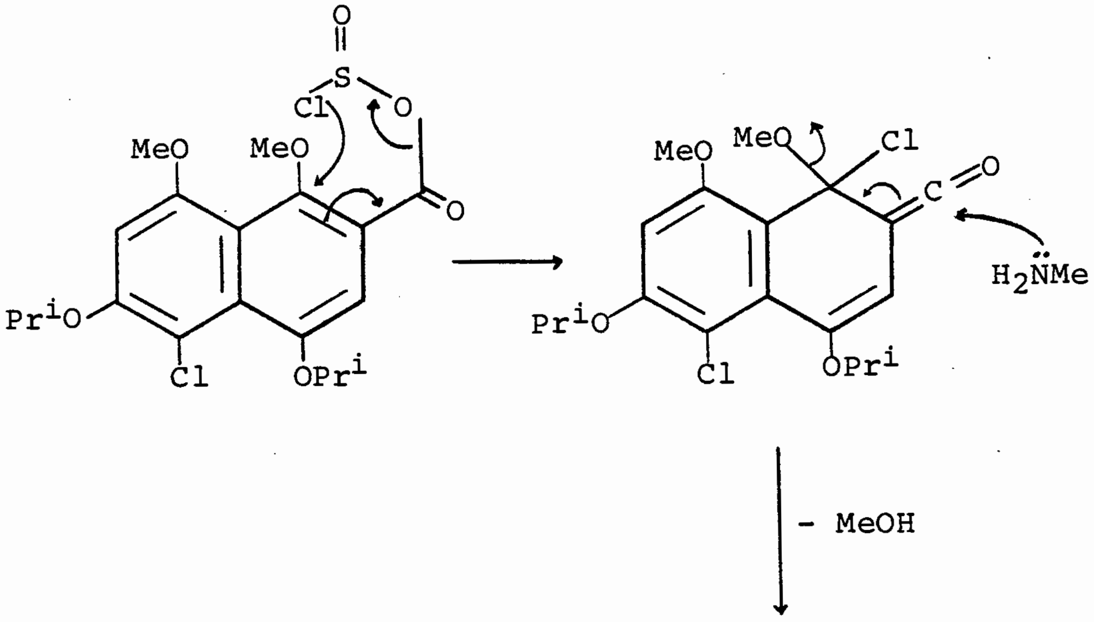
It was evident from the ^1H n.m.r. spectral characteristics of this compound that it was not the expected amide (196). Micro elemental analyses and mass spectrometry studies of this compound both complied with the molecular formula $C_{19}H_{23}O_4NCl_2$. In view of this information, structure (197) was assigned to the product which may arise as shown below


MeO
OMe
CONHMe
Pr^{i}O
OPr^i

(196)

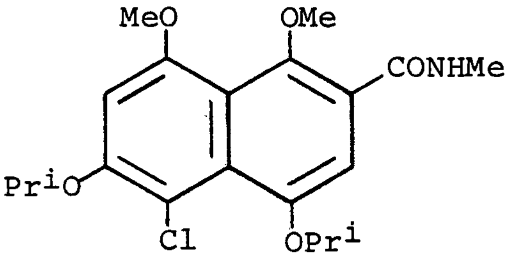

MeO
Cl
CONHMe
Pr^{i}O
Cl
OPr^i

(197)


O
S
Cl
O
O
MeO
MeO
Pr^{i}O
Cl
OPr^i
MeO
MeO
Cl
C
O
H$_2$NMe
Pr^{i}O
Cl
OPr^i
- MeOH

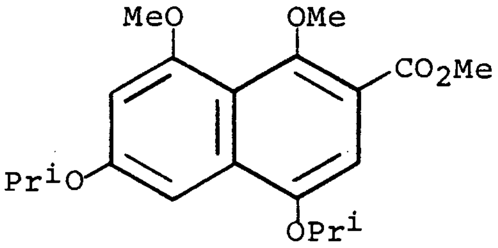
(197)

When the acid (193) was treated with thionyl chloride at room temperature, followed by treatment with methylamine, the amide (198) was isolated as the sole product.



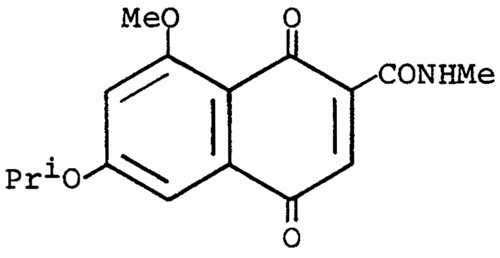
(198)

The target amide (196) was eventually prepared *via* ammonolysis of the ester (199) readily available by methylation of the acid (193) with iodomethane in the presence of potassium carbonate in dry acetone.



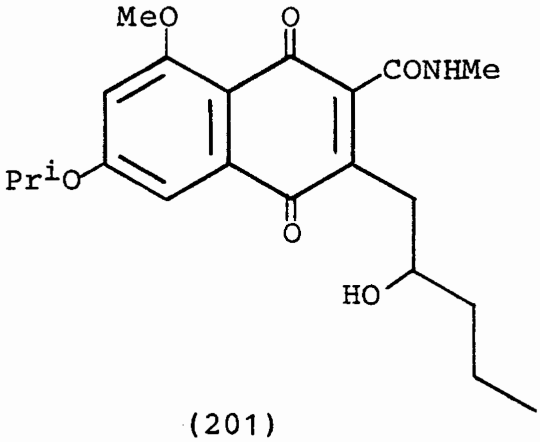
(199)

Oxidative demethylation of amide (196) with silver(II) oxide afforded the quinone (200) in poor yield. (24% after chromatography). This disappointing yield is in contrast with the good yield of quinone (190) obtained under similar reaction conditions.



(200)

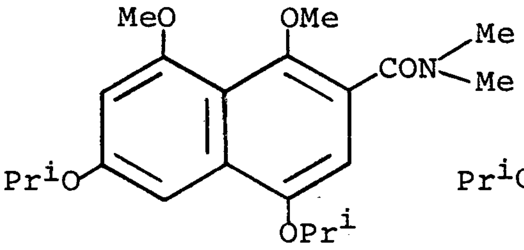
Treatment of quinone (200) with 3-hydroxyhexanoic acid as for quinone (190) afforded a mixture from which the unstable hydroxypentyl derivative (201) was isolated in a yield of 14%, at best, although this result was not readily reproducible. On several occasions no product corresponding to (201) was obtained.



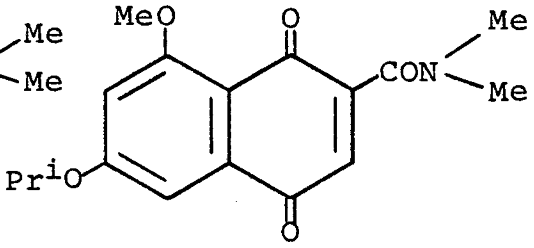
(201)

In the light of the poor overall yields obtained for compounds (200) and (201), as well as the instability of quinone (201), this route to the lactone (194) was not further investigated.

It was then decided to convert the amide (196) to the tertiary amide (202) in order to determine whether the oxidative demethylation of the latter amide would afford a higher yield of the corresponding quinone (203).



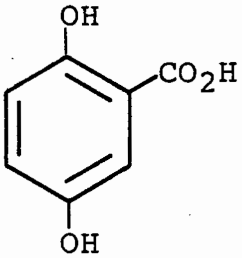
(202)



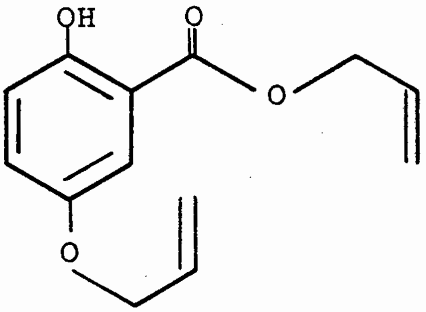
(203)

Amide (196) was smoothly converted in high yield (93%) to the analogue (202) by treatment with sodium hydride followed by iodomethane. Unfortunately, oxidative demethylation of the latter compound also gave the quinone (203) in low yield (14%).

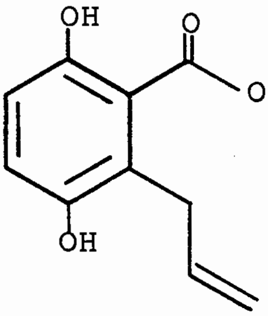
Harwood[75] recently reported a facile synthesis of the naturally occurring dihydroisocoumarin (207) which has been identified in extracts of Brazilian wood infected by fungi. His route to (207) involved the conversion of gentisic acid (204) to the allyl 5-allyloxy-2-hydroxy-benzoate (205) with allyl bromide and potassium carbonate in acetone. Trifluoroacetic acid-catalysed rearrangement of compound (205) afforded the target lactone (207) (41%), together with the dihydrobenzofuran (208) (14%), presumably *via* the intermediate product of Claisen-rearrangement (206).



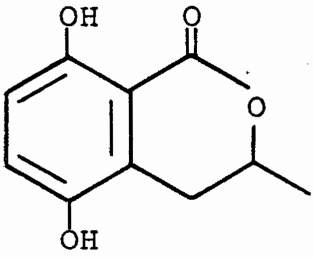
(204)



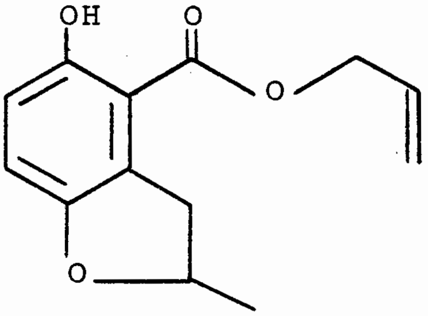
(205)



(206)

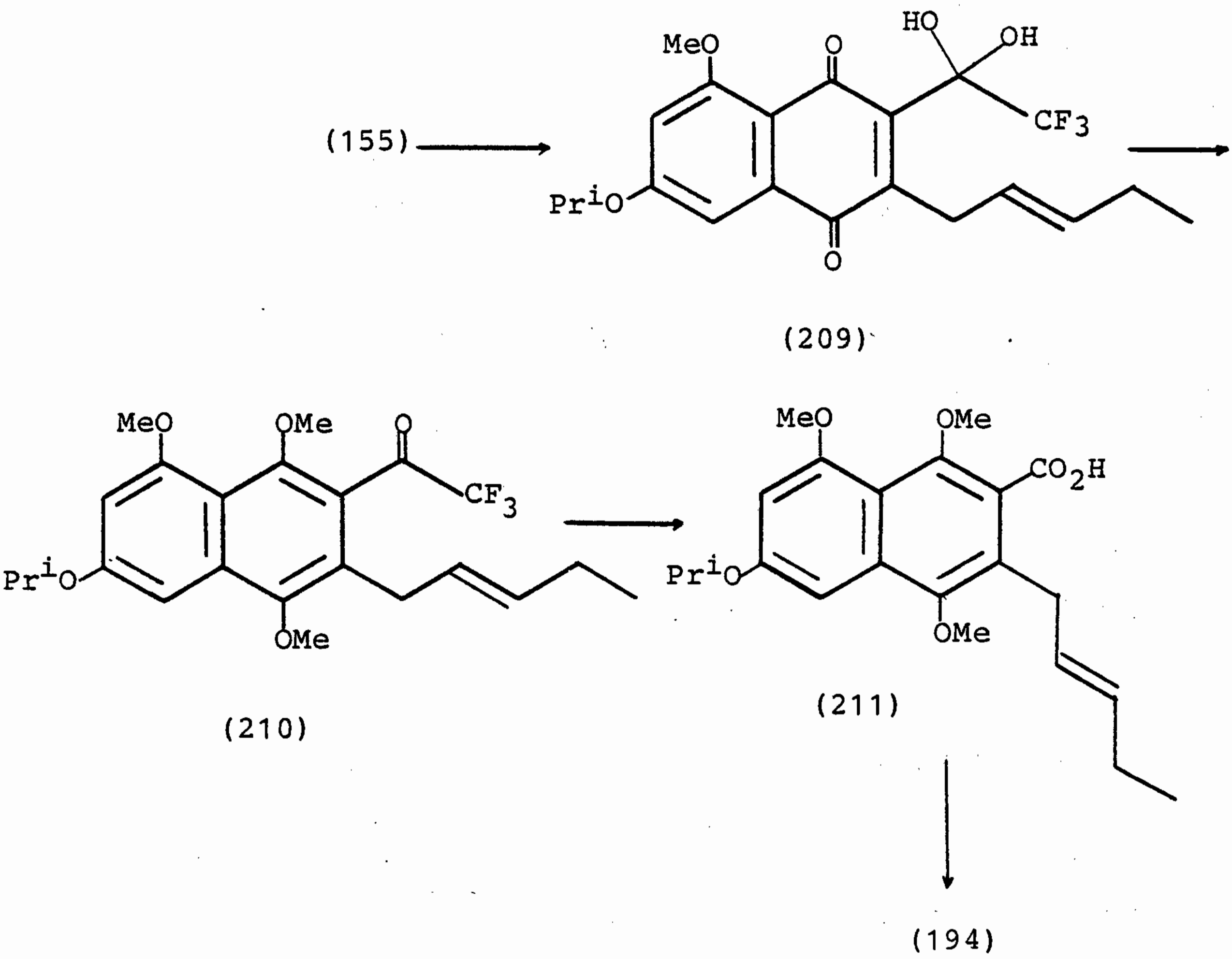


(207)



(208)

In the light of Harwood's work discussed above, the following potential synthetic sequence (Scheme N) in which the olefinic side-chain would be directly introduced by the Jacobsen and Torssell method,[42] was investigated.

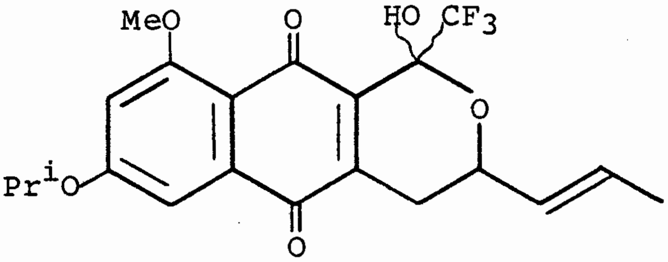


Scheme N

It was anticipated that treatment of quinone (155) with *trans*-3-hexenoic acid[76] would afford quinone (209) which could be converted to the trifluoroacetylnaphthalene

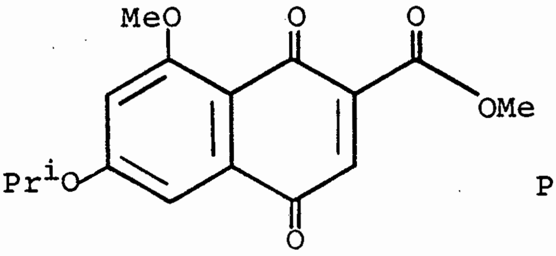
(210) by reductive methylation. This product would be an ideal precursor for the acid (211) by employing the conditions for the conversion of the analogue (195) to the acid (193). It was further envisaged that the acid (211) would cyclise to afford lactone (194) by treatment with trifluoroacetic acid.

However, in practice the reaction of quinone (155) with *trans*-3-hexenoic acid afforded a mixture in which compound (209) was not identified. Purification of the reaction mixture by preparative layer chromatography (p.l.c.) gave two fractions. The ^1H n.m.r. spectrum of the fraction of higher R_F was inconclusive but the ^1H n.m.r. spectrum of the other fraction showed *inter alia*, a three-proton doublet (J 5 Hz) at δ1.67, a poorly-defined pattern of signals between δ2.3 and 3.2 integrating for two protons, a deuterium oxide exchangeable signal at δ4.95 and a two-proton multiplet centred at δ5.47. Double irradiation at this multiplet resulted in the collapse of the three-proton doublet at δ1.67 to a singlet while the molecular mass of this compound was measured as 426. On the basis of this information, the structure (212) is tentatively proposed for this compound which may have arisen by cyclisation of quinone (209).

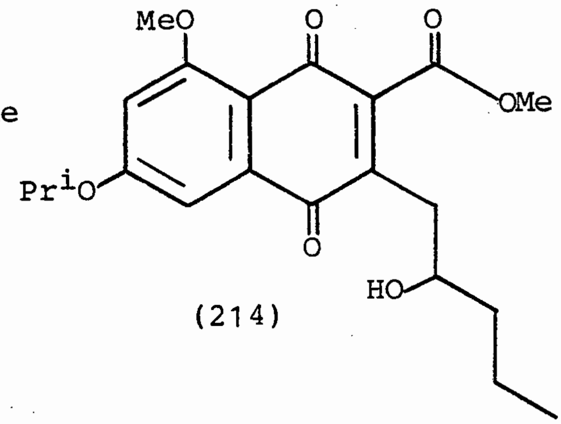


(212)

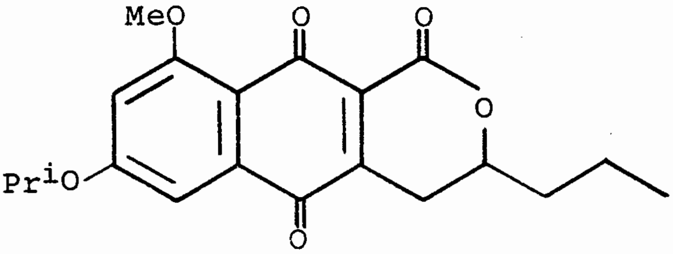
Attention was then focussed on the possible oxidation of the ester (199) to the quinone (213), followed by hydroxypentylation of the latter quinone to afford the derivative (214). It was further hoped that (214) would undergo cyclisation to afford the quinonoid lactone (215).



(213)



(214)



(215)

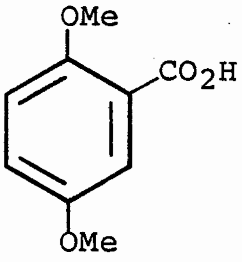
Oxidative demethylation of the ester (199) using silver(II) oxide afforded the ester (213) as an unstable oil in a yield of 18% after chromatography. Alternative oxidation of (199) using C.A.N. resulted in excessive decomposition of starting material with the quinone (213) not being observed in the complex reaction mixture. Due to this low yield of (213) obtained in the first step and the instability of the product, this route was not further investigated.

In recent years organothallium compounds have become increasingly useful as synthetic intermediates in organic chemical syntheses.[77-83] Thallium(III) trifluoroacetate (T.T.F.A.) in particular has been found to be extremely efficient as a reagent for electrophilic aromatic thallations. The thallium moiety can be substituted by several functional groups affording new routes to many substituted arenes.

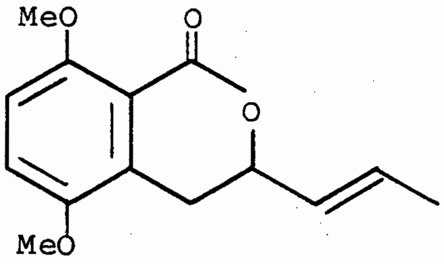
Taylor *et al.*[79] prepared several aromatic iodides *via* thallation of substituted aromatic substrates followed by treatment of the intermediate arylthallium ditrifluoroacetates with aqueous potassium iodide. It was found that *meta* substitution is usually observed under conditions of thermodynamic control, whereas under the conditions of kinetic control *ortho* substitution results as in the case of benzoic acid by means of *ortho* delivery of thallium.

Larock *et al.*[80] have synthesised several 3,4-dihydroisocoumarins from β-phenylethyl alcohols as substrates employing the direct thallation-carbonylation of the substrate alcohols. Larock and co-workers[81] also developed attractive routes to several isocoumarins *via* the thallation-olefination of several benzoic acid derivatives.

In the light of the results obtained by Larock and other groups, the thallation reaction was extended in this laboratory to the dimethoxybenzoic acid (216). Treatment of this compound with T.T.F.A. in trifluoroacetic acid followed by palladium(II) chloride and 1,3-pentadiene, afforded the 3,4-dihydroisocoumarin (217) in a yield of 41%.



(216)



(217)

The ^{1}H n.m.r. spectrum of lactone (217) (Figure 14) showed *inter alia*, a three-proton doublet (J 5 Hz) at δ1.72 due to methyl of the 3-(1')-propenyl side-chain, a one-proton doublet of doublets (J 12 and 17 Hz) at δ2.65 due to the *pseudo*-axial 4-H, and another one-proton doublet of doublets (J 3 and 17 Hz) due to the *pseudo*-equatorial 4-H.

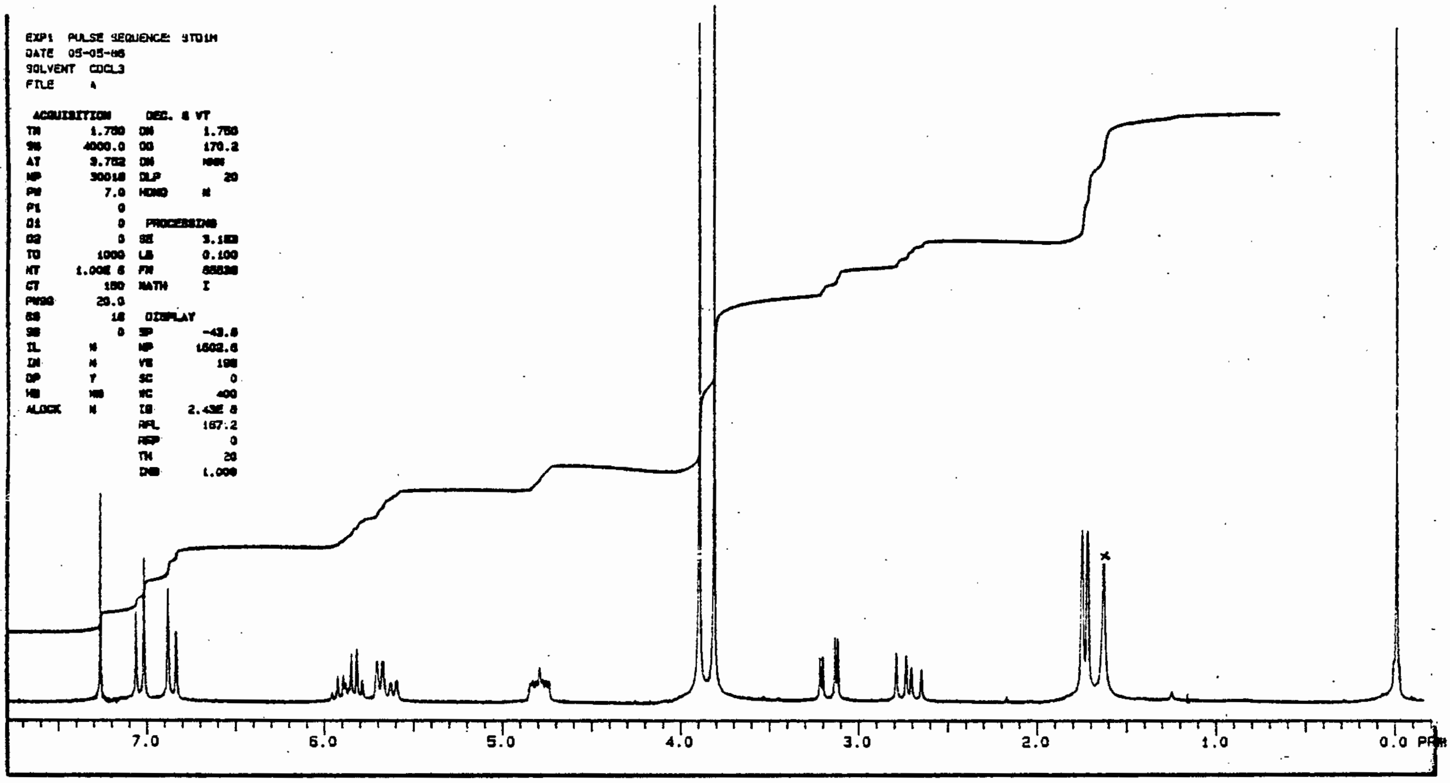
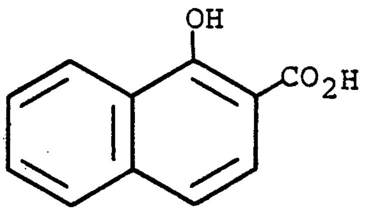
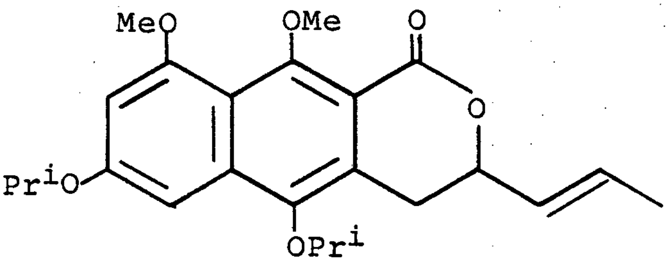


Fig. 14

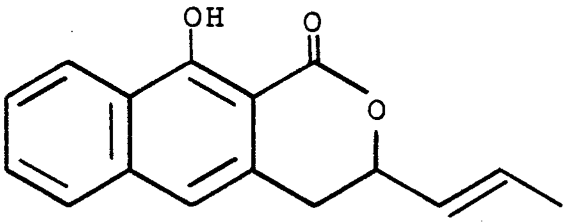
When this thallation reaction was repeated with the naphthalenic acids (193), (218) and (186) under the same conditions, none of the corresponding lactones (219), (220) and (221) were obtained.



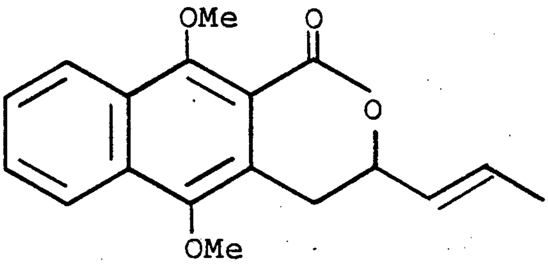
(218)



(219)



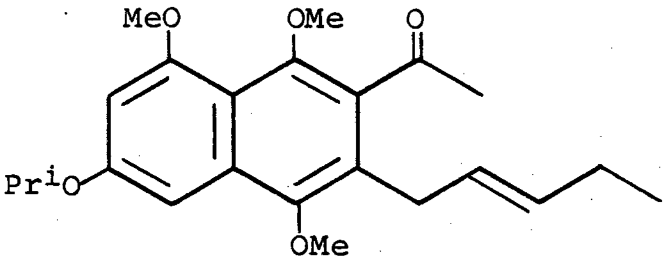
(220)



(221)

In all these cases a mixture of unreacted starting material and tars was observed.

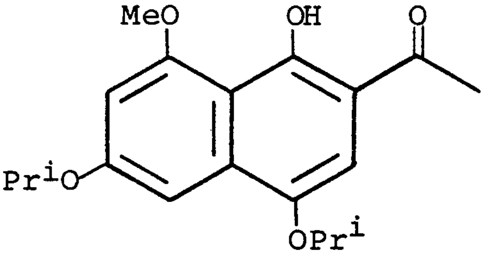
Attention was then focussed on the synthesis of the naphthalenic acid (211) *via* the acetylnaphthalene derivative (222), by oxidation of the acetyl group employing the haloform reaction.



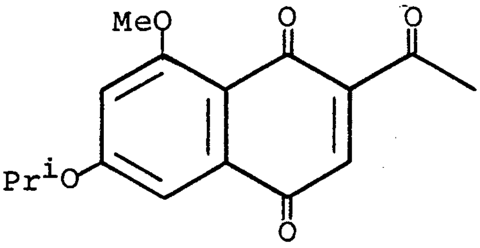
(222)

It was anticipated that the acid (211) would afford a lactone either by acid-catalysed cyclisation as for (206) to afford lactone (207), or by the palladium-catalysed cyclisation of aromatic olefinic acids as effected by Larock,[81] or by the photo-catalysed lactonisation described by Giles *et al*[68].

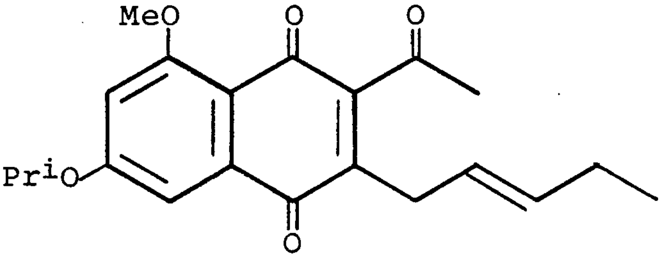
The naphthol (223)[65a] was envisaged as a suitable synthetic precursor for the naphthalene (222) since oxidation of (223), as for naphthol (55), would afford the corresponding quinone (224) which in turn should afford (222) on treatment with *trans*-3-hexenoic acid by the Jacobsen-Torssell reaction, followed by reductive - methylation of the pentenylquinone (225).



(223)

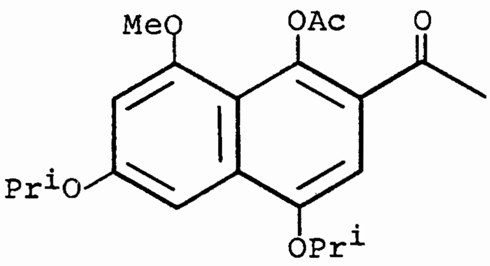


(224)

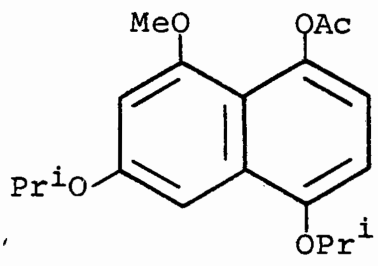


(225)

The synthesis of naphthol (223) was readily accomplished by treatment of naphthol (145) with premixed trifluoroacetic anhydride and glacial acetic acid to afford the acetates (226) (65%) and (227) (33%) based on unrecovered starting material. The latter compound could be hydrolysed to the naphthol (145) and recycled, thereby increasing the overall yield of (226).



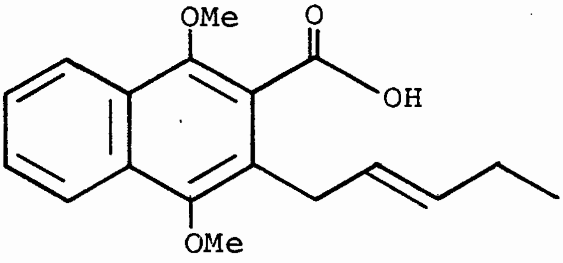
(226)



(227)

The acetate (226) afforded naphthol (223) on alkaline hydrolysis with a methanolic potassium hydroxide solution, in a yield of 84%.

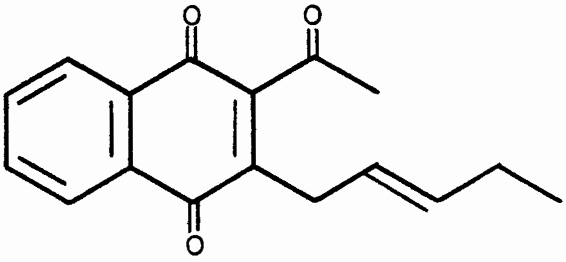
To avoid the possible loss of valuable material, it was at this stage decided to synthesise the acid (228) as the model on which the conditions necessary for the cyclisation reaction may be determined.



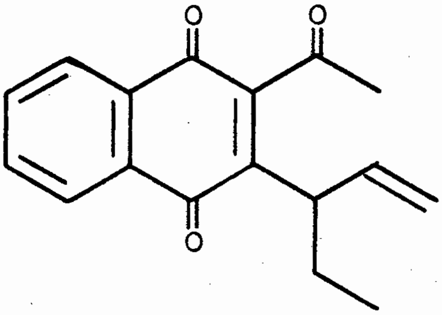
(228)

The quinone (28), available by oxidation of (185), afforded the olefin (229) [25% from (185)] on treatment with *trans*-3-hexenoic acid in the presence of ammonium persulphate and silver nitrate. The C-1 protons of the *trans*-2-pentenyl chain resonated as a sharp doublet of doublets (J 1 and 4 Hz) at δ3.23 which collapsed to a broad singlet on double irradiation at δ5.4, the centre of the multiplet of the olefinic protons.

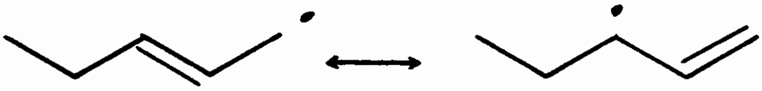
It is noteworthy that none of the isomeric (230) was observed which may arise by reaction of the quinone (28) with the radical (232) equivalent to radical (231), which gave rise to the product (229) under the Jacobsen-Torssell conditions.[42]



(229)

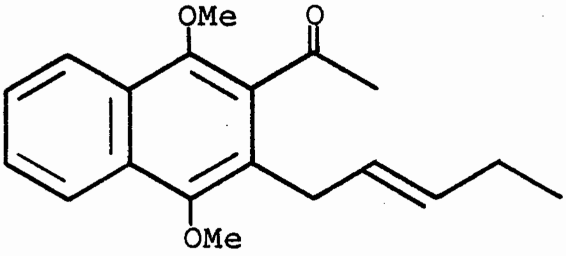


(230)



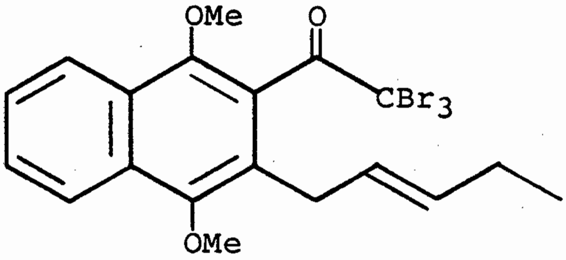
(231) (232)

Reductive methylation of quinone (229) employing the usual conditions, afforded the dimethyl ether (233) in a yield of 69%.



(233)

Treatment of this product in dioxane with a freshly prepared sodium hypobromite solution[84] for several hours, afforded the tribromacetyl derivative (234) as the sole product (86%).



(234)

In contrast to the above finding, the same hypobromite solution converted the acetylnaphthalene (185) to the acid (186) within forty minutes in almost quantitative yield (98%).

Treatment of (234) with an excess of a 12% aqueous potassium hydroxide solution for several hours also failed to afford the corresponding acid (228). In this case only starting material and tar were recovered. Sodium hypochlorite treatment had no effect on naphthalene (233) whatsoever and it was recovered quantitatively.

This resistance of (234) to alkaline hydrolysis is undoubtedly due to the higher steric congestion (in the vicinity of the carbonyl carbon of the tribromoacetyl group) caused by the pentenyl chain, thus preventing nucleophilic attack by the hydroxyl anion at the carbonyl carbon.

In conclusion it can be said that although the potential synthetic routes to oxygenated lactones of the type (194) investigated so far have not proved to be successful, valuable new information has been attained from these investigations which may be helpful in our further synthetic strategies currently being actively examined.

EXPERIMENTAL

GENERAL

^1H n.m.r. spectra were recorded using the following instruments: 60 MHz, Varian EM-360; 90 MHz, Bruker WH-90 100 MHz, Varian XL-100 and 200 MHz, Varian XL-200. Unless otherwise stated, all ^1H n.m.r. spectra were recorded at ambient temperature in deuterochloroform using tetramethylsilane as an internal standard. 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. High resolution mass spectra were recorded on a Varian MAT 311 A spectrometer at the University of Stellenbosch. Unless otherwise stated, infrared spectra were measured for Nujol mulls. Melting points are quoted uncorrected and were recorded on a Fischer-John apparatus. Elemental analyses were performed on a Heraeus CHN-RAPID analyser.

Column chromatography was carried out on dry columns with Merck Kieselgel 60 (70 - 230 mesh) as adsorbent. 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.

Light petroleum refers to the fraction of boiling point 60 - 80°C, and ether to diethyl ether. Sodium hydride (Merck) was supplied as a dispersion in paraffin oil. 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.

C.A.N. refers to cerium(IV) ammonium nitrate while T.F.A.A. refers to trifluoroacetic anhydride. The phrase 'residue obtained upon work-up' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

*trans-3,4-Dihydro-9-methoxy-1,3-dimethyl-*1H*-Naphtho*[2,3-*c*] *pyran-5,10-quinone* [(±)*-Isoeleutherin*] (2)

The *trans* pyran (110) (134 mg) was dissolved in acetonitrile (10 ml) and a solution of C.A.N. (535 mg) in water (2ml) was added during 5 min. Stirring was continued for a further 10 min, then the mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the *product* (99 mg, 83%), m.p. 152 - 153°C (methanol) (lit.[45], 154 - 155°C).

(±)*-cis-3,4-Dihydro-7,9-dimethoxy-1,3-dimethyl-*1H*-naphtho* [2,3-*c*]*pyran-5,10-quinone* (19)

Compound (122) (16 mg), silver(II) oxide (40 mg), and dioxane (3 ml) were stirred together at room temperature. Nitric acid (6M; 0.2 ml) was added and the reaction mixture stirred for 4 min. A mixture of chloroform (4 ml) and water (1 ml) was added and the organic layer was separated. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with water. The residue obtained upon work-up gave the *product* (19) (11 mg, 75%) as a yellow powder, m.p. 185 - 186°C (dichloromethane - light petroleum) (lit.[54], 179 - 180°C).

(±)-*trans*-3,4-*Dihydro*-7,9-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (22)

The tetramethyl ether (119) (60 mg) was oxidised as described for compound (122) above with silver(II) oxide (5 equiv.) to give the *product* (22) (45 mg, 82%), m.p. 239.5 - 240.5°C (ethanol) (lit.[54], 228 - 230°C).

(1R,3R,4R)-3,4-*Dihydro*-4-*hydroxy*-7,9-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (23) *and its Enantiomer* [(±)-*Quinone* A' *Dimethyl ether*]

Compound (121) (130 mg) was oxidised as above with silver(II) oxide in dioxane to give the *product* (23) (105 mg, 88%) as small yellow rosettes, m.p. 200°C (decomp.) (propan-2-ol) (lit.[51] for the single enantiomer from natural sources, 201°C) (Found: C, 63.7; H, 5.9 $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%); νmax 3 422, 1 647, 1 599 and 1 560 cm^{-1}; δ1.38 (3 H, d, J 6 Hz, 3-CH_3), 1.51 (3H, d, J 7 Hz, 1-CH_3), 2.3 (1 H, br s, OH, D_2O exchangeable), 3.93 and 3.94 (3H each, s, OCH_3), *ca.* 3.95 (1 H, dq, J 2.5 and 6 Hz, 3-H obscured by OCH_3), 4.44 (1H, br s, 4-H, collapses to d, J 2.5 Hz on D_2O exchange), 4.99 (1 H, q, J 7 Hz, 1-H), 6.69 (1 H, d, J 2.5 Hz, 8-H) and 7.24 (1 H, d, J 2.5 Hz, 6-H).

(1R,3R,4S)-3,4-*Dihydro-4-hydroxy-7,9-dimethoxy-1,3-dimethyl-1H-naphtho*[2,3-*c*]*pyran-5,10-quinone* (24) *and its Enantiomer* [(±)-*Quinone* A *Dimethyl ether*]

Compound (120) (150 mg) was oxidised as above in dioxane (10 ml) to afford the *product* (24) (123 mg, 90%) as small yellow rosettes, m.p. 175.5 - 176.5 (propan-2-ol) (lit.[51], for the single enantiomer from natural sources, 172.5 - 174°C) (Found: C, 64.0; H, 5.75 $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%) νmax 3 555, 1 647, 1 630, 1 597, and 1 562 cm^{-1}; δ1.38 (3 H, d, J 6 Hz, 3-CH_3), 1.57 (3 H, d, J 7 Hz, 1-CH_3) 3.80 (1 H, s, OH, D_2O exchangeable), *ca.* 3.81 (1 H, dq, J 6 and 8 Hz, 3-H, partly obscured by OCH_3) 3.96 and 3.97 (3 H each, s, OCH_3), 4.44 (1 H, br d, J 8 Hz, 4-H, collapses to dd, J 1.5 and 8 Hz on D_2O exchange), 4.90 (1 H, dq, J 1.5 and 7 Hz, 1-H), 6.69 (1 H, d, J 2.5 Hz, 8-H), and 7.21 (1 H, d, J 2.5 Hz, 6-H)

(1R,3R,4S)-3,4-*Dihydro-4-hydroxy-9-methoxy-1,3-dimethyl-1H-naphtho*[2,3-*c*]*pyran-5,10-quinone* (25) *and its Enantiomer*

Compound (117) (26 mg) in acetonitrile (8 ml) and water (2 ml) was treated with C.A.N. (98 mg, 2.2 equiv.) in water (1 ml) dropwise during 3 min with stirring at room temperature. After being stirred for a further 7 min., the mixture was poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) to afford the *product* (25) (16 mg, 67%) m.p. 159 - 160°C (dichloromethane-light petroleum) (Found: C, 66.7; H, 5.65. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.55%); νmax. 3 560, 1 662, 1 650, 1 634, and 1 594 cm^{-1}; δ1.42 (3H, d, J 6 Hz, 3-CH_3), 1.60 (3 H, d, J 7.5 Hz, 1-CH_3), 3.80 (1 H, d, J 2 Hz, OH, D_2O exchangeable), 3.91 (1 H, dq, J 6 and 8 Hz, 3-H), 4.00 (3 H, s, OCH_3), 4.47 (1 H, br d, J 8 Hz, 4-H, collapses to dd, J 1.5 and 8 Hz on D_2O exchange), 4.93 (1 H, dq, J 1.5 and 7.5 Hz, 1-H), 7.31 (1 H, dd, J 3 and 8 Hz, 8-H), and 7.55 - 7.85 (2 H, m, 6- and 7-H).

(1R,3R,4R)-3,4-*Dihydro*-4-*hydroxy*-9-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (26) *and its Enantiomer*

Compound (118) (19 mg), silver(II) oxide (30 mg, 4 equiv.), and dioxane (2 ml) were stirred together at room temperature. Nitric acid (6 M; 0,2 ml) was added and the reaction mixture stirred for 3 min. A mixture of chloroform (8 ml) and water (2 ml) was added and the organic layer was separated. The aqueous layer was extracted with more chloroform, added to the first extract, washed with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was subjected to p.l.c. (eluant 50% ethyl acetate-light petroleum) to afford the *product* (15 mg, 88%) as yellow rosettes, m.p. 173.5 - 175°C (dichloromethane-light petroleum) (Found: M^+ 288.102 00. $C_{16}H_{16}O_5$ requires M 288.09975); νmax. 3 460, 1 663, 1 653, and 1 587 cm^{-1}; δ1.41 (d, J 6.5 Hz, 3-CH_3), 1.52 (d, J 7.5 Hz, 1-CH_3), 2.46 (1 H, br d, J 7 Hz, OH, D_2O exchangeable), *ca.* 4.0 (1 H, dq, J 2.5 and 6.5 Hz, 3-H), 4.01 (3 H, s, OCH_3), 4.49 (1 H, br d, J 7 Hz, 4-H, collapses to d, J 2.5 Hz, on D_2O exchange), 5.03 (1 H, q, J 7.5 Hz, 1-H), 7.32 (1 H, dd, J 2.5 and 8 Hz, 8-H), and 7.55 - 7.95 (2 H, m, 6- and 7-H).

3,4-*Dihydro*-3-*propyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (27)

To a stirred solution of compound (114) (104 mg) in acetonitrile (15 ml) and water (5 ml) was added a solution of C.A.N. (442 mg) in water (1 ml) during 10 min. The mixture was poured into water and extracted with dichloromethane. The residue obtained upon work-up gave the *product* (27) (83 mg, 90%), m.p. 123 - 124°C (methanol-chloroform). (Found: C, 74.6; H, 6.1. $C_{16}H_{16}O_3$ requires C, 74.95; H, 6.2%); δ0.98 (3 H, distorted t, J 7 Hz, CH_3), 1.2 - 1.95 (4 H, m, CH_2CH_2), 2.28 (1 H, dddd, J 3, 3.5, 10, and 19 Hz, *pseudo*-axial 4-H), 2.76 (1 H, dt, J 3.5 and 19 Hz, *pseudo*-equatorial 4-H), 3.3 - 3.7 (1 H, m, 3-H), 4.46 (1 H, dt, J 3.5 and 19 Hz, *pseudo*-axial 1-H), 4.88 (1 H, dd, J 3 and 19 Hz, *pseudo*-equatorial 1-H), 7.6 - 7.85 (2 H, m, 7- and 8-H), and 7.95 - 8.2 (2 H, m, 6- and 9-H)

3-*Acetyl-5-methoxy-1,4-naphthoquinone* (29)

(a) From compound (72):

A solution of C.A.N. (362 mg) in water (2 ml) was added dropwise with stirring over a period of 5 min to a solution of compound (72) (85 mg) in acetonitrile (10 ml). The solution was stirred for a further 15 min and then poured into water. This was extracted with dichloromethane and the residue obtained upon work-up gave the *product* (63 mg, 91%) as yellow needles, m.p. 102 - 103°C (dichloromethane-light petroleum) (lit.[12], 103.5 - 104.5°C).

(b) From compound (40):

A solution of C.A.N. (482 mg) in water (3 ml) was added dropwise with stirring over a period of 5 min to a solution of compound (40) (100 mg) in acetonitrile (7 ml). The solution was stirred for a further 15 min, worked-up and chromatographed as for (a) above to give the *product* (82 mg, 89%), identical with that obtained in (a) above.

3-*Acetyl*-5,7-*dimethoxy*-1,4-*naphthoquinone* (30)

(a) From compound (55):

A solution of C.A.N. (2.71 g) in water (20 ml) was added dropwise with stirring over a period of 10 min to a solution of compound (55) (620 mg) in acetonitrile (70 ml). The solution was stirred for a further 10 min and then poured into water. This was extracted with dichloromethane and the residue obtained upon work-up gave the *product* (550 mg, 94%) as orange crystals, m.p. 146 - 149°C (decomp.) (dichloromethane-light petroleum). (Found: C, 64.3; H, 4.8. $C_{14}H_{12}O_5$ requires C, 64.6; H, 4.6%); νmax 1 645 and 1 595 cm^{-1}; δ2.61 (3 H, s, CCH_3), 3.95 and 3.97 (3 H each, s, OCH_3), 6.74 (1 H, d, J 2 Hz, 6-H); 6.83 (1 H, s, 2-H), and 7.24 (1 H, d, J 2 Hz, 8-H).

(b) From compound (75)

Compound (75) (116 mg) in acetonitrile (7 ml) was oxidised as above with C.A.N. (493 mg) in water (3 ml) to give the *product* (94 mg, 90%) identical with the material described in (a) above.

1,3-*Dimethoxycyclohexa*-1,3-*diene* (47)

Prepared by an application of a literature method[30b] with minor modifications as follows:

(a) Recorcinol dimethyl ether (45) (53 g) and absolute ethanol (65 ml) were added to anhydrous liquid ammonia (2 l) and the solution was vigorously stirred. Sodium (36 g) was added in small pieces over a period of 90 minutes, each piece being added after the blue colour disappeared. Stirring was continued for 1 hour after final addition of sodium during which time the solution attained a reddish colouration. Water (750 ml) was slowly added and much ammonia was blown off by a stream of air. The crude diene was extracted with light petroleum (3 x 400 ml) and dried ($MgSO_4$). Evaporation of the solvent gave the crude *product* [30a] (47) [(45 g), which contained *ca.* 25% of diene (46), estimated by ^1H n.m.r. integration].

(b) The diene (46) (45 g) in dry ether (50 ml) was added to a stirred solution of potassium amide from potassium (2,46 g) in anhydrous ammonia (1 l). Ferric nitrate hydrate (70 mg) was added whereupon the brownish solution turned red. Stirring was continued for 30 minutes. Dry methanol (15 ml) was added, followed by water (500 ml). Some ammonia was blown off and work-up as in (a) gave the crude *product* (47) [(43 g), which contained *ca.* 27% of diene (46), estimated by ^{1}H n.m.r. integration].

1,4,4a,8a-*Tetrahydro*-1,3-*dimethoxy*-1,4-*ethanonaphthalene*-5,8-*dione* (48)

Prepared by the literature method[30a] with minor modifications as follows: The crude diene (47) (23 g) was taken up in dry benzene (500 ml) and the solution was brought to reflux. 1,4-Benzoquinone (9 g) was added portionwise, each portion being added after no more benzoquinone could be detected by t.l.c. The solution was boiled for 1 hour after the final addition of benzoquinone. The volume was reduced to *circa* 200 ml under reduced pressure and light petroleum (140 ml) was added. The yellow solution was left overnight in the cold to complete crystallisation. Filtration gave the *product* (15,32 g) m.p. 120° - 121°C (petroleum) (lit.[30a], 123° - 125°C).

1,4-*Dihydro*-1,4-*ethano*-1,3,5-*trimethoxy*-8-*naphthol* (49b)

The adduct (48)[30a] (9,61 g) was dissolved in dry acetone (100 ml). Dimethyl sulphate (11 ml) and potassium carbonate (32 g) were added and the solution was vigorously stirred and boiled under nitrogen for three hours whereupon the solution was cooled and the potassium carbonate removed by filtration. The solvent was removed under reduced pressure and the oily residue was taken up in ether. The excess of dimethyl sulphate was decomposed by careful addition of aqueous ammonia solution. The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil which solidified. Recrystallisation of the crude solid from light petroleum gave the *product* (4,63 g, 46%) m.p. 144 - 145°C (light petroleum). (Found: C, 68.9; H, 6.8 $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%) ν_{max}. 3 380 (sharp) and 1 615 cm^{-1}; δ1.78 (4 H, m, 2 x CH_2), 3.46, 3.64 and 3.72 (each 3 H, s, OCH_3) 4.04 (1 H, d, J 2.5 Hz, 4-H), 5.2 (1 H, d, J 2.5 Hz, 2-H) 6.5 (2 H, s 6- and 7-H), and 8.54 (1 H, s, OH, D_2O exchangeable). The mother liquor was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford *compound* (52b) (473 mg, 5%) m.p. 124 - 125°C (light petroleum) (Found: C, 67.55; H, 6.35. $C_{14}H_{16}O_4$ requires C, 67.8; H, 6.4%) ν_{max} 3 380 (sharp) and 1 725 cm^{-1}; δ1.77 (4 H, m, CH_2-CH_2), 2.33 (2 H, m, CH_2), 3.27 and 3.43 (each 3 H, s, OCH_3), 3.7 (1 H, m, C-H), 6.17 (2 H, s, Ar-H), and 8.0 (1 H, s, OH, D_2O exchangeable).

5,7-*Dimethoxy*-1,4-*naphthoquinone* (51)

The method by Birch *et al*[29] gave the *product* (5.23 g, 42%) m.p. 168 - 169°C (methanol) (Lit.[29] 152 - 154°C) from the adduct (48) (14,32 g).

1,5,7-*Trimethoxy*-4-*naphthol* (53)

(a) Quinone (51) (1,00 g) was dissolved in dichloromethane (60 ml) and shaken with an aqueous solution (200 ml) containing sodium dithionite (10 g) in a separating funnel. The residue obtained upon work-up of the colourless organic phase was immediately dissolved in dry acetone (75 ml), and anhydrous potassium carbonate (3,90 g) and dimethyl sulphate (1,5 ml) were added, and the mixture boiled under nitrogen for 2h. The cooled reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue was chromatographed (eluant 15% ethyl acetate in light petroleum) to give the *product* (870 mg, 81%), m.p. 131 - 132°C (light petroleum) (Found: C, 66.8; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%); νmax. 3 390 and 1 620 cm^{-1}; δ3.92 (6 H, s, 2 x OCH_3), 4.01 (3 H, s, OCH_3), 6.51 (1 H, d, J 2 Hz, 6-H), 6.62 and 6.76

(1 H each, d, J 8 Hz, 2- and 3-H), 7.15 (1 H, d, J 2 Hz, 8-H), and 8.72 (1 H, s, OH, D_2O exchangeable).

(b) The naphthol (49b) (325 mg) was heated under nitrogen (bath 160°C) for 10 minutes. Chromatography (eluant 15% ethyl acetate in light petroleum) afforded the *product* (188 mg, 65%) identical with the material described in route (a) above.

4-*Acetoxy*-1,5,7-*trimethoxynaphthalene* (54)

The naphthol (53) (860 mg), acetic anhydride (6 ml), and pyridine (30 ml) were boiled together for 2h and then thrown onto ice. The white crystalline solid was filtered off, washed with water, and dried to afford the *product* (860 mg, 85%), m.p. 145 - 146°C (ethanol) (Found: C, 65.1; H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.1; H, 5.8%); νmax. 1 750, 1 630, and 1 610 cm^{-1}; δ2.33 (3 H, s, CCH_3), 3.88, 3.91, and 3.97 (3 H each, s, OCH_3), 6.54 (1 H, d, J 2 Hz, 6-H), 6.73 and 6.85 (1 H each, d, J 8 Hz, 2- and 3-H), and 7.19 (1 H, d, J 2 Hz, 8-H).

3-*Acetyl*-1,5,7-*trimethoxy*-4-*naphthol* (55)

The acetate (54) (332 mg) and boron trifluoride diethyl ether (4 ml) were stirred together for 30 min at 60°C (bath temp.) The reaction mixture was thrown onto ice and extracted with dichloromethane. The residue obtained upon work-up of the organic phase was chromatographed (30% ethyl acetate in light petroleum) to give first the naphthol (53) (50 mg, 19%), followed by the *product* (222 mg, 67% or 83% based on unrecovered starting material) as yellow-green crystals, m.p. 174 - 175°C (ethanol) (Found: C, 64.9; H, 5.9. $C_{15}H_{16}O_5$ requires C, 65.1; H, 5.8%); νmax. 1 600 br cm^{-1}; δ2.63 (3 H, s, CCH_3) 3.92 (6 H, s, OCH_3), 3.99 (3 H, s, OCH_3), 6.52 (1 H, d, J 2 Hz, 6-H), 6.86 (1 H, s, 2-H), 7.10 (1 H, d, J 2 Hz, 8-H), and 14.00 (1 H, s, OH, D_2O exchangeable).

1-*Acetoxy*-5-*methoxy*-4-*naphthol* (63)

Juglone methyl ether (36) (520 mg) in chloroform (15 ml) was treated with acetic anhydride (0.7 ml), pyridine (0.7 ml), and zinc dust (2 g), and the mixture was gently boiled under nitrogen with vigorous stirring for 15 min. It was cooled, filtered, and the filtrate was poured into water and stirred for 10 min. The organic phase was briefly shaken with water (30 ml) containing concentrated hydrochloric acid (1 ml), followed by water (2 x 30 ml). The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate in light petroleum) to yield the *product* (468 mg, 72%) as colourless needles, m.p. 82 - 83°C (ethyl acetate-light petroleum) (Found: C, 67.2; H, 5.0. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); νmax. 3 370 and 1 740 cm^{-1}; δ2.41 (3 H, s, CCH_3), 4.03 (3 H, s, OCH_3), 6.78 (1 H, dd, *J* 6 and 3 Hz, 6-H), 6.81 (1 H, d, *J* 9 Hz, 3-H), 7.12 (1 H, d, *J* 9 Hz, 2-H), 7.3 - 7.5 (2 H, m, 7- and 8-H), and 9.25 (1 H, s, OH, D_2O exchangeable).

1-*Acetoxy*-4,5-*dimethoxynaphthalene* (65)

Compound (63) (160 mg) in dry acetone (30 ml) was treated with an excess of potassium carbonate (1,6 g) and dimethyl sulphate (1.4 ml) and the mixture boiled with vigorous stirring for 3h. It was then cooled, filtered, the solvent evaporated, and the residue chromatographed (eluant 15% ethyl acetate in light petroleum) which also removed the excess of dimethyl sulphate. The *product* (135 mg, 79%) was obtained as colourless crystals, m.p. 62°C (dichloromethane-light petroleum) (Found: C, 68.0; H, 5.7. $C_{14}H_{14}O_4$ requires C, 68.3; H, 5.7%) $\nu_{max.}$ 1 750 cm^{-1}; δ2.42 (3 H, s, CCH_3), 3.06 (6 H, s, OCH_3), 6.81 (1 H, d, J 9 Hz, 3-H), 6.8 - 7.0 (1 H, m, 6-H), 7.16 (1 H, d, J 9 Hz, 2-H), and 7.3 - 7.5 (2 H, m, 7- and 8-H).

1-*Acetoxy*-3-*acetyl*-5-*methoxy*-4-*naphthol* (72)

(a) From compound (63):

Compound (63) (100 mg) was stirred in boron trifluoride-diethyl ether (1 ml) at 65°C (bath temp.) for 30 min under nitrogen after which the mixture was poured into cold water, stirred for 10 min and extracted with dichloromethane. The residue obtained upon work-up was dissolved in chloroform (20 ml) and acetic anhydride (0,2 ml), pyridine (0,2 ml), and zinc dust (0,4 g) [to ensure that any quinone present by oxidation of (66) was reduced to the hydroquinone level] were added. The mixture was gently boiled with vigorous stirring under nitrogen for 15 min. The reaction mixture was cooled, filtered, and the filtrate poured into water (20 ml) and stirred for 10 min. The organic phase was briefly shaken with water (30 ml) containing concentrated hydrochloric acid (1 ml), separated, and washed with water (2 x 30 ml). The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate in light petroleum) to yield starting material (63) (35 mg, 35%) followed by the *product* (43 mg, 36 or 66% based on unrecovered starting material) as yellow needles, m.p. 130 - 131°C (methylene chloride-light petroleum) (Found: C, 65,5; H, 5.1. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5,1%); νmax. 1 750 and 1 620 cm^{-1}; δ2.44 (3 H, s, $OCOCH_3$), 2.67 (3 H, s, $CCOCH_3$) 4.05 (3 H, s, OCH_3), 6.94 (1 H, d, J 8 Hz, 6-H), 7.32 (1 H, d, J 8 Hz, 8-H) 7.45 (1 H, s, 2-H), 7.54 (1 H, t, J 8 Hz, 7-H), and 14.08 (1 H, s, OH, D_2O exchangeable).

(b) From compound (29):

A mixture of compound (29) (75 mg) in chloroform (20 ml) containing acetic anhydride (0,2 ml), pyridine (0,2 ml), and zinc dust (0,4 g) was gently boiled for 15 min with vigorous stirring under nitrogen. The reaction mixture was worked up and chromatographed as for compound (63) to give the *product* (57 mg, 63%), identical with that obtained in (a) above.

1-*Acetoxy*-5,7-*dimethoxy*-4-*naphthol* (73)

Quinone (51) (1,00 g) in chloroform (30 ml) was treated with acetic anhydride (1 ml), pyridine (1 ml) and zinc dust (3 g), and the mixture was gently boiled under nitrogen with vigorous stirring for 15 min. It was cooled, filtered, and the filtrate was poured into water and stirred for 10 min. The organic phase was briefly shaken with water (30 ml) containing concentrated hydrochloric acid (1 ml), followed by water (2 x 30 ml). The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate in light petroleum) to yield the *product* (960 mg, 80%) as colourless needles, m.p. 134 - 135°C (ethyl acetate-light petroleum) (Found: C, 63.9; H, 5.2. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); ν_{max} 3 375 and 1 750 cm^{-1}; δ2.40 (3 H, s, CCH_3), 3.87 and 3.98 (3 H each, s, OCH_3), 6.46 (1 H, d, J 2 Hz, 6-H), 6.63 (1 H, d, J 2 Hz, 8-H), 6.68 (1 H, d, J 9 Hz, 3-H), 7.08 (1 H, d, J 9 Hz, 2-H), and 9.07 (1 H, s, OH, D_2O exchangeable).

1-*Acetoxy*-3-*acetyl*-5,7-*dimethoxy*-4-*naphthol* (75)

(a) From compound (73):

Compound (73) (100 mg) was treated as for compound (63) [route (a)], and chromatography (eluant 25% ethyl acetate in light petroleum) gave starting material (31 mg, 31%) followed by the *product* (59 mg, 51 or 86% based on unrecovered starting material) as light yellow needles m.p. 183 - 184°C (dichloromethane-light petroleum) (Found: C, 63.2; H, 5.3. $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.2%); $\nu_{max.}$ 1 748 and 1 600 cm^{-1}; δ2.43 (3 H, s, $OCOCH_3$), 2.61 (3 H, s, $CCOCH_3$), 3.90 and 3.99 (3 H, each s, OCH_3), 6.53 and 6.62 (1 H, each d, J 2.5 Hz, 6- and 8-H), 7.40 (1 H, s, 2-H), and 14.46 (1 H, s, OH, D_2O exchangeable).

(b) From compound (30):

Compound (30) (50 mg) was reductively monoacetylated as for compound (29) (route b) to yield the *product* (46 mg, 78%), identical with the material described above.

1-*Acetoxy*-4,5,7-*trimethoxynaphthalene* (76)

Compound (73) (170 mg) was methylated as for compound (63), and the reaction mixture was chromatographed (eluant 15% ethyl acetate in light petroleum) to yield the *product* (138 mg, 77%) as white cubes, m.p. 110 - 112°C (methylene chloride-light petroleum) (Found: C, 65.05; H, 5.85. $C_{15}H_{16}O_5$ requires C, 65.2; H, 5.8%); νmax 1 751, 1 640, 1 611, and 1 588 cm^{-1}; δ2.42 (3 H, s, CCH_3), 3.90 (3 H, s, OCH_3), 3.94 (6 H, s, 2 x OCH_3) 6.65 and 6.67 (1 H each, d, J 2.5 Hz, 6- and 8-H), 6.68 (1 H, d, J 9 Hz, 3-H), and 7.12 (1 H, d, J 9 Hz, 2-H).

2-*Acetyl*-1,4-*dimethoxy*-3-*prop*-1-*enylnaphthalene* (85)

Compound (98) (2.25 g) was dissolved in dry tetrahydrofuran (T.H.F.) under nitrogen. Solid potassium *t*-butoxide (3.73 g) was added and the solution was stirred and heated at 60°C for 1.5h during which time the nearly colourless solution turned dark red. The solution was treated with aqueous ammonium chloride (30%) and was extracted with methylene chloride. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to give the oily *product* (1.98 g, 88%), identical with authentic material.[40]

3-(1-*Hydroxyethyl*)-1,4,5-*trimethoxy*-2-*prop*-1-*enylnaphthalene* (87)

Compound (90) (630 mg) in dry ether (20 ml) was added to a stirred suspension of lithium aluminium hydride (320 mg) in dry ether (60 ml). When t.l.c. showed that all starting material had been converted into product (*ca.* 20 min), the reaction was worked up by addition of saturated ammonium chloride, followed by anhydrous magnesium sulphate. Work-up of the filtrate gave a residue which was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (87) (550 mg, 87%), as an oil (Found: C, 71.2; H, 7.4. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%); νmax (neat) 3 450, 1 608, 1 568, and 1 487 cm^{-1}; δ1.61 [3 H, d, J 7 Hz, CH(OH) CH_3], 1.96 (3 H, dd, J 2 and 7 Hz, CH = $CHCH_3$), 3.76, 3.90 and 4.00 (each 3 H, s, OCH_3), 4.2 (1 H, br s, OH), 5.22 [1 H, m, *CH*(OH)CH_3], 6.05 (1 H, dq, J 7 and 16 Hz, CH = *CH*CH_3), 6.56 (1 H, dq, J 2 and 16 Hz, *CH* = $CHCH_3$), 6.85 (1 H, d, J 8 Hz, 6-H), 7.38 (1 H, t, J 8 Hz, 7-H), and 7.72 (1 H, d, J 8 Hz, 8-H).

3-(1-*Hydroxyethyl*)-1,4,5,7-*tetramethoxy*-2-*prop*-1-*enylnaphthalene* (88)

Compound (107) (320 mg) was reduced as described for compound (90) above, with lithium aluminium hydride (250 mg) in dry ether (20 ml). Work-up and chromatography (eluant: 30% ethyl acetate-light petroleum) afforded the *product* (88) (280 mg, 88%), m.p. 98 - 99°C (light petroleum) (Found: C, 68.55; H, 7.25. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.25%); νmax (liquid film before crystallisation) 3 440, 1 614, 1 580, and 1 490 cm^{-1}; δ1.63 [3 H, d, *J* 7 Hz, CH(OH)C*H*$_3$], 1.99 (3 H, dd, *J* 2 and 7 Hz, CH = CHC*H*$_3$), 3.74, 3.87, 3.93, and 3.97 (3 H each, s, OCH_3), 3.90 (1 H, br s, OH, D_2O exchangeable), 5.35 [1 H, m, C*H*(OH)CH$_3$], 6.06 (1 H, dq, *J* 7 and 16 Hz, CH = C*H*CH$_3$), 6.55 (1 H, d, *J* 2.5 Hz, 6-H) 6.60 (1 H, dq, *J* 2 and 16 Hz, C*H* = CHCH$_3$), and 7.05 (1 H, d, *J* 2.5 Hz, 8-H).

3-*Acetyl*-1,4,5-*trimethoxy*-2-*prop*-1-*enylnaphthalene* (90)

(a) Compound (92) (252 mg) was treated with potassium *t*-butoxide (375 mg, 4 equiv.) in dry tetrahydrofuran (25 ml) at 60°C under nitrogen for 2h. The reaction mixture was cooled and added to aqueous ammonium chloride, then extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to afford the *product* (90) (203 mg, 81%), m.p. 78 - 79°C (light petroleum) (Found: C, 71.7; H, 6.65. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%); νmax 1 699, 1 612, 1 570, and 1 490 cm^{-1}; δ1.92 (3 H, d, J 6 Hz, CHC*H*$_3$), 2.50 (3 H, s, COC*H*$_3$), 3.91 (6 H, s, OCH$_3$), 3.99 (3 H, s, OCH$_3$), 6.20 (1 H, dq, J 6 and 16 Hz, C*H*CH$_3$), 6.54 (1 H, d, J 16 Hz, C*H* = CHCH$_3$), 6.86 (1 H, d, J 8 Hz, 6-H), 7.41 (1 H, t, J 8 Hz, 7-H), and 7.74 (1 H, d, J 8 Hz, 8-H).

(b) The naphthalene (89a) (156 mg), benzoyl peroxide (30 mg) and freshly recrystallised *N*-bromosuccinimide (109 mg) in dry carbon tetrachloride (20 ml) were heated under gentle reflux for 3.5h. The solution was cooled, filtered, and the solvent removed under reduced pressure to afford the oily crude *bromonaphthalene* (89b). Without further purification the crude bromide (89b) was taken up in dry dimethylformamide (60 ml) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene (0,5 ml) and stirred at 45°C (bath temp.) for 90 min. The solution was thrown into water (300 ml) containing concentrated hydrochloric acid (1 ml), and extracted with ether (5 x 100 ml). The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to afford the *product* (72 mg, 46%), identical to the material described in route (a) above.

3-*Acetyl*-5-*methoxy*-2-*prop*-2-*enyl*-1,4-*naphthoquinone* (91)

The quinone (29) (273 mg) was dissolved in acetonitrile (15 ml) and water (6 ml) was added, followed by vinylacetic acid (141 mg), and silver nitrate (126 mg) in water (1 ml). The flask was flushed with nitrogen and then potassium persulphate (600 mg) in water (10 ml) was added during 20 min to the stirred reaction mixture immersed in an oil-bath at 80 - 85°C, and the reaction mixture was stirred with heating for a further 30 min. The cooled solution was poured into water and extracted with dichloromethane (3 x 50 ml). The organic layer was then washed with a small amount of aqueous sodium hydrogen carbonate and the residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) to give the product (91) (176 mg, 52%) as light orange needles, m.p. 135 - 136°C (light petroleum) (Found: C, 71.15; H, 5.2. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%) νmax 1 708, 1 656, 1 637, and 1 578 cm^{-1}; δ2.48 (3 H, s, CCH_3), 3.23 (2 H, dd, J 1 and 6 Hz, CH_2), 4.01 (3 H, s, OCH_3), 5.0 - 5.25 (2 H, m, vinyl CH_2), 5.6 - 6.1 (1 H, m, vinyl CH), 7.32 (1 H, dd, J 2.5 and 8 Hz, 6-H), 7.6 - 7.8 (2 H, m, 7- and 8-H).

3-*Acetyl*-1,4,5-*trimethoxy*-2-*prop*-2-*enylnaphthalene* (92)

The quinone (91) (320 mg) in dichloromethane (50 ml) was shaken with an excess of aqueous sodium dithionite until the organic phase became pale yellow. The organic layer was dried and evaporated, and the residue immediately dissolved in dry acetone (30 ml). Anhydrous potassium carbonate (3.0 g) was added, followed by dimethyl sulphate (2 ml), and the mixture was vigorously stirred and boiled for 3h under nitrogen. The mixture was cooled, filtered, the solvent evaporated, and the residue was taken up in ether and washed successively with concentrated ammonia, water, dilute hydrochloric acid, and finally water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the *product* (92) (252 mg, 71%) as an oil. (Found: C, 72.0; H, 6.6. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%); νmax (neat) 1 684, 1 609, and 1 565 cm^{-1}; δ2.60 (3 H, s, CCH_3), 3.56 (2 H, dd, *J* 1 and 6 Hz, CH_2), 3.78, 3.87, 4.00 (3 H each, s, OCH_3), 4.85 - 5.15 (2 H, m, vinyl CH_2), 5.75 - 6.20 (1 H, m, vinyl CH), 6.89 (1 H, d, *J* 8 Hz, 6-H), 7.44 (1 H, t, *J* 8 Hz, 7-H), and 7.70 (1 H, d, *J* 8 Hz, 8-H).

3-(1-*Hydroxyethyl*)-1,4,5-*trimethoxy*-2-*prop*-2-*enylnaphthalene* (93)

Compound (92) (245 mg) was reduced with lithium aluminium hydride (10 equiv.) in dry ether (20 ml) as described in the preparation of compound (87) above. Work-up and chromatography (eluant 30% ethyl acetate-light petroleum) gave the *product* (93) (221 mg, 90%) as an oil whose spectral characteristics corresponded to those reported for this compound prepared by another route.[45]

2-*Acetyl*-3-*prop*-2-*enyl*-1,4-*naphthoquinone* (97)

A solution of freshly recrystallised 2-acetyl-1,4-naphthoquinone (28) (1,00 g) in acetonitrile (35 ml) containing vinylacetic acid (650 mg) was treated with a solution of silver nitrate (600 mg) in water (1 ml). The mixture was stirred at 70°C (bath temp.) while a solution of potassium persulphate (2.70 g) in water (30 ml) was added dropwise during 45 min. The mixture was stirred for a further 2h at the same temperature. The cooled solution was poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum). Early fractions afforded *compound* (101) (28 mg, 2%) which was further purified by p.l.c., m.p. 125°C (light petroleum) (Found: M^+, 240. $C_{15}H_{12}O_3$ requires M, 240); δ2.64 (3 H, s, CCH_3), 4.80 (2 H, dd, J 1 and 4 Hz, CH_2), 5.91 (1 H, dt, J 4 and 10 Hz, 3-H), 6.78 (1 H, dd, J1 and 10 Hz, 4-H) 7.5 - 7.8 (2 H, m, 8- and 9-H), 8.1 - 8.2 and 8.4 - 8.5 (each 1-H, m, together 7- and 10-H), and 13.86 (1 H, s, OH, D_2O exchangeable). Later fractions afforded the *product* (520 mg, 43%) as an oil. A portion was rechromatographed for analysis (p.l.c.) (Found: C, 74.7; H, 5.4. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%); νmax (neat), 1 707, 1 660, and 1 595 cm^{-1}; δ2.48 (3 H, s, CCH_3), 3.26 (2 H, dd, J 1 and 7 Hz, CH_2), 5.0 -

5.3 (2 H, m, vinyl CH_2), 5.6 - 6.1 (1 H, m, vinyl CH), 7.6 - 7.85 (2 H, m, 6- and 7-H), and 7.9 - 8.15 (2 H, m, 5- and 8-H).

2-*Acetyl*-1,4-*dimethoxy*-3-*prop*-2-*enylnaphthalene* (98) *and* 5-*Acetyl*-6-*methoxy*-2H-*naphtho*[1,2-*b*]*pyran* (102)

A solution of the quinone (97) above (200 mg) in diethyl ether (50 ml) was shaken with an aqueous solution of an excess of sodium dithionite (2 x 50 ml). The organic layer was dried and evaporated to give a red oil which was immediately dissolved in dry acetone (30 ml) and anhydrous potassium carbonate (575 mg) and dimethyl sulphate [525 mg (0,4 ml)] were added. The mixture was stirred under nitrogen and boiled under reflux for 18h. Work-up as for compound (49b) gave an oil which was chromatographed (eluant 10% ethyl acetate-light petroleum) to give, firstly, *product* (98) (145 mg, 64%) as an oil (Found: C, 75.6; H,6.9. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.65%); ν_{max} (neat) 1 709, 1 692, 1 640, and 1 590 cm^{-1}; δ2.60 (3 H, s, CCH_3), 3.61 (2 H, dd, J 1 and 6 Hz, CH_2), 3.86 and 3.88 (each 3 H, s, OCH_3), 4.8 - 5.15 (2 H, m, vinyl CH_2), 5.7 - 6.2 (1 H, m, vinyl CH), 7.4 - 7.65 (2 H, m, 6- and 7-H), and 7.95 - 8.2 (2 H, m, 5- and 8-H). Later fractions afforded the *naphthopyran* (102) as an oil (8 mg, 4%) (Found: C, 75.2; H, 5.6. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%); ν_{max} (neat) 1 673 br, 1 628, 1 601, and 1 585 cm^{-1}; δ2.64 (3 H, s, CCH_3), 3.84 (3 H, s, OCH_3), 4.87 (2 H, dd, J 1 and 4 Hz, CH_2), 5.78 (1 H, dt, J 4 and 10 Hz, 3-H), 6.45 (1 H, dd, J 1 and 10 Hz, 4-H), 7.3 - 7.7 (2 H, m, 8- and 9-H), and 7.9 - 8.2 (2 H, m, 7- and 10-H).

2-(1-*Hydroxyethyl*)-1,4-*dimethoxy*-3-*prop*-2-*enylnaphthalene* (99)

To a stirred suspension of lithium aluminium hydride (620 mg) in dry diethyl ether (100 ml) was added compound (98) in dry ether at a rapid drip rate. The mixture was stirred for 10 min after the addition was complete, by which time t.l.c. indicated the consumption of all starting material. The reaction was quenched by the addition of saturated ammonium chloride, followed by anhydrous magnesium sulphate. The solid material was filtered off and the filtrate was evaporated to give a residue which was chromatographed (eluant 15% ethyl acetate-light petroleum) to give the *product* (99) as an oil (1.05 g, 95%) (Found: C, 75.2; H, 7.35. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.35%); νmax 3 420, 1 638, and 1 594 cm^{-1}; δ1.63 (3 H, d, J 6.5 Hz, CCH_3), 3.68 (2 H, m, CH_2), 3.86 and 3.98 (each 3 H, s, OCH_3), 3.9 (1 H, br s, OH, D_2O-exchangeable), 4.8 - 5.15 (2 H, m, vinyl CH_2), 5.25 (1 H, m, $CHCH_3$), 5.85 - 6.3 (1 H, m, vinyl CH), 7.35 - 7.45 (2 H, m, 6- and 7-H), and 7.9 - 8.15 (2 H, m, 5- and 8-H).

3-*Acetyl*-5,7-*dimethoxy*-2-*prop*-2-*enyl*-1,4-*naphthoquinone* (104)

The quinone (30) (302 mg) was dissolved in acetonitrile (35 ml) and water (5 ml) was added, followed by vinylacetic acid (149 mg), and silver nitrate (115 mg) in distilled water (3 ml). The flask was flushed with nitrogen and then potassium persulphate (629 mg) in distilled water (4 ml) was added under nitrogen during 45 min to the reaction mixture, immersed in an oil-bath maintained at 80°C, and the reaction mixture was stirred with heating for a further 30 min. Work-up as described for the preparation of compound (91) above, followed by chromatography (eluant 30% ethyl acetate-light petroleum) afforded the *product* (104) (178 mg, 51%), m.p. 156 - 157°C (dichloromethane-light petroleum) (Found: C, 67.7; H, 5.3. $C_{17}H_{16}O_5$ requires C, 68.0; H, 5.3%); νmax 1 709, 1 660, 1 598, and 1 562 cm^{-1}, δ2.46 (3 H, s, CCH_3), 3.21 (2 H, dd, J 1 and 6 Hz, CH_2), 3.95 (6 H, s, 2 x OCH_3), 4.9 - 5.3 (2 H, m, vinyl CH_2), 5.6 - 6.1 (1 H, m, vinyl CH), 6.73 (1 H, d, J 3 Hz, 6-H), and 7.25 (1 H, d, J 3 Hz, 8-H).

3-*Acetyl*-1,4,5,7-*tetramethoxy*-2-*prop*-2-*enylnaphthalene* (105)

(a) The quinone (104) (373 mg) in dichloromethane (50 ml) was treated as described above for the preparation of compound (92) with an excess of aqueous sodium dithionite followed by treatment with anhydrous potassium carbonate (2.0 g) and dimethyl sulphate (2 ml) in dry acetone (30 ml). Work-up and chromatography (eluant 30% ethyl acetate-light petroleum) gave the *product* (105) as an oil (369 mg, 90%) (Found: C, 68.9; H, 6.75. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.65%); νmax (neat) 1 690, 1 620, and 1 583 cm^{-1}; δ2.58 (3 H, s, CCH_3), 3.55 (2 H, dd, J 1 and 6 Hz, CH_2), 3.76, 3.86, 3.93, and 3.98 (3 H each, s, OCH_3), 4.9 - 5.15 (2 H, m, vinyl CH_2), 5.75 - 6.2 (1 H, m, vinyl CH), 6.55 (1 H, d, J 2 Hz, 6-H), and 7.00 (1 H, d, J 2 Hz, 8-H).

(b) The naphthol (55) (1,0 g) in acetonitrile (100 ml) and water (25 ml) was treated with C.A.N. (5,10 g, 2.6 equiv.) in water (20 ml) during 8 min, and stirring was continued for a further 15 min. The mixture was thrown into water, extracted with dichloromethane, and the solution dried. The solution volume was reduced to about 60 ml, and this was then cooled to -78°C and the flask flushed with nitrogen. Boron trifluoride-ether (0.38 ml, 0.8 equiv. relative to the starting naphthol) was added, whereupon the solution turned dark brown. Allyltrimethylstannane (1.2 g, 1.5 equiv.) was added, and the reaction mixture stirred for 1h at -78°C, and warmed to room temperature. Water (200 ml) was then rapidly added and the whole extracted with dichloromethane (4 x 50 ml). The dried extract was filtered, and the resulting oil, on evaporation of the solvent, was dissolved in dry acetone (100 ml) and treated with potassium carbonate (5 g, 10 equiv.) and dimethyl sulphate (3.5 ml, 10 equiv.). The mixture was boiled with vigorous stirring for 5h. Work-up as under route (a) above gave a brown oil which was chromatographed (eluant 15% ethyl acetate-light petroleum) to give the *product* (105) (764 mg, 64%), identical with the material from route (a) above.

3-(1-*Hydroxyethyl*)-1,4,5,7-*tetramethoxy*-2-*prop*-2-*enylnaphthalene* (106)

Compound (105) (2.20 g) in dry ether (20 ml) was added dropwise during 3 min to a stirred suspension of lithium aluminium hydride (1.03 g) in dry ether (80 ml). The mixture was stirred for a further 10 min and the reaction was worked up by addition of saturated ammonium chloride, followed by anhydrous magnesium sulphate. Work-up of the filtrate gave a residue which was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (106) (2.01 g, 91%). A small portion was subjected to p.l.c. to provide an analytical sample of the oily product (Found: C, 68.85; H, 7.25; $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.25%); ν_{max} (neat) 3 480, 1 618, 1 580, and 1 492 cm^{-1}; δ1.63 (3 H, d, J 7 Hz, CCH_3), 3.70 (2 H, m, CH_2), 3.82, 3.84, 3.90, and 3.94 (3 H each, s, OCH_3), 4.10 (1 H, br s, OH, D_2O exchangeable), 4.8 - 5.2 (2 H, m, vinyl CH_2), 5.26 (1 H, m, C*H* CH_3), 5.9 - 6.3 (1 H, m, vinyl CH), 6.52 (1 H, d, J 2.5 Hz, 6-H), and 6.98 (1 H, d, J 2.5 Hz, 8-H).

3-*Acetyl*-1,4,5,7-*tetramethoxy*-2-*prop*-1-*enylnaphthalene* (107)

Compound (105) (504 mg) was treated with potassium *t*-butoxide (684 mg, 4 equiv.) in dry tetrahydrofuran (60 ml) at 60°C under nitrogen for 2h. The reaction mixture was cooled and added to aqueous ammonium chloride, then extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the *product* (107) (369 mg, 73%), m.p. 98 - 99°C (light petroleum) (Found: C, 68.9; H, 6.8. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.65%); νmax 1 704, 1 615, and 1 576 cm^{-1}; δ1.93 (3 H, d, J 6 Hz, CH *CH*$_3$), 2.50 (3 H, s, $COCH_3$), 3.79, 3.82, 3.95, and 3.99 (3 H each, s, OCH_3), 6.12 (1 H, dq, J 6 and 16 Hz, *CH*CH_3), 6.56 (1 H, d, J 16 Hz, *CH* = CH CH_3), 6.55 (1 H, d, J 2 Hz, 6-H), and 7.05 (1 H, d, J 2 Hz, 8-H).

trans-3,4-*Dihydro*-5,10-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (108) *and cis*-3,4-*Dihydro*-5,10-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*-[2,3-*c*]*pyran* (109)

(a) Nitrogen was bubbled through a solution of the alcohol (99) (106 mg) in dry dimethylformamide (10 ml) for 0.5h before the addition of potassium *t*-butoxide (175 mg, 4 equiv.). After the addition the flask was immersed in an oil-bath preheated to 60°C, the contents were stirred, and nitrogen was blown onto the surface of the solution. The reaction was quenched after 5 min by the addition of water (30 ml), and the mixture was cooled and extracted with diethyl ether (4 x 10 ml). The extract was backwashed with water (50 ml), dried ($MgSO_4$) and evaporated to give the *product* (108) virtually quantitatively, and which was shown to be pure by ^1H n.m.r. spectroscopy.

(b) Using the above procedure, the alcohol (99) (1.022 g), dry DMF (50 ml), and base (1.686 g, 4 equiv.) were warmed at 60°C under nitrogen for 1.25 h. Work-up gave an oil (955 mg, 93%). A portion (135 mg) was chromatographed by p.l.c. (developer 4% ethyl acetate-light petroleum) to give *compound* (109) as the product with the higher R_F value (55 mg, 40%) as cubes, m.p. 82 - 82.5°C (ethanol) (Found: C, 74.65; H, 7.4. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.4%); ν_{max} 1 590 cm^{-1}; δ1.43 (3 H, d, J 6 Hz, 3-CH_3), 1.73 (3 H, d, J 6 Hz, 1-CH_3), 2.60 (1 H, dd, J 11 and 16

Hz, *pseudo*-axial 4-H), 3.10 (1 H, dd, J 3 and 16 Hz, *pseudo*-equatorial 4-H), 3.4 - 3.9 (1 H, m, 3-H), 3.87 and 3.92 (each 3 H, s, OCH_3), 5.22 (1 H, q, J 6 Hz, 1-H), 7.4 - 7.6 (2 H, m, 7- and 8-H), and 8.0 - 8.15 (2 H, m, 6- and 9-H). *Compound* (108) (72 mg, 53%), of lower R_F value, was obtained as needles, m.p. 99.5 - 100.5°C (light petroleum) (Found: C, 74.6; H, 7.4. $C_{17}H_{20}O_3$ requires C, 74.95; H, 7.4%); ν_{max} 1 590 cm^{-1}; δ1.39 (3 H, d, J 6 Hz, 3-CH_3), 1.63 (3 H, d, J 6 Hz, 1-CH_3), 2.59 (1 H, dd, J 11 and 16 Hz, *pseudo*-axial 4-H), 3.11 (1 H, dd, J 3.5 and 16 Hz, *pseudo*-equatorial 4-H), 3.88 and 3.90 (each 3 H, s, OCH_3), 3.9 - 4.3 (1 H, m, 3-H), 5.35 (1 H, q, J 6 Hz, 1-H), 7.35 - 7.6 (2 H, m, 7- and 8-H), and 7.9 - 8.15 (2 H, m, 6- and 9-H).

trans-3,4-*Dihydro*-5,9,10-*trimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*] *pyran* (110)

Compound (93) (152 mg) was dissolved in dry dimethylformamide (20 ml) and dry nitrogen was passed through the solution for 5 min. Potassium *t*-butoxide (226 mg, 4 equiv.) was added and the mixture stirred under nitrogen at a bath temperature of

50 - 55°C for 15 min. The mixture was cooled, thrown into water, and extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the *product* (134 mg, 87%). This showed spectral characteristics identical with those reported for the same compound obtained by another method.[45]

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-5,10-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (112) *and its Enantiomer, and* (1R, 3R, 4R)-3,4-*Dihydro*-4-*hydroxy*-5,10-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (113) *and its Enantiomer*

(a) From compound (99):

The alcohol (99) (89 mg) and potassium *t*-butoxide (146 mg, 4 equiv.) were heated together at 70 - 80°C (bath) in dry dimethylformamide (15 ml) in the presence of air for 19h. The reaction mixture was cooled, thrown into water, and extracted with ether. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to give, firstly, racemic (112) (26 mg, 28%), followed by racemic (113) (7 mg, 7%). Both (112) and (113) were identical with authentic material.[40]

(b) From compound (108):

Air was bubbled through a solution of compound (108) (1.08 g) in dry dimethylformamide (20 ml) for 20 min. Potassium *t*-butoxide (1.78 g, 4 equiv.) was added and the flask was immersed in an oil-bath at 60°C and the contents were stirred for 2h. Water was added and the mixture was extracted with ether. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to afford, firstly, *compound (109)* (134 mg, 12%), followed by starting material (234 mg, 23%), then *compound (112)* (323 mg, 28%) as an oil. The last compound to be identified was compound (*113*) (76 mg, 7%), m.p. 166°C (lit.^{40}, 168°C), mixed m.p. with authentic material 166°C.

3,4-*Dihydro*-5,10-*dimethoxy*-3-*propyl*-1H-*naphtho*[2,3-*c*]*pyran* (114)

Alcohol (31) (106 mg) was dissolved in dry dimethylformamide (20 ml) which had been flushed with nitrogen. Potassium *t*-

butoxide (200 mg, 4 equiv.) was added and the reaction mixture, under nitrogen, was immersed in an oil bath, maintained at 65°C, for 20 min. Water was added to the cooled mixture and extracted with ether. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to afford the product (87 mg, 83%), m.p. 104 - 105°C (methanol) Found: C, 75.4; H, 7.75. $C_{18}H_{22}O_3$ requires C, 75.5; H, 7.75%); δ1.00 (3 H, distorted t, J 7 Hz, CH_3), 1.64 (4 H, m, CH_2CH_2), 2.66 (1 H, dd, J 11 and 17 Hz, *pseudo*-axial 4-H), 3.10 (1 H, dd, J 3.5 and 17 Hz, *pseudo*-equatorial 4-H), 3.5 - 3.9 (1 H, m, 3-H), 4.84 (1 H, d, J 16 Hz, *pseudo*-axial 1-H), 5.26 (1 H, d, J 16 Hz, *pseudo*-equatorial 1-H), 7.35 - 7.6 (2 H, m, 7- and 8-H), and 7.9 - 8.15 (2 H, m, 6- and 9-H).

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-5,9,10-*trimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (117) *and its Enantiomer*

Compound (87) (163 mg) was dissolved in dry dimethylformamide (20 ml) and potassium t-butoxide (242 mg, 4 equiv.) was added. Air was passed over the reaction mixture, which was heated at 60°C (bath) for 15 min. Work-up as for (114) afforded a residue which was chromatographed (eluant 30% ethyl acetate-light petroleum) to give, firstly, compound (110) (26 mg, 15%), followed by the *product* (117) (50 mg 31%) as an oil. (Found: C, 67,7; H, 6.8. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%); δ1.43 (3 H, d, J 6.5 Hz, 3-CH_3), 1.70 (3 H, d, J 7.5 Hz, 1-CH_3), 3.80, 3.97, and 4.01 (3 H each, s, OCH_3) *ca.* 3.97 (1 H, dq, J 6.5 and 8.5 Hz, 3-H, partially obscured by Me), 4.2 (1 H, br s, OH), 4.76 (1 H, d, J 8.5 Hz, 4-H), 5.26 (1 H, q, J 7.5 Hz, 1-H), 6.88 (1 H, d, J 8 Hz, 8-H), 7.40 (1 H, t, J 8 Hz, 7-H), and 7.64 (1 H, d, J 8 Hz, 6-H).

(1R,3R,4R)-3,4-*Dihydro*-4-*hydroxy*-5,9,10-*trimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (118) *and its Enantiomer*

Compound (87) (205 mg) was dissolved in acetonitrile (70 ml), and water (70 ml) was added. C.A.N. (743 mg, 2 equiv). in water (15 ml) was added during 5 min. Stirring was continued for a further 10 min, then the mixture was extracted into dichloromethane, and the extract was washed with water. The residue obtained upon work-up was subjected to p.l.c. (eluant 15% ethyl acetate-light petroleum) to give the *product* (118) (30 mg, 14%), m.p. 170 - 173 °C (light petroleum) (Found: M^+

318.1473. $C_{18}H_{22}O_5$ requires M, 318.1467); δ1.43 (3 H, d, J 6 Hz, 3-CH_3), 1.61 (3 H, d, J 7 Hz, 1-CH_3), 2.22 (1 H, d, J 8 Hz, OH, D_2O exchangeable), 3.81, 4.02, and 4.05 (3 H each, s, OCH_3), 4.14 (1 H, dq, J 2 and 6 Hz, 3-H), 4.76 (1 H, dd, J 2 and 8 Hz, 4-H, collapses to d, J 2 Hz on D_2O exchange), 5.34 (1 H, q J 7 Hz, 1-H), 6.89 (1 H, d, J 8 Hz, 8-H), 7.40 (1 H, t, J 8 Hz, 7-H), and 7.72 (1 H, d, J 8 Hz, 6-H).

trans-3,4-*Dihydro*-5,7,9,10-*tetramethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (119)

(a) Compound (88) (584 mg) was dissolved in dry dimethylformamide (25 ml) and dry nitrogen was passed through the solution for 5 min. Potassium *t*-butoxide (1.33 g, 4 equiv.) was added and the mixture stirred under nitrogen at a bath temperature of 55°C for 15 min. The mixture was cooled, thrown into water, and extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant: 30% ethyl acetate-light petroleum) to afford firstly the *naphthopyran (119)* (537 mg, 92%) (Found: C, 68,7; H, 7.40. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.25%); ν_{max} 1 615, 1 595, 1 578, and 1 500 cm^{-1};

δ1.39 (3 H, d, J 6 Hz, 3-CH_3), 1.63 (3 H, d, J 7 Hz, 1-CH_3), 2.56 (1 H, dd, J 10 and 17 Hz, *pseudo*-axial 4-H), 3.06 (1 H, dd, J 3.5 and 17 Hz, *pseudo*-equatorial 4-H), 3.79, 3.85, 3.94, and 3.98 (3 H each, s, OCH_3), 3.94 - 4.3 (1 H, m, 3-H), 5.31 (1 H, q, J 7 Hz, 1-H), 6.51 (1 H, d, J 2.5 Hz, 8-H), and 6.96 (1 H, d, J 2.5 Hz, 6-H). Later fractions afforded compound (*120*)) (12 mg, 2%), identical with the material described below.

(b) Similar treatment of the alcohol (106) (2.01 g) with potassium *t*-butoxide (4 equiv.) gave rise to the *product (119)* (1.73 g, 86%), identical with that described above. This was followed by compound *(120)* (100 mg, 5%), indistinguishable from the material described below. None of the isomeric compound (*121*) was observed in either reaction (a) or (b).

(1R,3R,4S)-3,4-*Dihydro-4-hydroxy-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* (120) *and its Enantiomer, and* (1R,3R,4R)-3,4-*Dihydro-4-hydroxy-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* (121) *and its Enantiomer and cis-3,4-Dihydro-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho [2,3-c]pyran* (122)

Compound (119) (193 mg) was dissolved in dry dimethylformamide (15 ml) and dry air was passed through the solution for 10 min. Potassium t-butoxide (440 mg) was added and the mixture stirred at a bath temperature of 55 - 60°C for 2h under a stream of dry air. The air was turned off, and stirring was continued for 1h, then the mixture was poured into water and extracted with ether. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to give firstly the *cis pyran (122)* (17 mg, 8%), m.p. 148.5 - 149.5°C (methylated spirits) (Found: C, 68.3; H, 7.55. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.25%); δ1.40 (3 H, d, J 6.5 Hz, 3-CH_3), 1.54 (3 H, d, J 6.5 Hz, 1-CH_3), 2.54 (1 H, dd, J 11 and 16 Hz, *pseudo*-axial 4-H), 3.04 (1 H, dd, J 2.5 and 16 Hz, *pseudo*-equatorial 4-H), 3.5 - 3.9 (1 H, m, 3-H, partially obscured), 3.73, 3.87, 3.93, and 3.98 (3 H each, s, OCH_3), 5.21 (1 H, q, J 6.5 Hz, 1-H), 6.51 (1 H, d, J 2.5 Hz, 8-H), and 6.98 (1 H, d, J 2.5 Hz, 6-H). The second fraction afforded starting material (15 mg, 8%), while the third fraction gave *product (120)* (70 mg, 35%) as white cubes, m.p. 119.5 - 120.5°C (dichloromethane-light petroleum) (lit.[51], for the single enantiomer from natural sources, 40°C. It is possible that the naturally derived sample was impure). (Found: C, 65.45; H, 7.0. $C_{18}H_{24}O_6$ requires C, 65.5; H, 6.9%). νmax 3 520, 1 620, 1 596, 1 584, and 1 497 cm^{-1}; δ1.42 (3 H, d, J 6.5 Hz, 3-CH_3), 1.68 (3 H, d, J 7.5 Hz, 1-CH_3), 3.76, 3.92, 3.94, and 3.96 (3 H each, s, OCH_3), 3.85 (1 H, br s, OH), *ca.* 3.97 (1 H, dq, J 6.5 and 9 Hz, 3 H, partially obscured by Me), 4.74 (1 H, d, J 9 Hz, 4-H), 5.21 (1 H, q, J 7.5 Hz, 1-H), 6.55 (1 H, d, J 2.5 Hz, 8-H), and 6.92 (1 H, d, J 2.5 Hz, 6-H). The last fraction gave rise to *compound (121)* (15 mg, 7%), m.p. 133 - 134°C (dichloromethane-light petroleum) (Found: C, 65.2; H, 7.0. $C_{18}H_{24}O_6$ requires C, 65.5; H, 6.9%); νmax 3 458, 1 618, 1 595, 1 578, and 1 496 cm^{-1}; δ1.42 (3 H, d, J 6.5 Hz, 3-CH_3), 1.61 (3 H, d, J 7 Hz, 1-CH_3), 2.22 (1 H, br s, OH, D_2O exchangeable), 3.79, 3.93, 3.98, and 4.04 (3 H each, s, OCH_3), *ca.* 4.13 (1 H, dq, J 2 and 6.5 Hz, 3-H), 4.72 (1 H, d, J 2 Hz, 4-H), 5.31 (1 H, q, J 7 Hz, 1-H), 6.56 (1 H, d, J 2.5 Hz, 8-H), and 7.02 (1 H, d, J 2.5 Hz, 6-H).

2-*Trifluoroacetyl*-1-*naphthol* (139) *and* 4-*trifluoroacetyl*-1-*naphthol* (140)

To 1-naphthol (138) (964 mg) in dry dichloromethane (5 ml) was added T.F.A.A. (5 ml) and the solution was stirred for 58h at room temperature after which it was poured into water. The residue obtained upon work-up was chromatographed (eluant 5% ethyl acetate-light petroleum and 20% ethyl acetate-light petroleum) and afforded firstly *product* (139) (602 mg, 64% based on unrecovered starting material) m.p. 87 - 88°C (light petroleum) (Found: C, 60.1; H, 2.95. $C_{12}H_7F_3O_2$ requires C, 60.01; H, 2.94%) ν_{max} 1 630 cm^{-1}; δ7.28 (1 H, d, J 9 Hz, 4-H), 7.4 - 7.85 (4 H, m, Ar-H), 8.45 (1 H, d, J 9 Hz, 3-H), and 12.85 (1 H, s, OH, D_2O exchangeable). Later fractions gave *product* (140) (135 mg, 14% based on unrecovered starting material) m.p. 183 - 187°C (dichloromethane-light petroleum) (Found: C, 59.9; H, 3.0%) ν_{max} 3 370 br and 1 655 cm^{-1}; δ3.3 - 4.2 (1 H, br s, OH, D_2O exchangeable), 7.2 (1 H, d, J 9 Hz, 2-H), 7.35 - 7.85 (2 H, m, Ar-H), 8.05 - 8.5 (2 H, m, Ar-H), and 8.9 - 9.2 (1 H, m, 5-H).

1,5-*Dimethoxy-3-trifluororacetyl-4-naphthol* (141).

1,5-Dimethoxy-4-naphthol (38) (51 mg) was dissolved in dry dichloromethane (2 ml) and trifluoroacetic anhydride (T.F.A.A.) (5 ml) was slowly added. The solution was stirred at room temperature for 40h. Evaporation of volatiles and chromatography of the residue (eluant 10% ethyl acetate in light petroleum) gave the *product* (63 mg, 84%) m.p. 126° - 127°C (ethanol). (Found C, 55.8; H, 3.5. $C_{14}H_{11}F_3O_4$ requires C, 56.0, H, 3.65%); νmax 1 632 cm^{-1}; δ3.94, 4.05 (3 H each, s, OCH_3), 6.91 (1 H, q, J 2 Hz, 2-H), 6.97 (1 H, d, J 9 Hz, 6-H), 7.58 (1 H, t, J 9 Hz, 7-H), 7.82 (1 H, d, J 9 Hz, 8-H), and 12.85 (1 H, s, OH, D_2O exchangeable).

1,5,7-*Trimethoxy-3-trifluoroacetyl-4-naphthol* (142) *and* 2,5-*di(trifluoroacetyl)*-4,6,8-*trimethoxy-1-naphthol* (143)

1,5,7-trimethoxy-4-naphthol (53) (24 mg) was dissolved in dry dichloromethane (5 ml) and T.F.A.A. (4 ml) was slowly added. The reaction mixture was stirred at room temperature for 4h, poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 20%

ethyl acetate-light petroleum) to afford first the *product* (142) (311 mg, 89%) m.p. 138 - 140°C (light petroleum) (Found: C, 54.9; H, 4.0. $C_{15}H_{13}F_3O_5$ requires C, 54.6; H, 4.0%); ν_{max} 1 630 cm^{-1}; δ3.93, 3.95, and 4.02 (each 3 H, s, OCH_3), 6.58 (1 H, d, J 2.5 Hz, 6-H), 6.86 (1 H, q, J 2 Hz, 2-H), 7.16 (1 H, d, J 2.5 Hz, 8-H), and 13.33 (1 H, s, OH, D_2O exchangeable). The second fraction gave *product* (143) (27 mg, 6%) m.p. 198 - 199°C (dichloromethane-light petroleum). (Found: C, 48.05; H, 2.9; $C_{17}H_{12}F_6O_6$ requires C, 47.90; H, 2.8%) ν_{max} 1 740, 1 620, and 1 580 cm^{-1}; δ3.6, 3.76 and 3.86 (each 3 H, s, OCH_3), 6.28 (1 H, s, 7-H), 6.52 (1 H, q, J 2 Hz, 3-H), and 12.64 (1 H, s, OH, D_2O exchangeable).

5-*Methoxy*-1,7-*di*(2-*propyl*)*oxy*-4-*naphthol* (145)

To the diene (149) (8.63 g) in dry benzene (100 ml) was added 1,4-benzoquinone (3.2 g, 0.7 equiv.) and the solution was boiled in a nitrogen atmosphere for 4h. The solvent was evaporated under reduced pressure and the oily residue was taken up in dry dimethylformamide (50 ml). Potassium carbonate (21 g) and 2-bromopropane (18 g) were added and the mixture was vigorously stirred at 55°C (bath) under nitrogen for 24h after which it was filtered. The filtrate was poured into water (2 l) and exhaustively extracted with ether. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the *product* (5.6 g, 64%) m.p. 52 - 53°C (25% water/methanol) (Found: C, 70.0; H, 7.8. $C_{17}H_{22}O_4$ requires C, 70.3; H, 7.6%) νmax 3 430 and 1 620; δ1.36 and 1.40 [each 6 H, 2 x d, each J 6.5 Hz, 2 x $CH(\mathit{CH}_3)_2$], 3.98 (3 H, s, OCH_3), 4.6 [2 H, m, 2 x $\mathit{CH}(CH_3)_2$], 6.40 (1 H, d, J 2.5 Hz, 6-H) 6.53 (1 H, d, J 9 Hz, 2-H), 6.78 (1 H, d, J 9 Hz, 3-H), 7.10 (1 H, d, J 2.5 Hz, 8-H), and 8.77 (1 H, s, OH, D_2O exchangeable).

5-*Methoxy*-1,7-*di*(2-*propyl*)*oxy*-3-*trifluoroacetyl*-4-*naphthol* (152) *and* 2,5-*di*(*trifluoroacetyl*)-8-*methoxy*-4,6-*di*(2-*propyl*)*oxy*-1-*naphthol* (153)

The naphthol (145) (456 mg) was dissolved in dry dichloromethane (3 ml) and treated with T.F.A.A. (2 ml). The solution was stirred at room temperature for 3 h, poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (25% ethyl acetate-light petroleum) to afford first the *product* 152 (515 mg, 85%)

m.p. 76 - 77°C (2-propanol) (Found: C, 59.0; H, 5.5. $C_{19}H_{21}F_3O_5$ requires C, 59.1; H, 5.5%) νmax 1 630 cm^{-1}; δ1.44 [12 H, d, J 6.5 Hz, 2 x CH(C*H*$_3$)$_2$], 4.03 (3 H, s, OCH$_3$), 4.73 (2 H, m, 2 x C*H*CH$_3$), 6.57 (1 H, d, J 2.5 Hz, 6-H), 6.93 (1 H, q, J 2 Hz, 2-H), 7.20 (1 H, d, J 2.5 Hz, 8-H), and 13.20 (1 H, s, OH, D_2O exchangeable). The second fraction gave *product* (153) (30 mg, 4%) m.p. 145 - 146°C (2-propanol) (Found: C, 52.35; H, 4.2. $C_{21}H_{20}F_6O_6$ requires C, 52.3; H, 4.2%) νmax 1 745, 1 630 and 1 585 cm^{-1}; δ1.37 [12 H, d, J 6.5 Hz, 2 x CH(C*H*$_3$)$_2$], 4.07 (3 H, s, OCH$_3$), 4.67 [2 H, m, 2 x C*H*(CH$_3$)$_2$] 6.6 (1 H, s, 7-H), 6.9 (1 H, q, J 2 Hz, 3-H), and 13.20 (1 H, s, OH, D_2O exchangeable).

3-(1,1-*Dihydroxy*-2,2,2-*trifluoroethyl*)-5-*methoxy*-1,4-*naphthoquinone* (154)

To a stirred solution of naphthol (141) (98 mg) in acetonitrile (20 ml) and water (15 ml), was added C.A.N. (358 mg, 2 equiv.) in water (5 ml) over 5 min at room temperature. The solution was stirred for a further 5 min, then poured into water, and the mixture was extracted with dichloromethane. The residue obtained upon work-up afforded the *product* (85 mg, 86%), m.p. 142 - 143°C (chloroform-light petroleum) which resolidified m.p. 156 - 157°C. (Found: C, 51.6; H, 2.9. $C_{13}H_9F_3O_5$ requires C, 51.7; H, 3.0%) νmax 3 250 br and 1 645 cm^{-1}; δ (acetone-d_6) 4.04 (3 H, s, OCH_3), 7.27 (3 H, s, two of which exchanged with D_2O leaving 2-H), and 7.5 - 8.0 (3 H, m, Ar-H).

3-(1,1-*Dihydroxy*-2,2,2-*trifluoroethyl*)-5-*methoxy*-7-(2-*propyl*)*oxy*-1,4-*naphthoquinone* (155)

To a stirred solution of naphthol (152) (416 mg) in acetonitrile (25 ml) and water (5 ml) was added C.A.N. (1.18 g, 2 equiv.) in water (8 ml) over 5 min at room temperature. The yellow solution was stirred for a further 5 min, poured into water and the mixture was extracted with dichloro-methane. The residue obtained upon work-up was rapidly chromatographed on a short column (eluant 25% ethyl acetate-light petroleum) to afford the *product* (357 mg, 92%), m.p. 104 - 106°C (dichloromethane-light petroleum) (Found: C, 53.4; H, 4.3. $C_{16}H_{15}F_3O_6$ requires C, 53.3; H, 4.2%) νmax 3 210 br, 1 670, and 1 640 cm^{-1}; δ (acetone-d_6) 1.38 [6 H, d, J 6.5 Hz, $CH(CH_3)_2$], 3.95 (3 H, s, OCH_3) 4.73 [1 H, septet, C*H*(CH_3)$_2$], 6.88 and 7.08 (each 1 H, d, J 3 Hz, 6- and 8-H respectively), 7.15 (1 H, s, 2-H) and 7.41 (2 H, s, 2 x OH, D_2O exchangeable).

1,4-*Dihydroxy-5-methoxy-7-(2-propyl)oxy-3-trifluoroacetyl-naphthalene* (156)

The quinone (155) (93 mg) was dissolved in dichloromethane (20 ml) and shaken with an aqueous solution of sodium dithionite in a separatory funnel until the organic phase became light-yellow. The organic layer was separated and dried ($MgSO_4$) in a nitrogen atmosphere. Rapid filtration and evaporation of the solvent gave the *product* (64 mg, 72% after recrystallisation from acetone-light petroleum), m.p. 148 - 149°C (acetone-light petroleum) (Found: C, 55.9; H, 4.5. $C_{16}H_{15}F_3O_5$ requires C, 55.8; H, 4.4%) νmax 3 570 br, 3 460 br, and 1 600 cm^{-1}; δ (acetone-d_6) 1.4 [6 H, d, J 6.5 Hz, CH(C*H*$_3$)$_2$], 4.05, (3 H, s, OCH_3), 4.87 [1 H, septet, C*H*(CH_3)$_2$], 6.63 (1 H, d, J 3 Hz, 6-H), 7.0 (1 H, q, J 2 Hz, 2-H), 7.17 (1 H, d, J 3 Hz, 8-H), 8.8 (1 H, br s, OH, D_2O exchangeable), and 12.18 (1 H, sharp s, OH, D_2O exchangeable).

1-*Hydroxy*-9-*methoxy*-3-(1-*propyl*)-1-*trifluoromethyl*-*naphtho*[2,3-*c*] *pyran*-5,10-*quinone* (158)

The quinone (154) (650 mg) was dissolved in acetonitrile (75 ml). 3-Hydroxyhexanoic acid (730 mg), distilled water (5 ml) and silver nitrate (200 mg) in distilled water (2 ml) were added and the stirred solution was treated dropwise with potassium persulphate (1.16 g) in distilled water (3 ml) under nitrogen over a period of 45 min at 78°C (bath). The solution was stirred for a further 75 min at the same temperature, poured into water (150 ml) and extracted with ether (3 x 50 ml). The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (640 mg, 80%), m.p. 168 - 170°C (dichloromethane-light petroleum); (Found: C, 58.3; H, 4.7. $C_{18}H_{17}F_3O_5$ requires C, 58.4; H, 4.6%); νmax 3 350 br, 1 665, and 1 645 cm^{-1}; δ0.95 (3 H, distorted t, J 6.5 Hz, CCH_3), 1.15 - 2.0 (4 H, m, 2 x CH_2), 2.13 (1 H, dd, J 11 and 18 Hz, *pseudo*-axial 4-H), 2.93 (1 H, dd, J 2.5 and 18 Hz, *pseudo*-equatorial 4-H), 3.8 (1 H, m, 3-H), 3.97 (3 H, s, OCH_3), 6.23 (1 H, s, OH, D_2O exchangeable), and 7.15 - 7.80 (3 H, m, Ar-H).

3,4-*Dihydro*-1-*hydroxy*-9-*methoxy*-3-(1-*propyl*)-7-(2-*propyl*)*oxy*-1-*trifluoromethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (159)

The quinone (155) (450 mg) and 3-hydroxyhexanoic acid (425 mg) in acetonitrile (30 ml) containing silver nitrate (120 mg) in distilled water (2 ml) was treated dropwise with potassium persulphate (676 mg) in distilled water (15 ml) under nitrogen over a period of 45 min at 72 - 78°C (bath). The solution was stirred for a further 75 min at the same temperature. Work-up as for compound (158) afforded a residue which was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the *product* (319 mg, 60%), m.p. 128 - 129°C (2-propanol) (Found: C, 58.7; H, 5.4. $C_{21}H_{23}F_3O_6$ requires C, 58.9; H, 5.4%); ν_{max} 3 385 br, 1 660, and 1 640 cm^{-1}; δ0.93 (3 H, distorted t, J 6 Hz, $-CH_2\mathit{CH_3}$), 1.37 [6 H, d, J 6.5 Hz, $CH(\mathit{CH_3})_2$], 1.15 - 2.0 (4 H, m, 2 x CH_2), 2.13 (1 H, dd, J 11 and 19 Hz, *pseudo*-axial 4-H), 2.90 (1 H, dd, J 2 and 19 Hz, *pseudo*-equatorial 4-H), 3.6 - 4.2 (1 H, m, 3-H), 3.95 (3 H, s, OCH_3), 4.73 [1 H, septet, $\mathit{CH}(CH_3)_2$], 6.50 (1 H, s, OH, D_2O exchangeable), 6.68 and 7.17 (each 1 H, d, J 2.5 Hz, 6- and 8-H).

3,4-*Dihydro*-1-*hydroxy*-7,9-*dimethoxy*-1-*methyl*-3-(1-*propyl*)-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (160)

The quinone (30) (800 mg) was dissolved in acetonitrile (50 ml). Distilled water (10 ml) was added followed by 3-hydroxyhexanoic acid (496 mg) and the solution was stirred at 78°C (bath). Silver nitrate (320 mg) in distilled water (4 ml) was added and the solution was treated dropwise with potassium persulphate (1.64 g) in distilled water (35 ml) under nitrogen over a period of 40 min. The solution was stirred for a further 3.5h at 78°C and then poured into water (250 ml) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford, firstly starting material (30) (44 mg), followed by the *product* (230 mg, 23% based on unrecovered starting material), m.p. 153 - 155°C (chloroform-light petroleum). (Found: M^+ 346.1398. $C_{19}H_{22}O_6$ requires M, 346.1416); νmax 3 600 - 3 100, 1 725 and 1 595 cm^{-1}; δ0.95 (3 H, distorted t, J 6 Hz, CH_2CH_3), 1.2 - 1.92 (4 H, m, 2 x CH_2), 1.70 [3 H, s, (C-1) CH_3], 2.05 (1 H, dd, J 11 and 18 Hz, *pseudo*-axial 4-H), 2.72 (1 H, dd, J 3 and 18 Hz, *pseudo*-equatorial 4-H), 3.9 (1 H, m, 3-H), 3.93 and 3.97 (each 3 H, s, OCH_3), 5.07 (1 H, br s, OH, D_2O exchangeable) 6.67 (1 H, d, J 3 Hz, 8-H), and 7.17 (1 H, d, J 3 Hz, 6-H).

6-*Chloro*-3,4-*dihydro*-1-*hydroxy*-9-*methoxy*-3-(1-*propyl*)-7-(2-*propyl*)*oxy*-1-*trifluoromethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (165)

The quinone (159) (218 mg) in dry dichloromethane (3 ml) was treated at -5°C with boron trichloride (a twentyfold excess) in dichloromethane. The solution was allowed to warm to room temperature and stirring was continued for 1h. The solution was poured into ethanol and this was stirred for 10 min. Water (50 ml) was added and the mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 35% ethyl acetate-light petroleum) to afford first a two-component fraction (18 mg) followed by starting material (45 mg) and finally the *product* (69 mg, 37% based on unrecovered starting material), m.p. 62 - 64°C (decomp.) (2-propanol) (Found: M^+ 462.1069. $C_{21}H_{22}{}^{35}ClF_3O_6$ requires M, 462.1057); ν_{max} 3 350 br and 1 650 br cm^{-1}; δ0.97 (3 H, distorted t, J 6.5 Hz, $CH_2\mathit{CH}_3$), 1.0 - 2.0 (4 H, m, 2 x CH_2), 1.48 [6 H, d, J 6.5 Hz, $CH(\mathit{CH}_3)_2$], 2.13 (1 H, dd, J 11 and 18 Hz, *pseudo*-axial 4-H), 3.10 (1 H, dd, J 2.5 and 18 Hz, *pseudo*-equatorial 4-H), 3.7 - 4.1 (1 H, m, 3-H), 4.02 (3 H, s, OCH_3) 4.77 [1 H, septet, $\mathit{CH}(CH_3)_2$], 6.83 (1 H, s, 8-H).

5-*Methoxy*-1,7-*di*(2-*propyl*)*oxy*-3-*trichloroacetyl*-4-*naphthol* (166)

The naphthol (145) (420 mg) in dry dichloromethane (4 ml) was treated with trichloroacetic anhydride (2 ml) and the solution was stirred at 55°C (bath) for 85h after which it was poured into water and the mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the *product* (240 mg, 38%), m.p. 152 - 153°C (acetone) (Found: M^+ 434.0378. $C_{19}H_{21}{}^{35}Cl_3O_5$ requires M, 434.0366); νmax 1 600 cm^{-1}; δ1.42 [12 H, d, J 6.5 Hz, 2 x CH(CH_3)$_2$], 4.0 (3 H, s, OCH_3), 4.63 [2 H, m, 2 x *C*H(CH_3)$_2$], 6.53 (1 H, d, J 3 Hz, 6-H), 7.17 (1 H, d, J 3 Hz, 8-H), 7.47 (1 H, s, 2-H), and 13.03 (1 H, s, OH, D_2O exchangeable).

1,4,5,7-*Tetramethoxynaphthalene* (167)

The naphthol (53) (172 mg) was dissolved in dry acetone (10 ml). To this solution was added potassium carbonate (1 g) and iodomethane (3 ml) and the mixture was stirred and boiled under reflux for 4h after which it was cooled, filtered and volatiles evaporated. The oily residue was chromatographed (eluant 15% ethyl acetate-light petroleum) to afford the *product* (158 mg, 87%), m.p. 115 - 116°C (light petroleum) (Lit.[29], 131 - 132°C) (Found: C, 67.55; H, 6.55. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.45%); νmax 1 623 and 1 597 cm^{-1}; δ3.90 and 3.92 (3 H, each s, OCH_3), 3.95 (6 H, s, OCH_3), 6.57 (1 H, d, J 2 Hz, 6-H), 6.63 and 6.74 (each 1 H, d, J 8 Hz, 2- and 3-H), and 7.09 (1 H, d, J 2 Hz, 8-H).

1,4,5,7-*Tetramethoxy*-8-*trifluoroacetylnaphthalene* (170)

The tetramethoxynaphthalene (167) (102 mg) in dry dichloromethane (4 ml) was treated with T.F.A.A. (1 ml) and the solution was stirred at room temperature for 3h and poured into water. The mixture was extracted with dichloromethane and the residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (97 mg, 69%), m.p. 156 - 157°C (ethanol) (Found: C, 55.9; H, 4.4. $C_{16}H_{15}F_3O_5$ requires C, 55.8; H, 4.4%); νmax 1 740 cm^{-1}; δ3.79, 3.89, 3.92, and 4.0 (each 3 H, s, OCH_3), 6.64 (1 H, s, 6-H), and 6.64 and 6.78 (each 1 H, d, J 9 Hz, 2- and 3-H).

1,4,5-*Trimethoxy*-8-*trifluoroacetylnaphthalene* (171) *and*
1,4,5-*trimethoxy*-3-*trifluoroacetylnaphthalene* (172)

To the trimethoxynaphthalene (168) (600 mg) in dry dichloromethane (3 ml) was added T.F.A.A. (4 ml) and the solution was stirred at room temperature for 10 days. The solution was poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford *product* (172) (50 mg; 14% based on unrecovered starting material) as a yellow oil. (Found: M^+ 314.07776. $C_{15}H_{13}F_3O_4$ requires M, 314.07657); ν_{max} 1 695 cm^{-1}; δ3.83, 4.0, and 4.03 (each 3H, s, OCH_3), 6.89 (1 H, s, 2-H), 7.00 (1 H, dd, J 2 and 8 Hz, 6-H), 7.57 (1 H, t, J 8 Hz, 7-H), and 7.90 (1 H, dd, J 2 and 8 Hz, 8-H). Later fractions afforded starting material (340 mg) followed by *compound* (171) (100 mg; 28% based on unrecovered starting material), m.p. 138 - 139°C (methanol-light petroleum); (Found: C, 57.5; H, 4.2. $C_{15}H_{13}F_3O_4$ requires C, 57.3; H, 4.2%); ν_{max} 1 730 cm^{-1}; δ3.82, 3.89, and 3.97 (each 3 H, s, OCH_3), 6.78 (2 H, s, 2- and 3-H), 6.80 (1 H, d, J 9 Hz, 6-H), and 7.28 (1 H, d, J 9 Hz, 7-H).

Methylation of 1,5 *dimethoxy-3-trifluoroacetyl-4-naphthol* (141)

The naphthol (141) (210 mg) in dry acetone (40 ml) was treated with potassium carbonate (2 g) and iodomethane (4 ml), and the mixture was heated under reflux with vigorous stirring for 4h. The cooled solution was filtered and volatiles were removed under reduced pressure. P.l.c. gave the *product* (172) (161 mg, 73%) as a yellow oil, identical by t.l.c., and by i.r. and ^{1}H n.m.r. spectroscopy, with material obtained by the trifluoroacetylation of the trimethoxynaphthalene (168).

5,10-*Dimethoxy*-3-*propyl*-3,4-*dihydronaphtho*[2,3-*c*]*pyran*-(1H)-1-*one* (180)

Compound (192) (140 mg) was heated under nitrogen at 170 - 200°C (bath) for 5h. The cooled material was taken up in dichloromethane (2 ml) and subjected to p.l.c. in the dark (eluant 50% ethyl acetate-light petroleum) to give the *product* (51 mg, 37%) identical by ^{1}H n.m.r. spectroscopy to the material obtained by Giles *et al*[68]; m.p. 105 - 106°C (methanol) (Lit.[68], 98 - 99°C).

2-*Acetyl*-1,4-*dimethoxynaphthalene* (185)

The dimethoxynaphthalene (169) (9.07 g) was treated with a premixed solution of T.F.A.A. (26.5 ml) and glacial acetic acid (7 ml) for 45 min at 60°C (bath). The solution was poured into water and the mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the *product* (8.6 g, 95%) m.p. 60 - 61°C (light petroleum) (Lit.[13b], 61 - 62°C).

1,4-*Dimethoxy*-2-*naphthoic acid* (186)

(a) A solution of compound (185) (1 g) in dioxane (40 ml) was added dropwise over a period of 1h to a stirred sodium hypochlorite solution (90 ml of a 10 - 14% m/v) at 75°C. The solution was stirred at the same temperature for a further 70 min. The solution was cooled, sodium metabisulphite (5 g) in water (30 ml) was slowly added and any organic material was extracted into dichloromethane. The aqueous phase was acidified, (dilute hydrochloric acid) filtered and the residue was taken up in dichloromethane. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) on a short column to afford the *product* (720 mg, 72%), m.p. 167 - 168°C (acetone-light petroleum) (Found: C, 67.1; H, 5.25 $C_{13}H_{12}O_4$ requires C, 67.25; H, 5.15%); νmax 3 200 - 2 300 and 1 675 cm^{-1}; δ4.03 (3 H, s, OCH_3), 4.10 (3 H, s, OCH_3), 7.3 (1 H, s, 3-H), 7.5 - 8.35 (4 H, m, Ar-H), and 9.1 (1 H, br s, COOH).

(b) Compound (185) (120 mg) was dissolved in dioxane (2 ml) and this was added to a stirred sodium hypobromite solution (7 ml). The solution was protected from light and stirred for a further 40 min at room temperature after which sodium metabisulphite (2 g) in water (15 ml) was added. The reaction mixture was extracted with dichloromethane and acidification and filtration of the aqueous phase (dilute hydrochloric acid) afforded the *product* (119 mg, 98%), identical to the material obtained in (a) above.

2-N-*methylcarboxamido*-1,4-*naphthoquinone* (190)

The amide (189) (600 mg) and silver(II) oxide (1.52 g) were stirred in dioxane (10 ml) at room temperature and nitric acid (6 mol.dm^{-3}, 4 ml) was added dropwise over a period of 5 min. The reaction was quenched by the addition of a chloroform-water mixture (26:6ml). The organic layer was separated and the water layer was extracted with dichloromethane. The combined organic extracts were washed with water and the residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) on a short column protected from light to afford the product (490 mg, 92%), m.p. 127 - 128°C (chloroform-light petroleum) (Found: C, 66.75; H, 4.35; N, 6.5. $C_{12}H_9NO_3$ requires C, 67.0; H, 4.2, and N, 6.5%); νmax 3 350, 1 680 and 1 665 cm^{-1}; δ3.05 (3 H, d, J 5 Hz, CH_3), 7.6 - 8.2 (5 H, 3-H and Ar-H), and 8.65 (1 H, br s, NH).

3-(2'-*Hydroxypentyl*) 2-N-*methylcarboxamido*-1,4-*naphthoquinone* (191)

A mixture of the quinone (190) (518 mg) and 3-hydroxyhexanoic acid (795 mg) in acetonitrile (30 ml) containing silver nitrate (200 mg) in distilled water (3 ml) was treated dropwise with potassium persulphate (1.3 g) in distilled water (30 ml) under nitrogen over a period of 40 min at 78°C (bath). The solution was stirred for a further 90 min at the same temperature and then poured into water (200 ml) and extracted with ether (3 x 50 ml). The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to give the *product* (377 mg, 52%) as a yellow oil. (Found: M^+ 301.1283. $C_{17}H_{19}NO_4$ requires M, 301.1314); ν_{max} (neat) 3 430 (br), 1 725 and 1 665 (br) cm^{-1}; δ0.9 (3 H, distorted t, J 6.5 Hz, 5'-CH_3) 1.2 - 1.8 (4 H, m, 3'- and 4'-CH_2), 2.45 (2 H, m, 1'-CH_2), 2.85 (3 H, d, J 5 Hz, CH_3), 3.8 (1 H, m, 2'-H), 5.2 (1 H, br s, OH, D_2O exchangeable) 7.01 (1 H, br s, N-H), 7.5 - 8.0 (4 H, m, Ar-H)

1,4-*Dimethoxy*-2-N-*methylcarboxamido*-3-(2'-*hydroxypentyl*)-*naphthalene* (192)

The quinone (191) (140 mg) was reductively methylated employing the usual conditions. Work-up and chromatography afforded the *product* (89 mg, 55%) as an oil. (Found: M^+ 331.1812. $C_{19}H_{25}NO_4$ requires M, 331.1783); νmax (neat) 3 370 (br) and 1 635 cm^{-1}; δ0,9 (3 H, distorted t, J 6.5 Hz, 5'-CH_3), 1.3 - 1.6 (4 H, m, 3'-CH_2 and 4'-CH_2), 2.65 (2 H, m, 1'-CH_2), 2.95 (3 H, d, J 5 Hz, CH_3), 3.80 (6 H, s, 2 x OCH_3) 3.9 (1 H, m, 2'-H), 6.55 (1 H, br s, N-H), 7.3 - 7.6 (2 H, m, 6- and 7-H), and 7.75 - 8.20 (2 H, m, 5- and 8-H).

4,5-*Dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-*naphthoic acid* (193)

Compound (195) (800 mg) in methanol (15 ml) was added over a period of 15 min to a stirred 12% aqueous potassium hydroxide solution (30 ml) at 70°C (bath). Stirring was continued for 40 min after which the dark solution was poured into water (200 ml) and extracted with dichloromethane. The aqueous layer was acidified with dilute hydrochloric acid and exhaustively extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and evaporation of the solvent afforded the *product* (571 mg, 82%), m.p. 127 - 128°C (dichloromethane-light petroleum) (Found: C, 65.5; H, 6.9. $C_{19}H_{24}O_6$ requires C, 65.5; H, 6.9%) ν_{max} 3 300 - 2 500, 1 660, and 1 610 cm^{-1}; δ1.43 [12 H, d, J 6.5 Hz, 2 x $CH(C\mathit{H}_3)_2$], 3.93 (3 H, s, OCH_3), 4.00 (3 H, s, OCH_3) 4.71 [2 H, m, 2 x $C\mathit{H}(CH_3)_2$] 6.6 (1 H, d, J 3 Hz, 6-H), 7.23 (1 H, d, J 3 Hz, 8-H), 7.37 (1 H, s, 2-H) 9.8 (1 H, br s, COOH).

4,5-*Dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-*trifluoroacetylnaphthalene* (195)

The naphthol (152) (300 mg) in dry acetone (20 ml) was treated with iodomethane (3 ml) and potassium carbonate (1 g) and the mixture was vigorously stirred and heated under reflux in a nitrogen atmosphere for 3.5h. The reaction mixture was filtered and evaporation of volatiles gave an oily residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the *product* (267 mg, 86%) m.p. 89 - 91°C (methanol) (Found: M^+ 400.1514. $C_{20}H_{23}O_5F_3$ requires M, 400.1497) ν_{max} 1 605 cm^{-1}; δ1.43 [12 H, d, J 6.5

Hz, 2 x CH(CH_3)$_2$], 3.83 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 4.73 (2 H, m, 2 x CH(CH_3)$_2$], 6.6 (1 H, d, J 2.5 Hz, 6-H), 6.95 (1 H, s, 2-H) and 7.27 (1 H, d, J 2.5 Hz, 8-H).

4,5-*Dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-N-*methylnaphthamide* (196)

The ester (199) (165 mg) in acetone (3 ml) was added to a 40% aqueous methylamine solution (20 ml) and the solution was stirred for 16h at 50°C (bath) after which it was poured into water (100 ml). The mixture was exhaustively extracted with dichloromethane and the residue obtained upon work-up was chromatographed (eluant 60% ethyl acetate-light petroleum) to afford the *product* (143 mg, 87%), m.p. 116 - 117°C (dichloromethane-light petroleum) (Found: C, 66.6; H, 7.45, and N, 3.9. $C_{20}H_{27}NO_5$ requires C, 66.5; H, 7.5, and N, 3.9%) ν_{max} 3 310 and 1 620 cm^{-1}; δ1.42 [12 H, d, J 6.5 Hz, 2 x CH(CH_3)$_2$], 3.03 (3 H, d, J 5 Hz, N-CH_3), 3.77 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 4.73 [2 H, septet, 2 x CH(CH_3)$_2$], 6.53 (1 H, d, J 2.5 Hz, 6-H), 7.2 (1 H, d, J 2.5 Hz, 8-H), 7.47 (1 H, s, 2-H), and 8.1 (1 H, br s, N-H).

4,8-*Dichloro*-5-*methoxy*-1,7-*di*(2-*propyl*)*oxy*-3-N-*methylnaphthamide* (197)

The acid (193) (400 mg) was treated with thionyl chloride (20 ml) and the solution was heated under reflux for 60 min. The excess of thionyl chloride was evaporated under reduced pressure and the oily residue was taken up in dry acetone (5 ml) and this was slowly added to a cold 40% aqueous methylamine solution (30 ml). The mixture was stirred for 3h and poured into water (100 ml) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (317 mg, 69%), m.p. 146 - 147°C (2-propanol) (Found: C, 56.95; H, 5.8; N, 3.55; $C_{19}H_{23}Cl_2NO_4$ requires C, 57.0; H, 5.75; N, 3.5) νmax 3 300 and 1 640 cm^{-1}; δ1.43 [12 H, d, 6.5 Hz, 2 x $CH(C\mathit{H}_3)_2$], 3.04 (3 H, d, J 5 Hz, N-CH_3), 3.73 (3 H, s, OCH_3), 4.67 [2 H, m, 2 x $C\mathit{H}(CH_3)_2$], 7.33 (1 H, s, 6-H), 7.53 (1 H, s, 2-H), and 7.9 (1 H, br s, N-H).

8-*Chloro*-4,5-*dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-N-*methylnaphthamide* (198)

The acid (193) (125 mg) was stirred with thionyl chloride (3 ml) at room temperature for 30 min. The excess of thionyl chloride was evaporated under reduced pressure and the oily residue was taken up in dry acetone (4 ml) and this was slowly added to a cold 40% aqueous methylamine solution (10 ml). The mixture was stirred for 18h. Work-up as for compound (197), followed by chromatography (eluant 50% ethyl acetate-light petroleum) gave the oily unstable *product* (132 mg, 93%) (Found: m/z 395; $C_{20}H_{26}{}^{35}ClNO_5$ requires M, 395) ν_{max} 3 300 and 1 635 cm^{-1}; δ1.43 [6 H, d, J 6.5 Hz, 2 x CH(C*H*$_3$)$_2$], 3.03 (3 H, d, J 5 Hz, N-CH$_3$), 3.75 and 3.95 (each 3 H, s, OCH$_3$), 4.67 [2 H, m, 2 x C*H*(CH$_3$)$_2$], 6.70 (1 H, s, 6-H), 7.57 (1 H, s, 2-H), and 8.1 (1 H, br s, N-H).

Methyl-4,5-*dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-*naphthoate* (199)

The acid (193) (440 mg) in dry acetone (40 ml) was treated with iodomethane (5 ml) and potassium carbonate (2 g) and the mixture was stirred and heated under reflux for 90 min. The reaction mixture was cooled, filtered and evaporation of volatiles gave an oily residue which was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the *product* (450 mg, 98%) as an oil. (Found: C, 66.35; H, 7.45. $C_{20}H_{26}O_6$ requires C, 66.3; H, 7.2%) νmax (neat) 1 700 and 1 610 cm^{-1}; δ1.43 [12 H, d, J 6.5 Hz, 2 x $CH(CH_3)_2$], 3.85, 3.93, and 3.95 (each 3 H, s, 2 x OCH_3 and CO_2CH_3), 4.67 [2 H, septet, 2 x $CH(CH_3)_2$], 6.52 (1 H, d, J 2.5 Hz, 6-H), 7.13 (1 H, s, 2-H), and 7.18 (1 H, d, J 2.5 Hz, 8-H).

5-*Methoxy*-7-(2*propyl*)*oxy*-3-N-*methylcarboxamido*-1,4-*naphthoquinone* (200)

To the amide (196) (50 mg) and silver(II) oxide (86 mg) in dioxane (4 ml) was added with stirring, nitric acid (6 mol. dm^{-3}; 2 ml) over a period of 4 min. The reaction was halted by the addition of a dichloromethane-water mixture (1:3) (20 ml) and then poured into water and extracted with dichloromethane. The residue obtained upon work-up was chromatographed on a short column (eluant 70% ethyl acetate-light petroleum) to afford the *product* (10 mg, 24%), m.p. 175

- 177°C (dichloromethane-light petroleum) (Found: C, 63.0; H, 5.9; N, 4.4. $C_{16}H_{17}NO_5$ requires C, 63.35; H, 5.65; N, 4.6%) νmax 3 300, 1 685 and 1 665 cm^{-1}; δ1.43 [6 H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$], 2.97 (3 H, d, *J* 5 Hz, *N*-CH$_3$), 3.95 (3 H, s, OCH$_3$), 4.73 [1 H, septet, C*H*(CH$_3$)$_2$], 6.70 (1 H, d, *J* 2.5 Hz, 6-H), 6.80 (1 H, d, *J* 2.5 Hz, 8-H), 7.68 (1 H, s, 2-H), and 8.9 (1 H, br s, N-H).

2-(2'-*hydroxypentyl*)-5-*methoxy*-7-(2-*propyl*)*oxy*-3-N-*methylcarboxamido*-1,4-*naphthoquinone* (201)

The quinone (200) (83 mg) in acetonitrile (30 ml), containing 3-hydroxyhexanoic acid (68 mg) and silver nitrate (120 mg) in distilled water (3 ml), was treated dropwise with potassium persulphate (122 mg) in distilled water (10 ml) under nitrogen over a period of 55 min at 75°C (bath). The solution was stirred for a further 90 min at the same temperature and then poured into water (150 ml) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 80% ethyl acetate-light petroleum) to afford the unstable *quinone* (201) (16 mg, 14%) as an oil. (Found: M$^+$ 389.1816 $C_{21}H_{27}NO_6$ requires M, 389.1838) νmax (neat) 3 400 (br), 1 723, and 1 664 cm^{-1}; δ0.93 (3 H, distorted t, *J* 6 Hz, 5'-CH_3) 1.43 [6 H, d, *J* 6.5 Hz, CH(CH_3)$_2$], 1.2 - 1.8 (4 H, m, 3'- and 4'-H) 2.5 (1 H, m, 2'-H) 2.86 (3 H, d, *J* 5 Hz, N-CH_3), 3.83 (3 H, s, OCH_3), 4.7 [1 H, septet *C*H(CH_3)$_2$], 6.55 (1 H, d, *J* 2.5 Hz, 6-H), 7.05 (1 H, d, *J* 2.5 Hz, 8-H), 7.35 (1 H, br s, N-H), and 7.90 (1 H, s, OH, D_2O exchangeable).

4,5-*Dimethoxy*-1,7-*di*(2-*propyl*)*oxy*-3-N,N-*dimethylnaphthamide* (202)

The amide (196) (357 mg) in dry tetrahydrofuran (20 ml) was treated with sodium hydride (475 mg of a 50% sodium hydride dispersion in oil) and the mixture was stirred for 15 min. Iodomethane (4 ml) was added and stirring was continued for a further 3h. A solution of saturated ammonium chloride (10 ml) was slowly added and the mixture was extracted with ether. The residue obtained upon work-up was chromatographed (eluant 60% ethyl acetate-light petroleum) to afford the product (345 mg, 93%), m.p. 93 - 94°C (ethyl acetate-light petroleum) (Found: M^+ 375.2017. $C_{21}H_{29}NO_5$ requires M, 375.2045) ν_{max} 1 615, 1 595, and 1 585 cm^{-1}; δ1.41 [12 H, d, 6.5 Hz, 2 x CH(CH_3)$_2$], 2.9 and 3.13 [each 3 H, s, N(CH_3)$_2$], 3.80 and 3.95

(each 3 H, s, OCH_3), 4.7 [2 H, septet, 2 x C*H*$(CH_3)_2$], 6.37 (1 H, d, J 2.5 Hz, 6-H), 6.63 (1 H, s, 2-H), and 7.16 (1 H, d, J 2.5 Hz, 8-H).

5-*Methoxy*-7-(2-*propyl*)*oxy*-3-N,N-*dimethylcarboxamido*-1,4-*naphthoquinone* (203)

To the amide (202) (330 mg) and silver(II) oxide (436 mg) was added with stirring, nitric acid (6 mol dm^{-3}; 3 ml) over a period of 4 min. Work-up as for compound (200), followed by chromatography (eluant ethyl acetate) gave the *product* (40 mg, 14%), m.p. 155 - 157°C (acetone-light petroleum) (Found: C, 64.35; H, 6.05; N, 4.50. $C_{17}H_{19}NO_5$ requires C, 64.3; H, 6.0; N, 4.4%) ν_{max} 1 635 and 1 590 cm^{-1}; δ1.41 [6 H, d, J 6.5 Hz, CH$(CH_3)_2$], 2.95 and 3.12 [each 3 H, s, $N(CH_3)_2$], 3.96 (3 H, s, OCH_3), 4.7 (1 H, septet, C*H*$(CH_3)_2$], 6.73 (1 H, d, J 2.5 Hz, 6-H) 6.8 (1 H, s, 2-H), and 7.2 (1 H, d, J 2.5 Hz, 8-H).

3,4-*Dihydro*-1-*hydroxy*-9-*methoxy*-7-(2-*propyl*)*oxy*-3-(*trans*-1'-*propenyl*)-1-*trifluoromethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (212)

A mixture of the quinone (155) (372 mg) and *trans*-3-hexenoic acid (235 mg) in acetonitrile (30 ml) containing silver nitrate (178 mg) in distilled water (3 ml) was treated dropwise with potassium persulphate (419 mg) in distilled water (15 ml) under nitrogen over a period of 30 min at 78°C (bath). The solution was stirred for a further 5h at the same temperature and then poured into water (200 ml) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford, first a fraction (60 mg) of which the ^{1}H n.m.r. spectrum was inconclusive, followed by the *product* (212) (77 mg) contaminated with the first fraction. The second fraction was further purified by p.l.c. to afford the *product* (67 mg, 15%) as an oil. (Found: M^+ 426. $C_{21}H_{21}F_3O_6$ requires M, 426) ν_{max} (neat) 3 440, 1 655, and 1 590 cm^{-1}; δ1.43 [6 H, d, J 6.5 Hz, CH(C*H*$_3$)$_2$], 1.68 (3 H, d, J 5 Hz, 3'-CH$_3$), 2.3 - 3.1 (2 H, m, 4-H), 3.93 (3 H, s, OCH$_3$), 4.0 (1 H, m, partially obscured by methoxyl signal, 3-H), 4.71 [1 H, septet, C*H*(CH$_3$)$_2$], 4.9 (1 H, br s, OH, D$_2$O exchangeable), 5.43 (1 H, m, J 15 Hz, 2'-

H), 5.71 (1 H, m, J 15 Hz, 1'-H), 6.6 (1 H, d, 2.5 Hz, 8-H), and 7.1 (1 H, d, J 2.5 Hz, 6-H).

3-*Carbomethoxy*-5-*methoxy*-7-(2-*propyl*)*oxy*-1,4-*naphthoquinone* (213)

To a mixture of the ester (199) (400 mg) and silver(II) oxide (712 mg) in dioxane (6 ml) was added nitric acid (6 mol.dm^{-3}; 3 ml) with stirring over a period of 4 min. Work-up, as for compound (190), and chromatography (eluant 50% ethyl acetate-light petroleum) afforded the unstable *product* (60 mg, 18%) as an oil. (Found: M$^+$ 304.0945. $C_{16}H_{16}O_6$ requires M, 304.0947) ν_{max} (neat) 1 730, 1 640 (br), and 1 590 cm^{-1}; δ1.42 [6 H, d, J 6.5 Hz, CH(C*H*$_3$)$_2$], 3.87 and 3.90 (each 3 H, s, OCH$_3$), 6.7 (1 H, d, J 2.5 Hz, 6-H), 6.98 (1 H, s, 2-H), 7.13 (1 H, d, J 2.5 Hz, 8-H).

5,8-*Dimethoxy*-3-(*trans*-1'-*propenyl*)-3,4-*dihydroisocoumarin* (217)

Thallium(III) trifluoroacetate (2.289 g) was dissolved in nitrogen-saturated trifluoroacetic acid (10 ml). 2,5-

Dimethoxybenzoic acid (216) (500 mg) was added to this solution and the contents were stirred and gently boiled in a flask immersed in an oil bath (80°C) under nitrogen for 20h. Trifluoroacetic acid was removed under reduced pressure, dry acetonitrile (5 ml) was added to the dark-brown oil followed by palladium(II) chloride (460 mg) and 1,3-pentadiene (piperylene) (354 mg). After stirring for 72h at room temperature under nitrogen, ether (30 ml) was added and the mixture filtered through celite. The residue was washed with more ether and the combined ether solutions were washed with saturated ammonium chloride solution, dried ($MgSO_4$) and chromatographed (eluant 60% ethyl acetate-light petroleum) to afford the *product* (280 mg, 41%) m.p. 102° - 103°C (acetone-light petroleum) (Found: C, 67.7; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.5%) νmax 1 710 and 1 585 cm^{-1}; δ1.72 (3 H, d, J 5 Hz, 3'-CH_3), 2.65 (1 H, dd, J 12 and 17 Hz, *pseudo*-axial 4-H), 3.18 (1 H, dd, J 3 and 17 Hz, *pseudo*-equatorial 4-H), 3.8 and 3.91 (3 H each, OCH_3), 4.6 - 5.0 (1 H, m, 3-H), 5.40 (1 H, m, J 15 Hz, 2'-H), 5.83 (1 H, m, J 15 Hz, 1'-H), 6.83 (1 H, d, J 9 Hz, 7-H), and 7.07 (1 H, d, J 9 Hz, 6-H).

3-*Acetyl*-5-*methoxy*-1,7-*di*(2-*propyl*)*oxy*-4-*naphthol* (223)

Compound (226) (280 mg) was treated with a 0.5% methanolic potassium hydroxide solution (83 ml) for 8 min at room temperature after which the solution was poured into water (200 ml) and acidified with dilute hydrochloric acid. The mixture was extracted with dichloromethane and the residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the *product* (210 mg, 84%); m.p. 91 - 92°C (2-propanol) (Found: C, 68.7; H, 7.3; $C_{19}H_{24}O_5$ requires C, 68.7; H, 7.2%) ν_{max} 1 630, 1 615, and 1 590 cm^{-1}; δ1.42 [12 H, d, J 6.5 Hz, 2 x CH(CH_3)$_2$], 2.65 (3 H, s, $COCH_3$), 3.97 (3 H, s, OCH_3), 4.71 [2 H, septet, 2 x *CH*(CH_3)$_2$], 6.52 (1 H, d, J 2.5 Hz, 6-H), 7.02 (1 H, s, 2-H), 7.15 (1 H, d, J 2.5 Hz, 8-H), and 14.07 (1 H, s, OH, D_2O exchangeable).

3-*Acetyl*-4-*acetoxy*-5-*methoxy*-1,7-*di*(2-*propyl*)*oxy-naphthalene* (226) *and* 4-*Acetoxy*-5-*methoxy*-1,7-*di*(2-*propyl*)*oxy-naphthalene* (227)

The naphthol (145) (3.0 g) was dissolved in dry chloroform (70 ml) and the solution was stirred and brought to reflux. A premixed solution of T.F.A.A. (3.26 g, 1.5 equiv.) and glacial acetic acid (931 mg, 1.5 equiv.) was added to the hot solution and stirring was continued under reflux for 10 min after which the same amount of the mixed anhydride solution was added. The solution was stirred for an additional 10 min under reflux and methanol (30 ml) was added. Volatiles were removed under reduced pressure and the oily residue was chromatrographed (eluant 20% ethyl acetate-light petroleum) to afford first starting material (1.74 g), followed by the *acetate* (227) (470 mg, 33% based on unrecovered starting material) m.p. 140 - 141°C (light petroleum) (Found: C, 69.0; H, 7.4. $C_{19}H_{24}O_5$ requires C, 68.7; H, 7.3%); νmax 1 770 and 1 610 cm^{-1}; δ1.4 [12 H, d, J 6.5 Hz, 2 x CH(C*H*$_3$)$_2$], 2.28 (3 H, s, OCOCH$_3$), 3.83 (3 H, s, OCH$_3$), 4.7 [2 H, septet, 2 x C*H*(CH$_3$)$_2$], 6.47 (1 H, d, J 2.5 Hz, 6-H), 6.7 (2 H, s, 2- and 3-H), and 7.17 (1 H, d, J 2.5 Hz, 8-H). Later fractions gave the *product* (226) (1.06 g, 65% based on unrecovered starting material) m.p. 104 - 105°C (methanol) (Found: C, 67.5; H, 6.9. $C_{21}H_{26}O_6$ requires C, 67.4; H, 7.0%) νmax 1 750, 1 670, and 1 600 cm^{-1}; δ1.42 [12 H, d, J 6.5 Hz, 2 x CH(C*H*$_3$)$_2$], 2.4 (3 H, s, OCOCH$_3$), 2.62 (3 H, s, COCH$_3$), 3.87 (3 H, s, OCH$_3$), 4.7 [2 H, septet, 2 x C*H*(CH$_3$)$_2$], 6.50 (1 H, d, J 2.5 Hz, 6-H), 7.17 (1 H, s, 2-H), and 7.20 [1 H, d, J 2.5 Hz, (partially obscured by signal of 2-H), 8-H].

2-*Acetyl*-3-(*trans*-2'-*pentenyl*)-1,4-*naphthoquinone* (229)

Compound (185) (500 mg) was oxidatively demethylated with silver(II) oxide (1.09 g) in the usual manner to afford the crude quinone (28) after work-up. This was dissolved in acetonitrile (20 ml) and the solution was stirred at 75°C (bath). Distilled water (15 ml), *trans*-3-hexenoic acid (376 mg) and silver nitrate (150 mg) in distilled water (3 ml) were added in that order and the flask was flushed with nitrogen. The solution was treated dropwise with ammonium persulphate (904 mg) in distilled water (15 ml) over a period of 25 min. The solution was stirred for a further 1h at the same temperature. Work-up as for compound (191), afforded an oil which was chromatographed (eluant 40% ethyl acetate-light petroleum) to give the *product* [150 mg, 26% overall from (185)] as an oil. (Found: M^+ 268.1071. $C_{17}H_{16}O_3$ requires M, 268.1099); ν_{max} (neat) 1 665 (br) and 1 595 cm^{-1}; δ0.98 (3 H, t, J 8 Hz, 5'-CH_3), 2.05 (2 H, m, 4'-H), 2.57 (3 H, s, $COCH_3$), 3.2 (2 H, dd, J 1 and 4 Hz, 1'-H), 5.4 (2 H, m, J 15 Hz established by double irradiation experiments, 2'- and 3'-H), 7.73 (2 H, m, 6- and 7-H), and 8.06 (2 H, m, 5- and 8-H).

2-*Acetyl*-1,4-*dimethoxy*-3-(*trans*-2'-*pentenyl*)-*naphthalene* (233)

Quinone (229) (300 mg) was reductively methylated employing the usual conditions. Work-up and chromatography (eluant 20% ethyl acetate-light petroleum) afforded the *product* (230 mg, 69%) an oil. (Found: M^+ 298.1594. $C_{19}H_{22}O_3$ requires M, 298.1569); ν_{max} (neat) 1 695 and 1 590 cm^{-1}; δ0.92 (3 H, t, J 8 Hz, 5'-CH_3), 2.02 (2 H, m, 4'-H), 2.58 (3 H, s, $COCH_3$), 3.53 (2 H, m, 1'-CH_2), 3.87 and 3.90 (each 3 H, s, OCH_3), 5.43 [2 H, m, (J 15 Hz established by double irradiation experiments), 2'- and 3'-H], 7.53 (2 H, m, 6- and 7-H), and 8.07 (2 H, m, 5- and 8-H).

2-*Tribromoacetyl*-1,4-*dimethoxy*-3-(*trans*-2'-*pentenyl*) *naphthalene* (234)

Compound (233) (180 mg) in dioxane (2 ml) was treated with a freshly prepared sodium hypobromite solution[84] (10 ml) for 3h at room temperature and then for 2 h at 60°C (bath) protected from light. Sodium metabisulphite (3 g) in water (15 ml) was added and the mixture was poured into water and extracted with dichloromethane. The organic extract was dried ($MgSO_4$) and evaporation of the solvent gave the *product* (277 mg, 86%) as an oil, virtually pure by t.l.c. (Found: M^+ 537.8787. $C_{19}H_{19}{}^{81}Br_3O_3$ requires M, 537.8827) ν_{max} (neat) 1 720 and 1 585 cm^{-1}; δ0.92 (3 H, t, J 8 Hz, 5'-CH_3), 2.02 (2 H, m, 4'-H), 3.52 (2 H, m, 1'-CH_2), 3.95 (6 H, s, 2 x OCH_3), 5.5 [2 H, m, (J 15 Hz established by double irradiation experiments), 2'- and 3'-H], 7.53 (2 H, m, 6- and 7-H), and 8.07 (2 H, m, 5- and 8-H).

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