THE SYNTHESES OF SOME NATURALLY DERIVED NAPHTHOQUINONES

a thesis submitted to the

U N I V E R S I T Y O F C A P E T O W N

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the degree of

DOCTOR OF PHILOSOPHY

by

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ABSTRACT

The synthesis of the naphthalene core of the ansamycin antibiotics, 8-acetyl-3-acetylamino-5,7-dihydroxy-1,4-naphthoquinone from benzoquinone by means of simple reactions including, Diels-Alder adduct formation, mild acetylation, oxime formation and Beckmann rearrangement in five steps with an overall yield of 22% is described in Chapter 1.

The synthesis of the naturally occurring naphthoquinone derivative, possessing antitumour and antiprotozoal properties, bikaverin is described in Chapter 2.

Starting from vanillin the key intermediate 2-(2'-benzyloxy-6'-methyl-4'-methoxybenzoyl)-1,4,5,6,8-pentamethoxynaphthalene was prepared in six simple steps in an overall yield of 18%. This key intermediate was converted into bikaverin utilizing two independent routes.

In the first route the benzyl group was removed from the key intermediate by hydrogenolysis followed by oxidative spiro ring formation with 2,3-dichloro-5,6-dicyanobenzoquinone. After effecting xanthone ring formation and removal of two methyl groups with lithium iodide, bikaverin was produced in six steps in an overall yield of 32%.

In the second route the key intermediate was first oxidised by silver(II) oxide this was followed by removal of the benzyl group and two methyl groups *peri*- to the quinone with boron trichloride, which led to spontaneous spiro ring

formation, ultimately bikaverin was produced in three steps in an overall of 34%.

The syntheses of the naturally occurring product ventiloquinone E and its *trans*-isomer as well as an isomer of the naturally occurring ventiloquinone J and its *trans*-isomer are described in Chapter 3.

Starting from 1,2,4,5,8-pentamethoxynaphthalene, the synthesis of which has been described in Chapter 2, ventiloquinone E was prepared in nine steps in an overall yield of 7%. Similarly an isomer of ventiloquinone J was also prepared from 1,2,4,5,8-pentamethoxynaphthalene in ten steps in an overall yield of 6%.

In both cases a mixture of *cis*-and *trans*-isomers was obtained, a successful resolution of both mixtures was accomplished by thin layer chromatography.

By two other methods the *trans*-isomer of ventiloquinone E could be prepared in either nine steps in an overall yield of 23% or in six steps with an overall yield of 30% starting from the same pentamethoxynaphthalene.

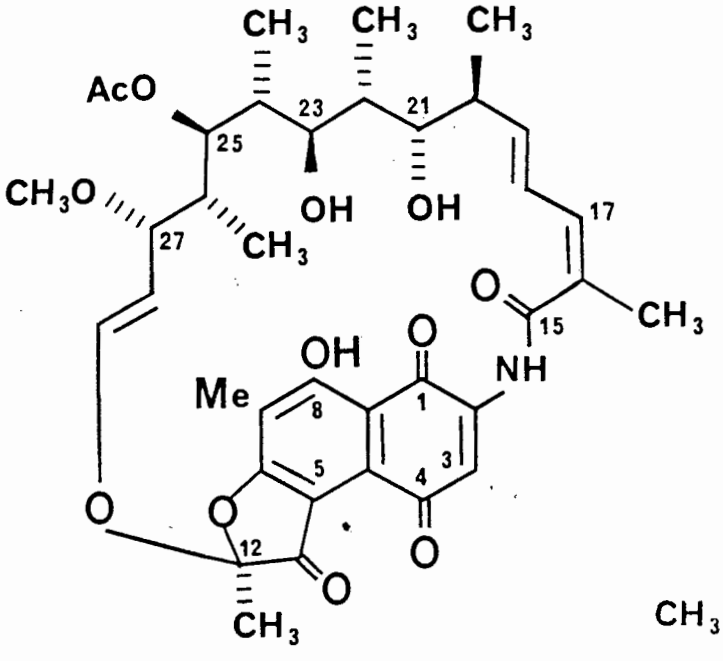
CHAPTER 1

SYNTHESIS OF THE NAPHTHALENE CORE OF THE RIFAMYCINS

INTRODUCTION

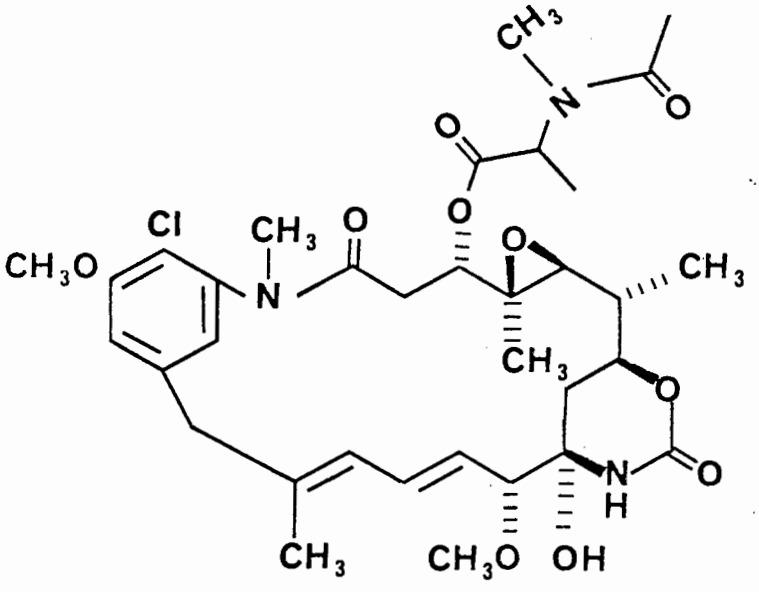
The ansamycins[1] are a class of macrocyclic lactams which possess interesting biological properties. These lactams are characterised by an aliphatic chain, known as an ansa chain, linked to non-adjacent positions on an aromatic nucleus.

The ansamycins can be divided into two sub-classes; namely the rifamycins[2] and streptovaricins,[1] and the maytansinoids,[1] the former having the ansa chain linked to a naphthoquinone or naphthalene nucleus and the latter having the chain attached to a benzene ring.



rifamycin S

maytansine



Many ansamycins are of great interest because of their structure, biogenesis, mechanism of action and therapeutic value. The rifamycins show an inhibitory effect against gram-positive bacteria,[3] while several semi-synthetic rifamycins show moderate activity against gram-negative bacteria[2] as well as antiviral properties,[4] a number of these being in clinical use. Of notable interest in the South African context is rifampicin[5] which is a broad-spectrum antibiotic used in the treatment of tuberculosis.[6]

The streptovaricins also show an inhibitory effect against gram-positive bacteria,[2] while various maytansenoids show antileukaemic and antitumour activity.[7]

As our synthetic study was aimed mainly at the rifamycins, only they will be discussed in more detail.

Although the rifamycins are produced as secondary metabolites by micro organisms belonging to the genus *Nocardia*[8] (orginally classified as *Streptomyces)* the laboratory synthesis is important for a number of reasons. First, as they are clinically important, an economical route for their synthesis has great value although it would probably be very difficult to devise a synthesis which could compete with the microbiological production of this material. Secondly, numerous antibiotics have unwanted side effects and if various analogues can be synthesised their activity might be such that they could alleviate or even eliminate these side effects.

Thirdly, as a number of bacteria and viruses have the ability to mutate this could render the antibiotic ineffective, so other antibiotics or derivatives have to be synthesised. Fourthly, by being able to make analogues, the mode of biological action could be investigated.

Studies[9] have shown that the rifamycins act on bacteria which block the synthesis of mammalian RNA, by inhibiting the DNA and RNA manufactured by the bacteria, making them chemotherapeutic agents, meaning they have a selective toxic effect.

Certain structural requirements[10] have to be present to afford this ability and by the use of numerous natural and semi-synthetic rifamycins it has been established that free hydroxyl groups are required on C-21 and C-23 (see diagram) in the ansa chain while it appears that the acetoxy group at C-25 and the methoxy group at C-27 are not essential. It has also been ascertained that rifamycins with functional modifications of the ansa chain which leave the hydroxyl groups in positions C-21 and C-23 intact, but produce important conformational changes elsewhere, are also not very active.[2]

Additionally, it has been accepted that a hydrogen bond between the functional groups on C-8 and C-1 of the aromatic ring is essential. This together with the hydroxyls in position C-21 and C-23 provide the binding sites of the rifamycin

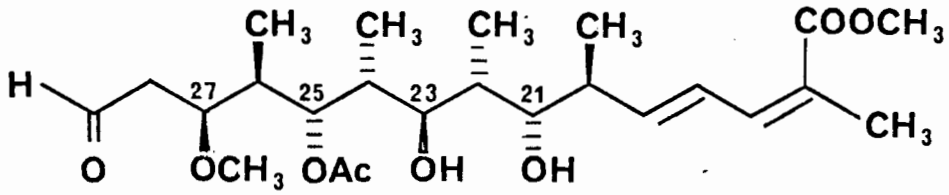
with the enzyme which produces the bacterial RNA and DNA (DNA - directed RNA polymerases, DDRP).

Apart from these requirements, the anti-bacterial activity of the ansamycin antibiotics withstands considerable variations.[2] Changes in substitution in position 3 and 4[11] do not dramatically influence the antibacterial activity, perhaps showing that this side of the molecule is not important in binding with the enzyme. Rather the differences in substitution at C-3 and C-4 seem to effect the ability of the antibiotic to penetrate the bacterial cell wall.

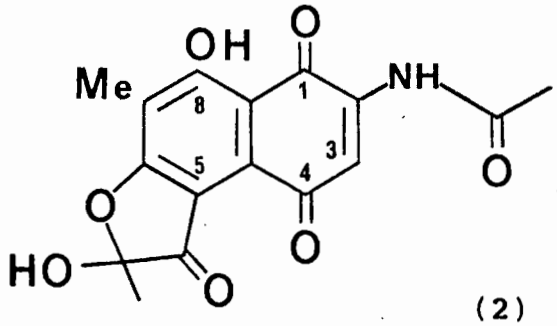
From the knowledge accumulated about the mode of action of the rifamycins it seems that as numerous changes in structure do not effect the activity, this will lead to the synthesis of many rifamycin analogues containing many structural differences, which may lead eventually to the synthesis of the "perfect" antibiotic.

The laboratory syntheses of the rifamycins in general involves the independent construction of the aromatic nucleus and the ansa chain, and their subsequent combination. Since our interest was mainly in the naphthalenic portion, syntheses of the ansa chain will not be discussed.

To date only one complete synthesis of rifamycin S (12) has been reported (c.f. Kishi).[12] This synthesis involved the combination of the aliphatic segment (1) and the aromatic portion (2).

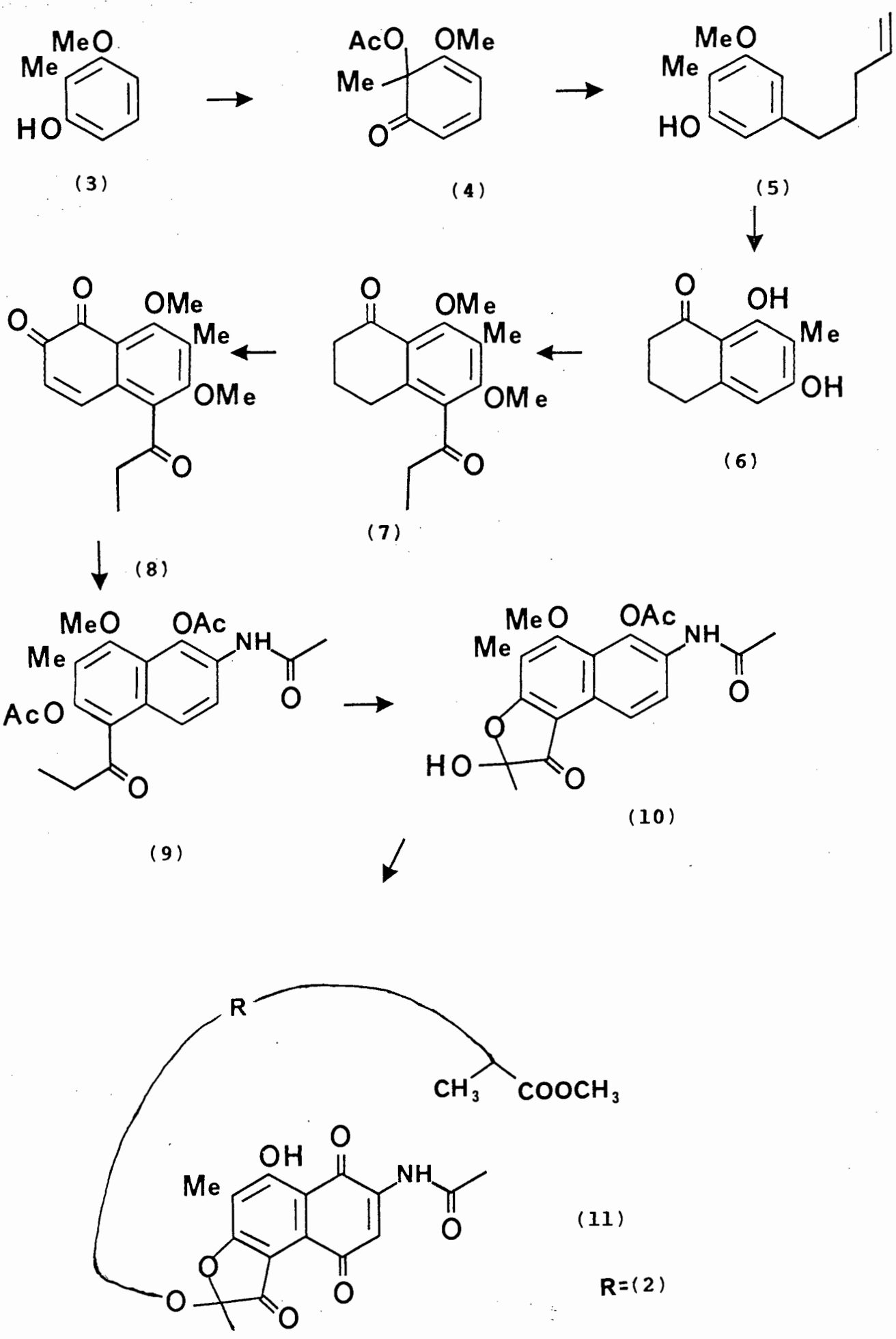


(1)



(2)

The naphthalenic portion was synthesised by an elaborate method in fourteen steps with an overall yield of 20%. The starting material 2-methylresorcinol monomethyl ether (3) was oxidised to the cyclohexadienone (4), which in turn was converted to the phenol (5). This was transformed to the tetralone (6). Using a second Friedel-Crafts reaction the acyl function was introduced to afford (7). The orthoquinone (8) was then prepared by oxidation using selenium dioxide. This was converted to the acetoamido derivative (9) by treatment with hydroxylamine hydrochloride, followed by reduction and acetylation. Further oxidation with selenium dioxide afforded the hemiacetal (10). After ansa chain attachment the naphthalene was oxidised to the naphthoquinone (11) which could be converted to Rifamycin S (12).


MeO
Me
HO
(3)
AcO
OMe
Me
O
(4)
MeO
Me
HO
(5)
O
OH
Me
OH
(6)
O
OMe
Me
OMe
O
(7)
O
O
OMe
Me
OMe
O
(8)
MeO
OAc
NH
Me
AcO
O
O
(9)
MeO
OAc
NH
Me
O
O
HO
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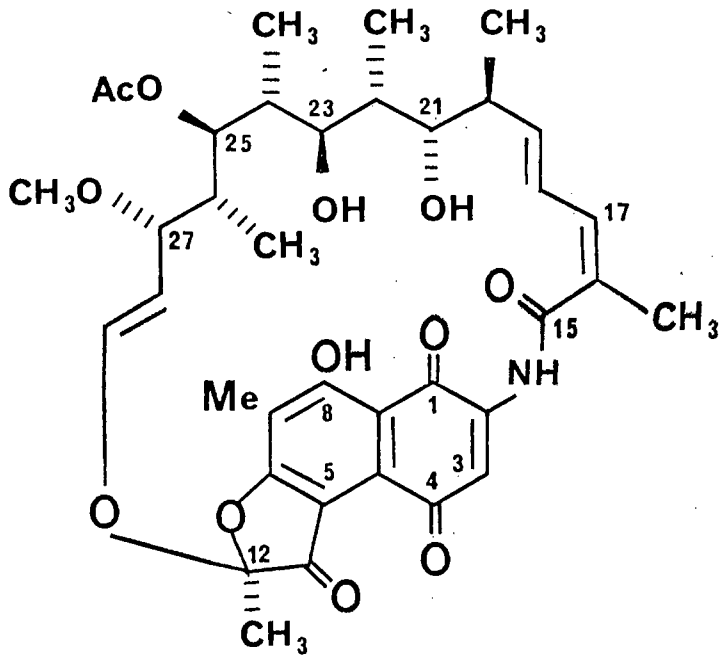
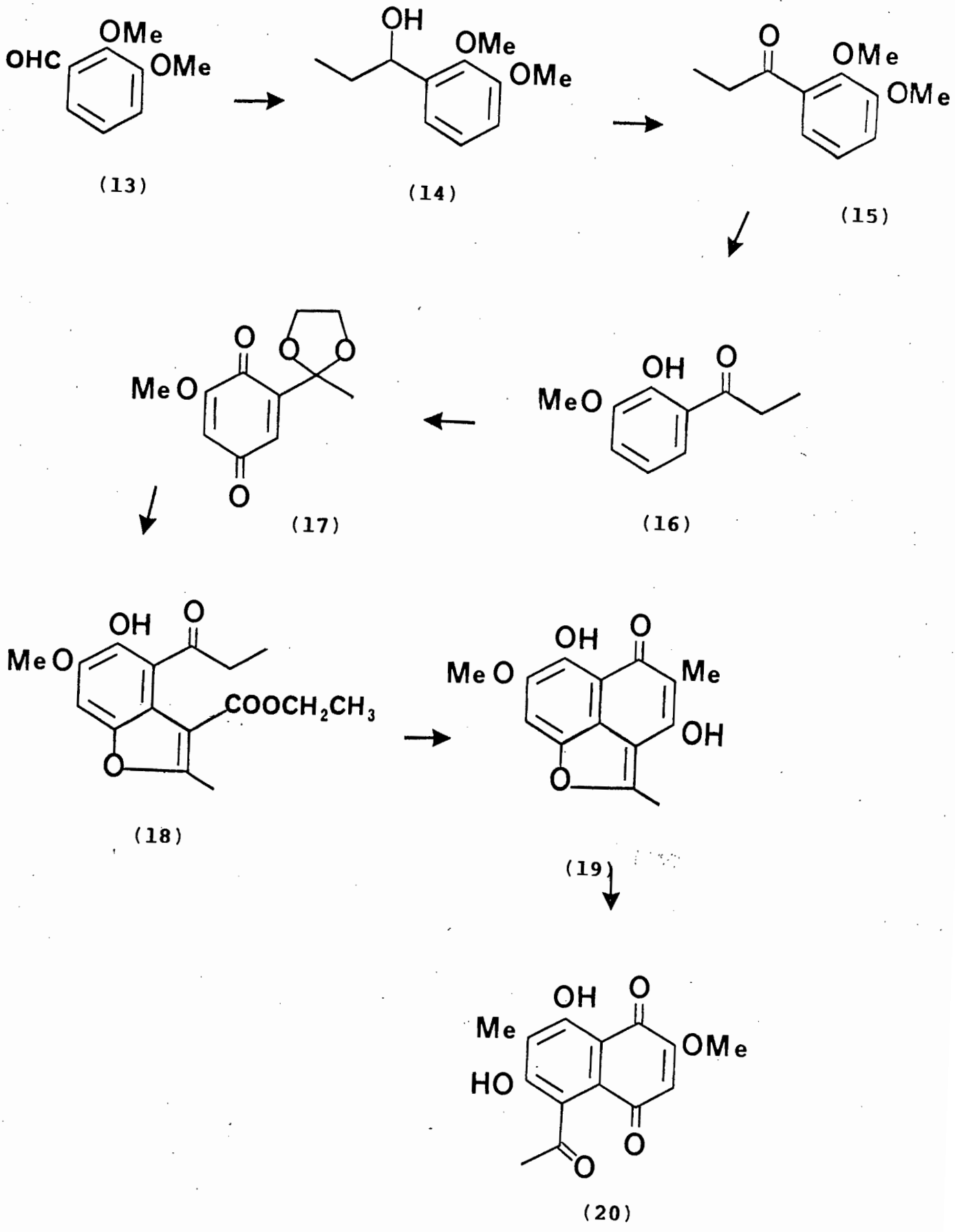
(11)
R=(2)



(12)

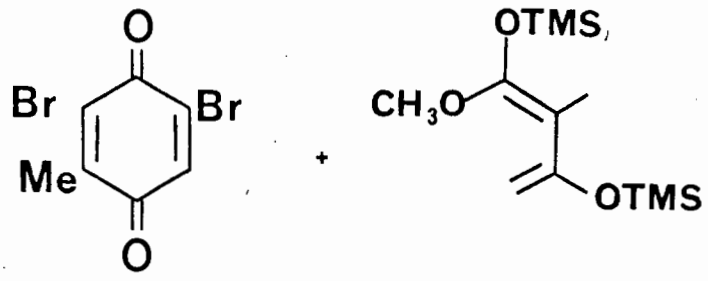
Four other syntheses of the aromatic portion of the rifamycin molecule have also been described recently.

Parker *et al.*[13] generated the rifamycin nucleus starting from the aldehyde (13). This was converted to the alcohol (14) which was subsequently oxidised to furnish the ketone (15). Demethylation afforded phenol (16), and protection of the ketone as a ketal, followed by oxidation gave the quinone (17). Michael addition of ethyl acetoacetate afforded the benzofuran (18), after affecting deketalization and dehydration of the adduct with hydrochloric acid. Intramolecular Claisen condensation by stirring (18) with sodium ethoxide furnished compound (19). Oxidative cleavage of this product with cerium(IV) ammonium nitrate gave the quinone (20).


OMe
OHC
OMe
(13)
OH
OMe
OMe
(14)
O
OMe
OMe
(15)
OH
O
MeO
(16)
O
O
O
MeO
(17)
OH
O
MeO
COOCH2CH3
(18)
OH
O
MeO
Me
OH
(19)
OH
O
Me
OMe
HO
O
O
(20)

Although this was a relatively short synthesis (seven steps), the overall yield was only 10%, mainly as a result of the Michael addition which proceeded in low yield (37%). In addition, Parker did not introduce a nitrogenous group in position 2 which is present in most of the rifamycins, although Day[14] claims this would be a simple reaction to perform.

Trost and Pearson[15] achieved the partial synthesis of the rifamycin nucleus by means of a cycloaddition reaction.



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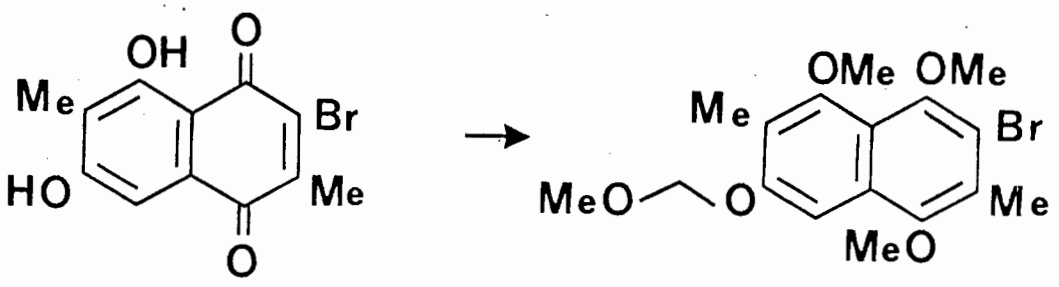
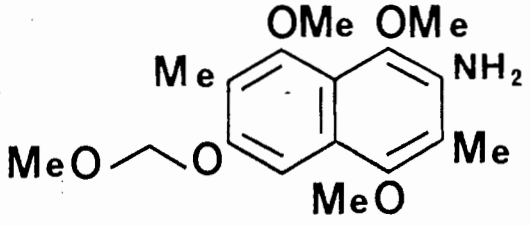


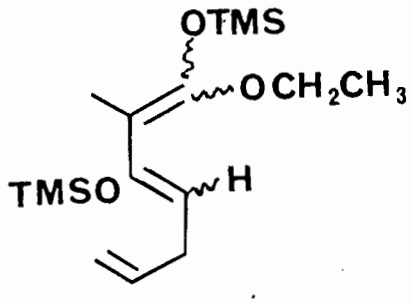
(23) (24)



(25)

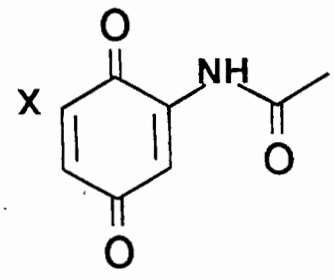
By using the dibromoquinone (**21**) and the diene (**22**), a regiochemical addition afforded the quinone (**23**). After protecting this naphthoquinone (**23**) to furnish the naphthalene (**24**), the amine (**25**) was synthesised by using azidomethylphenyl sulphide for the introduction of the amine function. Although the aromatic portion had been synthesised in only six steps with an overall yield of 22%, Trost had not introduced an acyl function at C-8. Had Trost attempted this introduction it would most likely have been problematic in view of the results obtained in our laboratory[16] and independent work reported by Ross Kelly.[17]

Ross Kelly *et al.*[17] have reported an elegant synthesis requiring eight steps to give the naphthalenic nucleus in overall yield of 37%. This was achieved by the cycloaddition of the diene (**26**) and the quinone (**27**), both readily prepared, to afford an adduct which was aromatised by treating with hydrochloric acid to give the naphthalene (**28**). Oxidation of the allyl side chain gave the chromophore (**29**).

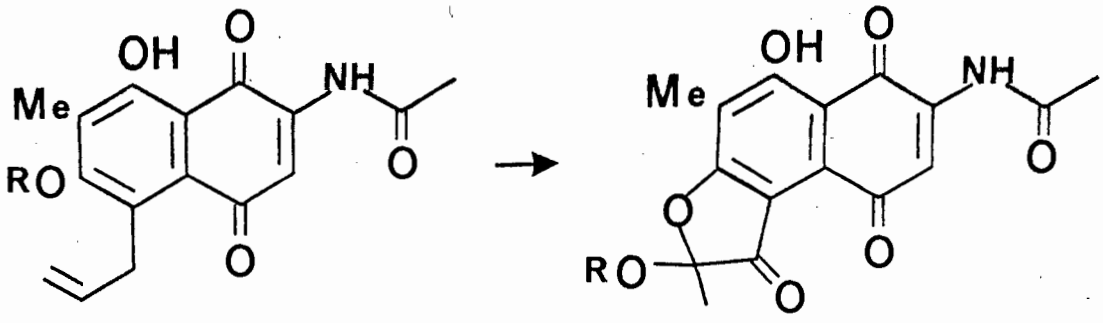


(**26**)

+



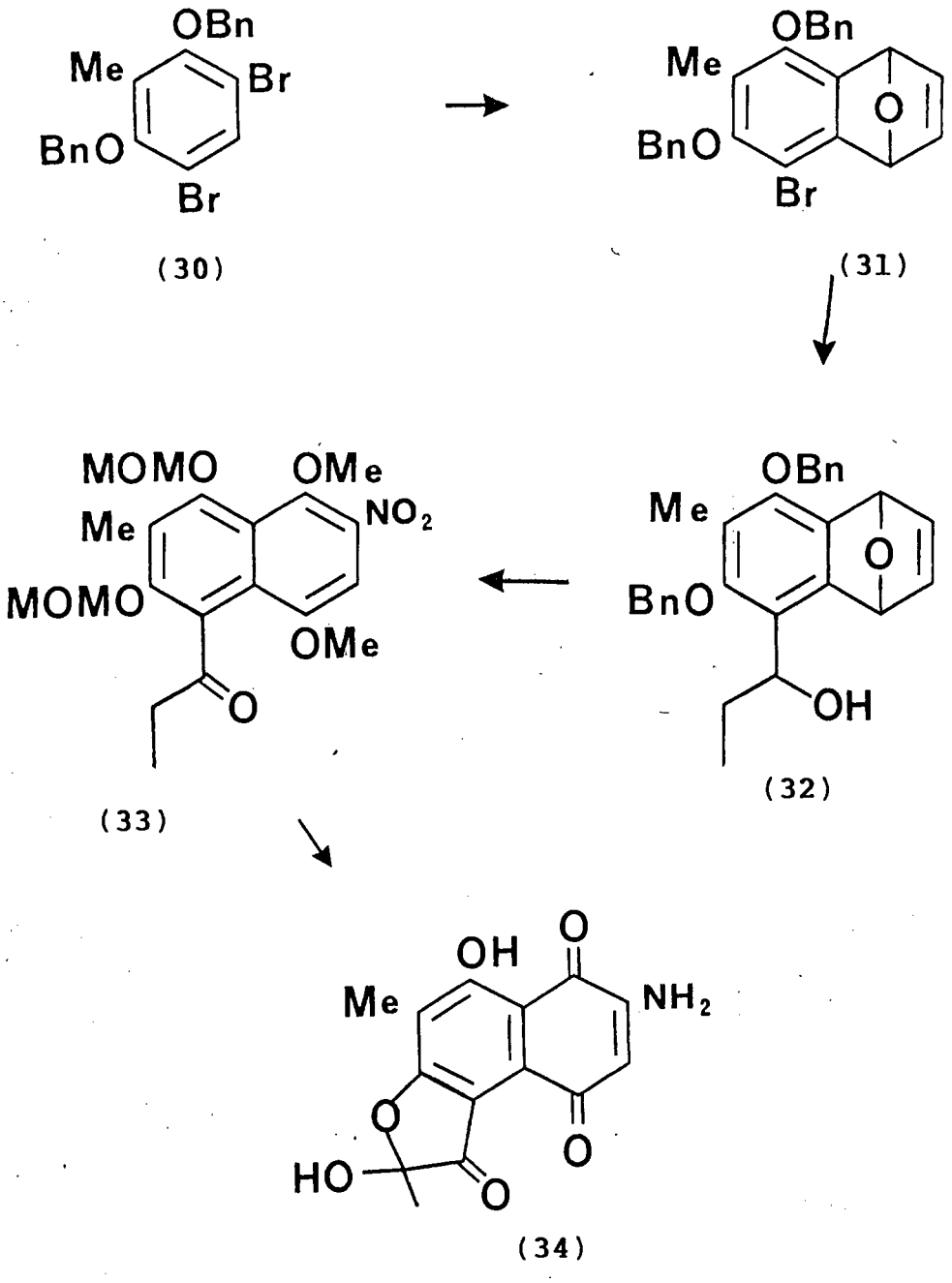
(**27**)



(28) (29)

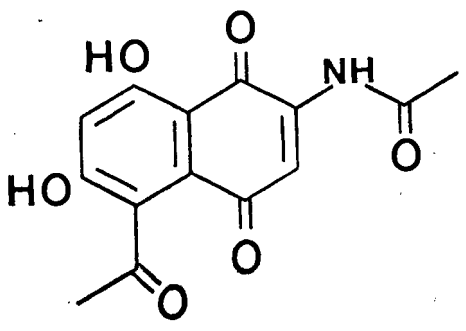
R= ether protecting group

More recently Kinoshita *et al.*[18] have described yet another synthesis of the rifamycin nucleus. This was done by generating the benzyne derivative of (30), and then reacting this with furan *in situ* to afford the bromoepoxide (31). Treatment of this with *n*-butyl lithium and propanal introduced the aliphatic side chain to furnish (32). Ring opening, oxidation, selective protection and nitration with copper nitrate yielded the nitro derivative (33), which was easily converted to the chromophore (34). This synthesis was achieved in thirteen steps with an overall yield of 18%. Although all the steps in the synthesis had good yields a cumbersome procedure of removing one protecting group and replacing it with another was utilized.

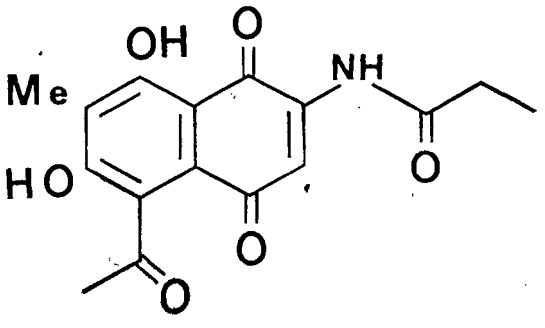


In our laboratory the synthesis of the rifamycin nucleus was also undertaken utilizing a mild Friedel-Crafts reaction recently developed.[19]

Two independent syntheses were attempted. The synthesis of the chromophore (35) lacking a methyl group at C-6, which is described in this thesis, and the other, the chromophore (36) possessing a methyl at C-6.[16]



(35)

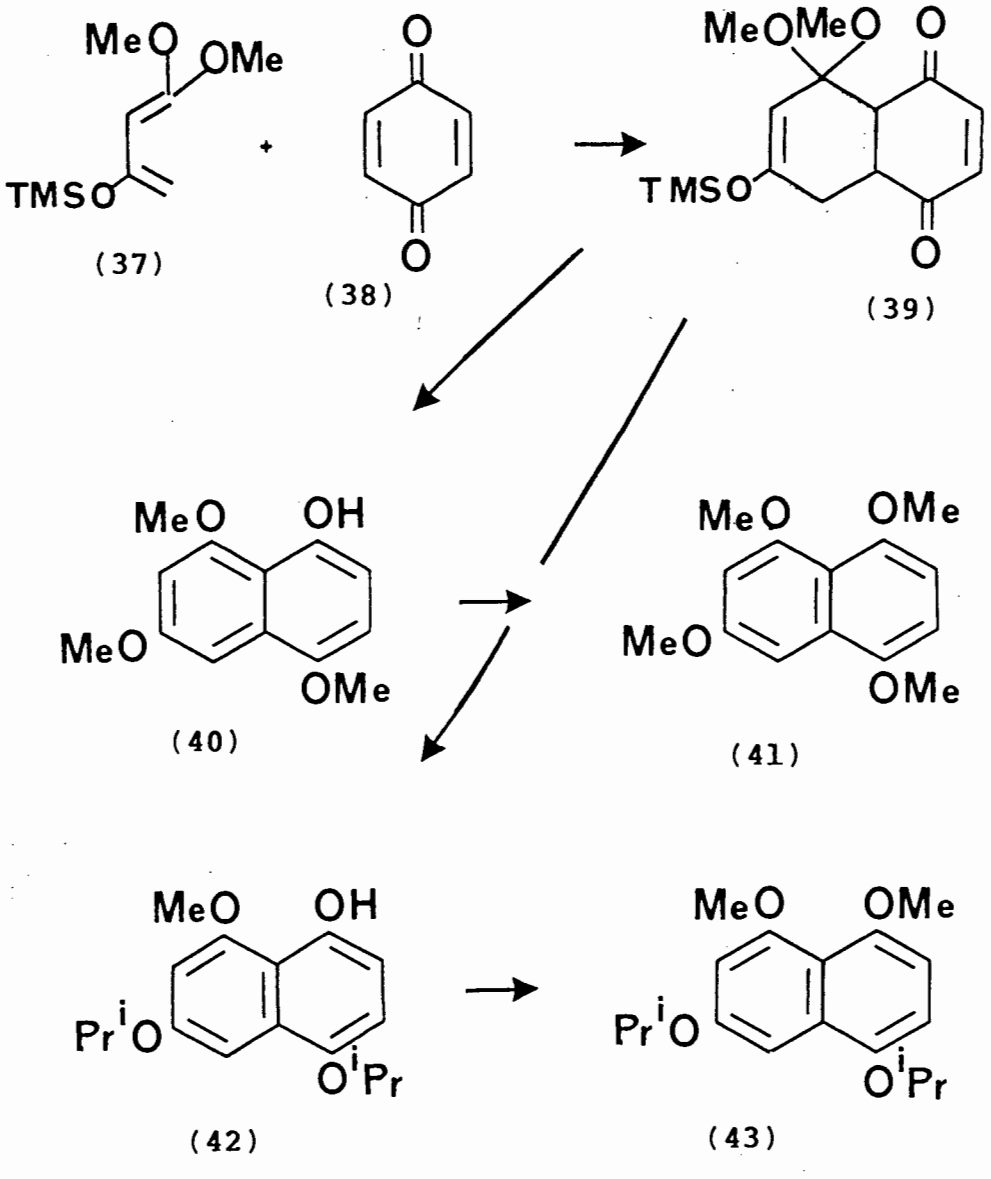


(36)

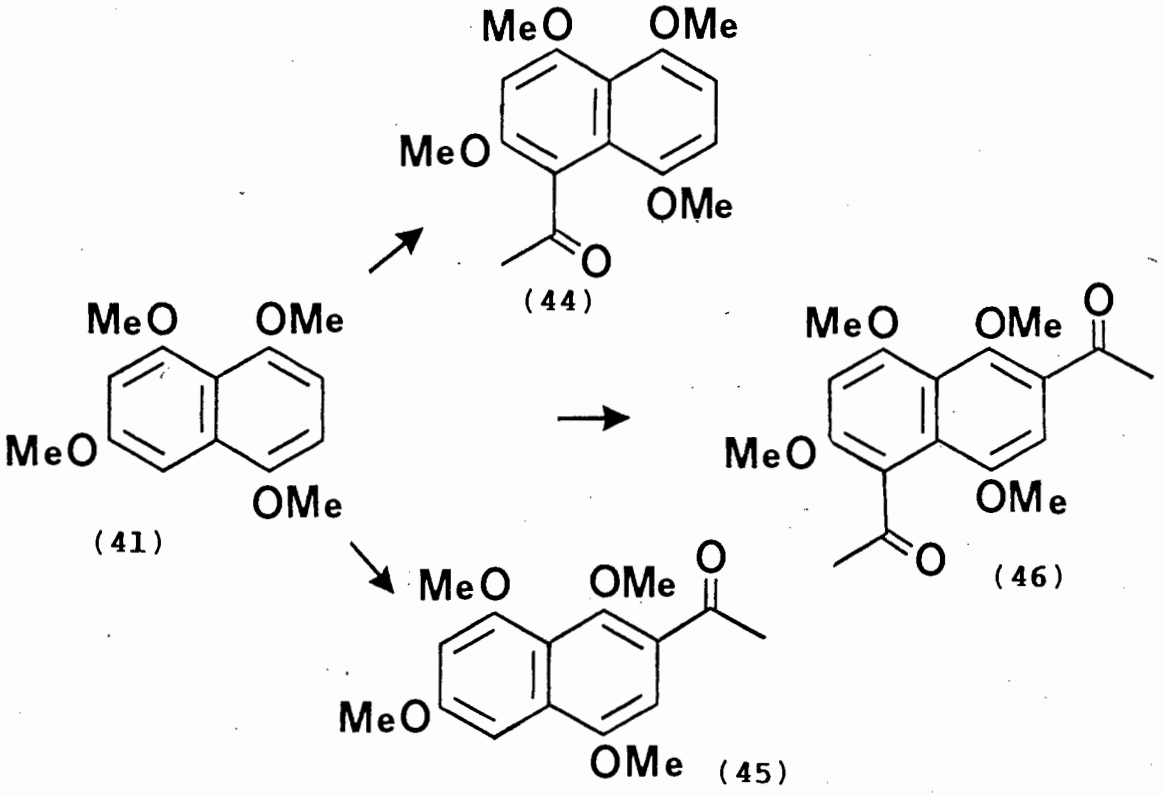
Both chromophore (**35**) and chromophore (**36**) were synthesised in overall yields of 22% and 20%, over five steps and six steps respectively.

RESULTS AND DISCUSSION

It has been found[21] that Brassard's diene (37)[20] reacts smoothly with benzoquinone (38) to afford the adduct (39). Methylation of the adduct (39) results in the formation of the naphthol (40), which on further methylation affords 1,4,5,7-tetramethoxynaphthalene (41). Alternatively, treatment of the adduct (39) with isopropyl bromide in the presence of potassium carbonate leads to the production of the naphthol (42), while further methylation affords the naphthalene (43).



Earlier work from our laboratory[19] has shown that 1,4,5,7-tetramethoxynaphthalene (**41**) undergoes monoacetylation with acetic acid in the presence of trifluoroacetic anhydride to yield 8-acetyl-1,4,5,7-tetramethoxynaphthalene (**44**) as the major reaction product and 3-acetyl-1,4,5,7-tetramethoxynaphthalene (**45**) as the minor product. In addition a trace of the 3,8-diacetylated product (**46**) was formed.



On examination of numerous rifamycins (for example rifamycin S (**12**)) it was noted that the naphthalene oxygenation pattern was identical to that of the system in 1,4,5,7-tetramethoxynaphthalene (**41**), and also that the ansa chain was connected at C-3 and C-8 of the naphthalenic nucleus, the positions where acetylation occurred in our system.

It was decided to try and generalize our acetylation reaction by performing acylations using various aliphatic acids, as the ansa chain could be considered to be derived from a long chain aliphatic dicarboxylic acid.

To simplify the reaction, it was initially thought advantageous to carry out the acylations with a variety of simple aliphatic monocarboxylic acids. In view of the fact that it was already known that monoacetylation of the naphthalene (**41**) gave rise to the two products (**44**) and (**45**), the possibility of altering the protection on one or more of the oxygens to give a single product of substitution at either C-3 or C-8 was first investigated.

This was readily achieved by replacing the electron donating methoxy group in the 4-position by the less electron donating acetoxy group thus making position 3 less susceptible to electrophilic attack.

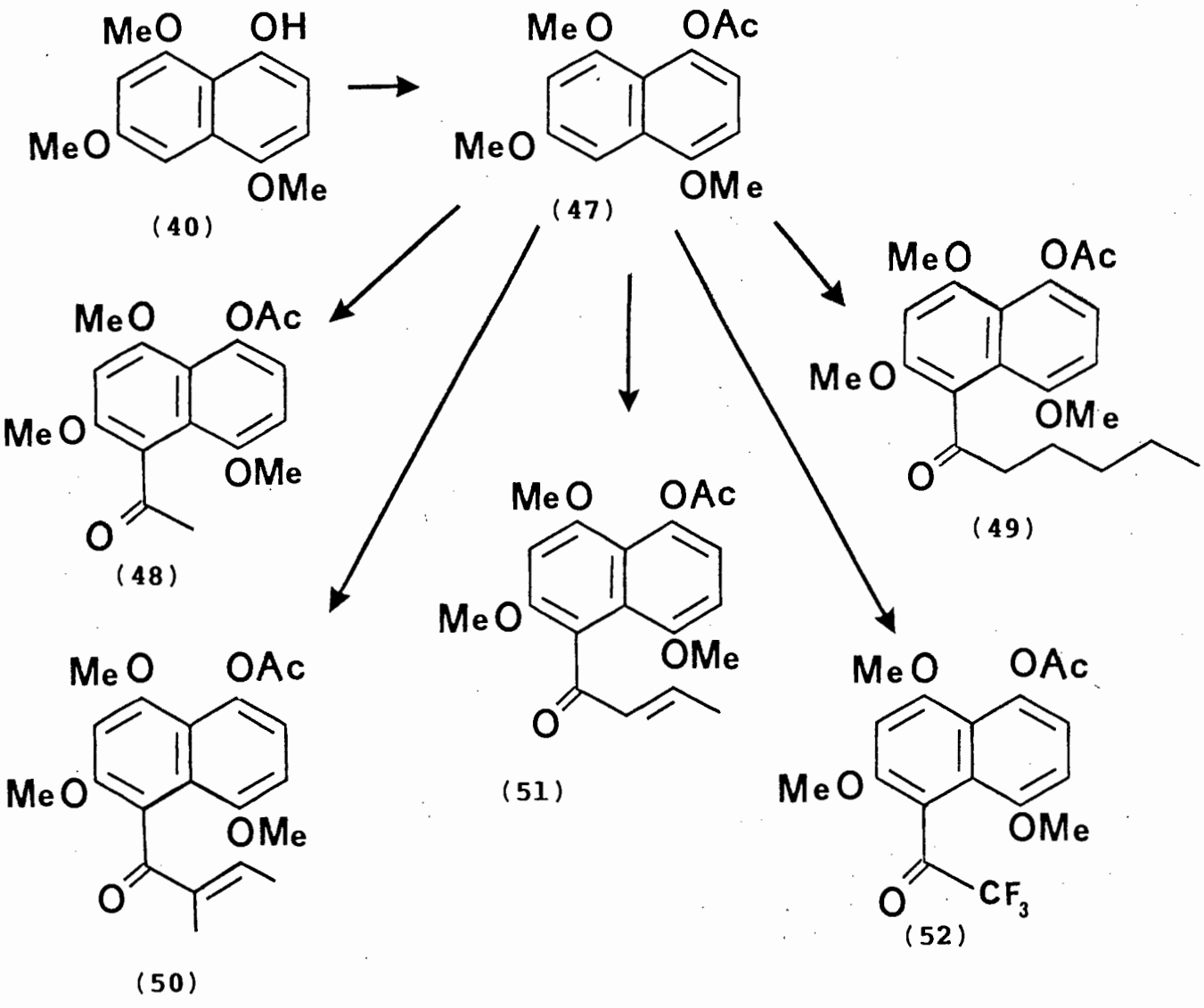
The naphthol (**40**) was acetylated with acetic anhydride in the presence of pyridine to give the acetate (**47**). This substance showed in the ^{1}H n.m.r. spectrum a characteristic acetyl peak at δ 2.33, three methoxy groups at δ 3.88, δ 3.91 and δ 3.97, two *meta*-coupled aromatic protons at δ 6.54 and δ 7.19 with J 2Hz and two *ortho*-coupled protons at δ 6.73 and δ 6.85 having J 8Hz respectively.[19]

Acetylation of the acetate (**47**) with acetic acid and trifluoroacetic anhydride gave 8-acetyl-4-acetoxy-1,5,7-trimethoxynaphthalene (**48**) as the sole product in a yield of 77%. The ^{1}H n.m.r. spectrum of this compound showed, as expected, the loss of the signals of the *meta*-coupled protons, these being replaced by an aromatic singlet at δ 6.73. Furthermore the two *ortho*-coupled protons at δ6.80 and δ6.97, with a coupling constant of *J* 8Hz were still present. The infrared spectrum showed two characteristic carbonyls at 1765 and 1710 cm^{-1}, (the former due to the acetate carbonyl and the later due to the C-8 acetyl group) and the mass spectrum showed a molecular ion at *m/z* 318. Although the assignment could have been reasoned to be the 6-acetyl isomer this was discounted on the basis that the higher field of the two *meta*-coupled protons at δ6.54 and δ7.19 in the starting material (**47**) was closer to the value of the chemical shift of the singlet (δ 6.73) in the product (**48**) and that this minor deshielding was due to the electron-withdrawing acetyl group *meta*- to it in the product. Other arguments favouring C-8 acetylation would also include the known preference for α-rather than β-substitution of naphthalenes, as well as the fact that resorcinol dimethyl ether is known to undergo electrophilic substitution at the 4- rather than the 2-position. This assignment was consistent also with the assignment of the 8-acetyl derivative (**44**) as the major product of acetylation of naphthalene (**41**), rather than the isomeric 6-acetyl compound. The assignment was finally confirmed in the determination of the crystal structure of the derivative (**55**) of the analogue (**53**) of the naphthalene

(**46**), itself the product of exhaustive acetylation of compound (**44**).

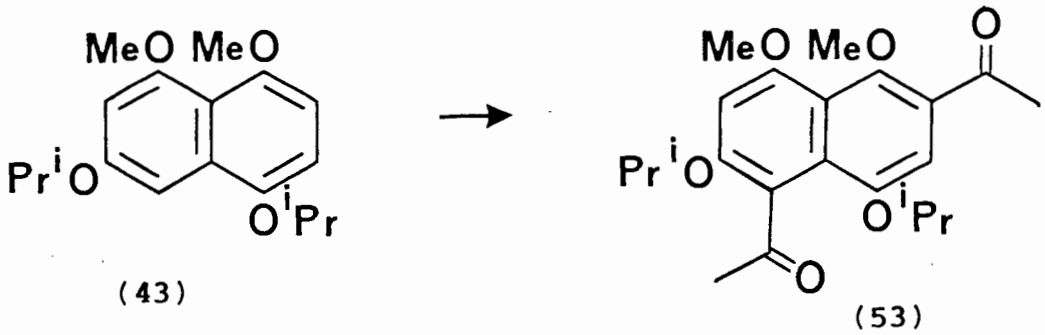
Replacement of the acetic acid in the acetylation by hexanoic, tiglic and crotonic acid yielded solely the hexanoyl, tiglyl and crotonyl derivatives (**49**), (**50**) and (**51**) respectively, as shown by spectroscopic techniques. The ^{1}H n.m.r. spectra of (**50**) and (**51**) showed that no isomerization of the tiglyl and crotonyl residues had taken place.

In these syntheses a slight excess of the organic acid and trifluoroacetic anhydride was required. However, it was found that with more of the latter anhydride, trifluoroacetylation also occurred as illustrated by the isolation of a by-product (**52**) in both the tiglic acid and crotonic acid reactions. This product still showed the two characteristic carbonyls at 1762 and 1744 cm^{-1} in the infrared spectrum. The ^{1}H n.m.r. spectrum indicated the loss of the signal of the *meta*-coupled protons, which were replaced by an aromatic high field proton at δ6.57, but there were no acyl methyl protons. The mass spectrum showed a molecular ion at *m/z* 372. From this information it was reasoned that trifluoroacetylation had occurred to afford product (**52**).



It was therefore possible to show that a simple change in the protection of the C-4 oxygen of naphthalene (**41**) from methyl to acetyl eliminated acylation at C-3. Interestingly, however, the substitution of the C-7 methoxy group in (**41**) to yield the C-7 acetate did not effect the converse change, that is, the exclusion of acetylation at C-8, since a separate study[22] of the acetylation of 7-acetoxy-1,4,5-trimethoxy-naphthalene showed that, under the same conditions, the C-8 acetyl derivative was the major product, the C-3 isomer being formed in minor amounts.

As noted earlier, it appeared that a 3,8-diacetyl derivative such as (**43**) was a suitable precursor to the nucleus of various rifamycins. It was thought that treatment of 1,7-di-isopropoxy-4,5-dimethoxynaphthalene (**43**) with an excess of acetic acid and trifluoroactic anhydride would result in the formation of the 3,8-diacetyl derivative (**53**) as the only product. Thus reaction of the naphthalene (**43**) with nine molar equivalents of acetic acid and trifluoroacetic anhydride afforded the diacetyl derivative (**53**) in 72% yield. The ^{1}H n.m.r. spectrum showed, *inter alia*, two methyl signals at δ 2.55 and δ 2.72 and two aromatic singlets at δ 6.64 (H-6) and δ 7.03 (H-2) respectively (H-2 being more deshielded than H-6 as it is *ortho*- to a carbonyl group). Further support for the structure was obtained from the infrared spectrum which showed carbonyl stretching frequencies at 1707 cm^{-1} and 1660 cm^{-1}, and the mass spectrum which showed a molecular ion at *m/z* 388.



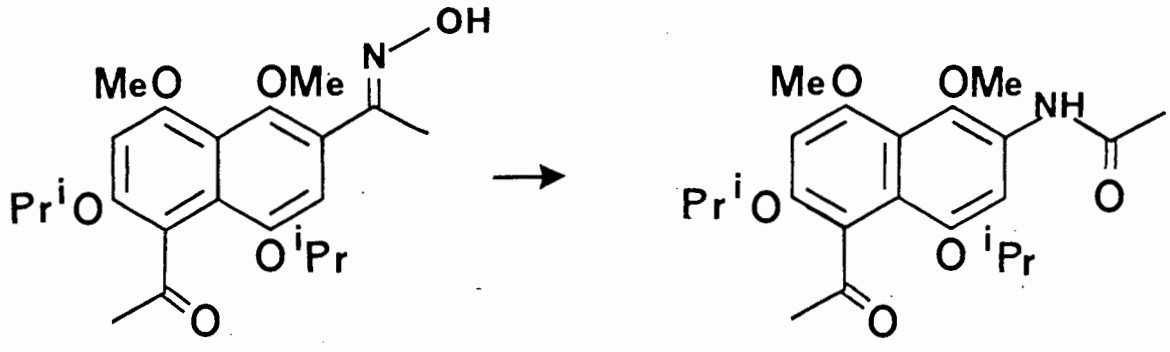
(**43**) (**53**)

Subsequently a nitrogen had to be inserted between the naphthalene ring and the acetyl group at C-3 to afford the acylamino substituent at this point, which is common to the rifamycin class of compounds. It appeared reasonable to try and effect this *via* a Beckmann rearrangement. While appreciating that there were two carbonyl groups which could both undergo reaction to form an oxime prior to the Beckmann rearrangement, it was thought that the 8-acetyl, flanked by an *ortho*- and a *peri*-isopropoxy group, would sterically be more crowded, than the 3-acetyl group which only had a methoxy group *ortho*- to it. It was for this reason that the reaction was first investigated on the di-isopropoxy derivative (**53**) rather than the corresponding methoxy derivative (**46**), since the bulk of the larger groups in the former compound would provide a greater impediment to nucleophilic attack on the C-8 acetyl group. Spectroscopic evidence also pointed towards the C-8 acetyl being more crowded since the ^{1}H n.m.r. spectrum showed the 3-acetyl methyl hydrogens' signal at δ 2.72 and the 8-acetyl methyl hydrogens' signal at δ2.55, while the infrared spectrum showed the C-3 acetyl carbonyl at 1660 cm^{-1} and the C-8 acetyl carbonyl at 1707 cm^{-1}. This suggested that the C-8 carbonyl was not in the same plane as the naphthalene ring.

The other important requirement was that the monoxime (**54**), which was formed prior to the Beckmann rearrangement, had to have the hydroxyl group *anti* relative to the naphthyl group. This appeared to be reasonable on steric grounds,

and there would be no strong case for hydrogen bonding between the oxime hydroxyl group and the C-4 methoxy substituent.

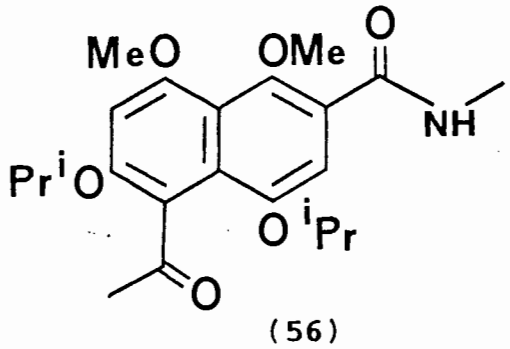
In the naphthalene (**53**) the carbonyl in position 3 was readily converted to the monoxime (**54**) by treatment with hydroxylamine hydrochloride in the presence of one molar equivalent of base. Treatment of the ketoxime (**54**) with phosphorus pentachloride at 0°C resulted in the Beckmann rearrangement, giving rise to the formation of the product (**55**).



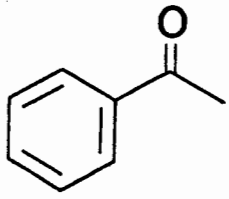
(**54**) (**55**)

The ^{1}H n.m.r. spectrum of compound (**55**) showed two aromatic singlets at δ 6.60 (H-6) and at δ 8.02 (H-2). The singlet at δ 8.02 was deshielded in relation to starting material (**53**), in which the corresponding signal was at δ 7.03. Also seen in the ^{1}H n.m.r. spectrum were a broad singlet at δ 7.93 corresponding to the amide proton and two three-proton singlets at δ 2.21 and δ 2.53 assigned to the methyl protons of the acetamido and the acetyl groups respectively.

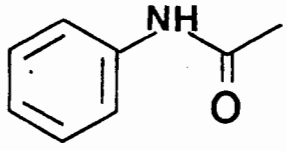
If the hydroxyl of the ketoxime (**54**) had not been *anti*- to the naphthyl group, rearrangement would have resulted in compound (**56**). The ^{1}H n.m.r. spectrum of this compound would have shown less of a deshielding influence on the aromatic singlet in position 2. Further evidence that the nitrogen had been inserted between the naphthalene ring and the acetyl at C-3 was provided by comparing the chemical shift and multiplicity of the methyl group in the three compounds, acetophenone (**57**), *N*-methylbenzamide (**58**) and acetanilide (**59**).[23]



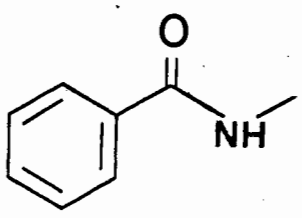
(**56**)



(**57**)



(**59**)



(**58**)

First, the methyl group of *N*-methylbenzamide (**58**) appeared as a doublet, which was not observed in our acetamide (**55**). Secondly, the chemical shift of the methyl group of *N*-methylbenzamide (**58**) showed a relative deshielding compared to acetophenone (**57**), to a value of δ 3.00, while our acetamide (**55**) displayed a relative shielding in relation to starting material (**53**). Comparison of the chemical shift of the methyl group of acetophenone (**57**) and acetanilide (**59**) showed a relative shielding ($\Delta\delta$ 0.56) from δ 2.64 to δ 2.08 respectively, which is similar to the difference in chemical shift ($\Delta\delta$ 0.51) of the methyl in the ketone (**53**) (δ2.72) and the acetamide (**55**) (δ2.21).

Confirmation of the fact that acetylation had occurred at position 3- and 8- and that the nitrogen had been inserted in the correct position was provided by a crystal structure determination carried out on compound (**55**) (Figure 1). This also showed, as expected, that, in the crystalline form, the C-8 acetyl group was twisted out of the plane of the naphthalene ring, and was approximately at right angles to it.

While this work was in progress efforts to make the analogue (**60**) possessing an extra methyl group in position 6 were independently being investigated in our laboratory.[16] These investigations revealed that acetylation of the 6-methyl isopropoxy derivative (**61**) only afforded the 3-acetyl derivative (**62**), presumably the introduction of a methyl at C-6

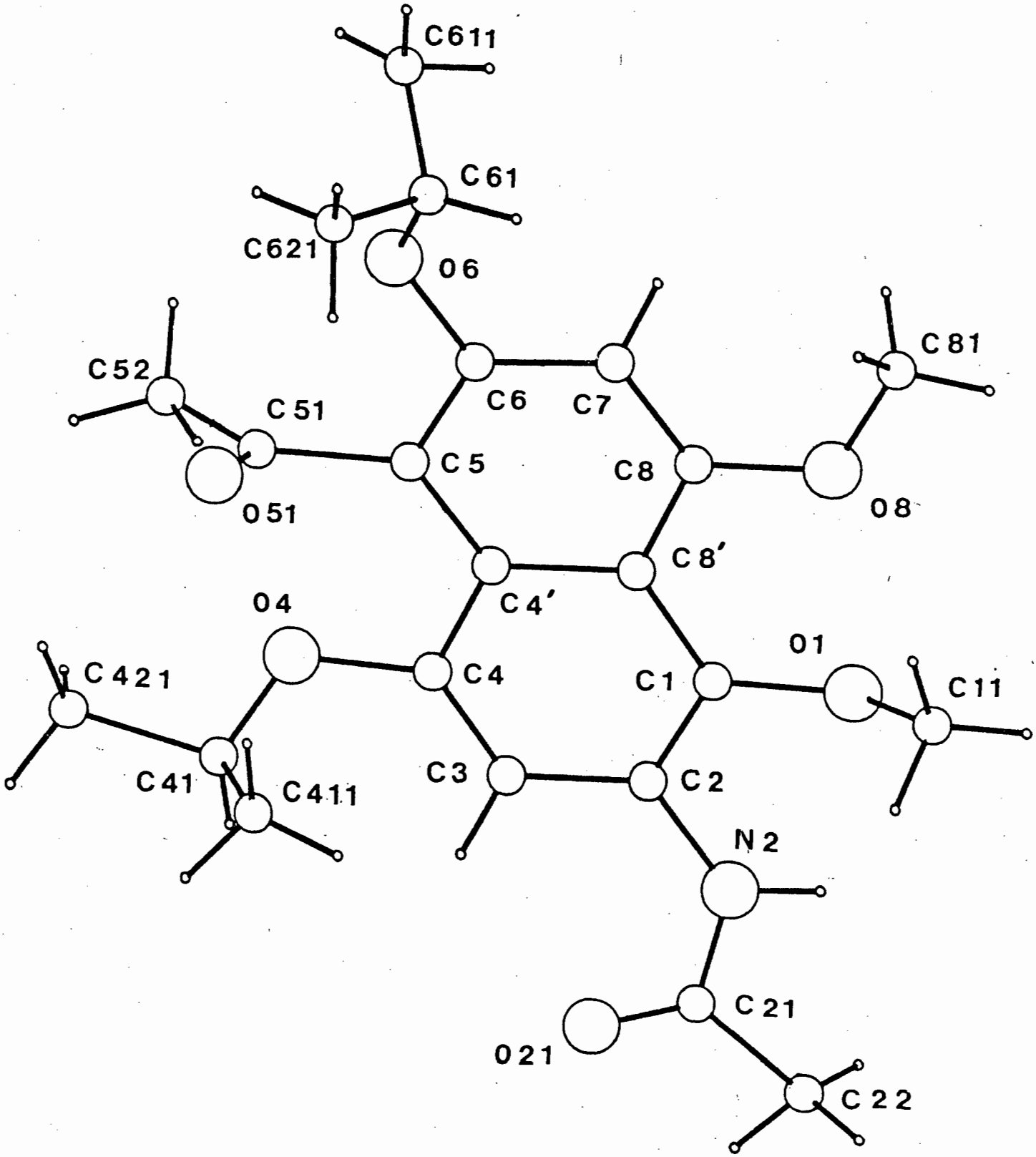
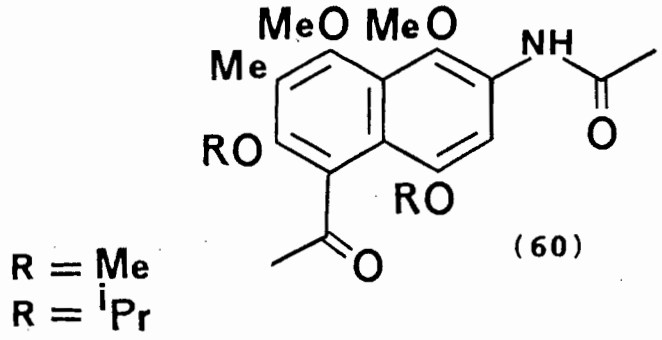
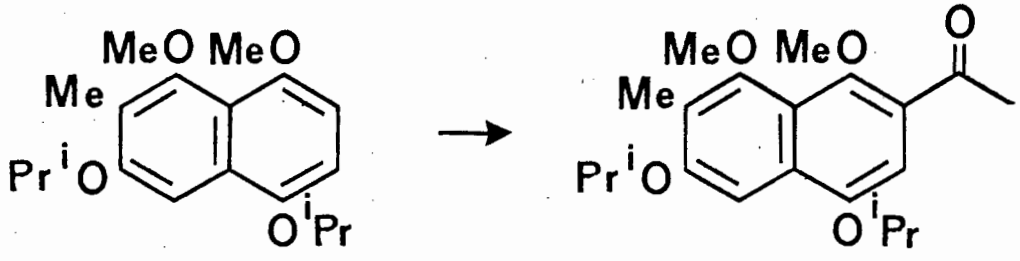

C611
C61
C621
O6
C52
C51
C6
C7
C81
C5
C8
O51
O8
C8'
C4'
O4
O1
C421
C4
C1
C11
C41
C411
C3
C2
N2
C21
O21
C22

figure 1

made position 8 inaccessible due to the buttressing effect of the methyl group. Therefore it was thought necessary to try and reduce possible overcrowding at C-8.



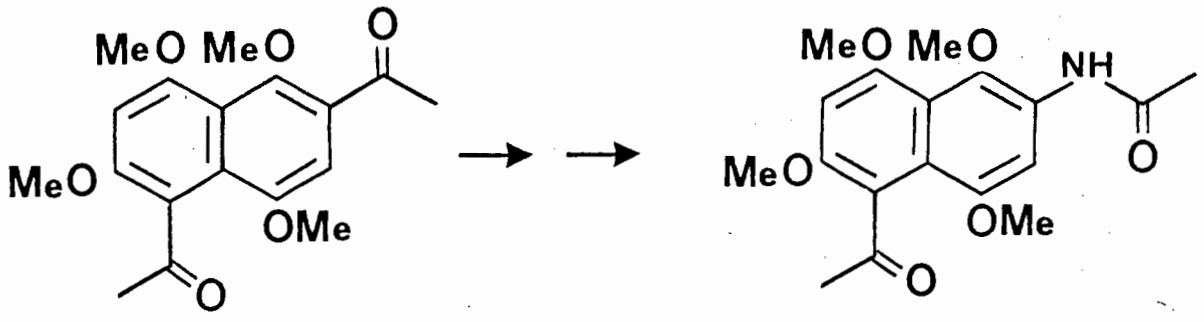
(60)



(61) (62)

Since 1,4,5,7-tetramethoxynaphthalene was readily available in our laboratory, the tetramethoxy amide derivative (63) was also synthesised. It was hoped that the reduction in size of the protecting group from isopropyl to methyl would still only lead to the formation of the monoxime derivative of the carbonyl in position 3.

Reaction of 1,4,5,7-tetramethoxynaphthalene (**41**) with an excess of acetic acid and trifluoroacetic anhydride afforded the 3,8-diacetyl derivative (**46**) in high yield (83%). Formation of the monoketoxime and the subsequent Beckmann rearrangement proceeded smoothly yielding the amide (**63**).



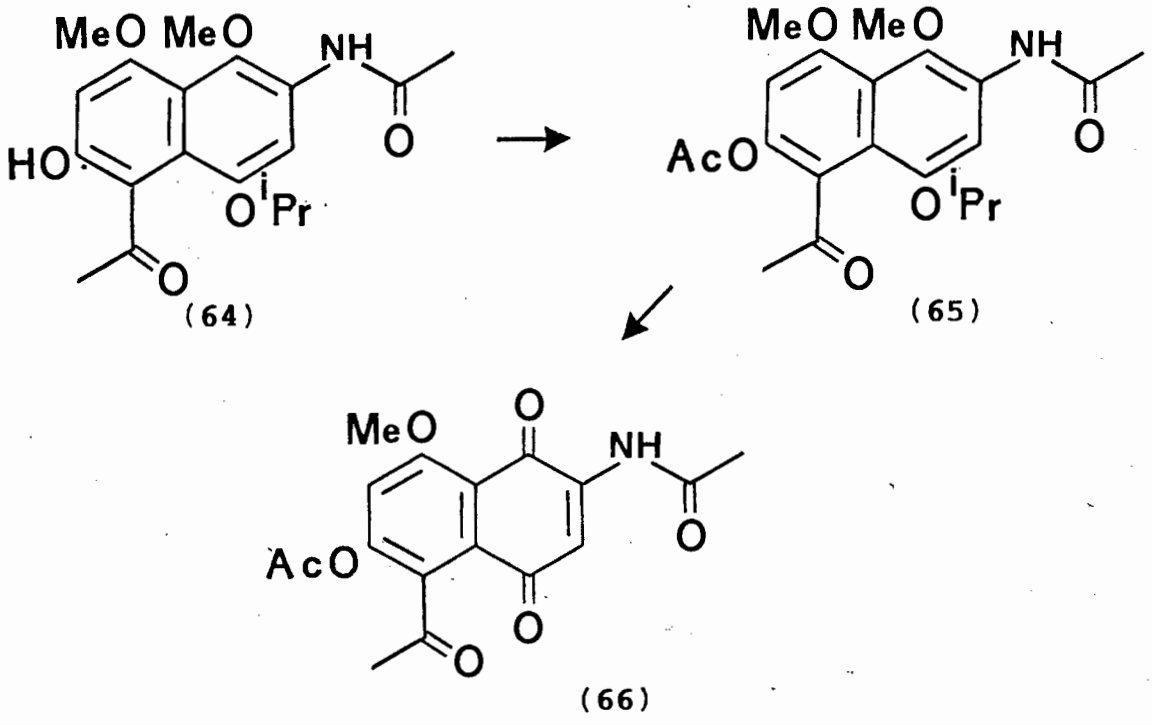
(**46**) (**63**)

At this stage the two naphthalenic systems (**55**) and (**63**) had been synthesised with the required substituents in the desired positions it was now necessary to remove the various protecting groups of the ether oxygens.

Initially, work was carried out on the system (**55**) possessing the isopropoxy groups in positions 1 and 7.

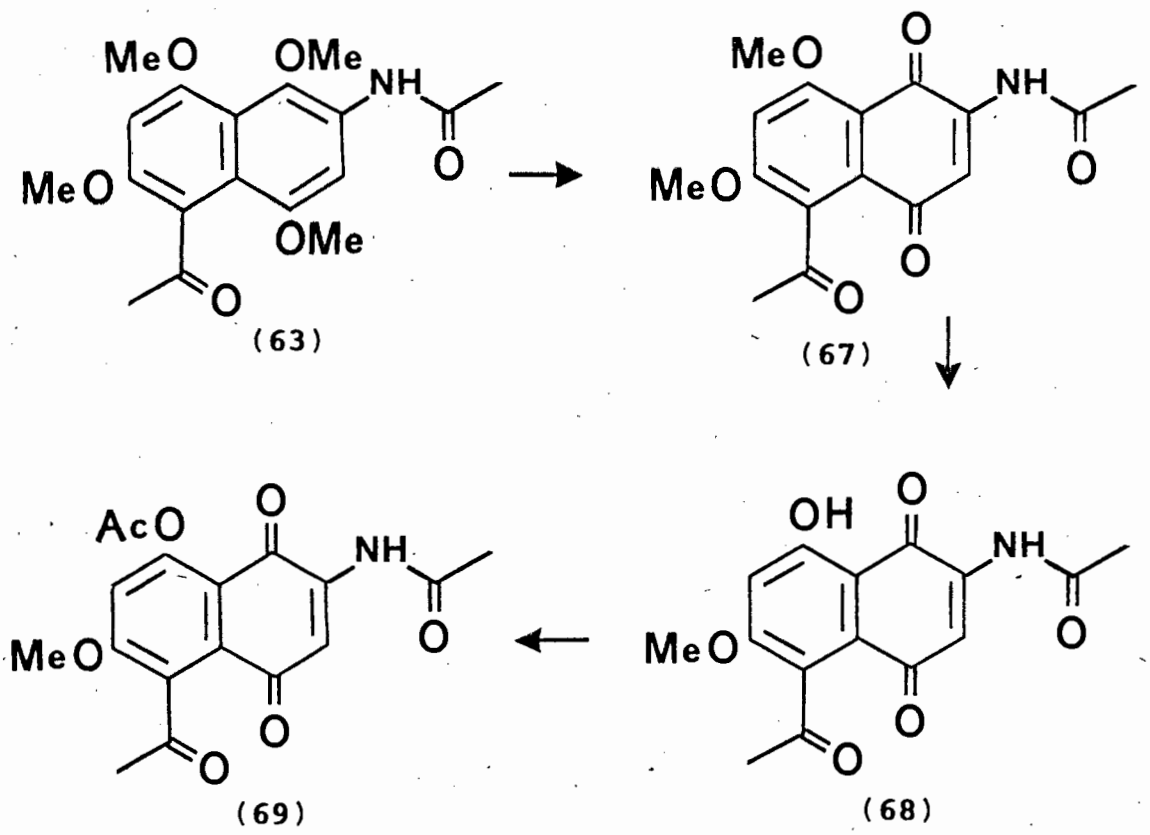
The naphthalene (**55**) was selectively deprotected with boron trichloride to afford the naphthol (**64**) lacking one isopropyl group. It was anticipated that the isopropyl group *ortho* - to the carbonyl at C-8 had been selectively removed. The naphthol (**64**) was then acetylated with acetic anhydride in the presence of pyridine to give the acetate (**65**), the

^1H n.m.r. spectrum of which clearly showed the presence of only one isopropyl group. The signal however appeared as two doublets at δ 1.27 and δ 1.45 each with a coupling constant of 6Hz. This indicated that each methyl group of the isopropyl group was in a different chemical environment, which is probably due to restricted rotation at the amide bond (similar to *N*-methyl benzamide (**58**) discussed earlier) to give the *(E)*-and-*(Z)*-isomers. In addition three acetyl groups at δ 2.22, δ 2.26 and δ 2.44 were observed. The infrared spectrum also showed the presence of three carbonyls with stretching frequences at 1770, 1703, and 1647 cm^{-1} respectively.



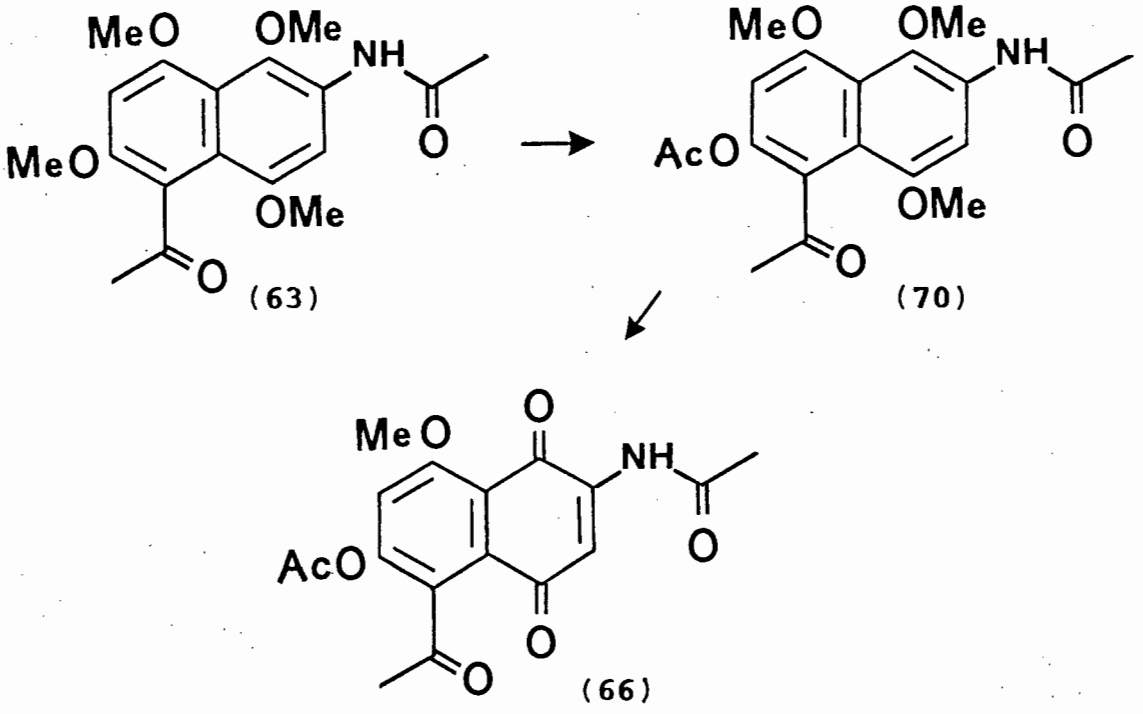
Oxidation of the acetate (**65**) with silver(II) oxide and nitric acid led in high yield to the quinone (**66**). The ^{1}H n.m.r. spectrum of the quinone still indicated the presence of three acetyl groups at δ2.26, δ2.28 and δ 2.44, one of which would not have been present if the alternative isopropyl group at C-1 in compound (**55**) had been removed confirming that the isopropyl *ortho*- to the carbonyl at C-8 had indeed been removed. Additionally, the ^{1}H n.m.r. spectrum of quinone (**66**) displayed a methoxy singlet at δ3.99, one naphthalene proton (H-7) at δ7.11, one quinonoid proton (H-2) at δ 7.69 as well as a broad singlet at δ8.47 for the amide proton. Further support for the structure (**66**) was provided by the mass spectrum which indicated a molecular ion at *m/z* 345, and the infrared spectrum which showed carbonyl stretching frequences at 1777, 1705, and 1655 cm^{-1}.

Further unambiguous proof of the correct structural assignment of the quinone (**66**) was provided by the successful synthesis of its structural isomer quinone (**69**), which was achieved by the following procedure. 1,4,5,7-tetramethoxynaphthalene (**63**) was initially oxidised to the quinone (**67**) which again showed the characteristic infrared stretching frequencies at 1695, 1654, 1638 and 1617 cm^{-1}. On selective deprotection of (**67**) with aluminium trichloride (known to deprotect methoxy groups *peri*- to carbonyls) naphthol (**68**) was formed which was acetylated with acetic anhydride in the presence of pyridine to afford the quinone (**69**), isomeric with the acetate (**66**).



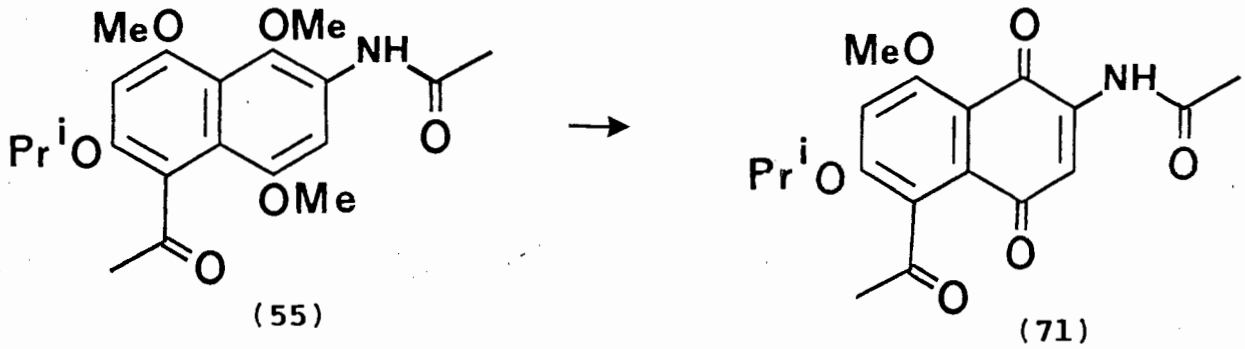
Comparison of melting points showed the former decomposed between 218-228 °C, while the latter melted between 232-233 °C. The ^{1}H n.m.r. spectrum of compound (**69**) showed the three acetyl groups with chemical shifts of δ 2.24, δ2.42 and δ 2.49 while in compound (**66**) the chemical shifts were δ 2.26, δ2.28 and δ 2.44, presumably the middle value of each set of three-proton singlets corresponded to the different acetoxy methyl groups reflecting their different chemical environments. It was also noted that the chemical shift (δ 6.81) of H-6 in compound (**69**) was different to that of substance (**66**) (δ7.11).

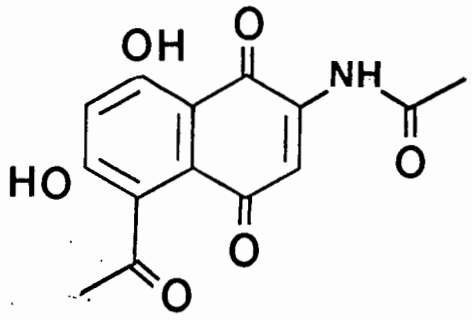
Alternatively, the tetramethoxynaphthalene (**63**) was first selectively deprotected with boron trichloride and then acetylated to afford the acetate (**70**) which was subsequently oxidised with silver(11) oxide in nitric acid to afford quinone (**66**), identical in all respects (spectroscopic and physical properties) to the same compound produced in the isopropyl series.



As the methoxy methyl group *peri-* to the carbonyl of the quinone (**65**) could readily be removed with aluminium trichloride and since an isopropyl group should also be more readily removed than a methyl group, it was decided to revert to the isopropyl series to synthesise the desired quinone (**35**). Thus the isopropyl amide (**55**) was oxidised with silver(11) oxide in nitric acid to the quinone (**71**) which

was subsequently treated with an excess of aluminium trichloride, to remove both the methyl and isopropyl groups to afford the target dihydroxynaphthoquinone (**35**) in a yield of 83%.





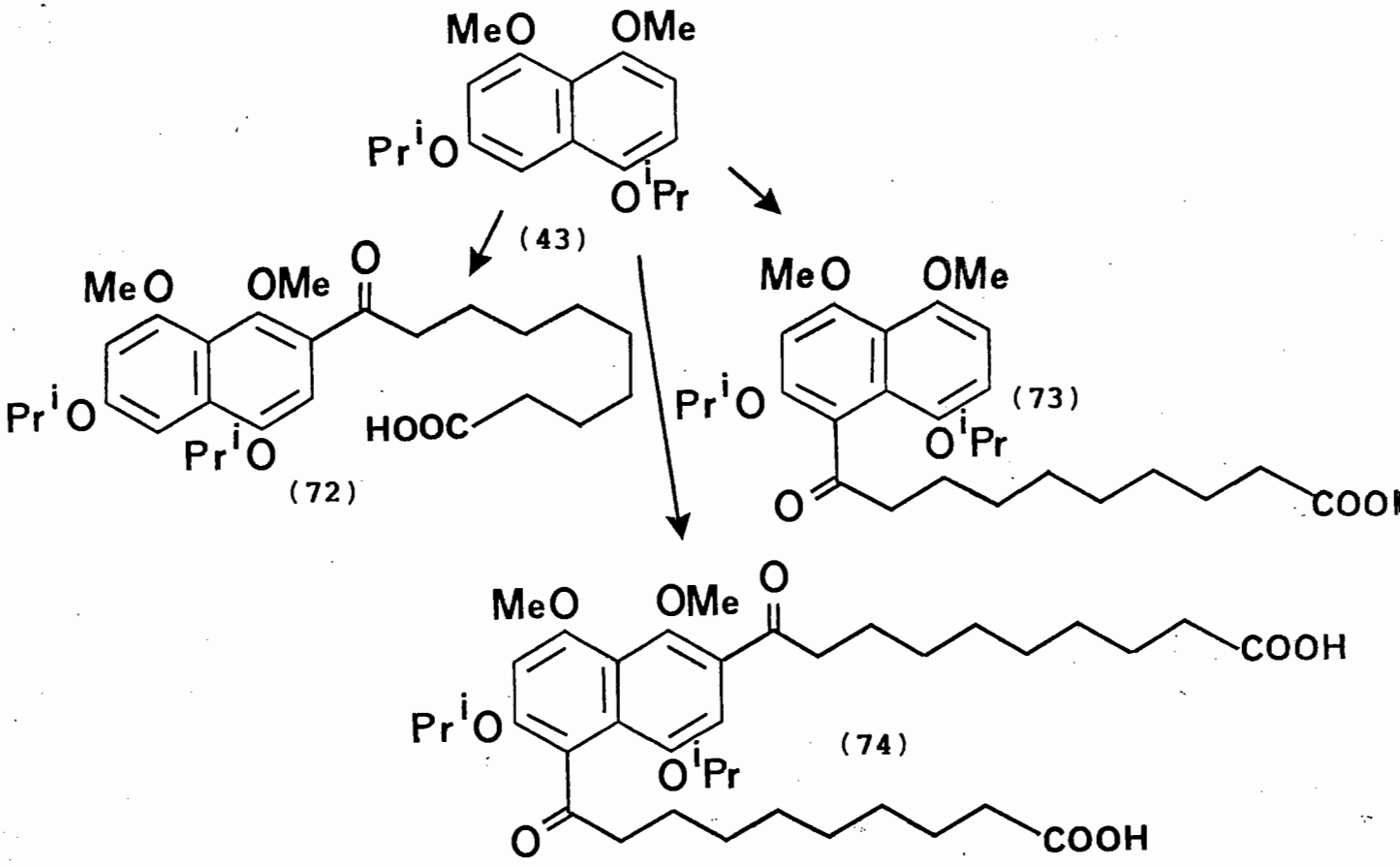
Evidence for the structure included a molecular ion of *m/z* 289 in the mass spectrum. This was further confirmed by the ^{1}H n.m.r. spectrum which showed an acetylamino three-proton singlet at δ 2.21 and the acetyl three-proton singlet at δ 2.29. Also present were two aromatic one-proton singlets at δ 6.56 (H-2) and δ 7.48 (H-6) as well as the amide proton at δ 8.49. The hydroxyl protons appeared as singlets at δ 11.87 and δ 9.86 respectively. Complementing this evidence

was the infrared spectrum which showed peaks at 1690 cm^{-1} (CO of acetyl), 1645 cm^{-1} (CO of quinone) and 1634 cm^{-1} (CO of amide).

A methodology for the synthesis of the ansamycin naphthalene nucleus (**35**) had been established. Subsequently a method had to be developed for the insertion of a methyl group in position 6 of the naphthalene nucleus. This was achieved by starting from naphthalene (**63**) the work being carried out by L S Knight.[16]

As our reactions resulting in the formation of the diacetylated compounds (**46**) and (**53**) had been successful and monoacylation at C-8 using different aliphatic acids had also been achieved (even though position 8 was more crowded than position 3), it was thought that if a long chain dicarboxylic acid was used it might result in the formation of an aliphatic chain linking the two non-adjacent positions at C-3 and C-8. On building a model using naphthalene (**43**) it was found that sebacic acid, the ten-carbon dicarboxylic acid would be the smallest one which was able to span across the two positions.

Acylation with sebacic acid unfortunately afforded the monoacylated products (**72**) and (**73**) as well as the diacylated product (**74**).

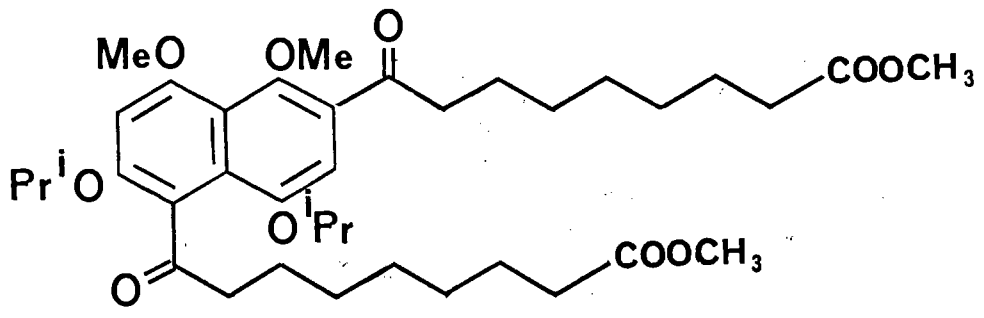


Evidence for this was provided by the mass spectra indicating molecular ions of *m/z* 488, *m/z* 488 and *m/z* 673 for each of the three compounds respectively. In the ^{1}H n.m.r. spectrum of the 3-acylated product (**72**) there were two *meta*-coupled protons at δ 6.56 and δ 7.20 with a coupling constant of 2Hz, as well as a singlet at δ 6.98. The 8-acylated product (**73**) showed two singlets at δ 6.65 and δ 6.59 with the former integrating for two protons. The diacylated product (**74**) showed two singlets at δ 6.64 and δ 6.88 as would be expected if the single dicarboxylic acid chain had spanned from position

3 to position 8, but the integration of the aliphatic portion of the spectrum indicated that two dicarboxylic acid moieties had been introduced.

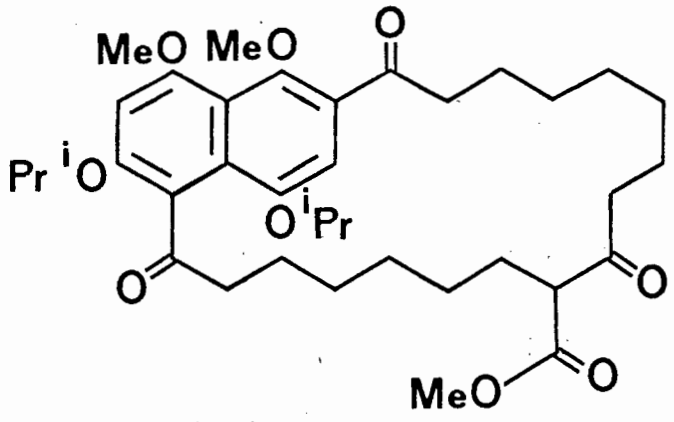
It was also noted, as earlier, that, if an excess of trifluoroacetic anhydride was used, trifluoroacetylation occurred in either position 8 or 3, with sebacic acid acylation occurring at the other site. The respective positions of acylation were not established but as the mass spectrum indicated a molecular ion of *m/z* 584 and the ^{1}H n.m.r. spectrum only indicated two aromatic singlets and based on earlier precedent, it was assumed that positions 3 and 8 had both been acylated.

As this reaction had proceeded in moderate yield, the readily obtainable half ester of the dicarboxylic acid, azelaic acid, was used instead. Diacylation proceeded smoothly to afford the derivative (**75**) in 58% yield as shown by spectroscopic properties.



(75)

It was postulated that Dieckmann condensation[24] of this diester (75) would result in the formation of ketone (76), but as our interest was mainly in the synthesis of the naphthalene core of the rifamycins this was not pursued.



(76)

In conclusion, the naphthalene core of the ansamycins had been synthesised, and the use of the acylation reaction with a carboxylic acid and trifluoroacetic anhydride had been explored, showing it to be very versatile and that it was possible to insert long chain acyl groups into positions 3- and 8- allowing further elaboration possibilities.

EXPERIMENTAL

All ^{1}H n.m.r. spectra were measured on a Brüker WH90 at 90MHz for solutions in ^{2}H chloroform with tetramethylsilane as internal reference, while infrared spectra were measured for Nujol mulls unless otherwise stated. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while column chromatography refers to dry-packed columns using the same gel (70-230 mesh). Light petroleum refers to the fraction of b.p. 60-80°C and ether to diethyl ether. 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.

4-Acetoxy-1,5,7-trimethoxynaphthalene (**47**).-
Compound (**40**)[19] (1.55 g, 66 mmol), acetic anhydride (2 ml), and pyridine (6 ml) were boiled together for 2 h and then thrown onto ice. The white crystalline solid was filtered off, washed with water, and dried to give the **product** (**47**) (1.55 g, 85%), m.p. 145-146°C.[19]

4-Acetoxy-8-acetyl-1,5,7-trimethoxynaphthalene (**48**).-
Acetic acid (26 mg, 0.43 mmol) premixed with trifluoroacetic anhydride (120 mg, 0.54 mmol) was rapidly added to naphthalene (**47**)(100 mg, 0.36 mmol) which was dissolved in dry methylene dichloride (2.5 ml). The mixture was stirred at room temperature for 87 h, with addition of further aliquots of the

mixed anhydride at 2, 20 and 65 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous sodium hydrogen carbonate solution. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 25-30% ethyl acetate-light petroleum) to afford the **product (48)** (89 mg, 77%) as white cubes, m.p. 164-165 °C (acetone) (Found: C, 64.15; H, 5.75. $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.70%); $\nu_{max.}$ 1765 ($COCH_3$) and 1710 (8 C=0) cm^{-1}; δ 2.35 and 2.53 (each 3H, s, $COCH_3$), 3.92, 3.87, and 3.95 (each 3H, s, OCH_3), 6.73 (1H, s, 6-H), 6.80 and 6.97 (each 1H, d, *J* 8Hz, 2- and 3-H); *m/z* 318 (M^+, 54%), 276 (100), 261 (98), and 245 (41).

4-Acetoxy-8-hexanoyl-1,5,7-trimethoxynaphthalene (**49**).-
In a manner similar to that described above, hexanoic acid (50 mg, 0.43 mmol) premixed with trifluoroacetic anhydride (120 mg, 0.54 mmol) was rapidly added to the naphthalene (**47**) (100 mg, 0.36 mmol) in dry methylene dichloride. The reaction was stirred at room temperature, with the addition of four more aliquots of the mixture of hexanoic acid and trifluoroacetic anhydride over a 38 h period. The residue obtained upon work-up (described above) was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford the desired **product** (**49**) (86 mg, 64%) as white needles, m.p. 124.5-125 °C (ethanol/acetone) (Found: C, 67.15; H, 7.05. $C_{21}H_{26}O_6$ requires C, 67.40; H, 6.95%); $\nu_{max.}$ 1751 ($COCH_3$) and 1689 (8 C=0) cm^{-1}; δ 1.08 - 2.02 (9H, m, $(CH_2)_3CH_3$), 2.37 (3H, s $OCOCH_3$), 2.58 - 3.00 (2H, m, $COCH_2$-), 3.87,

3.92 and 3.97 (each 3H, s, OCH_3), 6.77 (1H, s, 6-H), 6.83 and 7.00 (each 1H, d, *J* 9Hz, 2- and 3-H); *m/z* 374 (M^+, 38%), 332 (41), 303 (62), 261 (100), and 246 (26).

4-Acetoxy-8-tiglyl-1,5,7-trimethoxynaphthalene (**50**) and *4-Acetoxy-8-trifluoroacetyl-1,5,7-trimethoxynaphthalene* (**52**).-

The naphthalene (**47**) (100 mg, 0.36 mmol) in dry methylene dichloride (5 ml) was treated at room temperature with three aliquots of a mixture of tiglic acid (36 mg, 0.43 mmol) and trifluoroacetic anhydride (120 mg, 0.54 mmol) over 23 h. The residue obtained upon work-up (described above) was chromatographed (eluant 5-20% ethyl acetate-light petroleum) to afford first the **trifluoroacetyl naphthalene** (**52**) (28 mg, 21%) as white needles, m.p. 160-162°C (methanol) (Found: C, 55.05; H, 4.2. $C_{17}H_{15}F_3O_6$ requires C, 54.85; H, 4.05%); $\nu_{max.}$ 1762 and 1744 (C=O), and 1619 (C=C) cm^{-1}; 2.30 (3H, s, $COCH_3$), 3.78, 3.85, and 3.90 (each 3H, s, OCH_3), 6.57 (1H, s, 6-H), 6.67 and 6.85 (each 1H, d, *J* 8Hz, 2- and 3-H); *m/z* 372 (M^+, 26%), 330 (58), 261 (100), 246 (39), and 231 (15). This was followed by the **naphthalene** (**50**) (98 mg, 72%) as yellow needles, m.p. 213-214°C (methanol) (Found: C, 66.9; H, 6.2. $C_{20}H_{22}O_6$ requires C, 67.05; H, 6.2%); $\nu_{max.}$ 1753 ($COCH_3$) and 1647 (δ C=O) cm^{-1}; δ 1.73br. (3H, d, *J* 7Hz, CH_3CH), 1.97br. (3H, s, CH_3CCO), 2.33 (3H, s, $OCOCH_3$), 3.67, 3.80, and 3.92 (each 3H, s, OCH_3), 6.10 (1H, dq, *J* 7Hz and 1.5Hz, $CH{=}CCH_3$), 6.63 (1H, s, 6-H), 6.67 and 6.85 (each 1H, d, *J* 9Hz, 2- and 3-H); *m/z* 358 (M^+, 71%), 316 (100), 285 (48), 261 (50), 245 (24), and 43 (78).

4-Acetoxy-8-crotonyl-1,5,7-trimethoxynaphthalene (**51**).-

The naphthalene (**47**) (100 mg, 0.36 mmol) in dry methylene dichloride (5 ml) was treated at room temperature with two aliquots of a mixture of crotonic acid (31 mg, 0.43 mmol) and trifluoroacetic anhydride (100 mg, 0.43 mmol) over 26 h. The residue obtained upon work-up (described above) was chromatographed (eluant 5-20% ethyl acetate-light petroleum) to yield first the **product** (**52**) identical with that formed in the previous synthesis (34 mg, 26%) followed by the **naphthalene** (**51**) (92 mg, 73%) as pale yellow cubes, m.p. 184-185.5°C (methanol) (Found: C, 66.1; H, 6.05. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%); $\nu_{max.}$ 1751 ($COCH_3$) and 1654 (8 C=0) and 1620 (C=C) cm^{-1}; δ 1.80 (3H, dd, *J* 2 and 6Hz, $C=CHCH_3$), 2.30 (3H, s, $OCOCH_3$), 3.68, 3.78, and 3.88 (each 3H, s, OCH_3), 6.27 - 6.40 (2H, m, vinyl CH), 6.63 (1H, s, 6-H), 6.70 and 6.87 (each 1H, d, *J* 8Hz, 2- and 3-H); *m/z* 344 (M^+, 73%), 302 (100), 271 (98), 261 (29), and 231 (23).

3,8-Diacetyl-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene (**53**).-

A premixed solution of trifluoroacetic anhydride (3.1 g, 14.8 mmol) and acetic acid (0.9 g, 15.0 mmol) was added to 1,7-di-isopropoxy-4,5-dimethoxynaphthalene (**43**)[21] (500 mg, 1.6 mmol) in dry methylene dichloride (20 ml). The reaction was stirred for 66 h at room temperature. Upon quenching the reaction in the usual manner and chromatography (eluant 10-20% ethyl acetate-light petroleum) the **diacetyl naphthalene** (**53**) (433 mg, 72%) was obtained as white plates, m.p. 137-138°C (methanol) (Found: C, 67.8; H, 7.2. $C_{22}H_{28}O_6$ requires C, 68.05; H, 7.2%); $\nu_{max.}$ 1707 (8 C=0) and 1660

(3 C=0) cm^{-1}; δ 1.26 - 1.48 (12H, m, 2xCH(CH_3)$_2$), 2.55 (3H, s, 8-$COCH_3$), and 2.72 (3H, s, 3-$COCH_3$), 3.76 and 4.01 (each 3H, s, OCH_3), 4.68 (2H, septet, *J* 6Hz, 2xC**H**(CH_3)$_2$), 6.64 (1H, s, 6-H), and 7.03 (1H, s, 2-H); *m/z* 388 (M^+, 86%), 346 (54), 304 (85), 289 (84), 269 (21), 244 (11), and 72 (100).

8-Acetyl-3-acetylamino-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene (**55**).- The naphthalene (**43**) (650 mg, 1.7 mmol) dissolved in ethanol (40 ml) was treated with hydroxylamine hydrochloride (350 mg, 5 mmol) and a solution of potassium hydroxide (90 mg, 1.7 mmol) in water (10 ml). The solution was boiled for 2 h. The reaction mixture was diluted with water (100 ml) and acidified with 5M hydrochloric acid. The derived oxime (**54**) was extracted into ether, and the residue obtained upon work-up was dissolved in dry ether (150 ml). After treatment of the solution with phosphorus pentachloride (410 mg, 2.04 mmol) at 0 °C for 2 h, water was added to quench the reaction. The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) to give the **amide** (**55**) (459 mg 68%) as white needles, m.p. 149-150 °C (light petroleum-methylene dichloride) (Found: C, 65.35; H, 7.1; N 3.5. $C_{22}H_{29}NO_6$ requires C, 65.35; H, 7.2; N, 3.5%); $\nu_{max.}$ 3316 (NH), 1703 (8 C=0), and 1658 (amide C=0) cm^{-1}; δ1.32 and 1.34 (each 6H, d, *J*7Hz, CH(CH_3)$_2$), 2.21 (3H, s, CH_3CONH), 2.53 (3H, s, 8-$COCH_3$), 3.75 and 3.96 (each 3H, s, OCH_3), 4.57 and 4.73 (each 1H, septet, *J*7Hz, C**H**(CH_3)$_2$), 6.60 (1H, s, 6-H), 7.93br. (1H, s, NH), and 8.02 (1H, s, 2-H); *m/z* 403 (M^+, 100%), 346 (53), 304 (71), 260 (91), 246 (29), 220 (18), 43 (80), and 20 (77).

3,8-Diacetyl-1,4,5,7-tetramethoxynaphthalene (**46**).-

A premixed solution of trifluoroacetic anhydride (7.62 g, 36.3 mmol) and acetic acid (2.18 g, 36.3 mmol) was added to 1,4,5,7-tetramethoxynaphthalene (**41**)[19] (41) (1.00 g, 4.03 mmol) in dry methylene dichloride (20 ml). The reaction was stirred at room temperature for 44 h. Quenching of the reaction as above yielded after chromatography (eluant 20-30% ethyl acetate-light petroleum) the **product** (**46**) (1.02 g, 83%) as white needles, m.p. 132-133 °C (methanol) (Found: C, 65.1; H, 5.95. $C_{18}H_{20}O_6$ requires C, 65.1; H, 6.0%); $\nu_{max.}$ 1703 (8 C=O) and 1663 (3 C=O) cm^{-1}; δ 2.50 (3H, s, 8-$COCH_3$), 2.73 (3H, s, 3-$COCH_3$), 3.77, 3.82, 3.91, and 4.03 (each 3H, s, OCH_3), 6.70 (1H, s, 6-H), and 7.06 (1H, s, 2-H); *m/z* 332 (M^+, 100%), 317 (91), 301 (44), 287 (17), and 15 (11).

8-Acetyl-3-acetylamino-1,4,5,7-tetramethoxynaphthalene (**63**).-

The naphthalene (**46**) (883 mg, 2.6 mmol) dissolved in ethanol (50 ml) was treated with hydroxylamine hydrochloride (0.35 g, 5 mmol) in a solution of potassium hydroxide (0.14 g, 2.6 mmol) in water (20 ml). The solution was boiled for 2.5 h. The reaction mixture was diluted with water (150 ml) and acidified with 5M hydrochloric acid. The derived oxime was extracted into methylene dichloride and the residue obtained upon work-up was dissolved in dry tetrahydrofuran (150 ml). After treatment of the solution with phosphorus pentachloride (0.65 g, 3.1 mmol) at 0 °C for 3 h, an excess of water was added to quench the reaction. The residue obtained upon work-up was chromatographed (eluant ethyl

acetate) yielding light brown crystals of the **amide** (**63**) (683 mg, 70%), m.p. 192-193°C (2-propanol) (Found: C, 62.05; H, 6.1; N, 4.0. $C_{18}H_{21}NO_6$ requires C, 62.25; H, 6.05; N, 4.0%); $\nu_{max.}$ 3310 (NH), 1710 (8 C=0), and 1655 (amide C=0) cm^{-1}; δ2.23 (3H, s, $NHCOCH_3$), 2.51 (3H, s, 8-$COCH_3$), 3.75, 3.84, 3.88, and 4.00 (each 3H, s, OCH_3), 6.66 (1H, s, 6-H), 7.98br. (1H, s, NH), and 8.05 (1H, s, 2-H); *m/z* 347 (M^+, 76%), 332 (25), 290 (100), 260 (13), and 93 (22).

7-Acetoxy-8-acetyl-3-acetylamino-4,5-dimethoxy-1-(2-propyloxy)naphthalene (**65**).- The amide (**55**) (200 mg, 0.05 mmol) in dry methylene dichloride (20 ml) was treated at -78°C with boron trichloride (348 mg, 0.33 mmol) in the same solvent. After 30 min the solution was allowed to warm to room temperature and then hydrolysed with an excess of water. The residue obtained upon work-up was dissolved in pyridine (5 ml) and acetic anhydride (1 ml) and heated at 70°C for 2 h. The reaction mixture was cooled and added to an excess of water. The organic material was then extracted with methylene dichloride while keeping the pyridine in the aqueous layer by carefully acidifying with 5M hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **product** (**65**) (148 mg, 74%), as white flakes, m.p. 173-174°C (2-propanol)(Found: C, 62.55; H, 6.15; N, 3.45. $C_{21}H_{25}NO_7$ requires C, 62.5; H 6.2; N, 3.5%); $\nu_{max.}$ 1770 (AcO), 1703 (8 C=0), 1647 (amide C=0) cm^{-1}; δ1.27 and 1.43 (each 3H, d, *J*6Hz, each one CH_3 of $CH(CH_3)_2$), 2.22 and 2.26 (each 3H, s, $NCOCH_3$ and $OCOCH_3$) 2.44 (3H, s, $COCH_3$), 3.75 and 3.94 (each 3H, s, OCH_3), 4.70

(1H, septet, J6Hz, CH$(CH_3)_2$), 6.56 (1H, s, 6-H), 8.01br.(1H, s, NH), and 8.14 (1H, s, 2-H); *m/z* 403 (M^+, 62%), 361 (54), 346 (12), 319 (60), 364 (85), 262 (100), 244 (13), and 226 (20).

7-Acetoxy-8-acetyl-3-acetylamino-5-methoxy-1,4-naphthoquinone (**66**).- The naphthalene (**65**) (100 mg, 25 mmol), silver(II) oxide (80 mg, 0.65 mmol) and dioxane (10 ml) were stirred together at room temperature and then nitric acid (6M, 0.8 ml) was added and the reaction mixture stirred for another 3 min. A mixture of methylene dichloride (20 ml) and water (5 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) affording the **quinone** (**66**) (65 mg, 76%) as yellow needles, m.p. darkens 212°C, 218-228°C decomp. (methanol) (Found M^+, 345.0859. $C_{17}H_{15}NO_7$ requires M, 345.0849); $\nu_{max.}$ 1777 (AcO), 1705 (8 C=O), 1655 (quinone C=O), and 1624 and 1587 (C=C); δ2.26, 2.28 and 2.44 (each 3H, s, $COCH_3$), 3.99 (3H, s, OCH_3), 7.11 (1H, s, 6-H), 7.69 (1H, s, 2-H), and 8.47br. (1H, s, NH); *m/z* 345 (M^+, 22%), 330 (11), 303 (27), 288 (14), 246 (100), and 43 (41).

8-Acetyl-3-acetylamino-5,7-dimethoxy-1,4-naphthoquinone (**67**).- The naphthalene (**63**) (267 mg, 0.77 mmol), silver(II) oxide (380 mg, 3.08 mmol) and dioxane (10 ml) were stirred together at room temperature and then nitric acid (6M, 1.1 ml) was added and the reaction mixture stirred for another 4 min. A mixture of methylene dichloride (40 ml) and water (10 ml)

was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) affording the **quinone** (**67**) (186 mg, 76%) as pale yellow needles, m.p. 235-238°C (methanol) (Found: C, 60.15; H, 4.8; N, 4.4. $C_{16}H_{15}O_6N$ requires C, 60.6; H, 4.8; N, 4.4%); $\nu_{max.}$ 2922 (NH), 1695 (δ C=0) 1654 and 1638 (amide and quinone C=0) cm^{-1}; δ 2.23 (3H, s, $NCOCH_3$), 2.46 (3H, s, 8-$COCH_3$), 3.91 and 4.00 (3H, s, OCH_3), 6.63 (1H, s, 6-H), 7.62 (1H, s, 2-H), and 8.52br. (1H, s, NH); *m/z* 317 (M^+, 9%), 302 (17), 260 (100), and 43 (41).

5-Acetoxy-8-acetyl-3-acetylamino-7-methoxy-1,4-naphthoquinone (**69**).- The quinone methyl ether (**67**) (89 mg, 0.28 mmol) in dry methylene dichloride (20 ml) containing anhydrous aluminium trichloride (760 mg, 5.6 mmol) was stirred at room temperature for 30 min. Water was added and the aqueous layer washed with ethyl acetate. The residue obtained upon work-up was dissolved in pyridine (2 ml) and acetic anhydride (1 ml) and heated at 70°C for 2 h. The reaction mixture was cooled and added to an excess of water. The organic material was then extracted with methylene dichloride while keeping the pyridine in the aqueous layer by carefully acidifying with 5M hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **quinone** (**69**) (50 mg, 51%) as pale yellow needles, m.p. darkens above 220°C melts 232-233°C (methanol) (Found C, 59.4; H, 4.35; N, 4.1. $C_{17}H_{15}NO_7$ requires C, 59.1; H, 4.35; N, 4.05%), $\nu_{max.}$ 1773 (OAc), (δ C=0) 1711,

1648, and 1624 (amide and quinone C=0) cm^{-1}; δ 2.24 (3H, s, $NCOCH_3$) 2.42 and 2.49 (each 3H, s, $COCH_3$), 3.89 (3H, s, OCH_3), 6.81 (1H, s, 6-H), 7.71 (1H, s, 2-H), and 8.38br.(1H, s, NH); *m/z* 345 (M^+, 13%), 330 (17), 288 (17), 246 (100), and 43 (25).

7-Acetoxy-8-acetyl-3-acetylamino-1,4,5-trimethoxynaphthalene (**70**).- The amide (**63**) (105 mg, 0.30 mmol) in dry methylene dichloride (10 ml) was treated at -78°C with a solution of boron trichloride (210 mg, 1.8 mmol) in the the same solvent. After 40 min the solution was allowed to warm to room temperature and then hydrolysed with an excess of water. The residue obtained upon work-up was dissolved in pyridine (5 ml) and acetic anhydride (1 ml) and heated at 70°C for 2 h. The reaction mixture was cooled and added to excess water. The organic material was then extracted with methylene dichloride while keeping the pyridine in the aqueous layer by carefully acidifying with 5M hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate-light petroleum) to afford the **product** (**70**) (95 mg, 83%) as white needles, m.p. 187-188°C (2-propanol) (Found: C, 60.85; H, 5.65; N, 3.8. $C_{19}H_{21}NO_7$ requires C, 60.80; H, 5.6; N, 3.7%); $\nu_{max.}$ 1759 (OAc), 1688 (C=0), and 1614 cm^{-1}; δ 2.24 and 2.28 (each 3H, s, $NCOCH_3$ and $OCOCH_3$) 2.42 (3H, s, $CCOCH_3$), 3.77, 3.86 and 3.96 (each 3H, s, OCH_3), 6.59 (1H, s, 6-H), 8.04br.(1H, s, NH), and 8.16 (1H, s, 2-H); *m/z* 375 (M^+, 34%), 333 (73), 276 (100), and 318 (29).

7-Acetoxy-8-acetyl-3-acetylamino-5-methoxy-1,4-naphthoquinone (**66**).-
The amide (**70**) (60 mg, 0.16 mmol) was treated in the same manner as the naphthalene (**65**) to afford the same **quinone** (**66**) prepared previously. (42 mg, 75%) identical with respect to physical and spectroscopic properties.

8-Acetyl-3-acetylamino-5-methoxy-7-(2-propyloxy)-1,4-naphthoquinone (**71**).-
The amide (**55**) (66 mg, 0.16 mmol), silver(11) oxide (80 mg, 0.64 mmol) and dioxane (10 ml) were stirred together at room temperature. Nitric acid (6M, 0.8 ml) was added and the reaction mixture stirred for 4 min. A mixture of methylene dichloride (20 ml) and water (5 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate-light petroleum) affording the **quinone** (**71**) (43 mg, 77%) as pale yellow flakes, m.p. 221°C (2-propanol) (Found: C, 62.7; H, 5.5; N, 4.1 $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.1%), $\nu_{max.}$ 3299 (NH), 1707 (8 C=0), 1653 (quinone C=0), and 1622 (amide C=0) cm^{-1}; δ1.38 (6H, d, *J* 7Hz, $CH(CH_3)_2$), 2.24 (3H, s, $NCOCH_3$), 2.47 (3H, s, $CCOCH_3$), 4.00 (3H, s, OCH_3), 4.68 (1H, septet, *J* 7Hz, $CH(CH_3)_2$), 6.64 (1H, s, 6-H), 7.64 (1H, s, 2-H) and 8.54br.(1H, s, NH); *m/z* 345 (M^+ 11%), 330 (22), 266 (21), and 245 (100).

8-Acetyl-3-acetylamino-5,7-dihydroxy-1,4-naphthoquinone (**35**).-
The quinone (**71**) (16 mg .046 mmol) in dry methylene dichloride (5 ml) containing anhydrous aluminium trichloride (122 mg, 0.92 mmol) was stirred at room temperature for 15 min. Water

was added and the aqueous layer washed with ethyl acetate. The residue obtained upon work-up was chromatographed (eluant ethyl acetate) to afford the **product** (**35**) (12 mg, 83%) as yellow needles, m.p. 222-226°C (methanol) (Found: M^+, 289.058. $C_{14}H_{11}NO_6$ requires M, 289.058); $\nu_{max.}$ 3315 (NH), 1690 (8 C=O), 1645 (quinone C=O), and 1634 (amide C=O) cm^{-1}; δ (DMSO - d_6) 2.21 (3H, s, $NHCOCH_3$), 2.29 (3H, s, $COCH_3$), 6.56 (1H, s, 6-H), 7.48 (1H, s, 2-H), 8.49br. (1H, s, NH), 9.86br. (1H, s, OH), and 11.87 (1H, s, OH); *m/z* 289 (M^+, 35%), 232 (100), and 43 (49).

3,8-Di(9-carboxydecanoyl)-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene (**74**), *3-(9-carboxydecanoyl)-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene* (**72**), and *8-(9-carboxydecanoyl)-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene* (**73**).- Sebacic acid (decanedioic acid) (350 mg, 2.15 mmol) premixed with trifluoroacetic anhydride (3.80 mg, 2.15 mmol) and dry methylene dichloride (2 ml) was rapidly added to the naphthalene (**43**) (100 mg, 0.34 mmol) dissolved in dry methylene dichloride (5 ml). The reaction was stirred at room temperature for 24 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous sodium hydrogen carbonate solution. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was subjected to p.l.c. (eluant 30% ethyl acetate-light petroleum) to afford first the 3-**acylated product** (**72**) (71 mg, 31%) as a light brown oil, (Found: C, 68.65; H, 8.0. $C_{28}H_{40}O_7$ requires C, 68.85; H, 8.2%); $\nu_{max.}$ (film) 1735 (C=O) and 1705 (CO_2H) cm^{-1}; δ 1.24 - 1.88 (24H, m, $CH(CH_3)_2$ and $-(CH_2)_6-$), 2.32 (2H, t, *J*8Hz,

$-CH_2COOH$), 3.11 (2H, t, *J* 7Hz, $COCH_2-$), 3.76 and 3.98 (each 3H, s, OCH_3), 4.71 (2H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.56 (1H, d, *J* 2Hz, 6-H), 6.98 (1H, s, 2-H), and 7.20 (1H, d, *J* 2Hz, 8-H); *m/z* 488 (M^+, 100%), 446 (29), 445 (18), 289 (14), and 247 (35). The second product was the **8-acylated product** (**73**) (55 mg, 24%) also obtained as a light brown oil, (Found: C, 68.65; H, 8.2. $C_{28}H_{40}O_7$ requires C, 68.85; H, 8.2%); $\nu_{max.}$(film) 1725 (C=O) and 1694 (CO_2H) cm^{-1}; δ 1.20 - 1.87 (24H, m, $CH(CH_3)_2$ and $-(CH_2)_6-$), 2.29 (2H, t, *J* 7Hz, $-CH_2COOH$), 2.62 - 2.92 (2H, m, $-COCH_2-$), 3.85 and 3.92 (each 3H, s, OCH_3), 4.55 (2H, septet, *J* 6Hz $CH(CH_3)_2$), 6.59 (1H, s, 6-H), and 6.65 (2H, s, 2- and 3-H); *m/z* 488 (M^+, 63%), 446 (36), 385 (10), 289 (45), and 247 (100). The third product was the **diacylated product** (**74**) (33 mg, 14%) as a brown oil (Found: C, 68.0; H, 8.4. $C_{38}H_{56}O_{10}$ requires C, 67.9; H, 8.3%); $\nu_{max.}$(film) 1704 (C=O) cm^{-1}; δ 1.22 - 1.85 (36H, m, $CH(CH_3)_2$ and $-(CH_2)_6-$) 2.32br (4H, t, *J* 7Hz, 2x CH_2COOH), 2.61-2.88 (2H, m, 8-$COCH_2-$), 3.09 (2H, t, *J* 7Hz, 3-$COCH_2$), 3.73 and 3.98 (3H, s, OCH_3), 4.64 (2H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.64 (1H, s, 6-H), and 6.88 (1H, s, 2-H); *m/z* 673 (M^+, 52%), 631 (34), 473 (13), 455 (27), 413 (20), 273 (53), 247 (23), 42 (100), and 28 (100).

3,8-Di(8-carbomethoxynonanoyl)-4,5-dimethoxy-1,7-di-2'-propyloxynaphthalene (**75**).- The monomethyl ester of azelaic acid (nonanedioic acid) (0.372 g, 1.65 mmol) premixed with trifluoroacetic anhydride (0.38 g, 1.65 mmol) dissolved in dry methylene dichloride (2 ml) was rapidly added to solution of the naphthalene (**43**) (100 mg, 0.33 mmol) in dry methylene dichloride (5 ml).

The reaction was stirred at room temperature for 115 h. After work-up as described above the residue was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **ester (75)** as a light brown oil (126 mg, 57%) (Found: C, 67.9; H, 8.25. $C_{38}H_{56}O_{10}$ requires C, 67.9; H, 8.4%), $\nu_{max.}$(film) 1736 (CO_2Me), 1704, 1662, and 1602 cm^{-1}; δ 1.23 - 1.80 (32H, m, $-(CH_2)_5-$ and $CH(CH_3)_2$), 2.28 (4H, t, *J* 9Hz, 2x CH_2COOCH_3), 2.68 - 2.92 (2H, m, 8-$COCH_2$-), 3.08 (2H, t, *J* 7Hz 3-$COCH_2$-), 3.65, 4.61, and 3.74 (each 3H, (except 3.65 6H), s, OCH_3), 4.60 (2H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.67 (1H, s, 6-H), and 6.92 (1H, s, 2-H); *m/z* 672 (M^+, 51%), 630 (23), 473 (18), 441 (9), 273 (49), 247 (12), 74 (18), and 93 (100).

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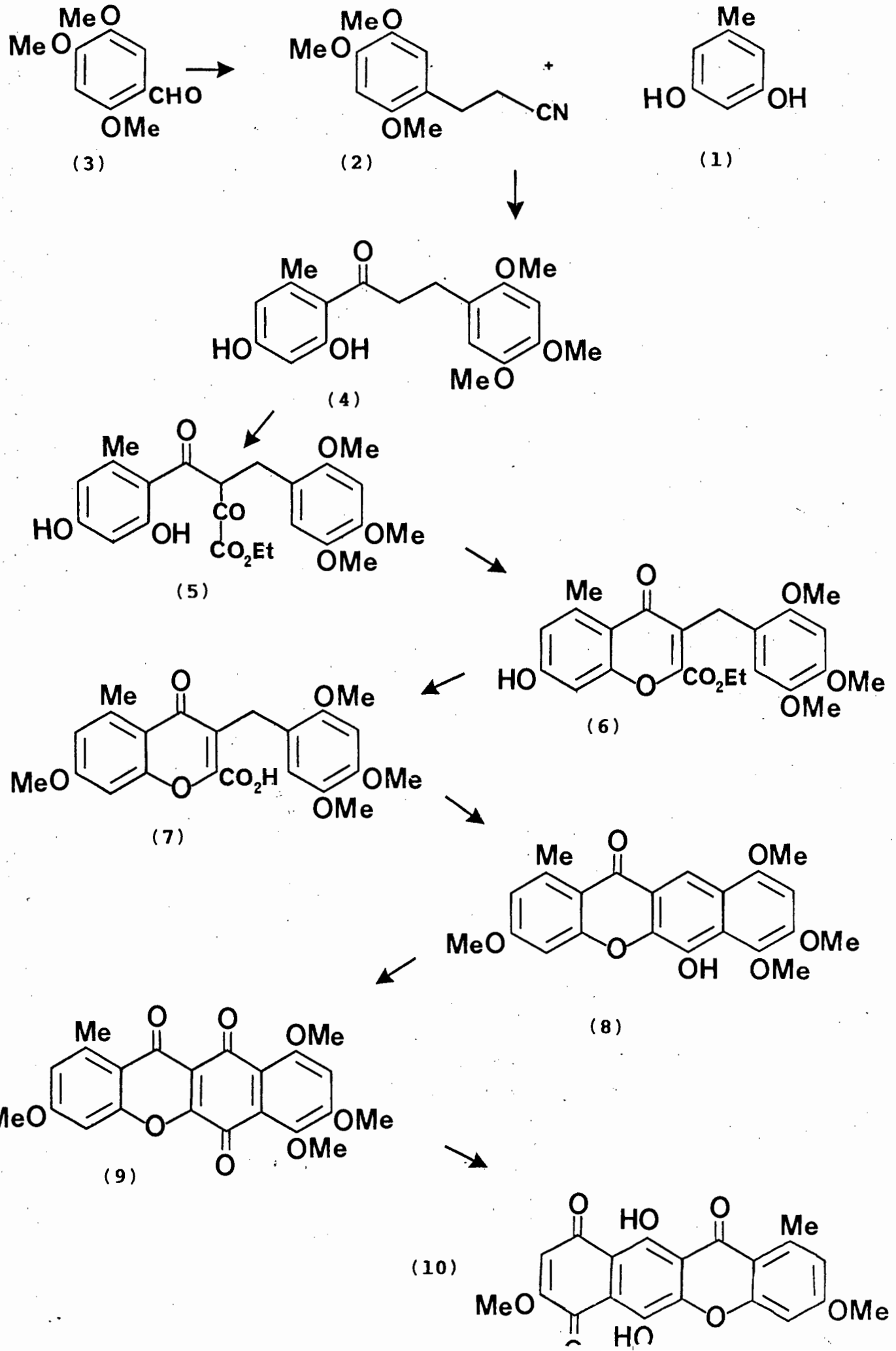
CHAPTER 2

CONVENIENT SYNTHESIS OF BIKAVERIN

INTRODUCTION

Bikaverin (**10**) is a wine-red pigment produced by species of the fungal genera *Fusarium*[1], *Gibberella*[2a,b] and *Mycogone*.[3] The pigment has been shown to have specific antiprotozoal,[4] antitumour,[5] and high vacuolation[1] properties. Bikaverin was isolated and characterised simultaneously by Cornforth[6] and Kjær,[2a] the structure being confirmed by X-ray crystallography.[7]

Bikaverin has recently attracted considerable attention which has led to three independent syntheses. In 1976 Barton[8] achieved the synthesis in ten steps with a 3% overall yield using orcinol (**1**) and 3-(2,4,5-trimethoxyphenyl)propiononitrile (**2**), which was obtained from 2,4,5-trimethoxybenzaldehyde (**3**), as starting materials. Condensation of the nitrile with orcinol gave a dihydrochalcone (**4**). This was treated with diethyl oxalate to give an ester (**5**) which condensed to give the chromone (**6**). This product on methylation followed by hydrolysis of the ester group produced the acid (**7**). Ring closure gave the xanthone (**8**), which upon oxidation afforded the quinone (**9**); this could be demethylated to give bikavarin (**10**).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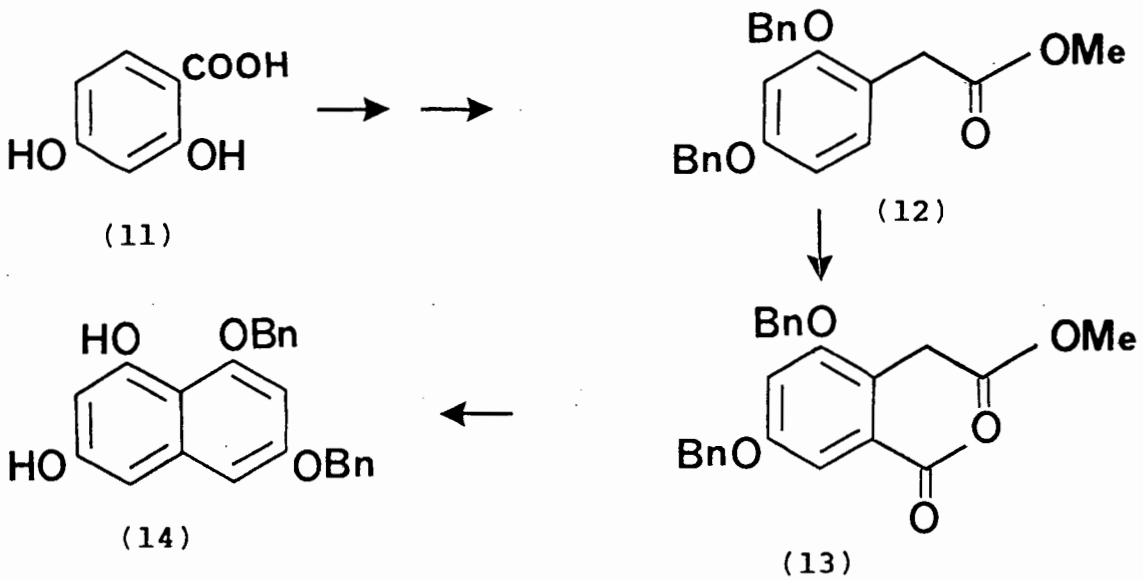
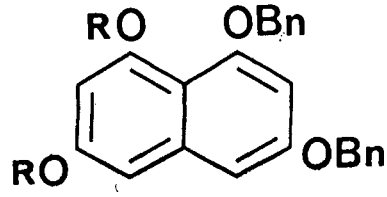
Five years later the Japanese workers, Kato, *et al.*[9] described a twelve-step synthesis of the pigment in an overall yield of 0,3%, using a novel rearrangement for transforming an angular orthoquinone into a linear benzoxanthone. In this synthesis 2,4-dihydroxybenzoic acid (**11**) was converted in three steps into the ester (**12**) which was acetylated to give the phenyl ester (**13**). Dieckmann condensation led to the production of a dihydroxynaphthalene (**14**). This substance was treated with an everninic acid chloride to produce the ester (**15**) which underwent Fries rearrangement to afford the phenol (**16**). This compound on ring closure gave the angular benzoxanthone (**17**). Conversion of this substance to the orthoquinone (**18**) was achieved by oxidation with potassium dichromate. Treatment of the orthoquinone (**18**) with silica gel, led *via* a novel rearrangement to the linear xanthone (**19**), which was in turn oxidised and suitably deprotected to yield norbikaverin (**20**) and subsequently bikaverin (**10**).





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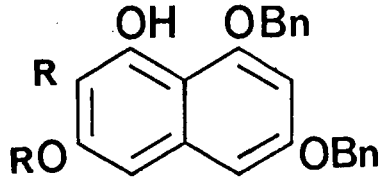

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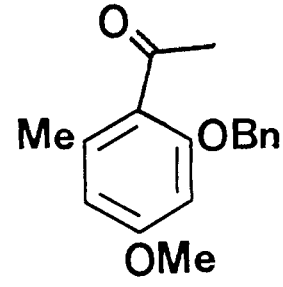

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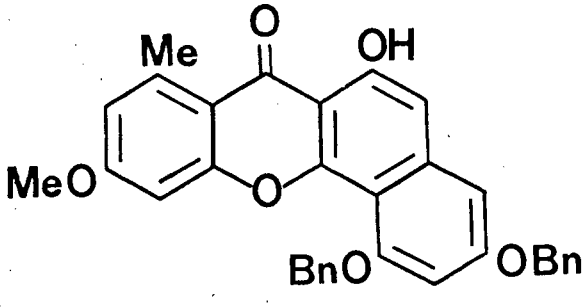

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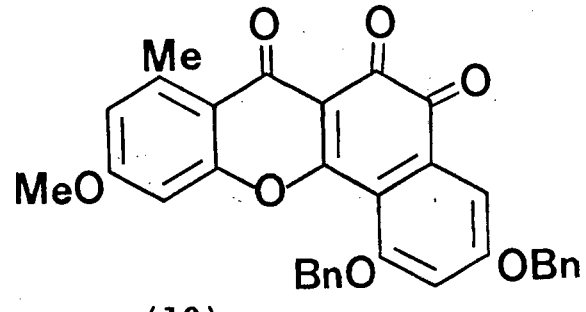

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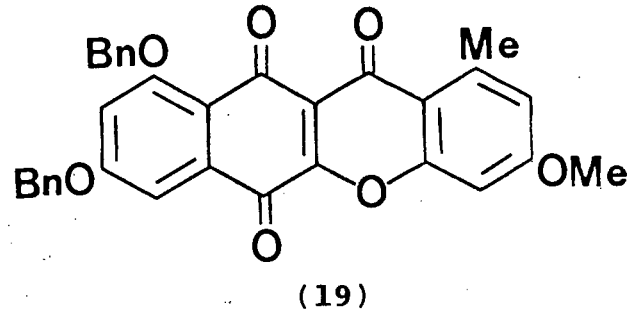

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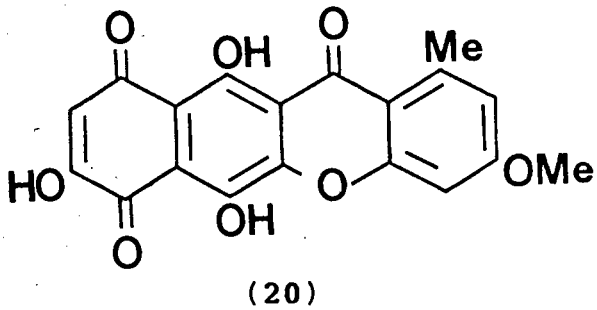

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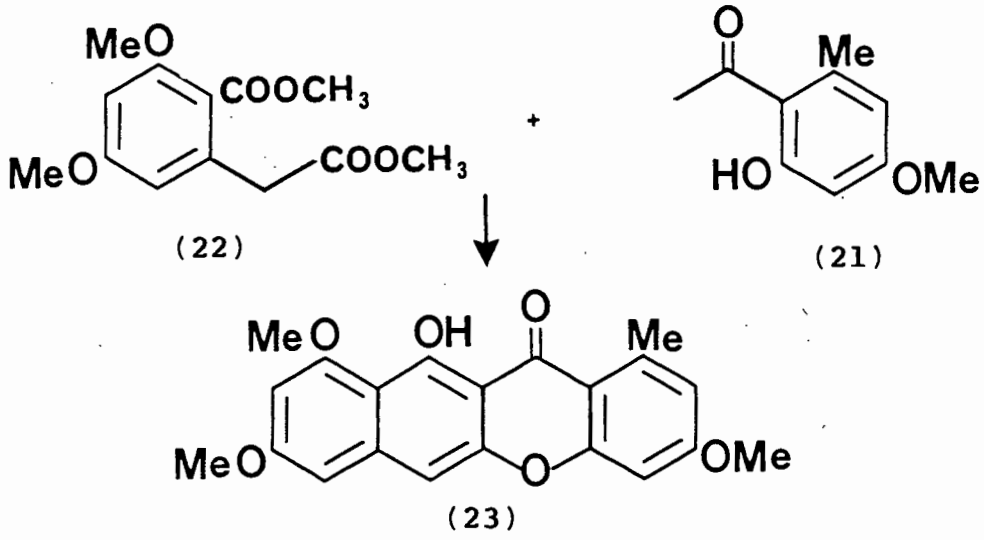
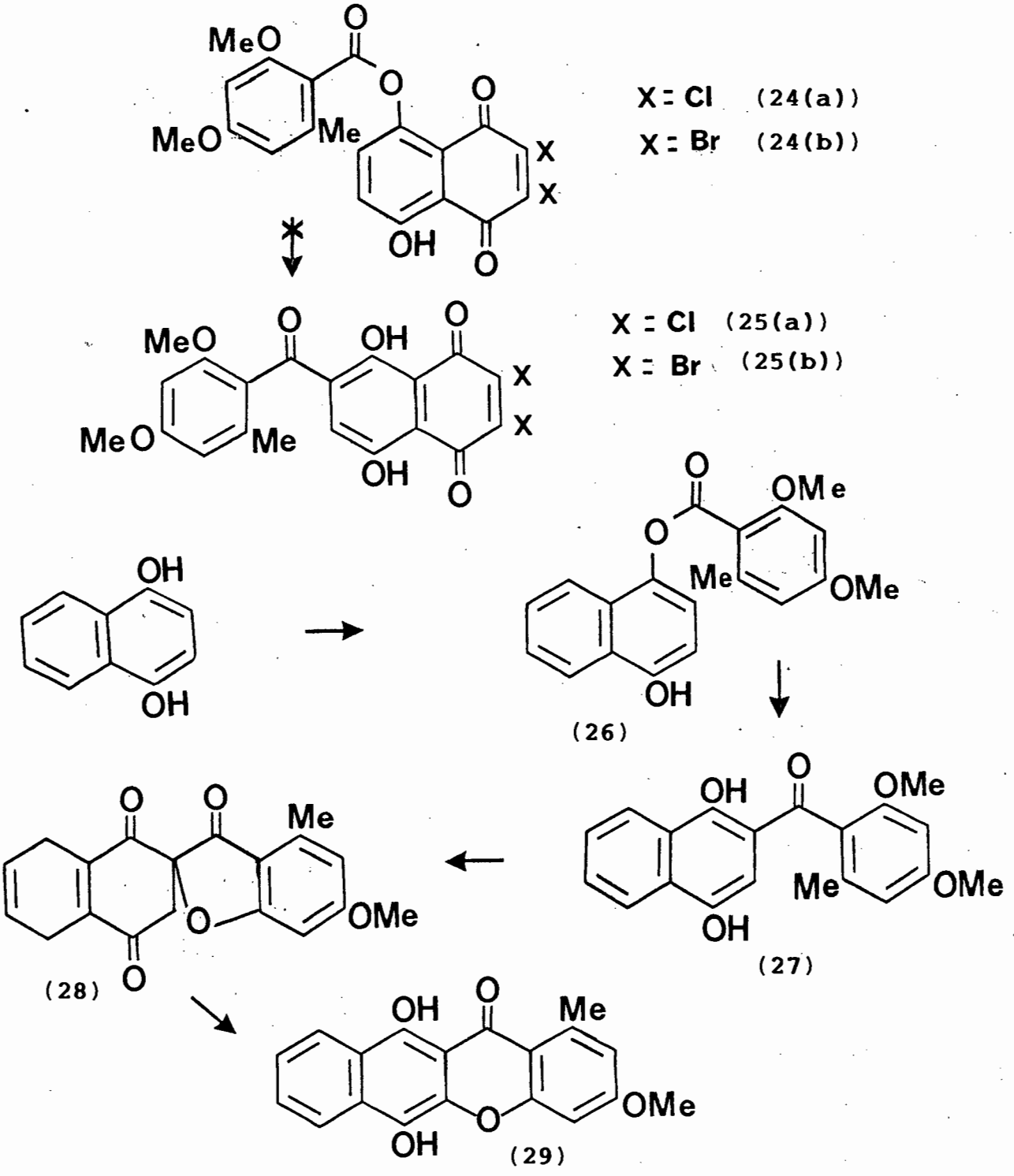
More recently, in 1983 Kjær[10] also successfully accomplished a six-step synthesis of bikaverin, in an overall yield of 4.5%. Kjær's synthesis involved a base-catalysed reaction of the acetophenone (**21**), with the dimethoxyhomophthalate (**22**) to give the hydroxybenzoxanthone (**23**) which was oxidised to bikaverin (**10**) in poor yield.



Another interesting approach to the synthesis of bikaverin, based on oxidative phenolic coupling was developed by Lewis.[11] Lewis attempted a rearrangement of the quinones (**24(a)** and **(b)**) which he hoped would lead to the acylated products (**25(a)** and **(b)**). These in turn would lead to bikaverin (**10**) *via* selective deprotection and oxidative coupling. The proposed strategy was however only successful with the acylated product (**27**), which was obtained from the ester of 1,4-naphthohydroquinone (**26**) by a Fries rearrangement. This compound, after partial demethylation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone produced the spirocyclohexene-dione (**28**) which was thermally converted into the xanthone (**29**).

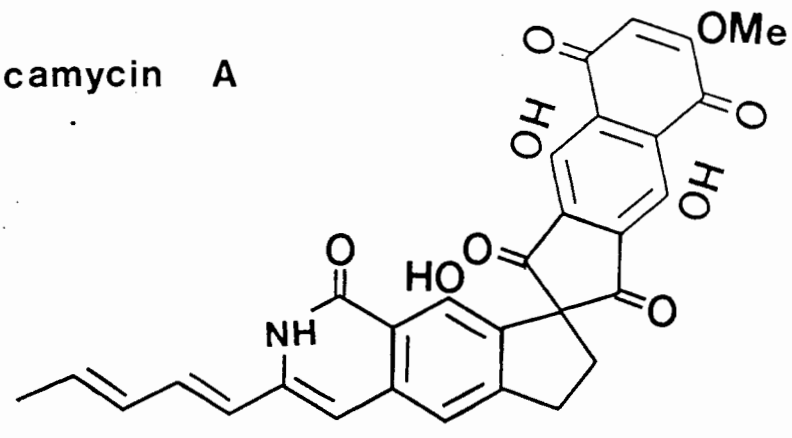


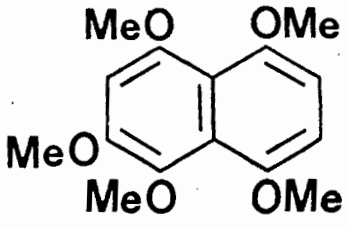
Recent work by Brassard[12,13] and Bekaert[14] shows that other synthetic strategies for the assembly of the wine-red pigment bikaverin are in progress.

Bikaverin has now been synthesised in our laboratory *via* two different routes, in either five steps with a 11% overall yield, or in eight steps with a 10% overall yield (yields based on 1,2-dibromo-3,4,6-trimethoxybenzene as starting material, which is readily obtained from vanillin).

Both syntheses use a pentamethylated leuconaphthopurpurin (**30**), which is produced from vanillin, as starting material. The oxygenation pattern of this naphthalene (**30**) is of interest in that a number of naturally occurring quinonoid compounds are based on it.[15] In addition to the bikaverins (**10**) and (**20**), it forms the skeleton of compounds as diverse as mompain,[15a] javanicin,[15b] solaniol,[15c] the fusarubins,[15d] the wilting agents marticin and isomarticin,[15e] the dactynaphins,[15f] erythrostominone,[15g] and purpuromycin.[15h] A compound whose synthesis is presently attracting considerable attention on account of its antitumour activity is the antibiotic fredericamycin A,[16a-j] which also possesses the same naphthalene skeleton.

fredericamycin A





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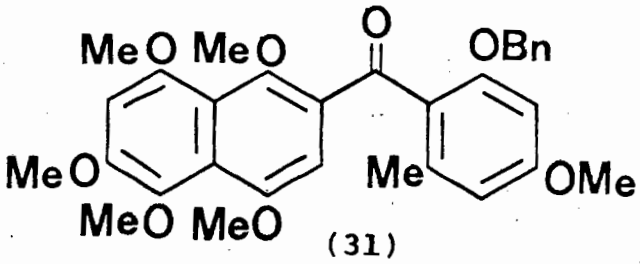

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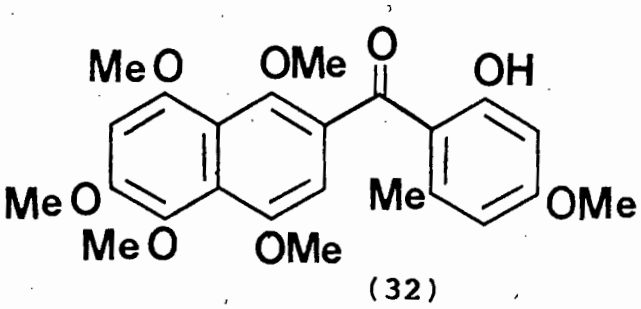

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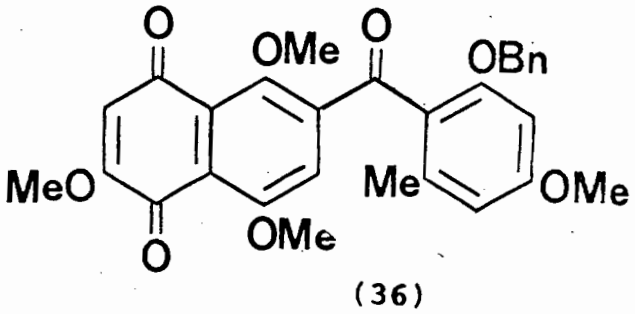

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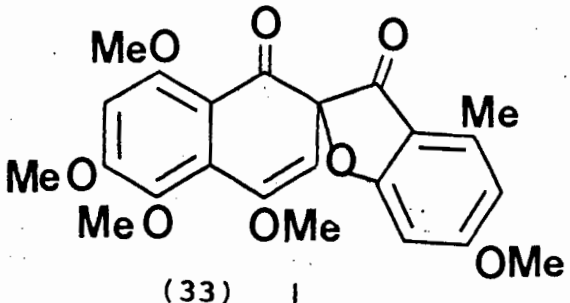

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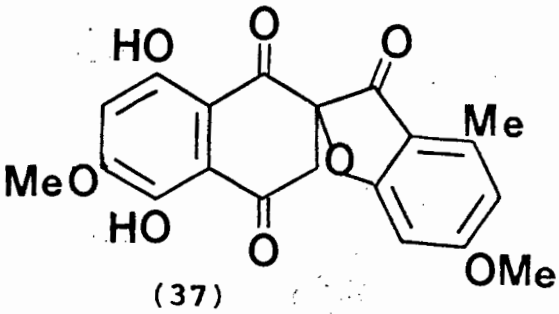

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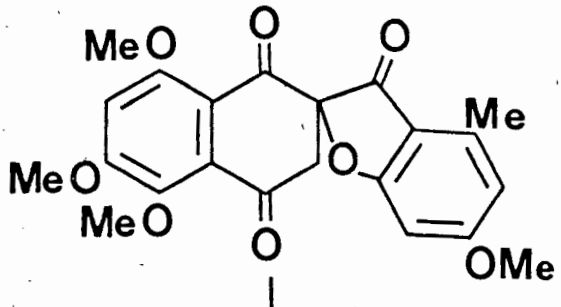

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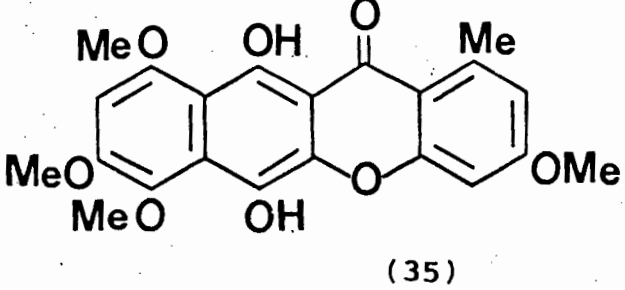

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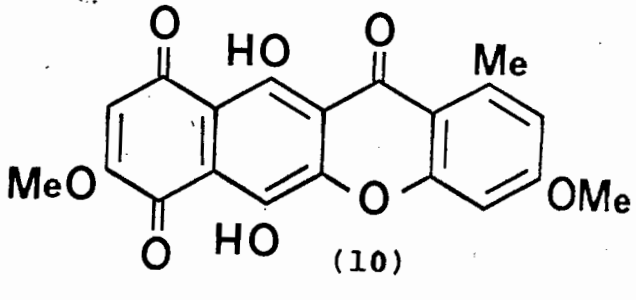


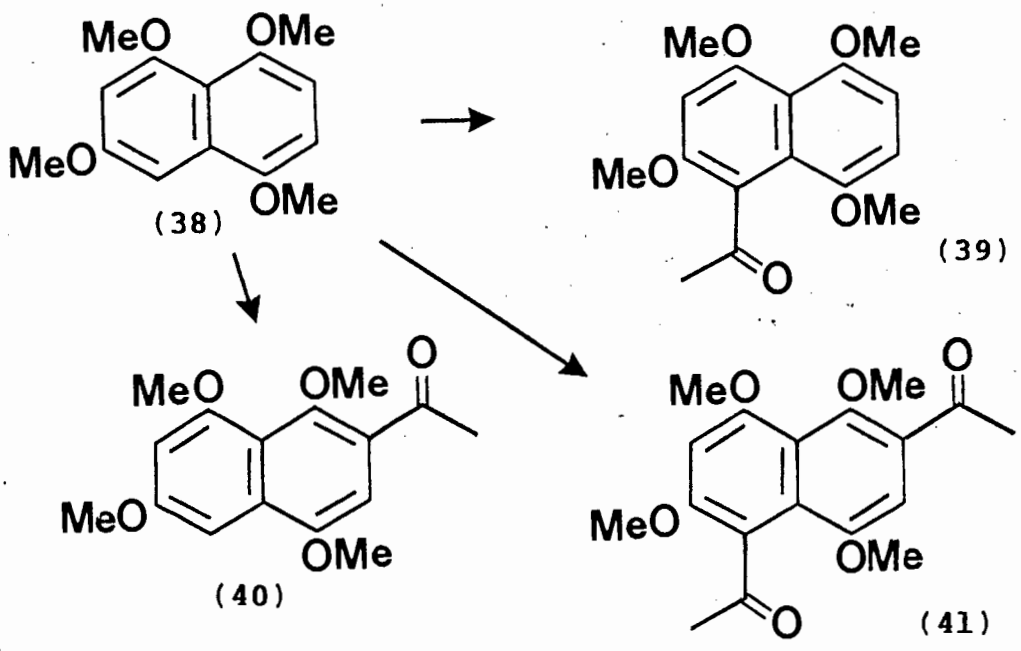
(10)

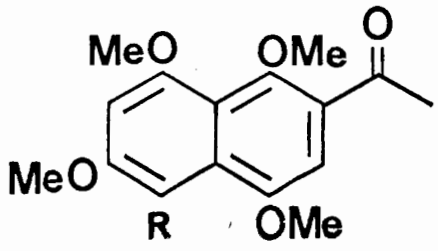
The next step in our synthesis was the important regiochemical acylation by means of mixed anhydrides of trifluoroacetic acid and a suitable organic acid, a procedure which was originally developed in our laboratory by Giles *et al.*[17] This yielded the common acylated intermediate (**31**). Removal of the benzyl group by hydrogenolysis in the presence of palladium on activated carbon afforded compound (**32**) which on oxidative coupling with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave the spiro-compound (**33**). Hydrolysis of this enol ether afforded the trione (**34**), which in turn was thermally converted to the hydroquinone (**35**). Oxidation of (**35**) with silver(I) oxide and the removal of the appropriate methyl groups with lithium iodide[8] afforded bikaverin (**10**). This constituted the eight-step procedure.

Alternatively, in the five step synthesis, compound (**31**) was oxidised with silver(II) oxide to yield the quinone (**36**). Treatment of this quinone with boron trichloride gave the spirocompound (**37**) directly, which on heating rearranged to bikaverin (**10**).

RESULTS AND DISCUSSION

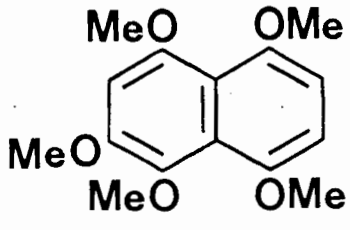
Earlier work from our laboratory[17] has shown that monoacetylation of 1,4,5,7-tetramethoxynaphthalene (**38**) with acetic acid in the presence of trifluoroacetic anhydride leads to the formation of the C-8 acetyl product (**39**) as the major component and the C-3 acetyl compound (**40**) as the minor component. If however, an excess of acetic acid and trifluoroacetic anhydride is used, the reaction leads to the production of the 3,8-diacetylated product (**41**) in good yield.[18] It was therefore envisaged that if C-8 were blocked by another substituent e.g. methoxy, the reaction would lead to acetylation in position 3 only to afford (**42**), in spite of the fact that an additional methoxy substituent at C-8 might, in conjunction with that already at C-1, militate against the regiochemical direction provided by the three methoxy groups at C-4, C-5, and C-7, thereby reducing the regioselectivity.





R = OMe (42)

Retrosynthetic analysis of bikaverin (10) shows that it could be considered to be composed of a pentaoxygenated unit (30) and a substituted aromatic acid, such as (43). Aromatic acylation would then lead, as postulated, to the 3-acylated product (31).



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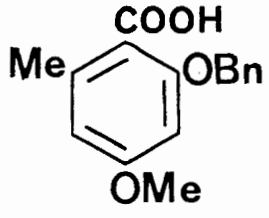

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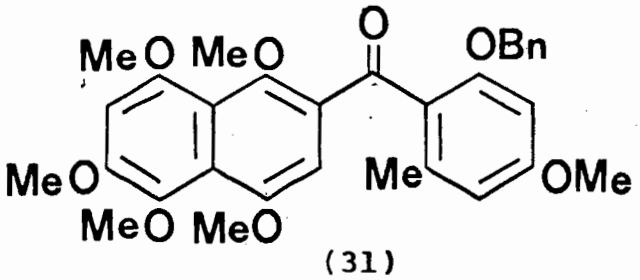
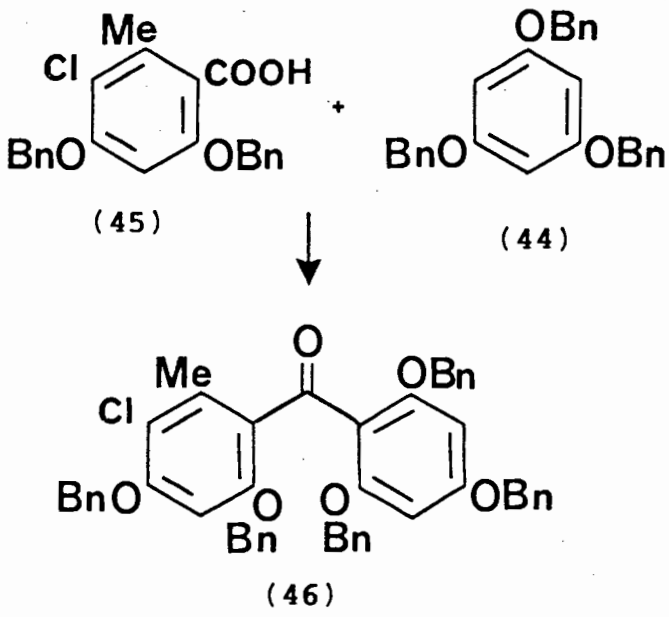


(31)

Sundholm[19] has shown that aromatic acylation using an oxygenated benzene compound such as (**44**) and a substituted benzoic acid such as (**45**) in the presence of trifluoroacetic anhydride proceeds to give product (**46**) in very high yield.

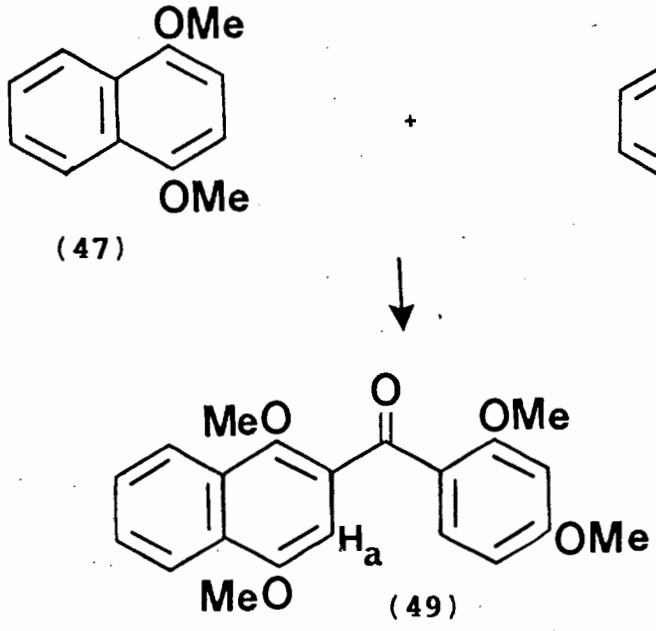


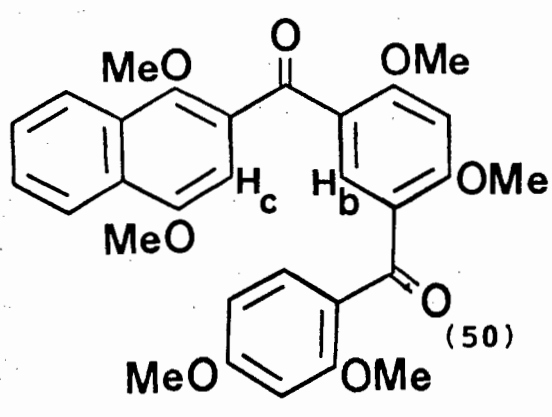
(45) (44) (46)

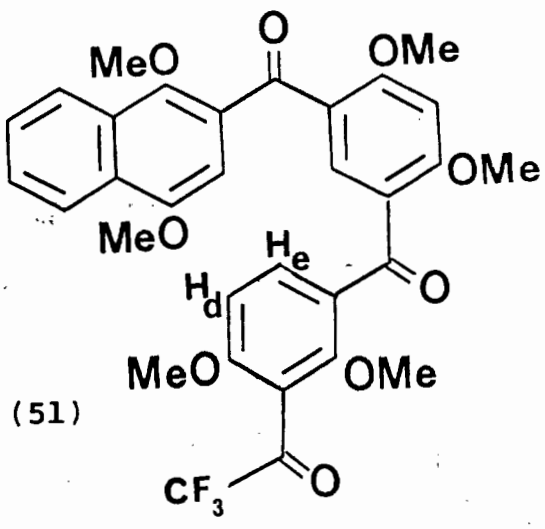
As acylation on our naphthalenic compounds had only been performed using aliphatic acids,[18] acylation of 1,4-dimethoxynaphthalene (**47**) with 2,4-dimethoxybenzoic acid (**48**) in the presence of trifluoroacetic anhydride was used as a model system.

Acylation occurred at position 2 of the naphthalene nucleus affording the product (**49**) in a yield of 51%. This showed a characteristic aromatic singlet (Ha) at δ 6.88 in the ^{1}H n.m.r. spectrum., a characteristic aromatic carbonyl at 1629 cm^{-1} in the infrared spectrum and a molecular ion at *m/z* 352 in the mass spectrum. It was found that further acylation of the benzene nucleus of the product (**49**) also

took place and as a by-product (50) was isolated. In the ^{1}H n.m.r. spectrum of this compound (50), two aromatic singlets Hb and Hc were observed at δ 7.82 and δ 6.90 respectively, the proton at δ 7.82 (Hb) being *ortho*-to two deshielding carbonyl groups, and the proton at δ 6.90 (Hc) being *ortho*-to only one carbonyl group. Confirmation of the structure was obtained from the mass spectrum which indicated the presence of a molecular ion at *m/z* 516, and the presence of both carbonyl stretching vibrations in the





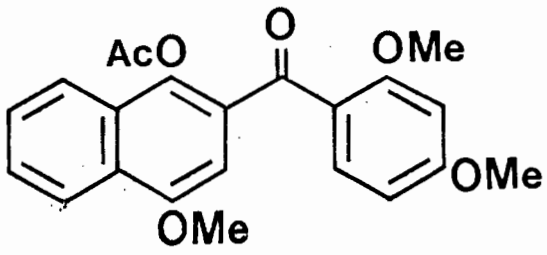


infrared spectrum at 1628 cm^{-1}, the absorption at 1607 cm^{-1} probably being too low for a carbonyl stretch, and being more likely due to a carbon carbon vibration.

Another minor product was identified by means of ^{1}H n.m.r. spectroscopy as the trifluoroacetylated product (51). Only two *ortho*-coupled protons at δ6.56 and δ7.37 (J10Hz) corresponding to the two aromatic protons Hd and He respectively were observed on the second benzene ring of compound (51).

On adding an excess of the mixture of trifluoroacetic anhydride and 2,4-dimethoxybenzoic acid in an attempt to increase the yield of compound (49), further acylation occurred, and the maximum yield was obtained when only one equivalent of the mixed anhydride was used.

In order to attempt ring closure to afford the xanthone on this simplified system (49), it was necessary to selectively demethylate the 2'-methoxy group on the benzenoid ring. Treatment of the acylated product (49) with four molar equivalents of boron trichloride resulted in the selective removal of one methyl group; undoubtedly it was one of the two methyl groups *ortho*- to the carbonyl group. To establish which one had been selectively deprotected the crude naphthol was acylated to afford either product (52) or (53).



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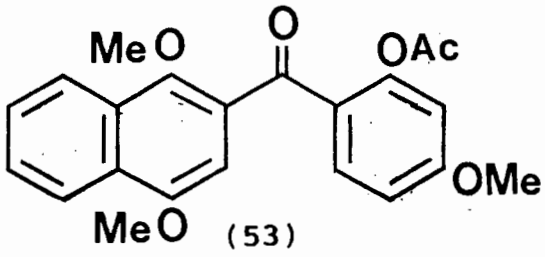
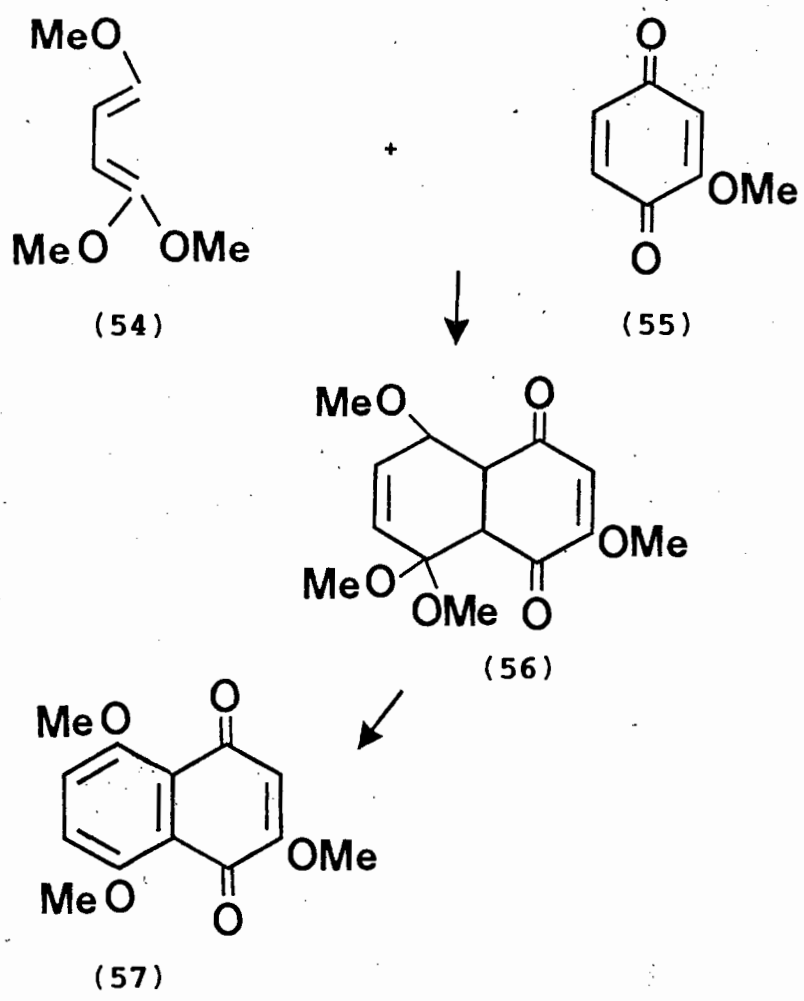


(53)

The ^{1}H n.m.r. spectrum of the resulting compound showed that the product was indeed (52) as the protons in position 5- and 8- no longer had similar chemical shifts. The 5-proton had been relatively shielded, from a multiplet at δ 8.03-8.36 to a multiplet at δ 7.69-7.90. It was therefore necessary to protect the benzenoid oxygen, which was subsequently to provide to xanthone ring oxygen, with a substituent other than methyl, so that this could be selectively deprotected in the projected assembly of bikaverin itself.

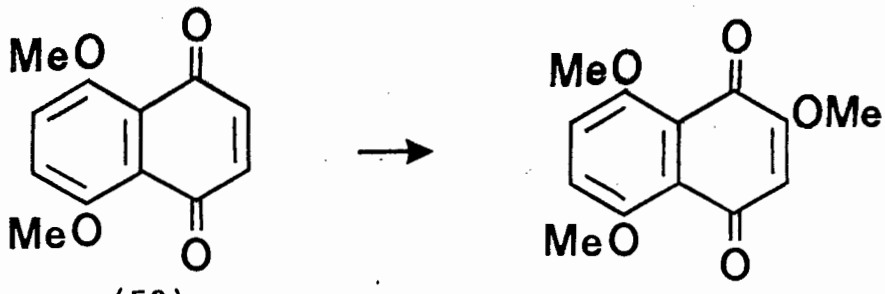
Since aromatic acylation of the model system to afford the naphthalene (49) had been successful, a synthesis had to be developed for a 1,2,4,5,8-pentaoxygenated naphthalene (30).



Cameron[20] has reported that 1,4,4-trimethoxybutadiene (**54**) and 2-methoxy-1,4-benzoquinone (**55**) react to form the Diels-Alder adduct (**56**). It was postulated that elimination of a molecule of methanol and two hydrogen atoms in substance (**56**) would lead to aromatisation. This quinone (**57**) could then be reductively methylated to form the pentamethoxy compound (**30**). In our laboratory reactions for the elimination were not successful. For this reason, and the fact that the yield of the Diels-Alder adduct (**56**) was low, this avenue was not further explored.

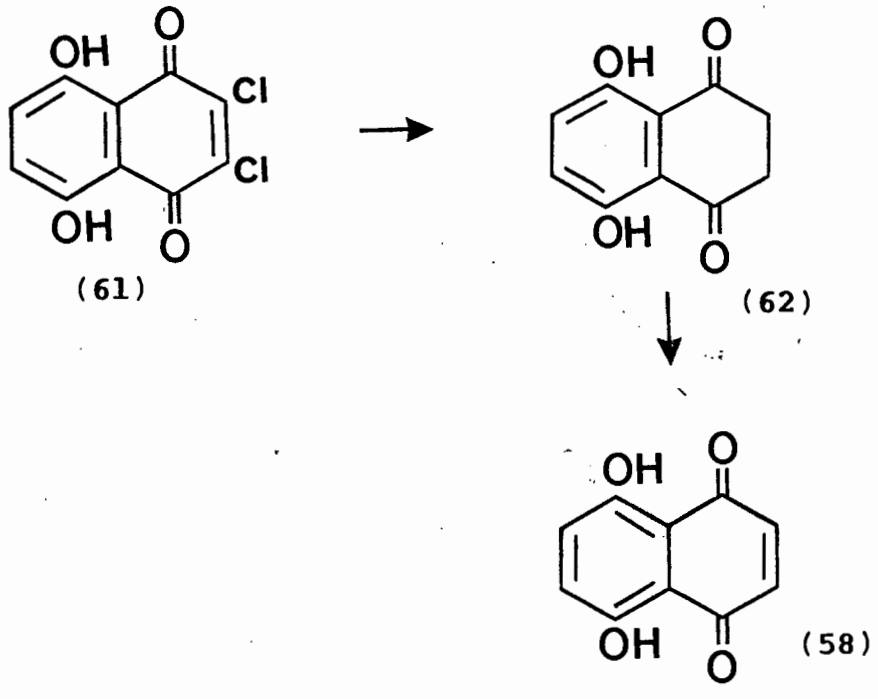
Various methods exist for the production of naphthopurpurin[e.g.21-24] and its derivatives, which in general rely on the ring oxygenation of the tetraoxygenated compound

naphthazarin (58). The most attractive method for our synthesis seemed to be that of Fariña.[25]



(59) (60)

He showed that the naphthazarin dimethyl ether (59) could be methoxylated in high yield to give the quinone (60). Reductive methylation of this would give rise to the desired product (30). The problem with this approach would be the initial production of naphthazarin which by the standard literature method[26] i.e. reaction of maleic anhydride and hydroquinone in the presence of molten aluminium trichloride and sodium chloride, proceeds in very low yield.



(61) (62)

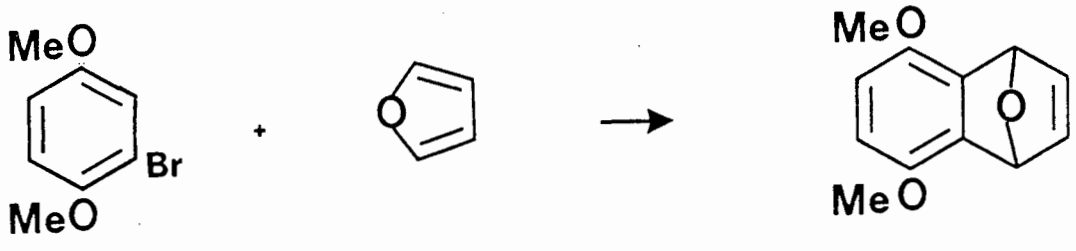
OH
O
OH
O

(58)

An alternative method for the synthesis of naphthazarin exists[27] in which 2,3-dichloronaphthazarin (**61**) (formed in high yield from 1,4-dimethoxybenzene and 2,3-dichloromaleic anhydride[28]) is reduced with tin(II) chloride to give the dihydronaphthazarin (**62**). Brief treatment of compound (**62**) with alkali affords naphthazarin (**58**). In our hands the yields of the reactions were poor and variable. Consequently a different approach was needed.

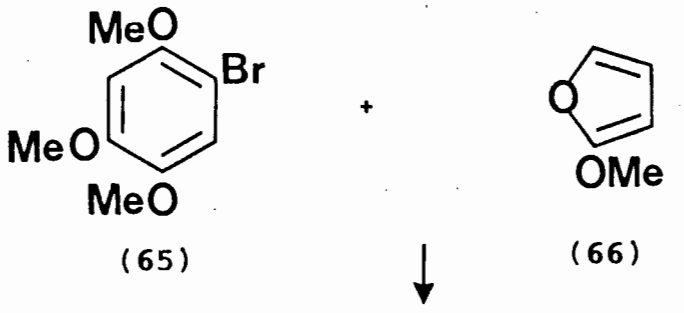
Since 1955[29] it has been known that benzynes react with furans to afford 1,4-epoxy-1,4-dihydronaphthalenes. It has also been established that benzynes can be generated in three general ways; (i) from aryl halides by treatment with a strong base,[30] (ii) by diazotisation of anthranilic acid derivates,[30] or (iii) by treatment of o-dibromoarenes with *n*-butyl lithium at -78 °C.[31,32]

Giles[33] and co-workers have shown that the benzyne generated from 1-bromo-2,5-dimethoxybenzene (**63**) with sodium amide readily undergoes Diels-Alder addition with furan to produce the epoxynaphthalene (**64**) in good yield.



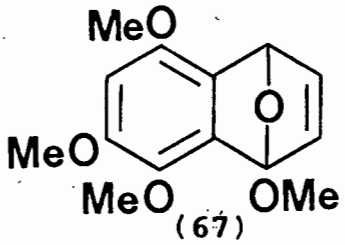
(**63**) (**64**)

It was envisaged that 1-bromo-2,4,5-trimethoxybenzene (65) would react in the presence of sodium amide with 2-methoxy-furan (66) to give the adducts (67) and (68).[34] These would on opening of the epoxy ring, e.g. with silica, give the two naphthols (69) and (70) which could be methylated to give the desired product (30) as a single compound.

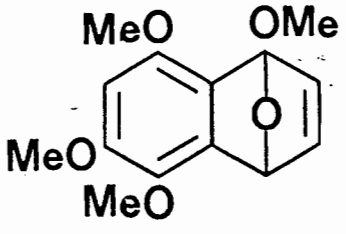


(65)

(66)



(67)



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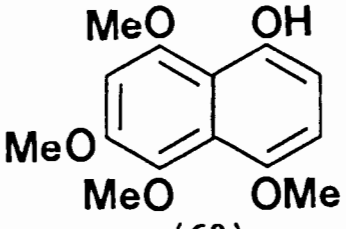

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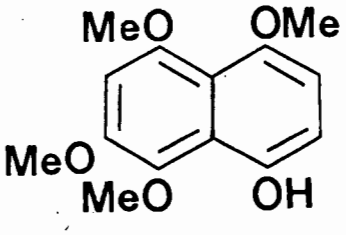

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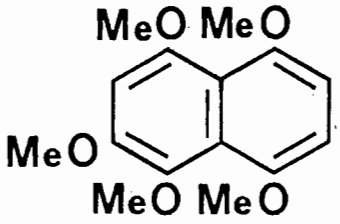
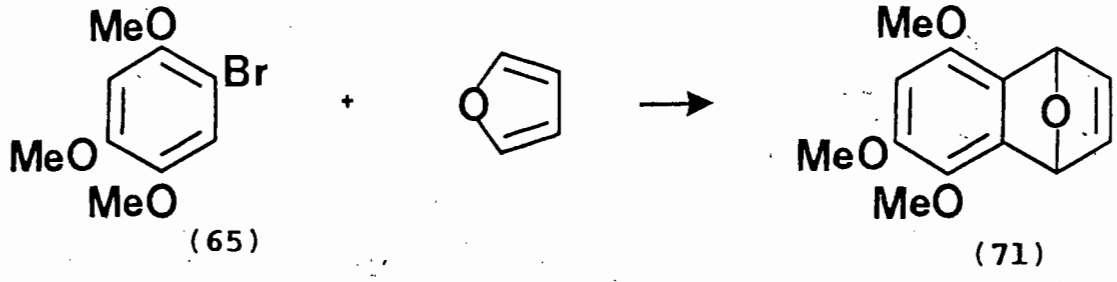


(30)

1-Bromo-2,4,5-trimethoxybenzene (**65**) was prepared in high yield according to the method of Jeffreys.[35]

Subsequently two model reactions using sodium amide were carried out. First, it was necessary to determine whether 1-bromo-2,4,5-trimethoxybenzene (**65**) did generate the benzyne when treated with base.

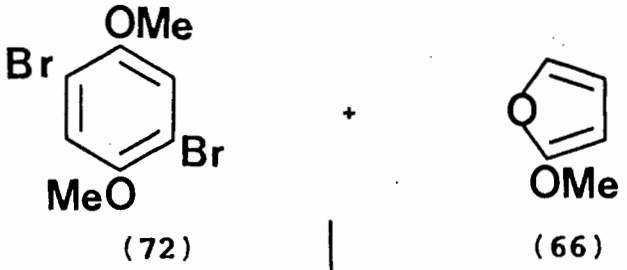
In a nitrogen atmosphere the trimethoxybenzene (**65**), furan and sodium amide were boiled in 1,2-dimethoxyethane for two hours. The resulting product (**71**) showed that the benzyne had indeed been formed and had reacted with furan to yield the Diels-Alder adduct (**71**), which was isolated in 58% yield.



(65) (71)

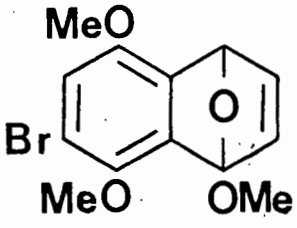
Secondly, it was necessary to determine whether the related 2-methoxyfuran underwent Diels-Alder additions. Treatment of 1,4-dibromo-2,5-dimethoxybenzene (**72**)[33] with 2-methoxyfuran (**66**) in the presence of sodium amide in boiling 1,2-dimethoxyethane for two hours produced the two adducts (**73**) and (**74**) which afforded the corresponding naphthols after opening of the epoxy ring by flash chromatography on silica gel. Both naphthols were eventually methylated to the single product (**75**). The yield of the product (**75**) was only moderate, but it was realized that some of the 2-methoxyfuran

could have added to both sides of the benzenoid ring to form compound (76). However since the reaction being discussed was a model reaction, only the major product was isolated, with minor components being observed in the reaction mixture using thin layer chromatography. Clearly, there was the possibility of forming two additional regioisomers of the bis-adduct, which would only form the single compound (76) after ring opening and subsequent methylation.

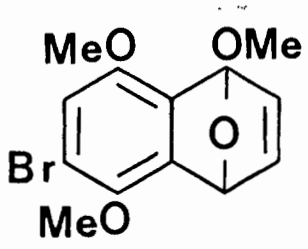


(72)

(66)



(73)



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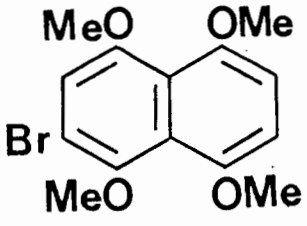

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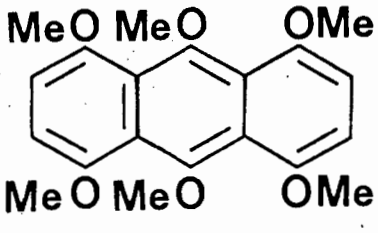


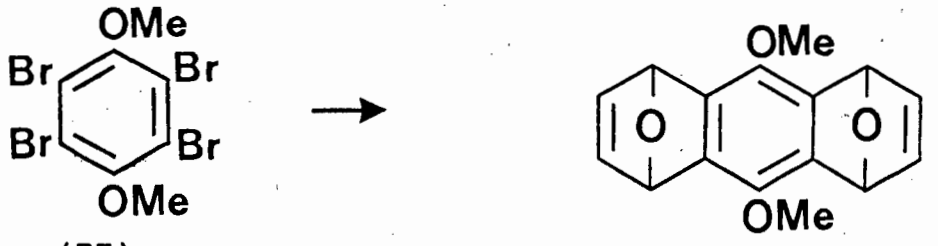
(76)

As both these reactions had been successful it was hoped that the trimethoxybenzene (**65**) would react with 2-methoxyfuran (**66**) to give the desired product (**30**), after hydrolysis and methylation. It was, however, realised that compound (**65**) also possessed an alternative aromatic hydrogen (*meta*- to the bromine atom) which might be more acidic than that *ortho*- to bromine, on account of the fact that the former proton is situated between two methoxy substituents, both of which would stabilise a derived anion situated between them. Were this to be so, it might prove difficult to remove the second proton leading to the formation of the required benzyne.

However, when the reaction was attempted by boiling in 1,2-dimethoxyethane for seven hours, followed by flash chromatography of the two adducts and methylation of the two naphthols, the pentaoxygenated naphthalene (**30**) was produced indicating that the difficulty that had been foreseen did not prevent the reaction from being relatively successful. The total yield of the two steps was 30%, suggesting perhaps that the reaction did not proceed as smoothly as the related reaction described earlier leading to the formation of (**71**), (58%).

A literature survey showed that other workers[36] had also encountered low yields in preparing substituted naphthalenes from benzynes. As the method was not entirely satisfactory other methods for generating the benzyne were therefore investigated.

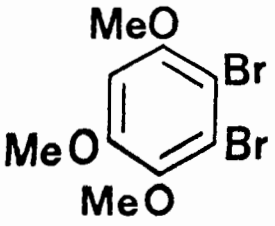
Hart[32] has described the conversion of ortho-dibromobenzenes such as (**77**) into anthracenes in two steps. Reactions of these potential bisarynes with *n*-butyl lithium in the presence of furan, led to Diels-Alder adducts such as (**78**).[33]



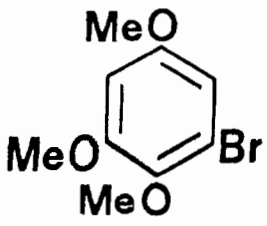
(**77**) (**78**)

In order to attempt this type of reaction for the production of the naphthopurpurin derivative (**30**), 1,2-dibromo-3,4,6-trimethoxybenzene (**79**) needed to be synthesised.

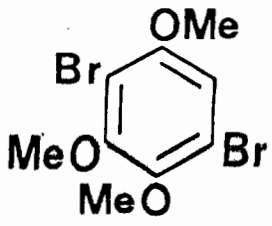
Dorn[37] in 1939 synthesised 1-bromo-2,3,5-trimethoxybenzene (**80**) from vanillin, by bromination of vanillin, followed by the replacement of the aldehyde group by a hydroxyl by the Dakin reaction and subsequent methylation. Further bromination according to Dorn[37] led to the supposed formation of 1,4-dibromo-2,3,5-trimethoxybenzene (**81**). More recent work by McOmie[38] and Crowther[39] has shown however that the alleged 1,4-dibromo-compound (**81**) was not formed but rather 1,2-dibromo-3,4,6-trimethoxybenzene (**79**). This latter substance was prepared in four steps with overall yield of 56% from vanillin.



(79)



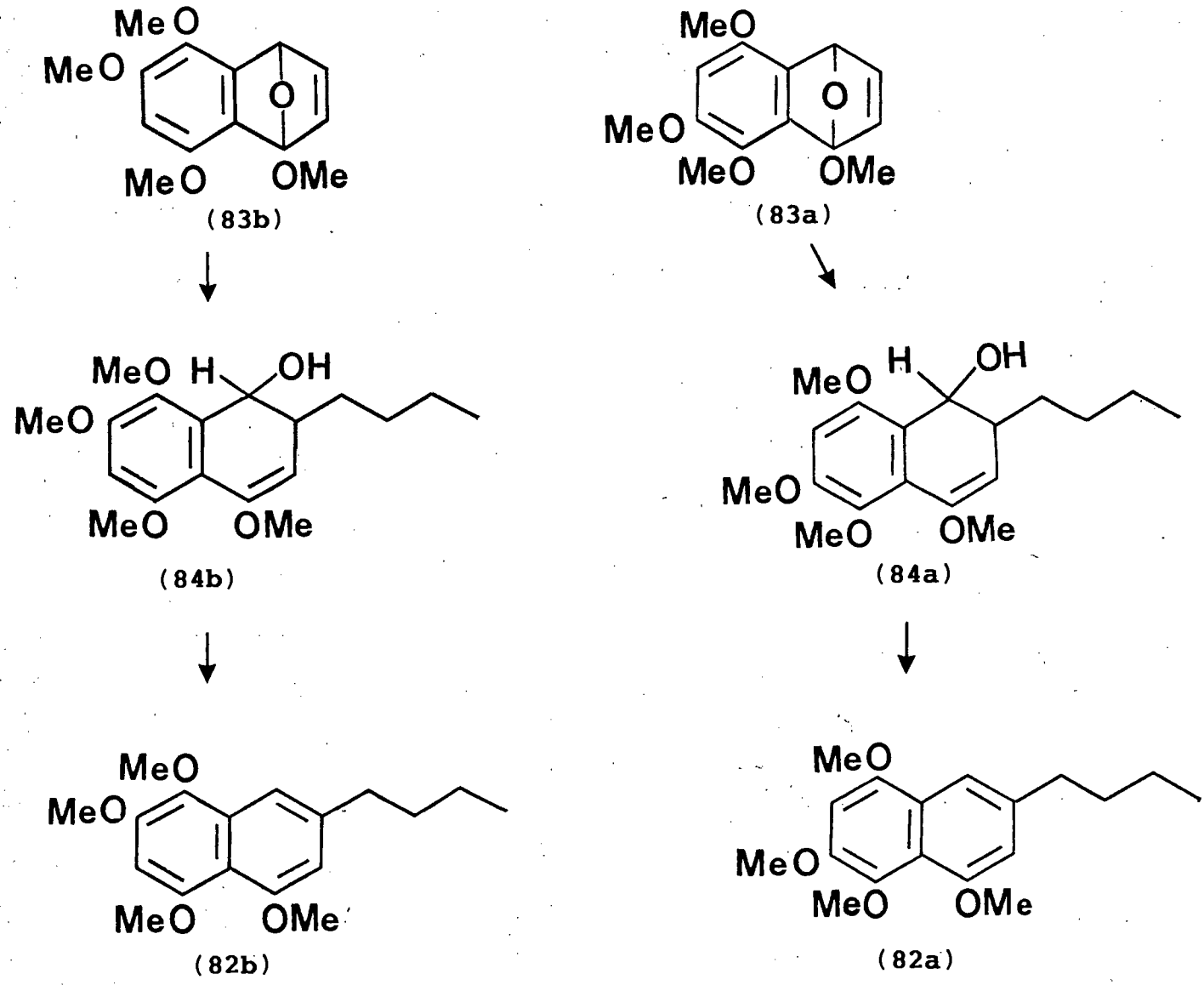
(80)



(81)

On a small scale a solution of 1,2-dibromo-3,4,6-trimethoxybenzene (**79**) and 2-methoxyfuran in dry tetrahydrofuran were treated at -78°C with one molar equivalent of *n*-butyl lithium in a nitrogen atmosphere. After work-up, flash chromatography of the two isomeric adducts and subsequent methylation gave product (**30**) in 53% yield.

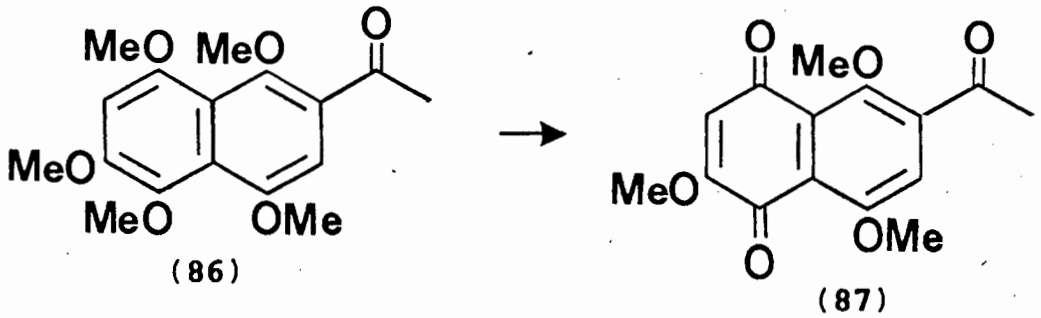
On scaling up the reaction it was noticed that a by-product was also formed, and that the larger the scale of the reaction, the more of this undesired compound was produced. The ^{1}H n.m.r. spectrum of the compound showed peaks characteristic of a butyl moiety and only four methoxy singlets as well as an aromatic singlet at δ 6.64 and two doublets at δ 6.73 and δ7.58 with a coupling constant of 2Hz. This suggested that the by-product was either (**82a**) or (**82b**), but not both as only a single product was isolated. This assignment was supported by the mass spectrum, which showed a molecular ion at *m/z* 304.



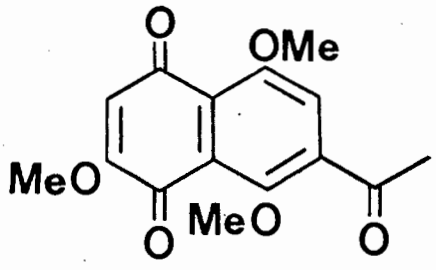
The formation of this by-product probably takes place by reaction of some of one of the Diels-Alder adducts (**83(a)** or **(b)**) with butyl anions to afford one of the butylated products either (**84a**) or (**84b**). Subsequent base catalysed methylation leads to the elimination of water to afford the product (**82(a)** or **(b)**). As this was an unwanted by-product it seemed unnecessary to determine the position of the methoxy group but rather to attempt to exclude the formation of this undesired compound.

Attempts to suppress the formation of the undesired product (**82**) by changing the solvent, shortening the reaction time, diluting the reaction mixture, or lowering the reaction temperature were unsuccessful. However, it was found that by using only 0.9 molar equivalents of *n*-butyl lithium the pentamethoxynaphthalene (**30**) was produced in a yield of 63% (calculated on converted (**79**)), with some starting material being recovered. This proved the best method for the synthesis of 1,2,4,5,8-pentamethoxynaphthalene (**30**). It's ^{1}H n.m.r. spectrum showed, *inter alia*, an aromatic singlet at δ 6.75 and two characteristic *ortho*- coupled protons at δ 6.65 and δ 6.80 with a coupling constant of 10Hz. The structure was supported by the mass spectrum which showed a molecular ion at *m/z* 278.

Acetylation of the pentamethoxynaphthalene (**30**) with acetic acid in the presence of trifluoroacetic anhydride produced only one product (**86**) in high yield with the ^{1}H n.m.r. spectrum showing, apart from the five methoxy groups, two aromatic singlets at δ 6.75 and δ 7.07, and an acetyl three-proton singlet at δ 2.72. It was expected that acetylation would have taken place in the 2-position relative to the methoxy group at C-6, as argued earlier, but it was necessary to prove this unequivocally.



(86) (87)



(88)

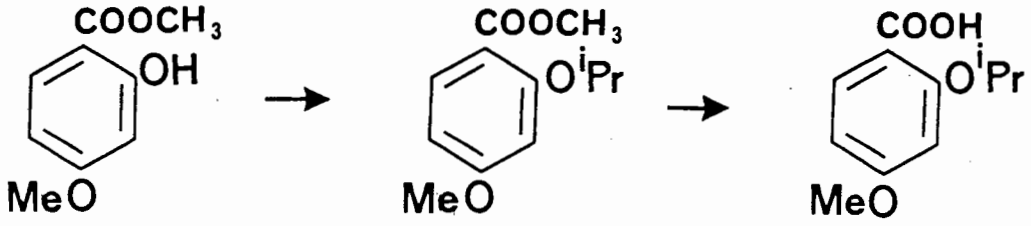
Fariña[25] has previously synthesised the pair of isomeric quinones 2-acetyl-1,4,6-trimethoxy-5,8-naphthoquinone (**87**) and 3-acetyl-1,4,6-trimethoxy-5,8-naphthoquinone (**88**). On oxidation of our naphthalene (**86**) with silver(II) oxide, quinone (**87**) was produced. It was to be expected that the more electronrich of the two naphthalene rings of compound (**86**) would be the one to be preferentially oxidised to afford the quinone (**87**). Support for this proposal was found in the ^{1}H n.m.r. spectrum of quinone (**87**) in that the quinonoid proton appeared at δ 6.10, typical of the chemical shift of such protons of methoxy-1,4-quinones.

As the ^{1}H n.m.r. spectrum and infrared spectrum of quinone (**87**) and quinone (**88**) were very similar, comparison of our quinone with each of the two quinones (**87**) and (**88**) (kindly supplied by Professor Fariña) by melting point and mixed melting point, as well as chromatographic behaviour in different solvents proved that our quinone was identical to

quinone (87) and different from compound (88).

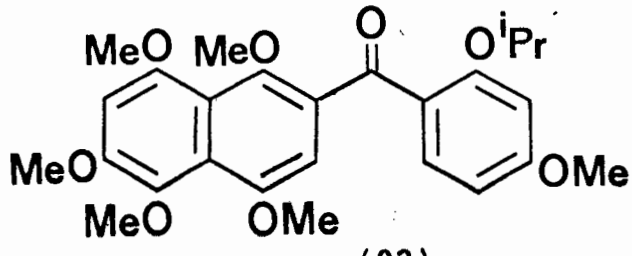
In the meantime, work was in progress, on the other portion, namely the production of a suitably protected aromatic acid. As 2,4-dihydroxybenzoic acid was readily commercially available it was decided to use derivatives of this acid as a model for acylation.

2,4-Dihydroxybenzoic acid was converted with methyl iodide and potassium carbonate[40] into the ester methyl 2-hydroxy-4-methoxybenzoate (89). This was treated with isopropyl bromide and potassium carbonate to afford the diether (90). On saponification of the ester (90) with boiling methanolic potassium hydroxide, the corresponding acid (91) was obtained.

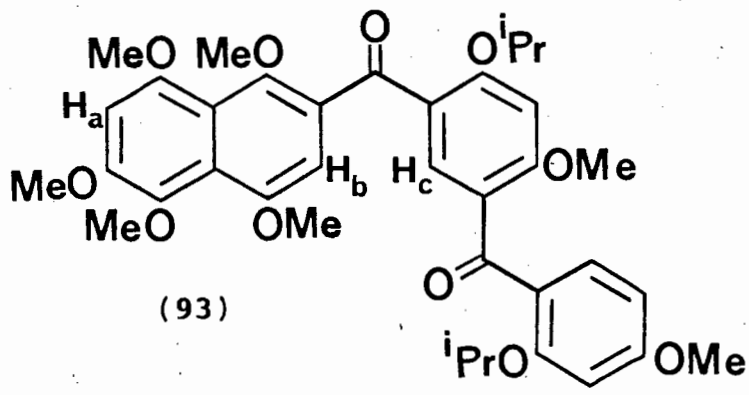


(89) (90) (91)

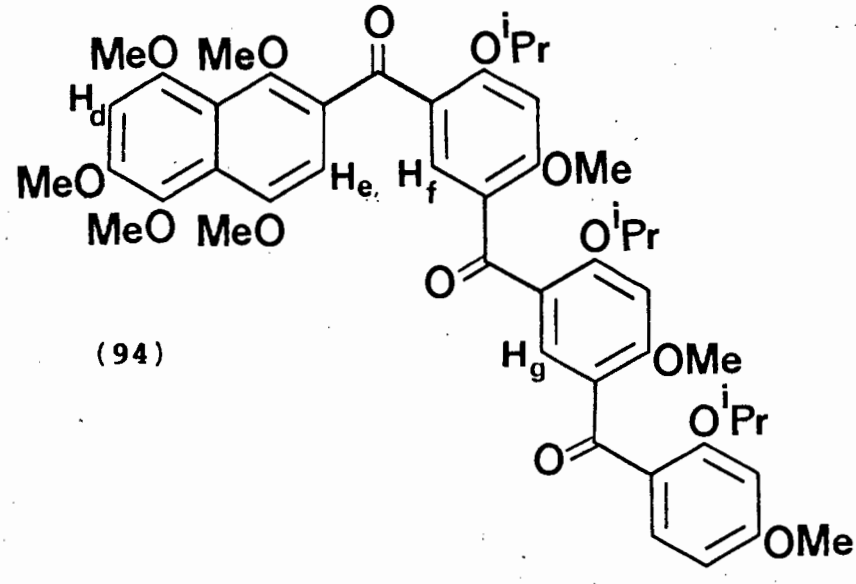
Acylation of the pentamethoxynaphthalene (30) with this model aromatic acid (91) in the presence of trifluoroacetic anhydride led to the desired monoacylated product (92). It was however noted that the diacylated (93) and triacylated products (94) were also formed in yields of 8 and 11% respectively.



(92)



(93)

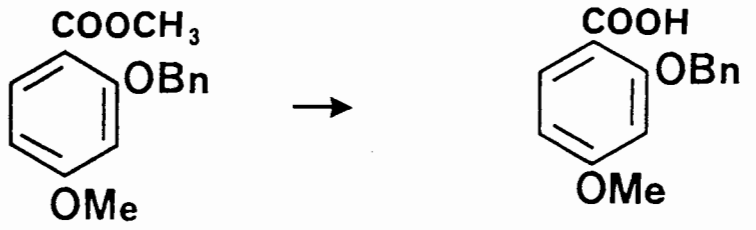


(94)

This was shown by the ^{1}H n.m.r. spectra which showed, apart from the other protons, characteristic singlets at δ 6.76 (Ha), δ 6.84 (Hb) and δ 7.96 (Hc) for compound (**93**), and aromatic singlets at δ 6.76 (Hd), δ 6.86 (He), and δ 7.79 (Hf or Hg) and δ 7.97 (Hg or Hf) for compound (**94**). The assignments

of (**93**) being supported by mass spectrometry.

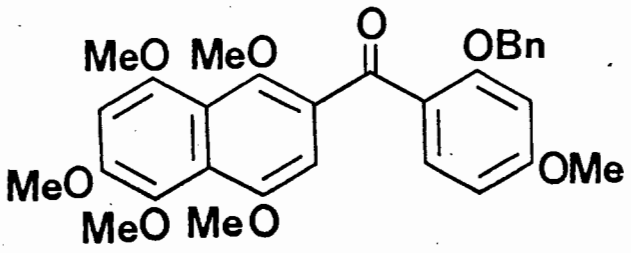
Selective deprotection of the monoacylated product (**92**) did not result in the clean removal of the isopropyl group and it was therefore decided to use another protecting group which could be removed more easily.



(**96**) (**95**)

2-Benzyloxy-4-methoxybenzoic acid (**95**) was synthesised in a manner similar to that of the isopropyl analogue (**91**), *via* the diether (**96**). Acylation of the naphthopurpurin derivative (**30**) using the acid (**95**) led to the formation of the acylated product (**97**) in 63% yield as a single compound. No di- and triacylation occurred in this case, presumably because of the greater bulk of the benzyl substituent in comparison with the isopropyl group in compound (**92**).

Selective removal of the benzyl moiety was achieved by treating the compound (**97**) with hydrogen in the presence of palladium on activated carbon as catalyst. This gave rise to phenol (**98**), as shown by ^{1}H n.m.r. spectroscopy indicating a hydrogen bonded proton at δ12.73 and mass spectrometry showing a molecular ion at *m/z* 428.



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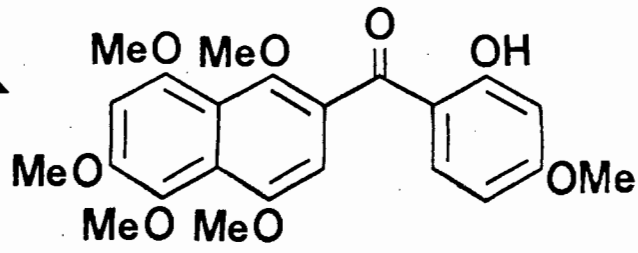
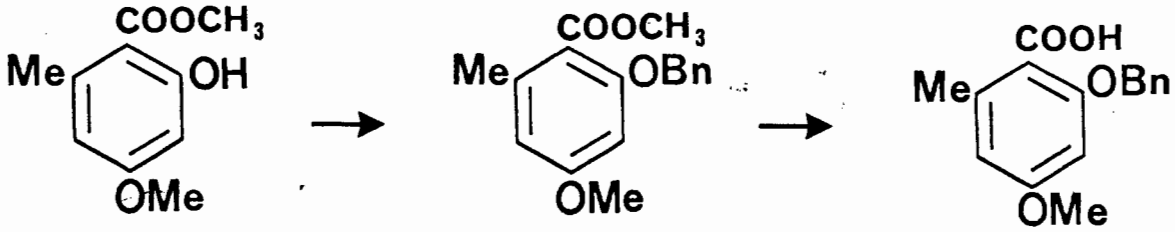


(98)

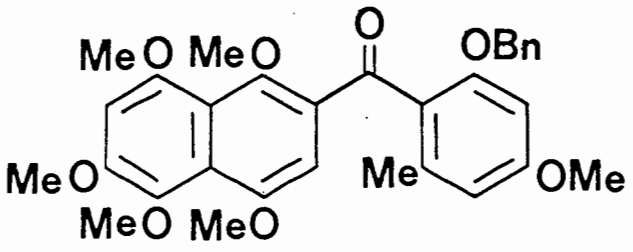
Since acylation with the model acid 2-benzyloxy-4-methoxy-benzoic acid and the selective removal of the benzyl group from the product (**96**) had been successful, the orsellinic acid derivative (**43**) was synthesised.

Methyl orsellinate prepared according to Sargent[41] was methylated[40] to yield the everninic methyl ester (**99**), and this was in turn treated with benzyl bromide and potassium carbonate to afford the ester (**100**). The ester (**100**) was hydrolysed with boiling methanolic potassium hydroxide to afford 2-benzyloxy-4-methoxy-6-methylbenzoic acid (**43**) which has previously been synthesised by Sundholm,[19] Nicollier,[47] Kato,[9] and Sargent.[48] Comparison of spectroscopic data showed identical characteristics.



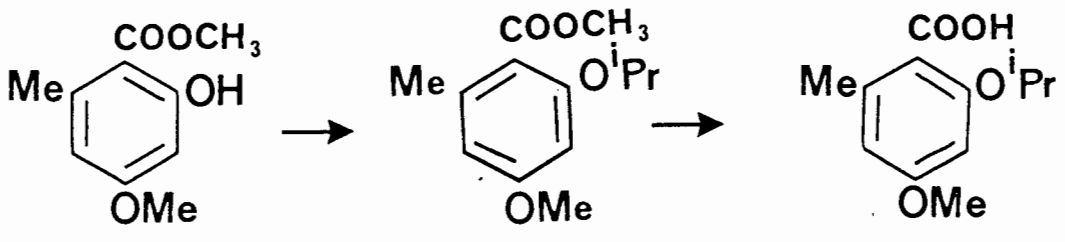
(99) (100) (43)

Acylation of pentamethoxynaphthalene (**30**) with this acid (**43**) yielded the desired product (**31**) in 51% yield, which proved to be the key intermediate for both syntheses of bikaverin (**10**). By ^{1}H n.m.r. spectroscopy, the product (**31**) showed (apart from the six methoxy groups and the benzyl group) a singlet at δ2.36 corresponding to the aryl methyl, an aromatic singlet at δ6.68 (the other aromatic singlet being situated under the aromatic benzyl proton signals), and two *meta*-coupled protons at δ6.32 and δ6.40 (*J*2.2Hz). The infrared spectrum showed the aromatic carbonyl at 1631cm^{-1}, while further evidence for the assignment was obtained from the mass spectrum which showed a molecular ion at *m/z* 532.

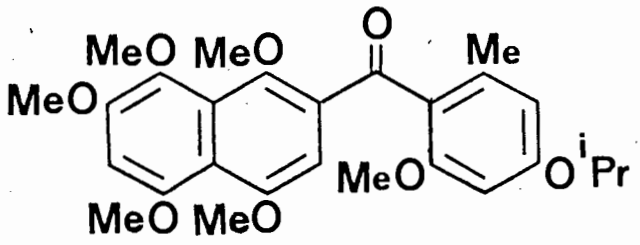


(**31**)

Strangely, acylation of the pentamethoxynaphthalene (**30**) with 2-isopropoxy-4-methoxy-6-methylbenzoic acid (**102**), produced similarly *via* the sequence (**99**) (**101**) (**102**), afforded in low yield a mixture of the two isomers (**103**) and (**104**) which were difficult to separate.



(**99**) (**101**) (**102**)



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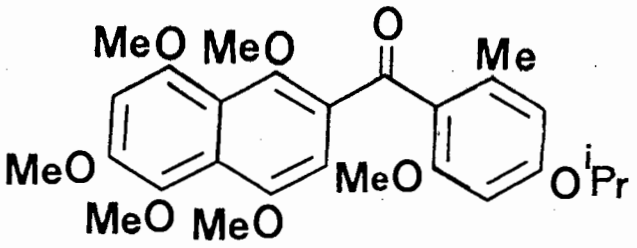
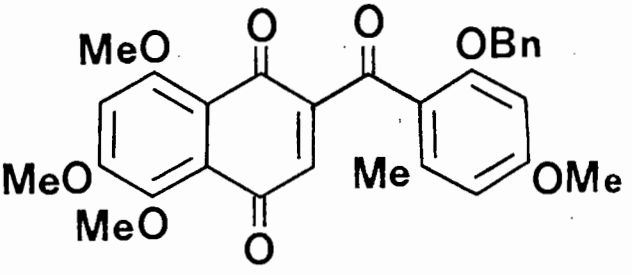
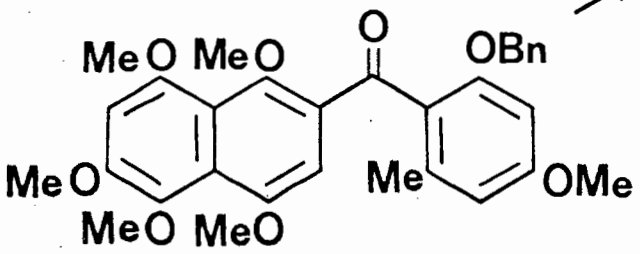


(104)

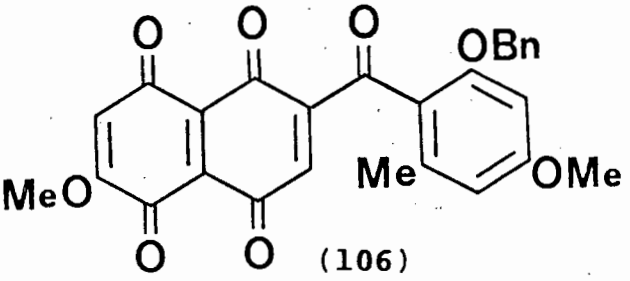
The next step in the synthesis of bikaverin was the formation of the xanthone ring. It was envisaged that if the naphthalene ring of compound (31) could be oxidised to produce either the quinone (105) or, better still, the diquinone (106), then on selective removal of the benzyl group this (106) would hopefully lead to spontaneous cyclisation to afford the xanthone bikaverin (10).



(105)



(31)

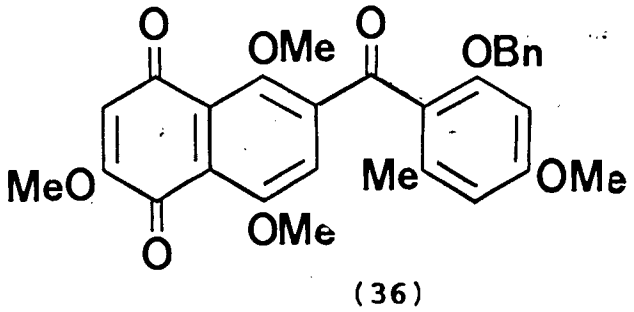


(106)

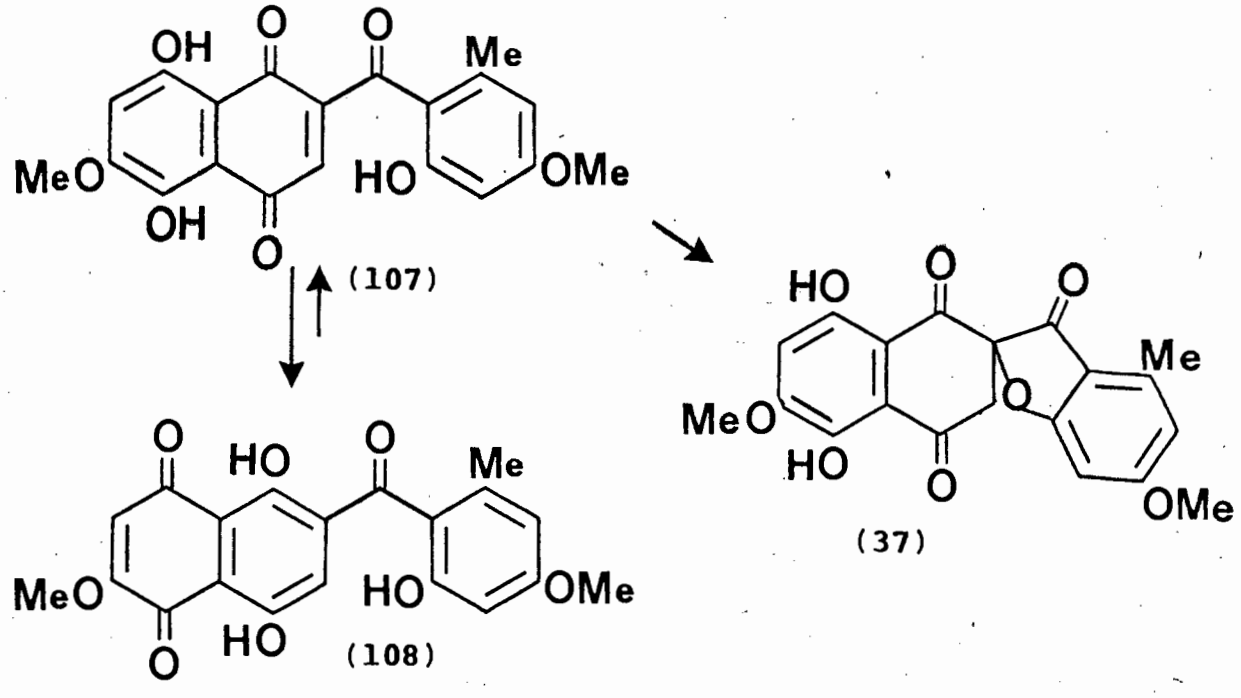
This would take place by 1,4-addition of the hydroxyl group to the α, β-unsaturated carbonyl system of the quinone. However, it was also anticipated that oxidation, if it were to afford a monoquinone, would once again take place preferentially at the more electron-rich ring. This was established in practice, since oxidation of the naphthalene (**31**) with various oxidising agents only led to the formation of the monoquinone (**36**).

In order to obtain the isomeric quinone (**105**), it was expected that one of the methyl protecting groups on the acylated ring of the naphthalene would have to be removed to permit selective oxidation of the derived *para*-methoxyphenol.

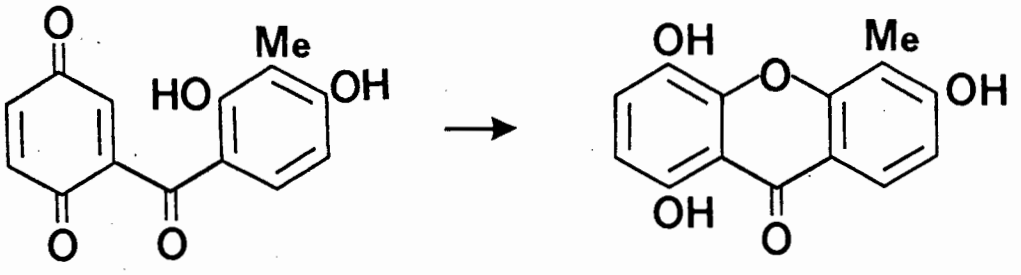
However, this route proved to be unnecessary, since treatment of the monoquinone (**36**) at 0°C with seven molar equivalents of boron trichloride produced the spirocompound (**37**). This presumably arose as a result of the removal of the benzyl moiety as well as the two remaining methyl groups in positions *peri*- to the carbonyl of the quinone (**36**). This was then followed by 1,2-addition of the hydroxyl group to the quinone (**107**) which exists in tautomeric equilibrium with the quinone (**108**).



(**36**)



The addition is in contrast to that encountered by Whalley[42] who found that the 1,4-benzoquinone (**109**) undergoes 1,4-Michael addition of the hydroxyl group to afford product (**110**).



Support for the assignment of structure (**37**) was provided by its ^{1}H n.m.r. spectrum (Figure 2), which clearly showed the presence of two doublets at δ 3.20 and δ 3.55 each with a coupling constant of 17.5Hz, corresponding to the methylene protons (c.f. Lewis[11]). Additional evidence was adduced from the mass spectrum which showed a molecular ion at *m/z* 384

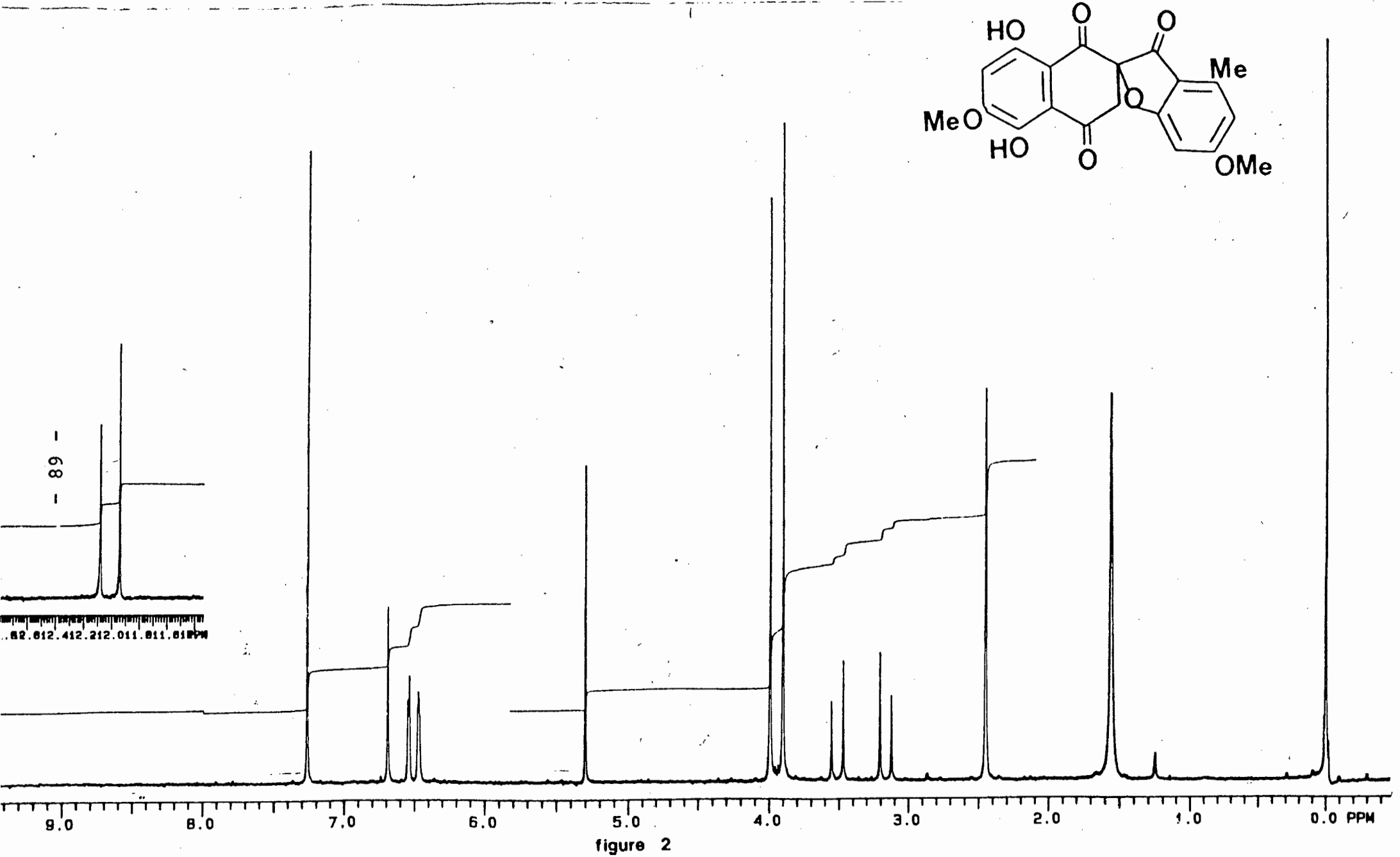
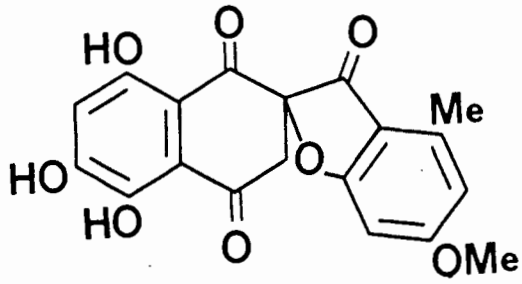


figure 2

Interestingly the base peak was at *m/z* 382. This presumably showed that the spirocompound (**37**) underwent rearrangement and oxidation to bikaverin (**10**) upon electron impact. This was encouraging as it seemed plausible that on heating the spirocompound it would rearrange to bikaverin (**10**). The infrared spectrum showed three carbonyls at 1702 cm^{-1} and 1653 cm^{-1} and 1628 cm^{-1} (c.f. Lewis' structure (**28**) 1703 cm^{-1}, 1677 and 1670 cm^{-1}).

It was also noted that the trihydroxyspirocompound (**111**) was formed as a by-product. This arose as a result of the additional removal of the methyl group *ortho*-to the quinone carbonyl during the reaction with boron trichloride.



(111)

This product (111) also showed two doublets at δ 3.16 and δ3.52, each with a coupling constant of 16.7Hz. In addition it only showed one methoxy signal in its ^1H n.m.r. spectrum (Figure 3). The mass spectrum showed the expected molecular ion at *m/z* 370 and the expected rearranged norbikaverin value of *m/z* 368.

Difficulties arose in the purification of both products. The elemental analyses of both spirocompounds were marginally low in carbon content, although the high resolution mass

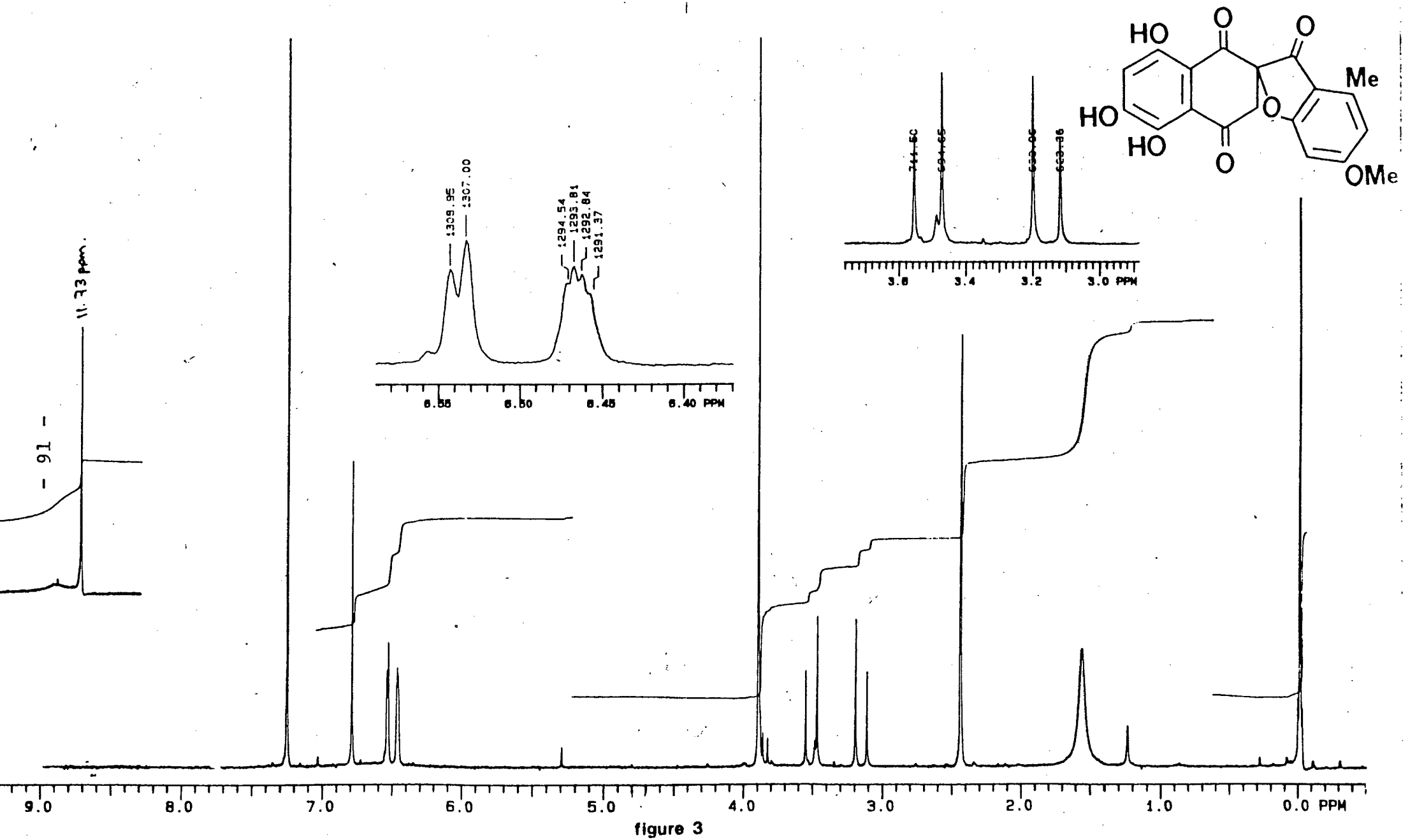

HO
HO
HO
O
O
O
O
Me
OMe
11.73 ppm
1309.95
1307.00
1294.54
1293.81
1292.84
1291.37
6.55
6.50
6.45
6.40 PPM
3.6
3.4
3.2
3.0 PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

figure 3

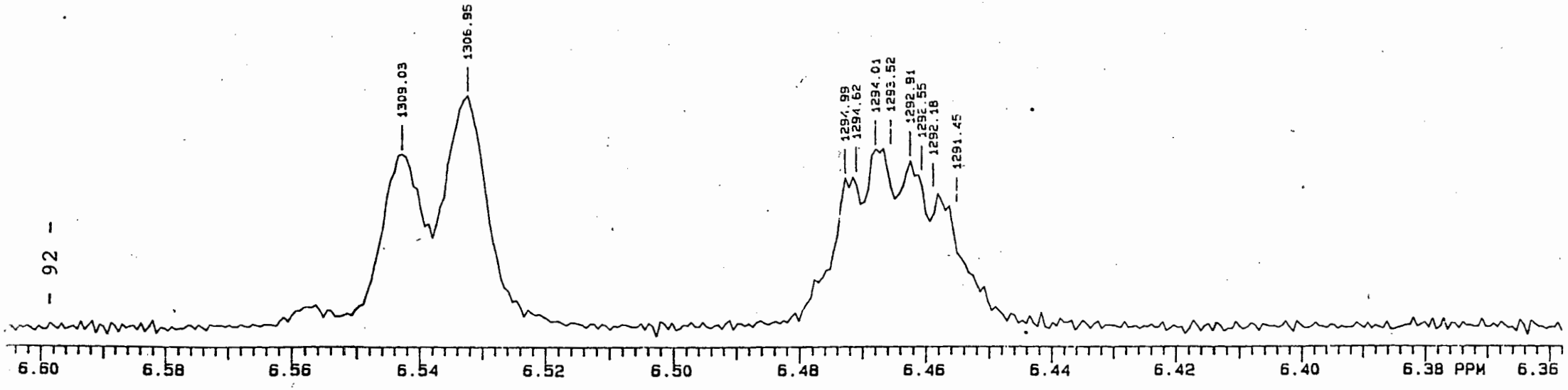
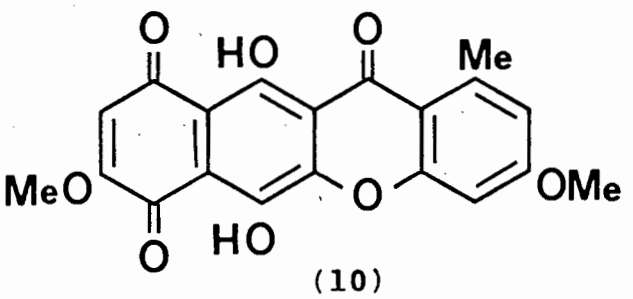

1309.03
1306.95
1294.99
1294.62
1294.01
1293.52
1292.91
1292.55
1292.18
1291.45
- 92 -
6.60
6.58
6.56
6.54
6.52
6.50
6.48
6.46
6.44
6.42
6.40
6.38 PPM
6.36

figure 3

spectra showed molecular ions of mass 370.0664 and 384.0867 which would be expected for the molecular formula $C_{19}H_{14}O_8$ and $C_{20}H_{16}O_8$ for the precursors of norbikaverin and bikaverin resepctively.



(10)

Rearrangement of the spirocompound (**37**) to bikaverin (which was microanalytically pure) was accomplished by heating in boiling nitrobenzene for two hours. The ^1H n.m.r. spectrum (Figure 4) clearly showed *inter alia*, the presence of only three high field protons: one singlet at δ 6.27 and two *meta*-coupled protons (*J* 2.7Hz) at δ6.73 and δ6.84. The doublet at δ6.73 showed long range coupling (*J* 0.5Hz) with the aryl methyl protons. An interesting difference between the ^1H n.m.r. spectrum of bikaverin (**10**) and the spirocompound (**36**) was the relative deshielding of the aryl methyl protons in bikaverin (**10**) (δ2.79) as compared to the spirocompound (δ 2.45). This difference was not observed in the two related compounds synthesised by Lewis[11], the spirocompound (**28**) and the xanthone (**29**) in which both aryl methyl protons appeared as singlets at δ 2.45.

The mass spectrum also confirmed that the rearrangement had taken place as a molecular ion of *m/z* 382 was observed. Comparison of an authentic sample of bikaverin of natural

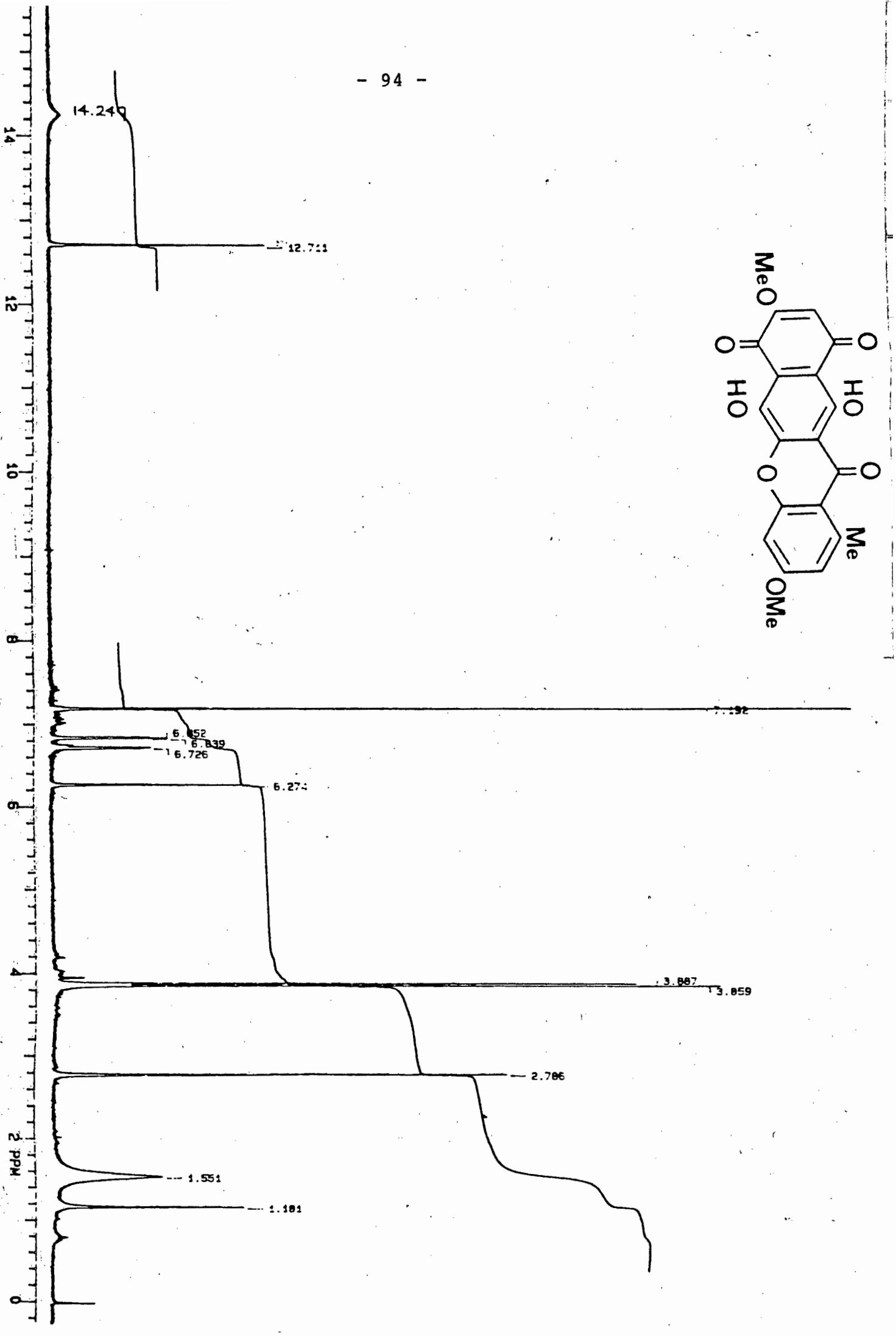

14.240
12.711
7.192
6.852
6.839
6.726
6.274
3.887
3.859
2.786
1.551
1.181
PPM
14
12
10
8
6
4
2
0
MeO
O
HO
HO
O
O
Me
OMe

figure 4

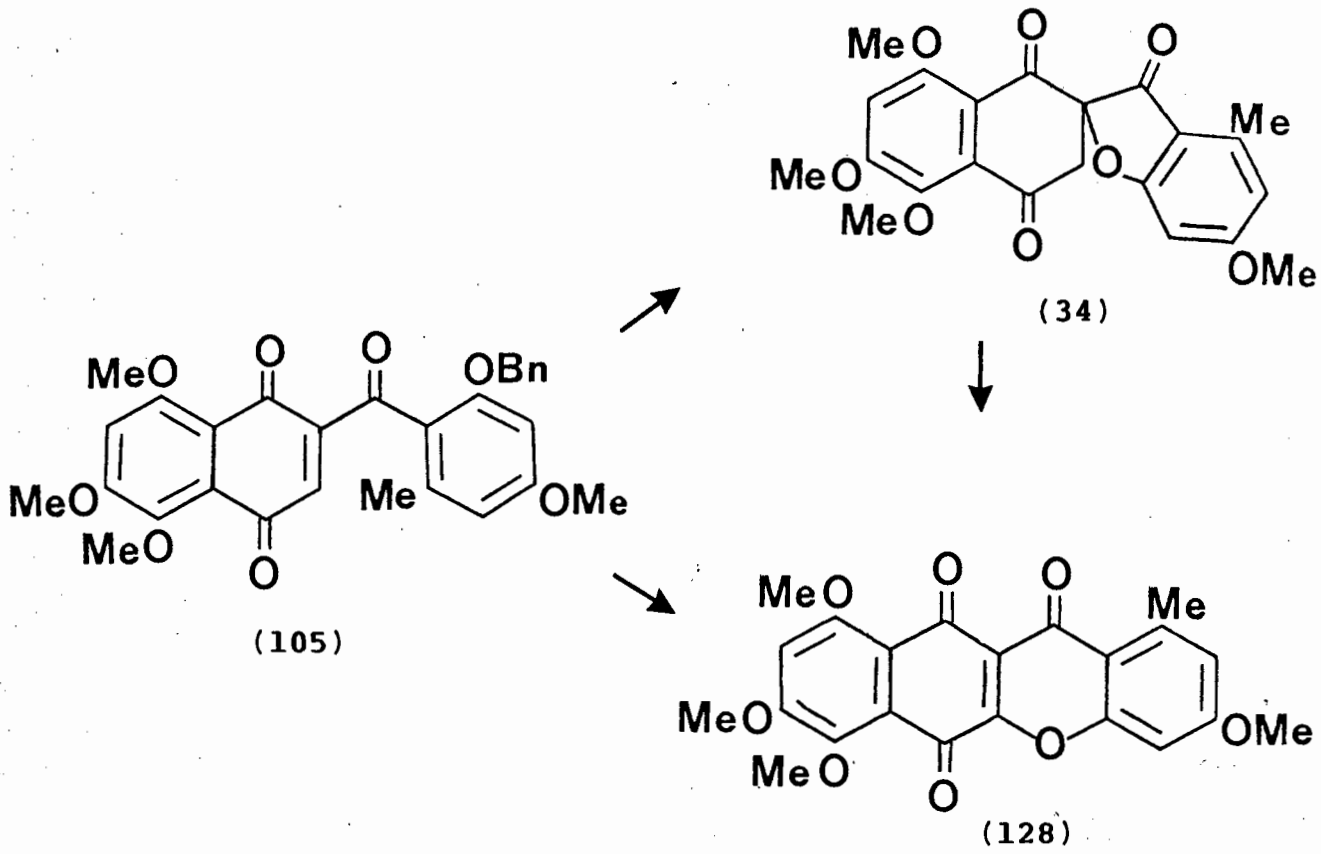
origin, kindly provided by Kjær, with our synthetic bikaverin showed them to be identical in respect of physical and spectroscopic characteristics.

The fact that 1,2-addition is preferred over 1,4-addition could be due to steric reasons, as in the spirostructure (**37**) the substituted benzene ring will be in a different plane to that of the naphthalene ring while in the xanthone structure it would have to be planar, this might mean that the spirocompound (**37**) is the kinetically controlled product and the xanthone (**10**) the thermodynamically controlled product.

A further possibility would be that the carbon *ortho*- to two carbonyls is more electron deficient than the carbon where Michael addition would be expected to take place.

As the work described above was in progress, alternative methods for ring closure were investigated.

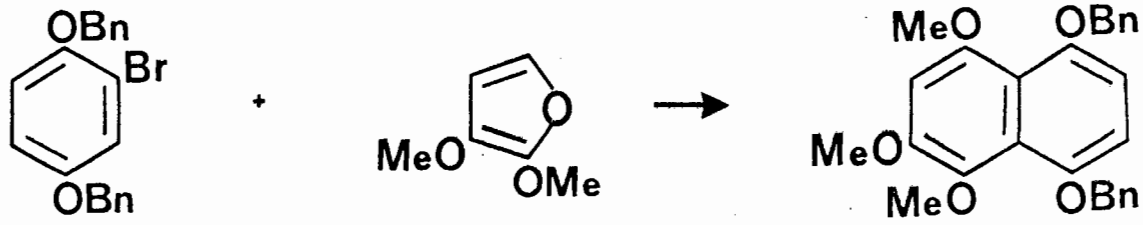
It was considered that the selective removal of the benzyl group in the quinone (**105**) would lead to spontaneous formation of either the spirocompound (**34**) or the xanthone (**128**).



Since these structures contain methyl ethers in the left hand ring (c.f. hydroxyl groups of structure (**36**)), it was believed that purification of these methyl ethers would not be as difficult as for (**37**) and bikaverin (**10**). The task was then to synthesise a pentaoxygenated naphthalene similar to structure (**30**) but with positions 5- and 8- protected by groups other than methyl, and which could be more easily removed. An example that was considered was the 5,8-dibenzyl ether (**112**). The synthesis of this compound (**112**) could be achieved in two ways:

(i) by starting with a 2-substituted furan bearing a group other than methoxy or

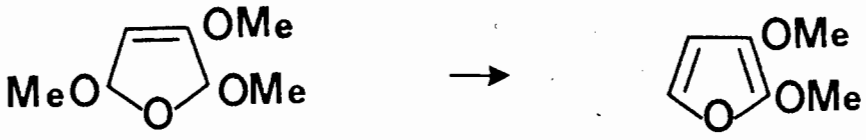
(ii) by starting with 2,3-dimethoxyfuran (**113**) and reacting this with 2-bromo-1,4-dibenzyloxybenzene (**114**) in the presence of sodium amide.



(114) (113) (112)

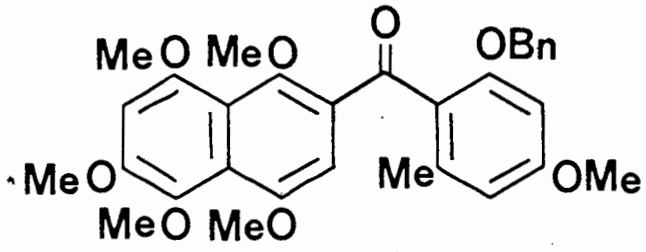
2-Isopropoxyfuran is a known compound,[43] synthesised from 2-furoic acid, the last step in the synthesis involving the decarboxylation of 2-isopropoxy-5-furoic acid with copper in the presence of quinoline. In our hands difficulty was experienced in separating the product from quinoline. Nevertheless the 2-isopropoxyfuran that was prepared was reacted with 5-bromo-1,2,4-trimethoxybenzene in the presence of sodium amide. The reaction failed to yield any identifiable product and was abandoned.

A literature search showed that 2,3-dimethoxyfuran (113)[44] is only postulated to be formed *in situ* by demethanolation of 2,3,5-trimethoxydihydrofuran and this envisaged route was therefore also not pursued further.

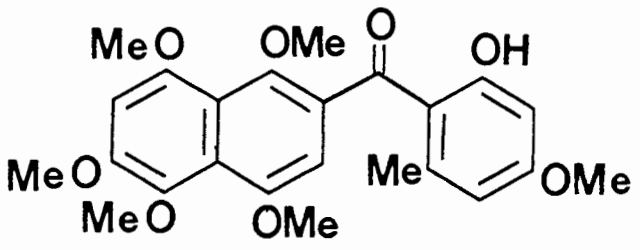


(113)

Returning to an earlier idea, the benzyl group in the acylated naphthalene (**31**) was selectively removed with hydrogen and palladium on activated carbon as catalyst to yield the naphthol (**32**). This compound showed *inter alia*, a characteristic hydrogen bonded proton at δ 12.97 in the ^{1}H n.m.r. spectrum, as well as molecular ion of *m/z* 442 and a characteristic hydroxyl stretching frequency of 3380 cm^{-1} in the infrared spectrum.



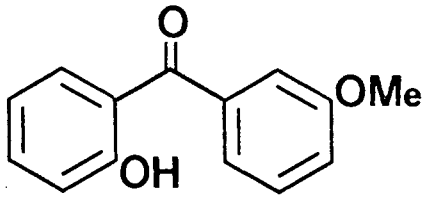
(31)



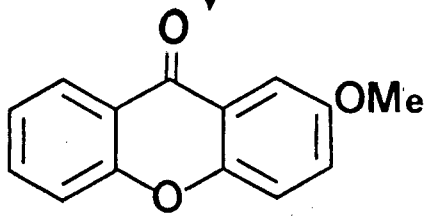
(32)

Methods were then investigated for ring closure in this product.

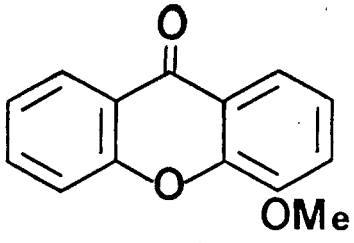
Lewis[45] has shown that 2-hydroxy-3'-methoxybenzophenones such as (115) undergo intramolecular oxidative cyclisation with 2,3-dichloro-5,6-dicyanobenzoquinone to form the corresponding methoxy xanthones (**116**) and (**117**).



(115)

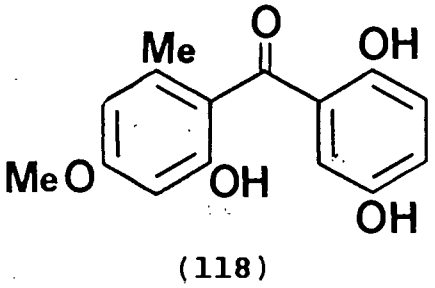


(116)

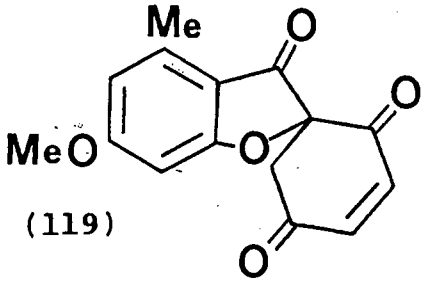


(117)

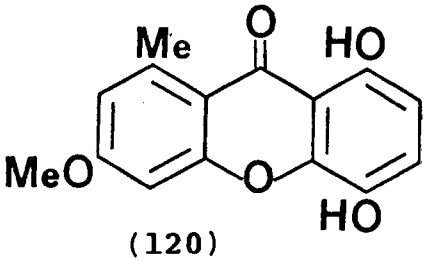
Lewis[11] later showed that the benzophenone (118) upon oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone yielded two products (119) and (120); compound (119) could in turn be converted into xanthone (120) by heating.



(118)



(119)



(120)

Although it was realized that the naphthol (32) did not posses the hydroquinone structure of (118) it was nevertheless considered worthwhile to attempt this type of reaction on our naphthol (32). Thus addition of 1.5 molar equivalents of 2,3-dichloro-5,6-dicyanobenzoquinone to (32) afforded one major product in a yield of 61%. Apart from the expected methoxy and methyl protons, the ^{1}H n.m.r. spectrum (Figure 5)

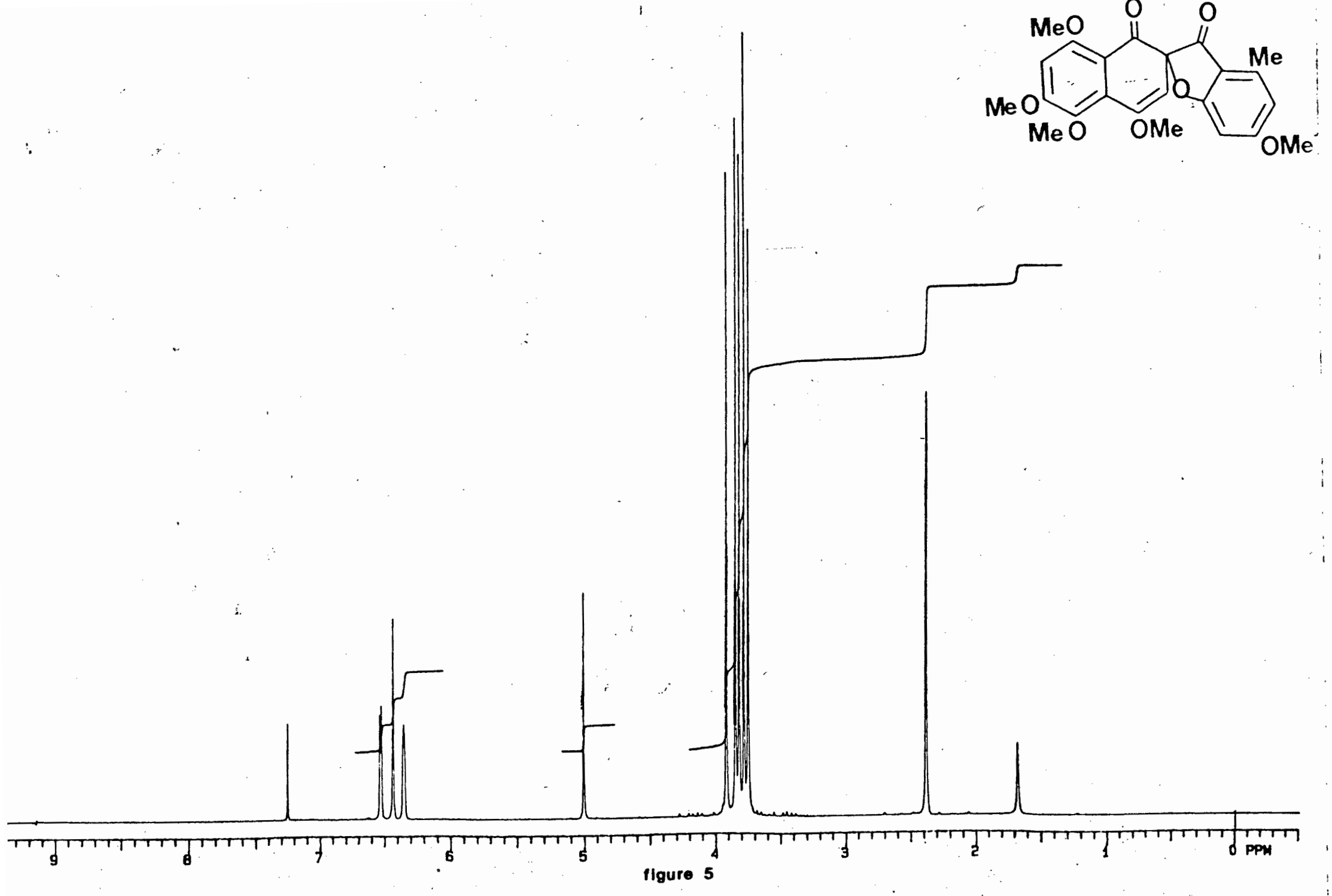
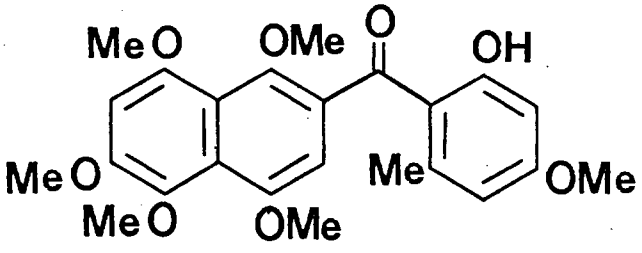
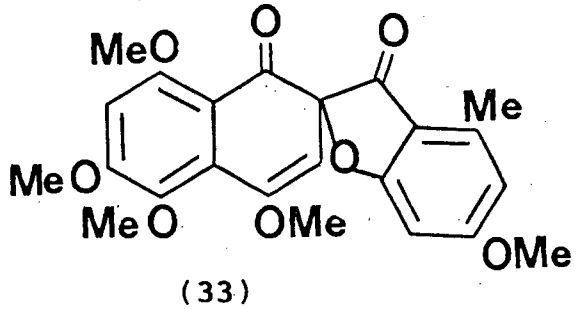


figure 5

showed a singlet integrating for one proton at δ 6.43, two aromatic *meta*-coupled protons at δ 6.35 and δ 6.53 respectively, and a singlet at δ 5.00 integrating for one proton. The structure was identified as the spiroenol ether (33). Confirmation of this was obtained from the presence of a molecular ion at *m/z* 426 in the mass spectrum and two carbonyl stretching bands in the infrared spectrum at 1710 cm^{-1} for the five-membered ring and 1676 cm^{-1} for the six-membered ring.

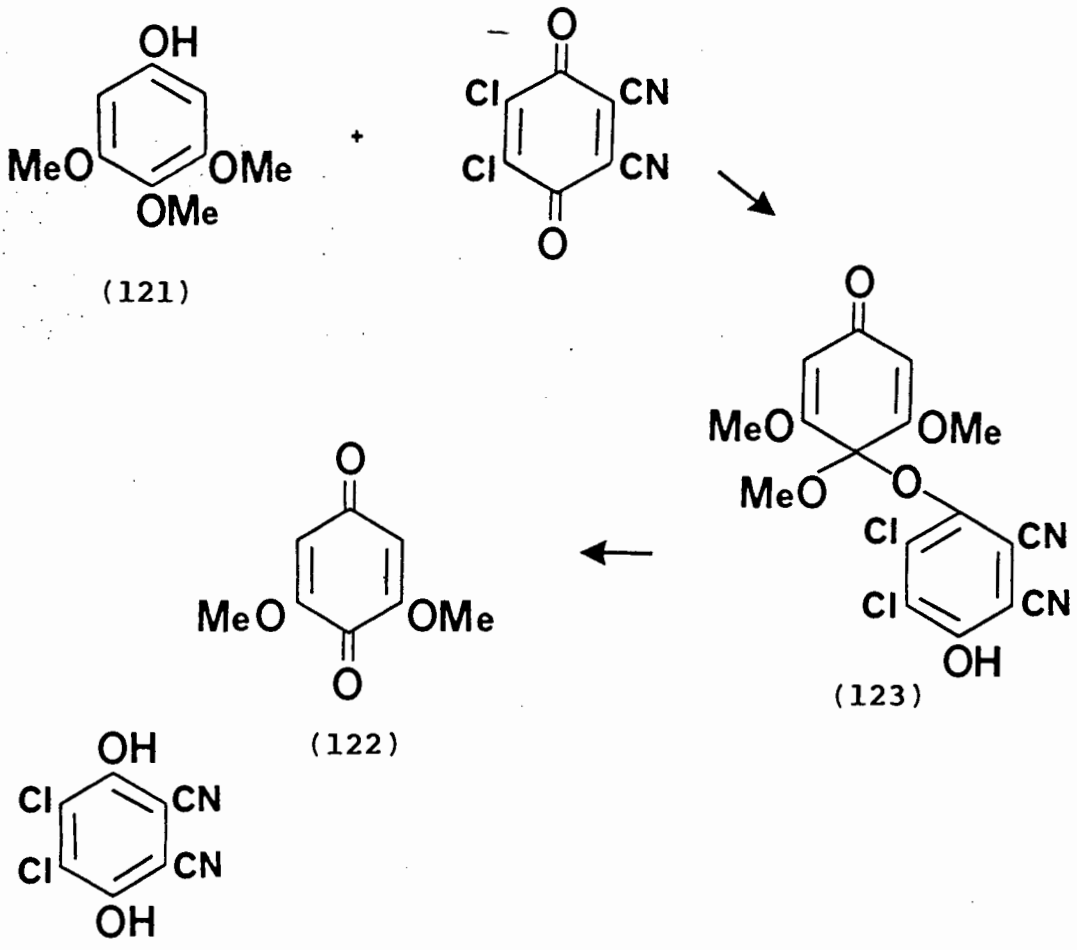


(32)

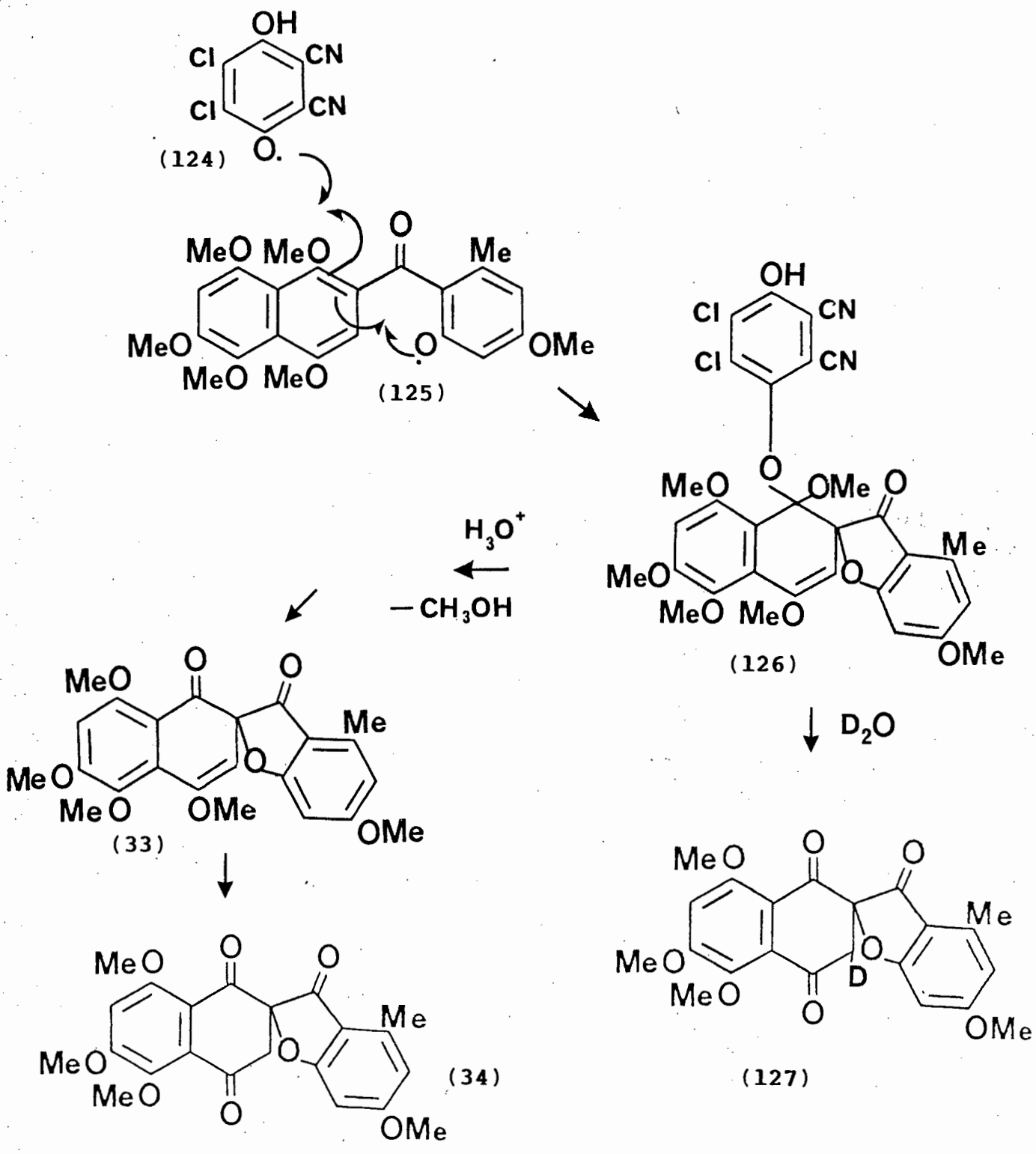


(33)

The mechanism for the formation of the spiroenol ether (33) was postulated to be similar to that of Becker,[46] who described the oxidation of 3,4,5-trimethoxyphenol (121) to 3,5-dimethoxybenzoquinone (122). The presence of the complex intermediate (123) was demonstrated by infrared spectroscopy.



In our system the naphthol (**32**) would undergo transfer of a hydrogen atom to give the phenoxy radical (**125**) and the 2,3-dichloro-5,6-dicyanhydroquinone radical (**124**). The two radicals could then combine to yield a "2,3-dichloro-5,6-dicyanbenzoquinonephenol adduct" (**126**). On subjection to chromatography the acidic conditions would result in the hydrolysis of the ketal to yield product (**33**). However, this would assume the more facile hydrolysis of the ketal function in compound (**126**) than that of the enol ether.



This product (**33**) was hydrolysed in turn to the triketone (**34**) in very high yield with trifluoroacetic acid in water. The ^1H n.m.r. spectrum showed *inter alia,* two doublets at δ 3.19 and δ3.46 each with a coupling constant of 15Hz and three

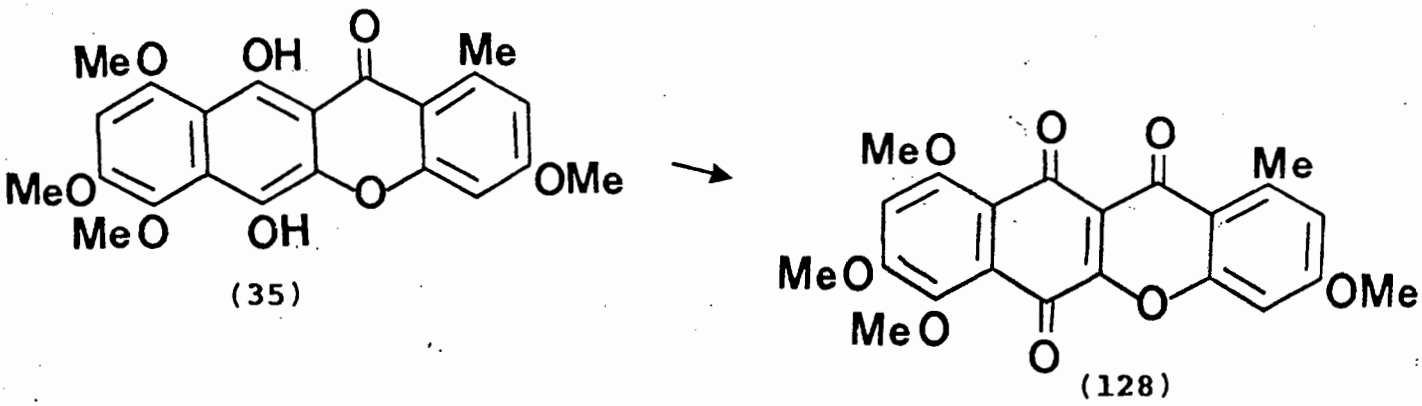
carbonyl stretching frequences in the infrared spectrum at 1707 and 1677 cm^{-1}. Interestingly, it was noted that on hydrolysing the product (**33**) with trifluoroacetic acid in deuterium oxide, deuterium was specifically incorperated in only one of the positions occupied by the methylene protons, as the deuterated product (**127**) showed in its ^{1}H n.m.r. spectrum a singlet at δ 3.15.

Although the original objective to prepare the quinone (**105**) as a potential precursor to the tetracyclic quinonoid (**128**) had not been accomplished, the need for its formation had now been obviated since the spirocompound (**34**) was now available which provided an alternative route to xanthone (**128**) from which bikaverin could be synthesised. Purification of this spirocompound (**34**) proved to be straight forward compared to the spirocompound (**37**), presumably, since the conversion of the enol ether (**33**) to the spirocompound (**34**) was a cleaner reaction than that of the corresponding conversion of quinone (**36**) to the analogue (**37**).

As predicted, rearrangement of compound (**34**) was accomplished by vacuum sublimation at 220°C to afford the hydroquinone (**35**) in excellent yield. The ^{1}H n.m.r. spectrum showed *inter alia,* a one-proton aromatic singlet at δ 6.53, two *meta*-coupled protons at δ 6.62 and δ 6.83, the signal at δ 6.62 actually being a doublet of quartets due to long range coupling with the methyl three-proton doublet at δ 2.86. This last value is at lower chemical shift ($\Delta\delta$ 0.50) than that observed for the methyl protons in the preceeding spiro-

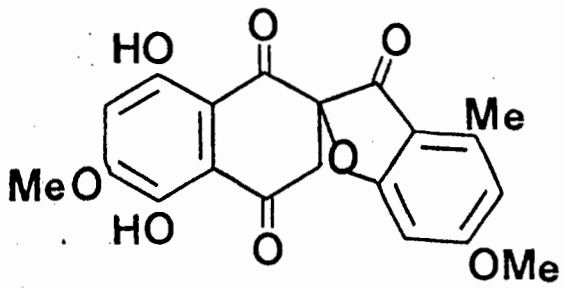
compound (34) (δ2.36), similar to that observed earlier (spirocompound (37) to xanthone (10)). The two hydroxyl protons were observed at δ 9.70 and δ 15.17 respectively. The latter signal arising from the proton of the hydroxyl group hydrogen bonded to the adjacent carbonyl function.

The hydroquinone (35) did not spontaneously oxidise in air to the quinone (128), but on stirring in chloroform in the presence of silver(I) oxide, the quinone (128) was formed in very good yield (93%). The spectroscopic and physical characteristics proved to be identical to a sample of natural origin[2a] kindly provided by Professor Kjær.



It has been shown[8] that this quinone (128) can be selectively demethylated with lithium iodide to afford bikaverin (10) in a yield of 80%.

During our work undertaken towards the synthesis of bikaverin (10) it was suggested that rearrangement of the spirocompounds (34) and (37) might arise through migration of the carbonyl carbon from the spiro carbon onto the carbon vicinal to it, rather than the alternative migration of the ether oxygen to the same carbon.



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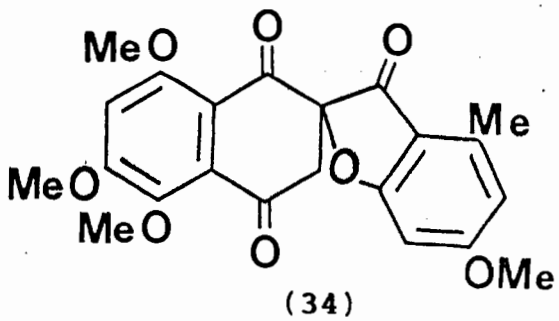

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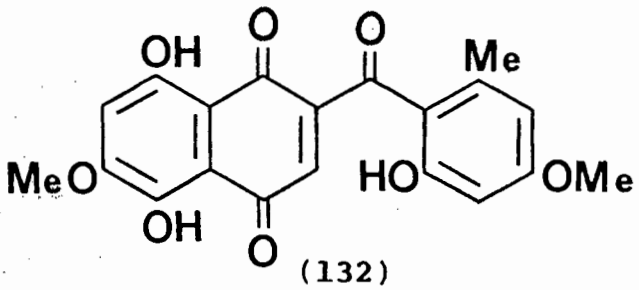

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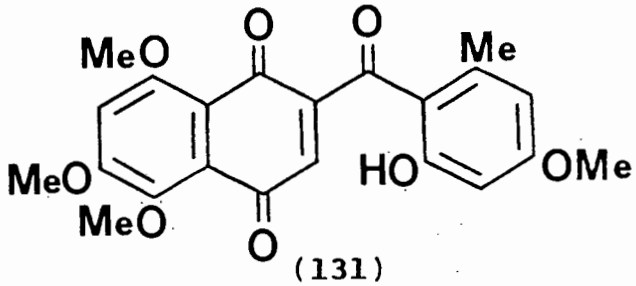
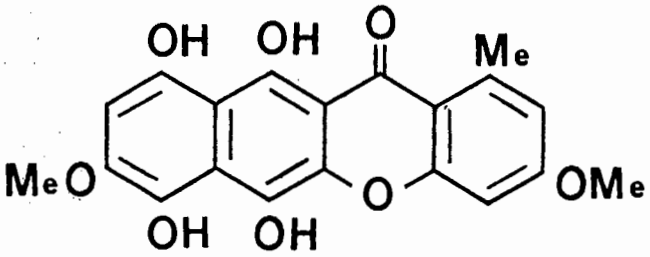
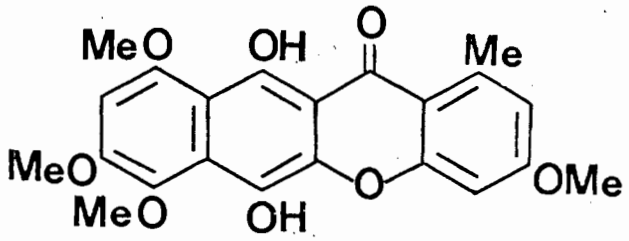


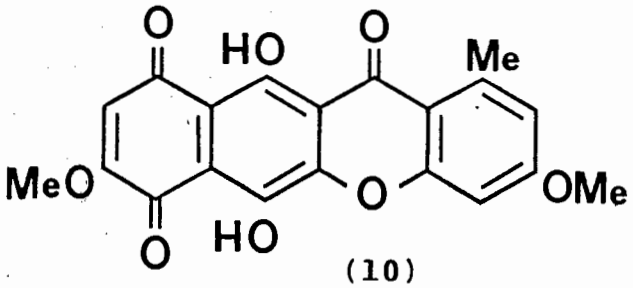
(131)



(133)



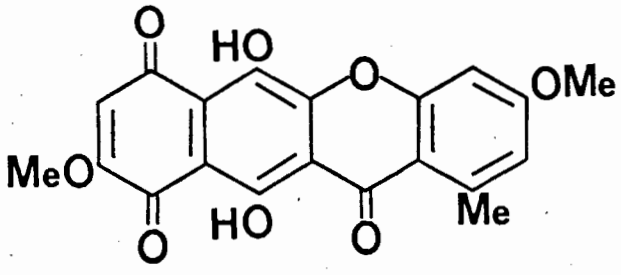
(35)



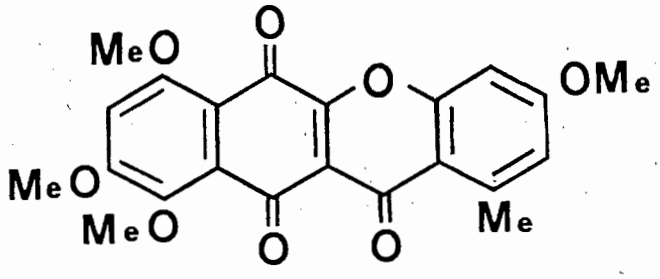
(10)

scheme 1

The latter possibility seemed far more reasonable, since it would only involve a reversal of the reactions which had led to the formation of spirocompound (34) and (37), and the subsequent nucleophilic addition of the derived phenolic oxygen to the α, β-unsaturated carbonyl group of the quinone in each compound (132) and (131) to afford the hydroquinones (133) and (35) respectively. (See Scheme 1). Subsequent oxidation in the former case took place readily in the more electron-rich ring to afford bikaverin (10), since that ring constituted an unprotected hydroquinone.



(130)



(129)

As the differences between bikaverin (10) and its isomer (129), and between the isomer (35) and (130) ((129) and (130) formed by migration of carbonyl carbon) might conceivably all be very small in terms of their physical and spectroscopic characteristics, differentiation on the basis of these criteria might be misleading. It was therefore decided

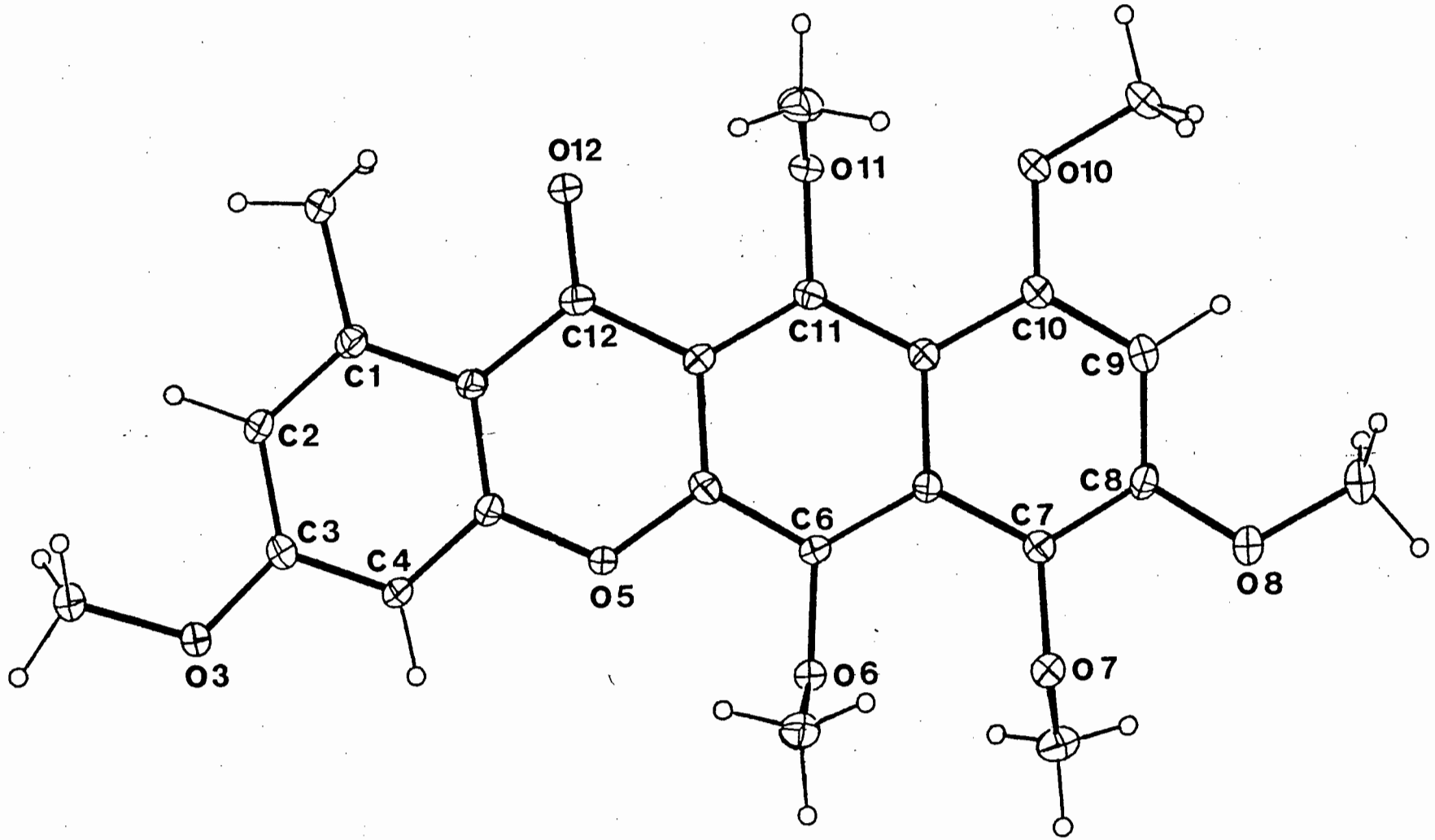
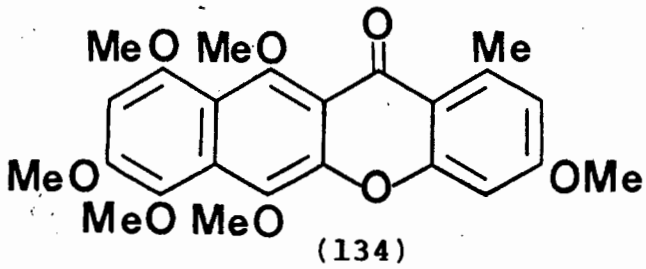


figure 6

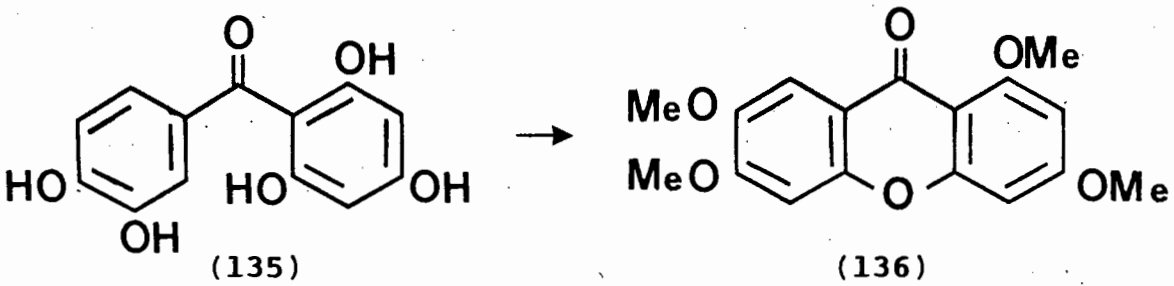
to determine the structure unambiguously using X-ray diffraction methods.



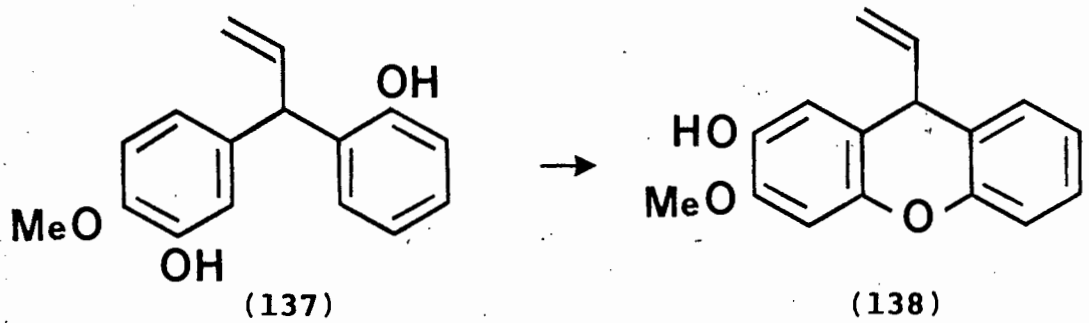
(134)

Suitable crystals of the xanthone (134) prepared by methylation of the hydroquinone (35) were grown. Analysis of the crystal structure (Figure 6) showed unequivocally that the desired isomer had been formed.

Whilst the methods for effecting ring closure of naphthol (32) into the xanthone (10) *via* spiro intermediates were being studied, alternative routes to afford xanthone (134) obviating the unnecessary spiro intermediates were investigated.



(135) (136)



(137) (138)

Scheinmann[49] has reported that ring closures of compounds

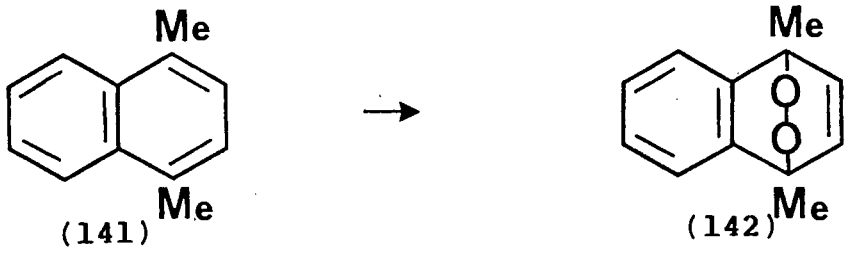
such as (**135**) to afford the xanthone (**136**) could be achieved by irradiation with ultraviolet light in the presence of oxygen. More recently Mukerjee[50] has also reported a similar reaction in which the naphthol (**137**) was treated in a similar manner to that described above to afford the xanthone (**138**). It was hoped therefore that irradiation of our naphthol (**32**) in the presence of oxygen would afford the xanthone (**134**), a precursor in the synthesis of bikaverin (**10**).

However, irradiation of the naphthol (**32**) in the presence of oxygen afforded two products of similar R_f value, neither of which proved to be the desired product (**134**). Nevertheless the results of the reaction proved to be very interesting.

Examination of the mass spectra of both products showed a molecular ion of *m/z* 474, indicating an increase of 32 atomic mass units, which led to the supposition that a molecule of oxygen had been added to the naphthol to afford two products. Microanalysis of the major product supported this supposition.

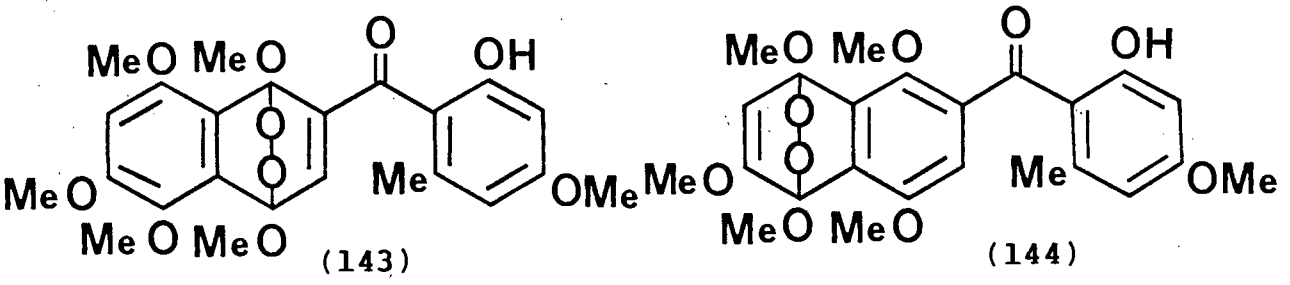
Examination of the ^1H n.m.r. spectra revealed the aryl methyl three-proton singlet at δ 2.00 for the major photochemical product (**139**) and at δ 1.89 for the minor photochemical product (**140**). This result indicated that ring closure had not been effected since earlier results had shown that the chemical shift for the aryl methyl group of the xanthones e.g. bikaverin (**10**) was at δ 2.79 and was at higher chemical shift value than the corresponding spiro

compound (37) where the methyl group appeared at δ 2.45. In the above case there is very little difference between the naphthol (32) and products (139)* and (140)*. The ^1H n.m.r. spectra also showed, *inter alia*, one-proton singlets at δ 5.36 and δ 5.00 for the major product (139)* and minor product (140)* respectively, which would also not be consistent with a xanthone structure. The problem was now to establish how the oxygen had been added to the naphthol (32).



(141) (142)

Wasserman[51] and Hart[52] have both described a photosensitised oxygenation of methyl naphthalenes, for example 1,4-dimethyl-naphthalene (141) to afford arene-peroxides such as (142). Rigaudy[53] has also described similar reactions of methoxy-anthracenes to give arene-peroxides. Initially it was thought that our reaction had also led to the formation of the two endoperoxides (143) and (144).

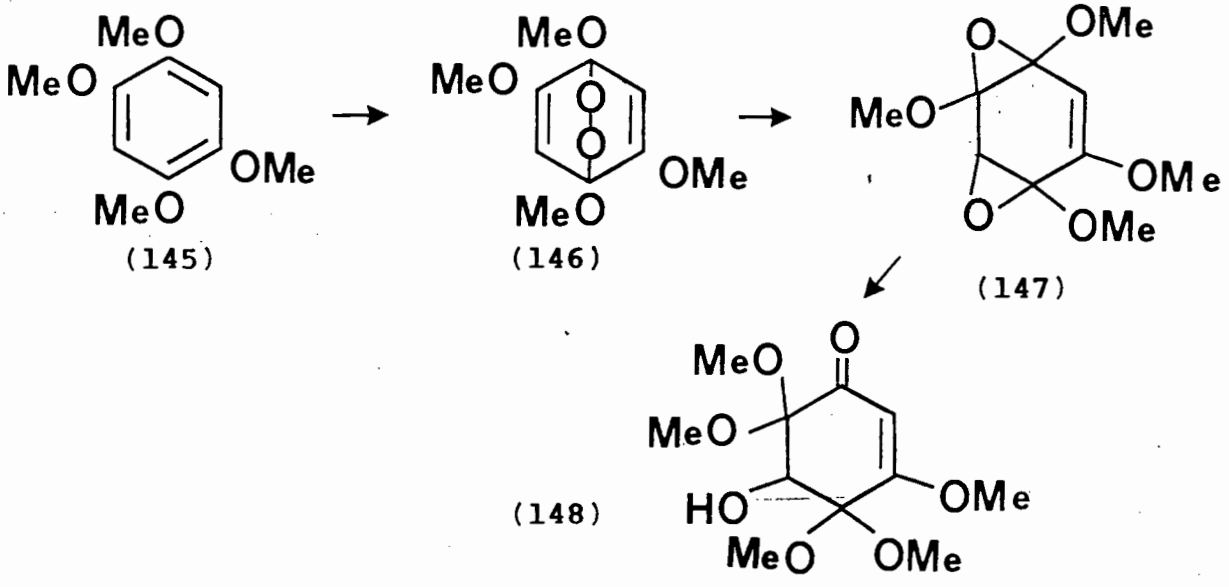


(143) (144)

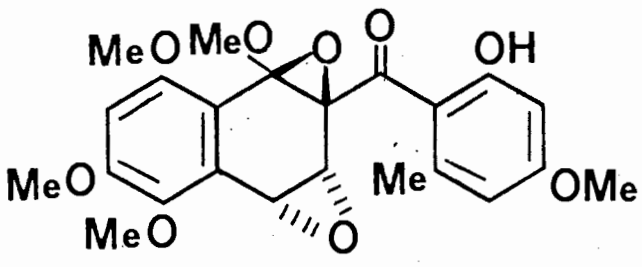
(At this stage in the work both are interchangeable).

However, the major product (**139**) exhibited two sharp bands at 1740 and 1716 cm^{-1}, which did not seem to be consistent with a conjugated carbonyl group attached to an aromatic ring. Furthermore Wasserman indicated that on heating endoperoxides, starting material would be reformed together with the loss of oxygen. Pyrolysis of our material did not lead to the formation of the starting material casting doubt upon the endoperoxide as a possible structure.

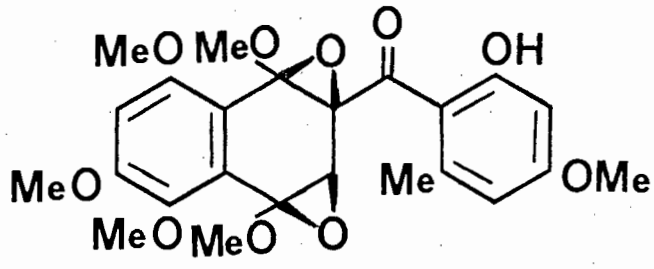
Examination of the fragmentation pattern of the mass spectra of both photo products provided further evidence that an endoperoxide had not been formed, as the loss of oxygen was not evident. The high resolution mass spectrum of the minor product (**140**) showed apart from the molecular ion at *m/z* 474.1471, two peaks at *m/z* 443.1346 and at *m/z* 412.1148, each of these corresponding to the loss of a methoxy group and not oxygen. Meanwhile the major product (**139**) showed two peaks at *m/z* 443.1350 and at *m/z* 411.1054, the first fragmentation being due to loss of a methoxy group and the second methanol and not oxygen.



A further literature survey[54] revealed that permethoxybenzenes, such as (**145**) when treated in a similar manner as above using methanol as a solvent afforded (**148**). It was proposed that the product (**148**) was formed by initially forming the endoperoxide (**146**) which underwent rearrangement to form the diepoxide (**147**) reaction of which with the solvent methanol could form the observed product (**148**). Since our reaction was performed in an aprotic solvent i.e. dry benzene the diepoxides (**139**) and (**140**) might be produced and not react further. As there were two products it was envisaged that one would be the *cis*-diepoxide (**139**) and the other the *trans*-diepoxide (**140**). All the spectroscopic evidence seemed to fit the proposed structures.



(**140**)



(**139**)

In order to verify our proposed structures, and to show which epoxide had the *trans*-structure and which one had the *cis*-structure crystals of the major product (**139**) were grown from various solvents but were found to be unsuitable for X-ray analysis. At present attempts to make a derivative of the naphthol of the major product (**139**) are in progress

with the aim of trying to grow crystals which will be suitable for X-ray analysis.

In summary, the goal of this work, namely the synthesis of bikaverin with improved yields, had been successfully achieved by two different methods.

EXPERIMENTAL

Procedures, equipment and abbreviations are identical to those described in chapter **1**, except where stated ^{1}H n.m.r. spectra were recorded on a Varian VXR-200 at 200 MHz, while all ^{13}C n.m.r. spectra were recorded on the same instrument at 50.1 MHz.

2-(2',4'-Dimethoxybenzoyl)-1,4-dimethoxynaphthalene (**49**), *2-(2',4'-Dimethoxy-5'-(2'',4''-dimethoxybenzoyl)benzoyl)-1,4-dimethoxynaphthalene* (**50**), and *2-(2',4'- Dimethoxy- 5'-(2'',4''-dimethoxy-3''-trifluoroacetylbenzoyl)benzoyl)-1,4-dimethoxynaphthalene* (**51**).-

(a) 2,4-Dimethoxybenzoic acid (**48**) (130 mg, 0.72 mmol) premixed with trifluoroacetic anhydride (190 mg, 0.90 mmol) was rapidly added to 1,4-dimethoxynaphthalene (**47**) (100 mg, 0.6 mmol) dissolved in dry methylene dichloride (3 ml). The mixture was stirred at room temperature for 22 h with one further aliquot being added after 6 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous sodium hydrogen carbonate solution. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **product** (**49**) (96 mg, 51%) as yellow diamonds, m.p. 109-109.5°C (2-propanol) (Found: C, 71.55; H, 5.65. $C_{21}H_{20}O_5$ requires C, 71.6, H, 5.7%); $\nu_{max.}$ 1629 (C=O) and 1603 (C=C) cm^{-1}; δ 3.65, 3.68, 3.84, and 3.96 (each 3H, s, OCH_3), 6.46br. (1H, s, 3'-H), 6.50 (1H, dd, *J*7 and 3Hz, 5'-H), 6.88 (1H, s, 3-H), 7.46-7.66 (3H, m, 6'-H and 6- and 7-H), and 8.03-8.36 (2H, m, 5- and 8-H);

m/z 352 (M^+, 100%), 337 (41), 201 (32), 165 (73), 151 (20), 129 (28), 122 (23), and 101 (21). The second **product** (**50**) (28 mg, 9%) eluted afterwards as opaque hexagons, m.p. 174-175°C (methanol)(Found: C, 69.65; H, 5.5. $C_{30}H_{28}O_8$ requires C, 69.8; H, 5.4%); $\nu_{max.}$ 1628 (C=O) and 1607 and 1590 (C=C) cm^{-1}; δ3.65 (6H, s, 2 x OCH_3), 3.70, 3.78, 3.81, and 3.96 (each 3H, s, OCH_3), 6.37 (1H, d, *J* 2Hz, 3"-H), 6.42 (1H, s, 3'-H), 6.45 (1H, dd, *J* 10 and 2Hz, 5"-H), 6.90 (1H, s, 3-H), 7.54 (1H, d, *J* 10Hz, 6"-H), 7.47-7.62 (2H, m, 6- and 7-H), 7.82 (1H, s, 6'-H), and 8.00-8.30 (2H, m, 5- and 8-H); *m/z* 516 (M^+, 65%), 363 (17), 329 (11), 215 (10), and 165 (100). A third **product** (**51**) (14 mg, 4%) was also identified only shown by ^1H n.m.r. spectrometry δ3.43, 3.64, 3.70, 3.77, 3.81, and 3.96 (each 3H, s, OCH_3), 6.42 (1H, s, 3'-H), 6.56 (1H, d, *J* 10Hz, 5"-H), 6.87 (1H, s, 3-H), 7.37 (1H, d, *J* 10Hz, 6"-H), 7.46-7.62 (2H, m, 6- and 7-H), 7.83 (1H, s, 6'-H), and 7.97-8.34 (2H, m, 5- and 8-H).

(b) Treatment of 1,4-dimethoxynaphthalene (**47**) (100 mg, 0.6 mmol) was described above with only one molar equivalent of the mixed anhydride resulted in the formation of (**49**) (114 mg, 61%) as the sole product, as well as unreacted starting material.

1-Acetoxy-2-(2',4'-dimethoxybenzoyl)-4-methoxynaphthalene (**52**).-
The naphthalene (**49**) (120 mg, 0.34 mmol) in dry methylene dichloride (5 ml) was treated at -78°C with boron trichloride (130 mg, 1.36 mmol) in the same solvent. After 25 min the solution was allowed to warm to room temperature and

then hydrolysed with an excess of water. The organic material was extracted into methylene dichloride. The residue obtained upon work-up was dissolved in dry pyridine (2 ml) and acetic anhydride (1 ml). The mixture was heated at 80°C for 2 h. The cooled reaction mixture was added to an excess of water, the organic material was then extracted into methylene dichloride, keeping the pyridine in the aqueous layer by careful acidification with dilute hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **acetate** (**52**) (114 mg, 88%) as white needles, m.p. 129-130°C (2-propanol)(Found: C, 69.6; H, 5.25. $C_{22}H_{20}O_6$ requires C, 69.5; H, 5.25%); $\nu_{max.}$ 1756 (OAc) and 1717 (C=O) cm^{-1}; δ2.18 (3H, s, CH_3CO), 3.62, 3.85, and 3.97 (each 3H, s, OCH_3), 6.47br. (1H, s, 3'-H), 6.54 (1H, dd, *J*10 and 3Hz, 5'-H), 6.96 (1H, s, 3-H), 7.56 (1H, d, *J*10Hz, 6'-H), 7.46-7.66 (2H, m, 6- and 7-H), 7.69-7.90 (1H, m, 5-H), and 8.16-8.40 (1H, m, 8-H); *m/z* 380 (M^+, 2%), 338 (21), 200 (100), and 43 (34).

2-Bromo-1,4,5,8-tetramethoxynaphthalene (**75**).-

A slurry of sodamide in light petroleum (1.0 g, excess) was weighed directly into a round bottom flask, to which a solution of 2-methoxyfuran (0.4 g, 4.1 mmol) in 1,2-dimethoxyethane (5 ml) was added followed by 2,5-dibromo-1,4-dimethoxybenzene (**72**)[33] (0.2 g, 0.68 mmol) in 1,2-dimethoxyethane (10 ml). The reaction mixture was boiled with stirring under nitrogen for 24 h. The cooled reaction mixture was quenched by the slow addition of *t*-butyl alcohol (20

ml), and then poured into water (100 ml). The organic material was extracted into ether (4 x 100 ml). The residue obtained upon work-up was flash chromatographed (eluant 50% ethyl acetate-light petroleum) to afford an oil which was immediately dissolved in dry acetone (50 ml), to which dry potassium carbonate (1.2 g, 6.8 mmol) and dimethyl sulphate (1.0 g, 0.78 ml, 6.8 mmol) were added, and the mixture heated under reflux with stirring for 20 h. The cooled reaction mixture was filtered and evaporated to produce a residue which was dissolved in ether (50 ml) and washed with a 25% ammonia solution (4 x 50 ml), followed by water (50 ml) dilute hydrochloric acid (50 ml) and finally water (50 ml). The ether solution was dried ($MgSO_4$) and evaporated yielding a residue which was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the **product (75)** (38%, 84 mg) as pale brown needles, m.p. 104-105.5°C (light petroleum-methylene dichloride)(Found: C, 51.65; H, 4.55. $C_{14}H_{15}O_4Br$ requires C, 51.4; H, 4.6%); $\nu_{max.}$ 1608 (C=C) and 1580 (C=C) cm^{-1}; δ 3.80 and 3.86 (each 3H, s, OCH_3), 3.89 (6H, s, 2 x OCH_3), 6.84 (2H, s, 6- and 7-H), and 6.97 (1H, s, 3-H); *m/z* 328 (M^+, 100%), 326 (M^+, 100%), 312 (16), 232 (41), 217 (32), and 203 (19).

1,4-Epoxy-1,4-dihydro-5,6,8-trimethoxynaphthalene (**71**).-
A slurry of sodamide in light petroleum (0.91 g, excess) was weighed directly in a round bottom flask, to which a solution of furan (3.0 g, 44.1 mmol) in 1,2-dimethoxyethane (10 ml) was added followed by 5-bromo-1,3,4,-trimethoxybenzene (**65**)[35] (0.20 g, 0.81 mmol) in 1,2-dimethoxyethane

(5 ml). The reaction mixture was boiled under nitrogen for 2 h. The cooled reaction mixture was quenched by the slow addition of *t*-butyl alcohol (20 ml), and then added to water (100 ml). The organic material was the extracted into ether (4 x 100 ml). The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the **product** (**71**) (110 mg, 58%) as opague diamonds, m.p. 95-97°C (light petroleum-methylene dichloride) (Found: C, 66.7; H, 5.85. $C_{13}H_{14}O_4$ requires C, 66.7; H, 5.9%); $\nu_{max.}$ 1626 and 1610 (C=C) cm^{-1}; δ 3.77 (6H, s, 2 x OCH_3), 3.80 (3H, s, OCH_3), 5.88br. (2H, d, *J*3.6Hz, bridgehead H's), 6.06 (1H, s, 7-H), and 6.95br. (2H, s, alkene H's); *m/z* 234 (M^+, 87%), 219 (51), 205 (57), 191 (100), and 175 (20).

1,2,4,5,8-Pentamethoxynaphthalene (**30**).-
A slurry of sodamide and light petroleum (3.9 g, 0.10 mol) was weighed directly into a round bottom flask, to this was added 2-methoxyfuran (2.5 g, 0.026 mol) in 1,2-dimethoxyethane (10 ml) and 1-bromo-2,4,5-trimethoxybenzene[35] (**65**) (5.0 g, 0.02 mol) in 1,2-dimethoxyethane (20 ml). The reaction mixture was boiled under nitrogen for 6 h. The cooled reaction mixture was quenched by the slow addition of *t*-butyl alcohol (40 ml), and then added to water (200 ml). The organic material was then extracted into ether (4 x 100 ml). The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) affording a light brown oil which was immediately dissolved in dry acetone (150 ml), to which dry potassium carbonate

(27.8 g, 0.2 mol) and dimethyl sulphate (19.1 ml, 0.2 mol) were added, and the mixture heated under reflux with stirring for 16 h. The cooled reaction mixture was treated as described in the following method to afford the **pentamethoxynaphthalene (30)** (1.66 g, 30%) as white needles, m.p. 105-106°C, identical to the product described in the following method.

1,2,4,5,8-Pentamethoxynaphthalene (**30**) and *7-Butyl-1,2,3,(or 4),5-tetramethoxynaphthalene* (**82**).-

(a) 1,2-Dibromo-3,4,6-trimethoxybenzene (**79**)[37] (6.10 g, 0.019 mol) and 2-methoxyfuran (2.20 g, 0.021 mol) were stirred in dry tetrahydrofuran (50 ml) at -78°C under nitrogen. *n*-Butyl lithium (1.21 M, 13.87 ml, 0.017 mol) was dripped in over 15 min and the solution stirred for another 10 min. The reaction mixture was allowed to warm to room temperature and poured into water (200 ml). The organic material was then extracted into ether (4 x 100 ml). The residue obtained upon work-up was flash chromatographed (eluant 40% ethyl acetate-light petroleum) to afford a light brown oil. This was immediately dissolved in dry acetone (150 ml), to which dry potassium carbonate (25.7 g, 0.19 mol) and dimethyl sulphate (17.7 ml, 23.5 g, 0.19 mol) were added, and the mixture heated under reflux with stirring for 16 h. The cooled reaction mixture was filtered and evaporated to give a residue which was dissolved in ether (200 ml) and washed with a 25% ammonia solution (4 x 100 ml), followed by water (150 ml), dilute hydrochloric acid (100 ml) and finally water (150 ml). The ether solution

was dried ($MgSO_4$) and evaporated, yielding a residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford, firstly, starting material (**79**) (0.56 g) followed by the **product** (**30**) (3.02 g, 63%) as white needles, m.p. 105-106°C (light petroleum) (Found: C, 64.6; H, 6.8. $C_{15}H_{18}O_5$ requires C, 64.75; H, 6.5%); $\nu_{max.}$ 1601 (C=C) cm^{-1}, ^1H n.m.r (200 MHz) δ 3.81, 3.88, 3.90, 3.92, and 3.98 (each 3H, s, OCH_3), 6.65 (1H, d, J10Hz, 6-H), 6.75 (1H, s, 3-H), 6.80 (1H, d, J10Hz, 7-H); ^{13}C n.m.r. δ57.30, 57.35, 57.61, 57.80, 61.88 (5 x OCH_3), 99.20 (C-3), 105.20 (C-6), 108.97 (C-7), 115.54 (C-8a)[a], 124.19 (C-4a)[a], 138.13 (C-5), 149.99 (C-8)[b], 150.13 (C-2)[b], 151.48 (C-1), 153.85 (C-4) (assignment with the same superscript may be interchanged); *m/z* 278 (M^+, 100%), 263 (58), and 249 (18).

(b) Using one molar equivalent of *n*-butyl lithium resulted in the formation of a butylated product (**82**), as well as the desired Diels-Alder products, the butylated product (**82**) increasing in yield as the scale of the reaction was increased. ^1H n.m.r. δ0.95 (3H, t, J7.2Hz, $-CH_2CH_3$), 1.3-1.5 (2H, m, CH_2-CH_3), 1.6-1.8 (2H, m, $-CH_2CH_2CH_3$), 2.71 (2H, t, J7.7Hz, $Ar-CH_2-$), 3.84 and 3.96 (each 3H, s, OCH_3), 3.98 (6H, s, 2 x OCH_3) 6.64 (1H, s, 2- or 3-H), 6.73 (1H, d, J2Hz, 6-H), and 7.58 (1H, d, J2Hz, 8-H); *m/z* 304 (M^+, 100%), 289 (63), and 261 (44).

2-Acetyl-1,4,5,6,8-pentamethoxynaphthalene (**86**).-

Acetic acid (220 mg, 0.37 mmol) premixed with trifluoroacetic anhydride (770 mg, 0.37 mmol) was rapidly added to 1,2,4,5,8-pentamethoxynaphthalene (**30**) (113 mg, 0.41 mmol) in dry

methylene dichloride (5 ml). The mixture was stirred at room temperature for 21 h. The reaction was quenched by successive additions of an excess of methanol and a saturated aqueous sodium hydrogen carbonate solution. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **product** (**86**) (108 mg, 83%) as pale yellow flakes, m.p. 108-109°C (light petroleum/methylene dichloride)(Found: C, 63.45; H, 6.2. $C_{17}H_{20}O_6$ requires C, 63.75; H, 6.25%); UV $\lambda_{max.}^{EtOH}$ nm (log *E*) 350 (3.87) and 380 (3.90); $\nu_{max.}$ 1679 (C=O) and 1594 (C=C) cm^{-1}; ^1H n.m.r. δ 2.72 (3H, s, $COCH_3$), 3.76, 3.78, 3.94, 3.98, and 4.00 (each 3H, s, OCH_3), 6.75 (s, 1H, 7-H), and 7.07 (1H, s, 3-H); ^{13}C n.m.r δ 31.03 (CH_3C), 56.32, 56.41, 56.61, 61.48, and 63.29 (5 x OCH_3), 97.61 (C-7), 105.31 (C-3) 116.15 (C-8a)[a], 126.00 (C-4a)[a], 126.34 (C-2), 137.82 (C-1), 151.52 (C-4), 152.05 (C-6), 152.52 (C-5), 153.91 (C-8), and 199.67 (CO) (assignments with the same superscript may be interchanged); *m/z* 320 (M^+, 100%), 305 (60), 290 (10), 277 (20), 273 (17), 247 (10), and 43 (20).

2-Acetyl-1,4,6-trimethoxy-5,8-naphthoquinone (**87**).-

The naphthalene (**86**) (67.5 mg, 0.21 mmols), silver(II) oxide (107 mg, 0.84 mmol) and dioxane (5 ml) were stirred together at room temperature. Nitric acid (6M, 0.8 ml) was added and the reaction mixture was stirred for 4 min. A mixture of methylene dichloride (20 ml) and water (5 ml) was added and the organic layer was separated and washed

with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to give the **quinone** (**87**) (57 mg, 93%) m.p. 187-188.5°C (methanol), identical to an authentic sample of 2-acetyl-1,4,6-trimethoxy-5,8-naphthoquinone (**87**) kindly provided by Fariña, but different from an authentic sample of 3-acetyl-1,4,6-trimethoxy-5,8-naphthoquinone[25] (**88**) also provided by Fariña. (m.p. 174-175°C). Literature melting points[25] of both these compounds were quoted to be 169-170°C and 179-180°C for the 2-acetyl compound (**87**) and the 3-acetyl compound (**88**) respectively, but in our laboratory these two samples provided by Fariña melted at 187-188°C and 174-175°C for the 2-acetyl compound (**87**) and the 3-acetyl compound (**88**) respectively.

Thin layer chromatography comparison also showed our quinone to be identical to the 2-acetyl compound provided by Fariña.

Methyl-2-hydroxy-4-methoxybenzoate (**89**).-
2,4-Dihydroxybenzoic acid (1.00 g, 6.5 mmol) was treated as described by Corey[40] and chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **ester** (**89**) (1.02 g, 88%).

Methyl-2-2'-propyloxy-4-methoxybenzoate (**90**).-
The ester (**89**) (1.02 g, 5.7 mmol) was dissolved in dry dimethylformamide (50 ml). Dry potassium carbonate (2.00 g, 14.3 mmol) and isopropyl bromide (1.75 g, 14.3 mmol) were added and the mixture stirred at 60°C for 23 h. The cooled

reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the **product** (**90**) (0.93 g, 79%) as a pale yellow oil, (Found: C, 64.45; H, 7.15. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.15%); $\nu_{max.}$ 1728 (C=O) cm^{-1}; δ 1.36 (6H, d, *J* 7Hz, $(CH_3)_2CH$), 3.83 and 3.80 (each 3H, s, OCH_3), 4.54 (1H, septet, *J* 7Hz, $CH(CH_3)_2$), 6.38-6.56 (2H, m, 3- and 5-H), and 7.81 (1H, d, *J* 9Hz, 6-H); *m/z* 224 (M^+, 11%), 182 (25), 150 (100), and 122 (15).

2-2'-Propyloxy-4-methoxybenzoic acid (**91**).-

The ester (**90**) (747 mg, 4.0 mmol) in a methanolic solution of potassium hydroxide (8% w/v, 6.0 mmol) was stirred under reflux for 12 h. The reaction mixture was cooled and neutralised with ice-cooled concentrated hydrochloric acid. The benzoic acid was extracted into ether (100 ml) and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the **product** (**91**) (615 mg, 88%) as white needles, m.p. 60-61°C (light petroleum-methylene dichloride)(Found: C, 62.8; H, 6.6. $C_{11}H_{14}O_7$ requires C, 62.86; H, 6.67%); $\nu_{max.}$ 1661 (C=O) cm^{-1}; δ 1.44 (6H, d, *J* 6Hz, $(CH_3)_2CH$), 3.84 (3H, s, OCH_3), 4.80 (1H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.50 (1H, d, *J* 3Hz, 3-H), 6.59 (1H, dd, *J* 10 and 3Hz, 5-H), and 8.10 (1H, d, *J* 10Hz 6-H), 10.64br.(1H, s, OH, D_2O exchangeable); *m/z* 210 (M^+, 15%), 168 (23), 150 (100), and 122 (20).

2-(2'-(2-Propyloxy)-4'-methoxybenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**92**), *2-(2'-(2-Propyloxy)-4'-methoxy-5'-(2''-(2-propyloxy)-4''-methoxybenzoyl)benzoyl)-1,4,5,6,8-pentamethoxynaphthalene* (**93**), and *2-(2'-(2-Propyloxy)-4'-methoxy-5'-(2''-(2-propyloxy)-4''-methoxy-5''-(2'''-(2-propyloxy)-4'''-methoxybenzoyl)benzoyl) benzoyl)-1,4,5,6,8-pentamethoxynaphthalene* (**94**).-

(a) 2-Isopropoxy-4-methoxybenzoic acid (**91**) (157 mg, 0.7 mmol) premixed with trifluoroacetic anhydride (147 mg, 0.7 mmol) in dry methylene dichloride (1 ml) was rapidly added to 1,2,4,5,8-pentamethoxynaphthalene (**30**) (194 mg, 0.7 mmol) dissolved in dry methylene dichloride (5 ml). The mixture was stirred at room temperature for 162 h with the addition of a further aliquot of the mixed anhydride after 144 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous solution of sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 30%-40% ethyl acetate-light petroleum) to afford firstly starting material (30 mg) and then the **product** (**92**) (196 mg, 60%) as yellow needles, m.p. 164-165°C (2-propanol)(Found: C, 66.3; H, 6.35. $C_{26}H_{30}O_8$ requires C, 66.4; H, 6.4%); $\nu_{max.}$ 1633 (C=O) and 1597 (C=C) cm^{-1}; δ 0.88 (6H, d, *J*5Hz, $(CH_3)_2CH$), 3.58, 3.81, 3.83, and 4.00 (each 3H, s, OCH_3), 3.92 (6H, s, 2 x OCH_3), 4.36 (1H, septet, *J*5Hz, $CH(CH_3)_2$), 6.37 (1H, d, *J*3Hz, 3'-H), 6.52 (1H, dd, *J*8 and 3Hz, 5'-H), 6.75 (1H, s, 7-H), 6.85 (1H, s, 3-H), and 7.77 (1H, d, *J*8Hz, 6'-H); *m/z* 470 (M^+, 100%), 455 (20), 381 (9), 289 (13), and 151 (37).

(b) If one further aliquot of the mixture of 2-isopropoxy-4-methoxybenzoic acid and trifluoroacetic anhydride were added to the same quantities of reaction mixture product (**92**) (184 mg, 56%) and two further products were isolated, eluting first (**93**) (37 mg, 8%) as shown by the ^{1}H n.m.r. spectrometry δ0.90 (6H, d, J6Hz, $(CH_3)_2CH$), 1.08 (6H, d, J6Hz, $(CH_3)_2CH$), 3.58, 3.74, 3.82, 3.84, and 4.00 (each 3H, s, OCH_3), 3.92 (6H, s, 2 x OCH_3), 4.43 (2H, septet, J6Hz, 2 x $CH(CH_3)_2$), 6.38 (1H, d, 3Hz, 3"-H), 6.51 (1H, dd, J8 and 3Hz, 5"-H), 6.63 (1H, s, 3'-H), 6.76 (1H, s, 7-H), 6.84 (1H, s, 3-H), 7.65 (1H, d, J8Hz, 6"-H), and 7.96 (1H, s, 6'-H); *m/z* 663 (M^+, 100%), 193 (35), and 151 (50). Eluting secondly product (**94**) (66 mg, 11%) as shown by ^{1}H n.m.r. spectrometry δ 0.90, 1.05, and 1.14 (each 6H, d, J6Hz, $(CH_3)_2CH$), 3.56, 3.74, 3.76, 3.82, 3.84, 3.92, 3.93, and 4.00 (each 3H, s, OCH_3), 4.46 (3H, septet, J6Hz, 3 x $CH(CH_3)_2$), 6.35 (1H, d, J2Hz, 3'''-H), 6.38 (2H, s, 3'- and 3"-H), 6.53 (1H, dd, J8 and 2Hz, 5'''-H), 6.76 (1H, s, 7-H), 6.86 (1H, s, 3-H), 7.66 (1H, d, J8Hz, 6'''-H), and 7.79 and 7.97 (each 1H, s, 6'- and 6"-H).

Methyl-2-benzyloxy-4-methoxybenzoate (**96**).-

The ester (**89**) (1.50 g, 8.4 mmol) was dissolved in dry acetone. Dry potassium carbonate (2.90 g, 21 mmol) and benzyl bromide (3.60 g, 21 mmol) were added and the mixture stirred under reflux for 21 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant light petroleum to 20% ethyl acetate-light petroleum) to afford the **product** (**96**) (2.17 g, 97%) as a pale yellow

oil, (Found: C, 70.75; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.5; H, 5.9%); $\nu_{max.}$ 1722 (C=O) cm^{-1}; δ 3.72 and 3.80 (each 3H, s, OCH_3), 5.08 (2H, s, CH_2-Ph), 6.44 (1H, dd, $\bar{J}$ 9 and 3Hz, 5-H) 6.54 (1H, d, *J*3Hz, 3-H), 7.20-7.54 (5H, m, **Ph**CH_2), and 7.82 (1H, d, *J*9Hz, 6-H); *m/z* 272 (M^+, 13%), 211 (31), 179 (11), 150 (13), 134 (42), 108 (53), 91 (100), 79 (62), 77 (52), 65 (49), and 51 (48).

2-Benzyloxy-4-methoxybenzoic acid (**95**).-

The ester (**96**) (2.18 g, 8.0 mmol) in a methanolic solution of potassium hydroxide (12% w/v, 12 mmol) was stirred under reflux for 20 h. The reaction mixture was cooled and neutralised with ice-cooled concentrated hydrochloric acid. The organic material was extracted into ether (150 ml) and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the **product** (**95**) (1.86 g, 90%) as white cubes, m.p. 100-101°C (light petroleum/methylene dichloride)(Found: C, 69.55; H, 5.35. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%); $\nu_{max.}$ 1680 (C=O), 1661 (C=O), and 1608 (C=C) cm^{-1}; δ 3.81, (3H, s, OCH_3), 5.20 (2H, s, **CH_2**-Ph), 6.59 (1H, d, *J*3Hz, 3-H), 6.62 (1H, dd, *J*10 and 3Hz, 5-H), 7.38 (5H, s, **Ph**-CH_2), 8.09 (1H, d, *J*10Hz, 6-H), and 10.26br. (1H, s, OH); *m/z* 258 (M^+, 67%), 240 (9), 150 (26), 91 (100), and 65 (48).

2-(2'-Benzyloxy-4'-methoxybenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**97**).-

2-Benzyloxy-4-methoxybenzoic acid (**95**) (91 mg, 0.36 mmol) premixed with trifluoroacetic anhydride (76 mg, 0.36 mmol) in dry methylene dichloride (1 ml) was rapidly added to

1,2,4,5,8-pentamethoxynaphthalene (**30**) (100 mg, 0.36 mmol) dissolved in dry methylene dichloride (5 ml). The mixture was stirred at room temperature for 92 h with the addition of one more aliquot of the mixed anhydride after 25 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous solution of sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 30-40% ethyl acetate-light petroleum) to afford the **product** (**97**) (117 mg, 63%), as yellow needles, m.p. 129-130°C (2-propanol)(Found: C, 69.2; H, 5.85. $C_{30}H_{31}O_8$ requires C, 69.35; H, 5.95%); $\nu_{max.}$ 1734 (C=O) cm^{-1}; δ3.49, 3.79, 3.83, and 3.97 (each 3H, s, OCH_3), 3.86 (6H, s, 2 x OCH_3), 4.85 (2H, s, CH_2-Ph), 6.47 (1H, d, *J*2.7Hz, 3'-H) 6.52 (1H, dd, *J* 8 and 2.7Hz, 5'-H), 6.68 (1H, s, 7-H), 6.82 (1H, s, 3-H), 6.82-7.12 (5H, m, **Ph**CH_2), and 7.72 (1H, d, 8Hz, 6'-H); *m/z* 518 (M^+, 100%), 503 (11), 381 (19), 353 (12), 91 (45), and 28 (100).

2-(2'-Hydroxy-4'-methoxybenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**98**).- The naphthalene (**97**) (111 mg, 0.22 mmol) in ethyl acetate (20 ml) was stirred together with 10% Pd/C (0.1 g) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 1 h. After filtration and evaporation of the solvent under reduced pressure the residue was chromatographed (eluant 50% ethyl acetate-light petroleum) to yield the **product** (**98**) (79 mg, 86%) as yellow crystals, m.p. 156-158°C (methanol)(Found: C, 64.2; H, 5.4. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.6%); $\nu_{max.}$ 3427 (OH),

1634 (C=O), and 1591 (C=C) cm^{-1}; δ3.68, 391, 3.96, and 4.00 (each 3H, s, OCH_3), 3.83 (6H, s, 2 x OCH_3), 6.32 (1H, dd, *J*9 and 2.5Hz 5'-H), 6.49 (1H, d, *J*2.5Hz, 3'-H), 6.66 (1H, s, 7-H), 6.78 (1H, s, 3-H), 7.31 (1H, d, *J*9Hz, 6'-H), and 12.73 (1H, s, OH, D_2O exchangeable); *m/z* 428 (M^+, 70%), 397 (100), 367 (26), 349 (11), 198 (12), and 151 (25).

Methyl-2-hydroxy-4-methoxy-6-methylbenzoate (**99**).-

Methyl orsellinate (3.0 g, 0.019 mol) prepared according to Sargent[41] was treated as described by Corey[40] and chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the **everninic methyl ester** (**99**) (2.6 g, 80%) m.p. 67-68°C (Lit.,[47] 66-67°C).

Methyl-2-benzyloxy-4-methoxy-6-methylbenzoate (**100**).-

The ester (**99**) (3.02 g, 15.3 mmol) was treated in a similar manner to Sargent[48] to yield the **product** (**100**) (4.89 g, 99%) as a pale yellow oil, (Found: C, 71.45; H, 6.3. $C_{17}H_{18}O_4$ requires C, 71.35; H, 6.3%); $\nu_{max.}$ 1724 (C=O) cm^{-1}; δ 2.26 (3H, s, Ar-CH_3), 3.68 and 3.80 (each 3H, s, OCH_3), 5.00 (2H, s, CH_2Ph), 6.28br. (2H, s, 3- and 5-H), and 7.2-7.4 (5H, m, **Ph**-CH_2); *m/z* 286 (M^+, 61%), 255 (26), 227 (15), 164 (26), 91 (100), and 65 (37). (^1H n.m.r. spectrum details being similar to those described by Sargent.[48])

2-Benzyloxy-4-methoxy-6-methylbenzoic acid (**43**).-

The ester (**100**) (4.89 g, 17.1 mmol) was treated in a similar manner to that described by Sargent[48] to yield the **product** (**43**) (3.86 g, 83%) as white needles, m.p. 103-104°C (lit.,[48] 99-100°C).

2-(2'-Benzyloxy-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**31**).-

2-Benzyloxy-4-methoxy-6-methylbenzoic acid (**43**) (0.83 g, 3.06 mmol) premixed with trifluoroacetic anhydride (0.64 g, 3.06 mmol) in dry methylene dichloride (5 ml) was rapidly added to 1,2,4,5,8-pentamethoxynaphthalene (**30**) (0.85 g, 3.06 mmol) dissolved in dry methylene dichloride (20 ml). The mixture was stirred at room temperature for 90 h with addition of further aliquots of the mixture of aromatic acid and trifluoroactic anhydride at 6 and 48 h. The reaction was quenched by the successive additions of an excess of methanol and a saturated aqueous solution of sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **product** (**31**) (0.83 g, 51%) as light yellow quartz clusters, m.p. 152.5-153°C (methanol) (Found: C, 69.9; H, 5.9. $C_{31}H_{32}O_8$ requires C, 69.9; H, 6.0%); $\nu_{max.}$ 1631 (C=O) and 1600 (C=C) cm^{-1}; δ 2.36 (3H, s, Ar-CH_3), 3.32, 3.82, 3.88, and 3.98 (each 3H, s, OCH_3), 3.80 (6H, s, 2 x OCH_3), 4.82 (2H, s, PhCH_2), 6.32 (1H, d, J2.2Hz, 5'-H), 6.40 (1H, d, J2.2Hz, 3'-H), 6.68 (1H, s, 7-H), and 6.75-7.12 (6H, m, **Ph**CH_2 and 3-H); *m/z* 532

(M^+, 100%), 517 (13), 410 (20), 395 (25), 366 (12), and 91 (37).

Methyl-2-(2-propyloxy)-4-methoxy-6-methylbenzoate (**101**).-

The ester (**99**) (426 mg, 2.17 mmol) was dissolved in dry dimethylformamide (30 ml). Dry potassium carbonate (750 mg, 5.43 mmol) and isopropyl bromide (670 mg, 5.43 mmol) were added, and the mixture stirred at 60°C for 19 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the **product** (**101**) (467 mg, 90%) as a pale yellow oil, (Found: C, 65.45; H, 7.5. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.55%); $\nu_{max.}$ 1728 (C=O) cm^{-1}; δ1.28 (6H, d, *J* 6Hz, $(CH_3)_2CH$), 2.24 (3H, s, Ar-CH_3), 3.75 and 3.84 (each 3H, s, OCH_3), 4.45 (1H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.28 (2H, s, 3- and 5-H); *m/z* 238 (M^+, 14%), 196 (12), 164 (100), 136 (14), 97 (15), and 57 (35).

2-(2-propyloxy)-4-methoxy-6-methylbenzoic acid (**102**).-

The ester (**101**) (358 mg, 1.50 mmol) in a methanolic solution of potassium hydroxide (5% w/v, 2.25 mmol) was boiled for 18 h. The reaction mixture was cooled and neutralised with ice-cooled concentrated hydrochloric acid. The organic material was extracted into ether (100 ml) and the residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the **acid** (**102**) (281 mg, 83%) as white needles, m.p. 68-71 °C (light petroleum/methylene dichloride)(Found: C, 64.3; H, 7.1. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.15%); $\nu_{max.}$ 1671 (C=O) cm^{-1}; δ1.40 (6H, d, *J* 6Hz, $(CH_3)_2CH$), 2.57 (3H, s, Ar-CH_3), 3.80 (3H, s, OCH_3),

4.68 (1H, septet, *J* 6Hz, $CH(CH_3)_2$), 6.40 and 6.46 (each 1H, d, *J* 3Hz, 3- and 5-H), and 8.64br. (1H, s, OH, D_2O exchangeable); *m/z* 224 (M^+, 23%), 164 (100), and 136 (19).

2-(2'(2-Propyloxy)-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**103**) and *3-(2'-(2-Propyloxy)-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxynaphthalene* (**104**).-

2-Isopropoxy-4-methoxy-6-methylbenzoic acid (**102**) (200 mg, 0.90 mmol) premixed with trifluoroacetic anhydride (190 mg, 0.90 mmol) in dry methylene dichloride (2 ml) was rapidly added to 1,2,4,5,8-pentamethoxynaphthalene (**30**) (124 mg, 0.45 mmol) dissolved in dry methylene dichloride (10 ml). The mixture was stirred at room temperature for 174 h with addition of one further aliquot of the mixture of aromatic acid and trifluoroacetic anhydride after 78 h. The reaction was quenched by the successive additions of an exces of methanol and a saturated aqueous solution of sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford a mixture of inseparable isomers (**103**) and (**104**) (47 mg, 22%) as shown by ^1H n.m.r. spectrometry δ 0.94 (6H, d, *J*6Hz, $(CH_3)_2CH$ of (**103**)), 1.06 (d, *J* 6Hz, $(CH_3)_2CH$ of (**104**)), 2.30 (s, Ar-CH_3 of (**104**)), 2.35 (3H, s, Ar-CH_3 of (**103**)), 3.39, 3.79, 3.89, and 3.97 (each 3H, s, OCH_3) 3.92 (6H, s, 2 x OCH_3), 4.55 (1H, septet, *J*6Hz, $CH(CH_3)_2$), 6.22 (1H, d, *J*3Hz, 5'-H), 6.36 (1H, d, *J* 3Hz, 3'-H), 6.72 (1H, s, 7-H), 7.03 (1H, s, 3-H of (**103**)), and 7.13 (s, 2-H of (**104**)). The ratio of (**103**) to (**104**) being approxi-

mately 4:1 as judged by ^{1}H n.m.r. spectrometry.

2-(2'-Benzyloxy-6'-methyl-4'-methoxybenzoyl)-1,4,6-trimethoxy-5,8-naphthoquinone (**36**).-

The naphthalene (**31**)(200 mg, 0.38 mmol), silver(II) oxide (280 mg, 2.24 mmol) and dioxane (10 ml) were stirred together at room temperature. Nitric acid (6M, 1.5 ml) was added and the reaction mixture was stirred for 15 min. A mixture of methylene dichloride (30 ml) and water (10 ml)was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **quinone** (**36**) (132 mg, 70%) as yellow diamonds, m.p. 210-212°C (methanol)(Found: C, 68.9; H, 5.1. $C_{29}H_{26}O_8$ require C, 69.3; H, 5.2%); $\nu_{max.}$ 1641 and 1627 (C=O) and 1602 (C=C) cm^{-1}; δ 2.46 (3H, s, Ar-CH_3), 3.32 and 3.71 (each 3H, s, OCH_3), 3.81 (6H, s, 2 x OCH_3), 4.69 (2H, s, PhCH_2), 5.92 (1H, s, 7-H), 6.32 (1H, d, *J*2.2Hz, 5'-H), 6.43 (1H, d, *J*2.2Hz, 3'-H), and 6.74-7.18 (6H, m, **Ph**CH_2 and 3-H); *m/z* 502 (M^+, 40%), 471 (36), 439 (15), 411 (95), 380 (17), 327 (21), 165 (22), 91 (100), and 65 (17).

2,3-Dihydro-5,8-dihydroxy-6',6-dimethoxy-4'-methylnaphthalene-2-spiro-2'-benzo[b] furan-1,3',4-trione (**37**) and *2,3-Dihydro-6'-methoxy-4'-methyl-5,6,8-trihydroxy naphthalene -2-spiro-2'-benzo[b]furan-1,3',4-trione* (**111**).-

The quinone (**36**) (237 mg, 0.47 mmol) in dry methylene dichloride (30 ml) was treated at 0°C with boron trichloride (415 mg, 3.53 mmol) in the same solvent. After 3 h, the solution was allowed to warm to room temperature and then

hydrolysed with an excess of water. The organic material was extracted into methylene dichloride. The residue obtained upon work-up was chromatographed (eluant toluene) using deactivated silica[9] to yield the **product (37)** as dark red needles, (92 mg, 51%) m.p. > 300°C (methanol/methylene dichloride)(Found: C, 61.9; H, 4.3; M^+, 384.0867. $C_{20}H_{16}O_8$ requires C, 62.5; H, 4.2%; M, 384.0845); $\nu_{max.}$ 3320(OH), 1702 and 1653 (C=O), and 1628 (C=O) cm^{-1}; δ (200MHz) 2.45 (3H, d, J0.5Hz, Ar-CH_3)*, 3.20 (1H, d, J17.5Hz, 3-CH_2), 3.55 (1H, d, J 17.5Hz, 3-CH_2), 3.93 and 4.00 (each 3H, s, OCH_3), 6.47 (1H, dq, J1.95 and 0.5Hz, 5'-H)*, 6.54 (1H, d, J1.95Hz, 7'-H), 6.69 (1H, s, 7-H), and 11.94 and 12.08 (each 1H, s, OH, D_2O exchangeable); *m/z* 384 (M^+, 63%), 383 (29), 382 (100), 368 (28), 367 (82), 366 (15), 339 (29), 311 (13), and 165 (29). A second **product (111)** eluting afterwards was also obtained as dark red needles (24 mg, 14%) m.p. > 300°C (methanol/methylene dichloride)(Found: C, 61.0; H, 3.75; M^+, 370.0664. $C_{19}H_{14}O_8$ requires C, 61.6; H, 3.8%; M, 370.0689.); $\nu_{max.}$ 3369(OH), 1700 (C=O), 1616 (C=O), and 1585 (C=C) cm^{-1}; δ (200MHz) 2.45 (3H, d, J 0.5Hz, Ar-CH_3)*, 3.16 (1H, d, J16.7Hz, 3-CH_2), 3.52 (1H, d, J16.7Hz, 3-CH_2), 3.90 (3H, s, 6'-OCH_3), 6.46 (1H, dq, J 2 and 0.5Hz, 5'-H)*, 6.54 (1H, d, J 2Hz, 7'-H), 6.84 (1H, s, 7-H), 11.73 (1H, s, OH, D_2O exchangeable), 11.77br. (1H, s, OH, D_2O exchangeable); *m/z* 370 (M^+, 100%), 368 (45), 353 (62), 324 (12), 233 (16), 191 (24), 165 (37), 138 (25), and 77 (19).

*(The long range coupling between the aryl methyl protons and the *meta*-coupled proton 5' only being apparent on formation of the spiro compound or the xanthones).

Bikaverin: 6,11-Dihydroxy-3,8-dimethoxy-1-methylbenzo[b]xanthen-7,10,12-trione **(10)**.-

The spirocompound (**37**) (56 mg, 0.15 mmol) was heated in nitrobenzene (10 ml) at 200°C for 2 h. After vacuum distillation to remove the bulk of the nitrobenzene, the crude product was dissolved in methylene dichloride and washed with water, followed by a dilute solution of potassium hydroxide, the product forming a blue suspension in the aqueous basic solution. The aqueous layer was washed with more methylene dichloride, the two layers separated, the aqueous layer acidified with dilute hydrochloric acid, and the product re-extracted into methylene dichloride. The residue obtained upon work-up was chromatographed (Sephadex LH-20, eluant methanol/methylene dichloride (1:9v/v), 5 drops 5M hydrochloric acid) to yield the **product** (**10**) (41 mg, 74%) as dark red needles, m.p. > 300°C (methanol/methylene dichloride)(Found: C, 62.9; 3.95. $C_{20}H_{14}O_8$ requires C, 62.8; H, 3.7%); $\nu_{max.}$ 1665 and 1643 (C=O), and 1614 and 1589 (C=C) cm^{-1}; δ (200MHz) 2.79 (3H, d, *J* 0.5Hz, Ar-CH_3), 3.86 and 3.89 (each 3H, s, OCH_3), 6.27 (1H, s, 9-H), 6.73 (1H, dq, *J* 2.5 and 0.5Hz, 2-H), 6.84 (1H, d, *J* 2.5Hz, 4-H), 12.70 (1H, s, OH, D_2O exchangeable), 14.25br. (1H, s, OH, D_2O exchangeable); *m/z* 382 (M^+, 100%), 367 (51), and 339 (25). These spectroscopic and physical properties were identical to a sample of natural origin kindly provided by Kjær.[2a]

2-(2'-Hydroxy-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxynaphthalene (**32**).-

The naphthalene (**31**) (559 mg, 0.105 mmol) in ethyl acetate (200 ml) was stirred together with 10% Pd/C (0.5 g) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 1 h. After filtration of the solution and evaporation of the solvent under reduced pressure, the residue was chromatographed (eluant 40% ethyl acetate-light petroleum) to yield the **product** (**32**) (372 mg, 80%) as yellow diamond clusters, m.p. 164-165°C (2-propanol) (Found: C, 65.0; H, 5.8. $C_{24}H_{26}O_8$ requires C, 65.0; H, 5.8%); UV $\lambda_{max.}^{CHCl_3}$ nm (log *E*) 248 (4.63), 295 (4.15), and 343 (4.05) shoulder; $\nu_{max.}$ 3380 (OH) and 1620 (C=O) cm^{-1}; ^1H n.m.r. δ (200MHz) 1.85 (3H, s, Ar-CH_3), 3.66, 3.76, 3.78, 3.88, 3.90 and 3.95 (each 3H, s, OCH_3), 6.18 (1H, d, *J* 2.6Hz 5'-H), 6.36 (1H, d, *J* 2.6Hz, 3'-H), 6.60 (1H, s, 7-H), 6.74 (1H, s, 3-H), 12.97 (1H, s, OH, D_2O exchangeable); ^{13}C n.m.r. δ 23.06 (Ar-CH_3), 55.35, 56.90 (x2), 57.16, 61.87, 63.75 (6 x OCH_3), 98.42 (C-7), 98.76 (C-5'), 104.80 (C-3'), 111.44 (C-3), 115.29 (C-8a)[a], 117.07 (C-1'), 124.73 (C-4a)[a], 130.72 (C-2), 138.08 (C-1), 143.29 (C-6'), 146.97 (C-4), 151.16 (C-6), 152.54 (C-5), 153.74 (C-8), 164.70 (C-4'), 166.41 (C-2'), and 200.46 (CO) (assignment with the same superscript may be interchanged); *m/z* 442 (M^+, 40%), 411 (100), 382 (13), and 165 (22).

1,2-Dihydro-4'-methyl-4,5,6,6',8-pentamethoxynaphthalene-2-spiro-2'-benzo[b]furan-1,3'-dione (**33**).-

2,3-Dichloro-5-6-dicyanobenzoquinone (287 mg, 1.26 mmol) was added to the naphthol (**32**) (372 mg, 0.84 mmol) in dry benzene (30 ml). The mixture was stirred at room temperature (23°C) for 68 h. The solvent was evaporated under reduced pressure and the residue obtained was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **product** (**33**) (219 mg, 61%) as white grains, m.p. 195-196°C (methanol)(Found: C, 64.5; H, 5.05. $C_{23}H_{22}O_8$ requires C, 64.8; H, 5.15%); $\nu_{max.}$ 1710 (furan C=0) and 1676 (C=0) cm^{-1}; δ (200MHz) 2.39 (3H, s, Ar-CH_3), 3.75, 3.78, 3.83, 3.85, and 3.93 (each 3H, s, OCH_3), 5.00 (1H, s, 3-H), 6.35br. (1H, d, *J* 2.2Hz, 5'-H), 6.53 (1H, d, *J* 2.2Hz, 7'-H), and 6.43 (1H, s, 7-H); *m/z* 426 (M^+, 62%), 411 (100), 383 (31), 368 (29), 367 (21), 353 (17), 351 (11), 247 (11), 120 (12), and 77 (19).

2,3-Dihydro-4'-methyl-5,6,6',8-tetramethoxynaphthalene-2-spiro-2' benzo[b]furan-1,3',4-trione (**34**).-

The enol ether (**33**) (80 mg, 0.19 mmol) in methylene dichloride (20 ml) was shaken with trifluoroacetic acid (1.0 ml) in water (20 ml) for 5 min. After removal of the aqueous layer, the organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate-light petroleum) to afford the **product** (**34**) (73 mg, 94%) as light brown needles, m.p. 214-217°C (2-propanol)(Found: C, 64.05; H, 4.95. $C_{22}H_{20}O_8$ requires

C, 64.1; H, 4.85%); $\nu_{max.}$ 1707 (furan C=0) 1677, and 1624 (C=C) cm^{-1}; δ(200MHz) 2.36 (3H, d, *J* 0.5Hz, Ar-CH_3), 3.19 (1H, d, *J*15.0Hz, 3-CH_2) 3.46 (1H, d, *J*15.0Hz, 3-CH_2), 3.81, 3.85, 3.90 and 3.94 (each 3H, s, OCH_3), 6.35 (1H, dq, *J*2 and 0.5Hz, 5'-H), 6.46 (1H, d, *J*2Hz, 7'-H), and 6.68 (1H, s, 7-H); *m/z* 412 (M^+, 100%), 397 (56), 233 (9), 193 (23), 165 (18), 134 (13), and 77 (15).

Hydrolysis of the enol ether with trifluoroacetic acid in D_2O afforded the deuterated product (**127**) as shown only by ^1H n.m.r. spectrometry δ 2.38(3H, d, *J* 0.5Hz, Ar-CH_3), 3.15 (1H, s, 3-H), 3.83, 3.87, 3.92, and 3.96 (each 3H, s, OCH_3), 6.37 (1H, dq, *J* 2 and 0.5Hz, 5'-H), 6.46 (1H, d, *J*2Hz, 7'-H), and 6.70 (1H, s, 7-H).

6-11-Dihydroxy-3,7,8,10-tetramethoxy-1-methylbenzo[b]xanthen-12-one (**35**).- The spiro compound (**34**) (55 mg, 0.13 mmol) was heated for 1 h at 200°C at 5 mmHg and then sublimed at the same temperature at a pressure of 0.06 mmHg for 6 h. The product was dissolved in methylene dichloride and chromatographed (eluant 40% ethyl acetate-light petroleum) to yield the **hydroquinone** (**35**) (51 mg, 93%) as red needles, m.p. 235-236°C (light petroleum/methylene dichloride)(Found: C, 63.90; H, 4.85. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.85%); $\nu_{max.}$ 3261 (OH), 1679 and 1654 (C=O) cm^{-1}; δ(200MHz) 2.86 (3H, d, *J*0.5Hz, Ar-CH_3), 3.88, 3.99, 4.00, and 4.03 (each 3H, s, OCH_3), 6.53 (1H, s, 9-H), 6.62 (1H, dq, *J*2.7 and 0.5 Hz, 2-H), 6.83 (1H, d, *J*2.7Hz, 4-H), and 9.70 and 15.17 (each 1H, s, OH, D_2O exchangeable); *m/z* 412 (M^+, 45%) and 397 (100).

3,7,8,10-Tetramethoxy-1-methylbenzo[b]xanthen-6,11,12-trione (**128**).- The hydroquinone (**35**) (10.0 mg, 0.024 mmol), silver(I) oxide (6 mg, 0.024 mmol) and chloroform (3 ml) were stirred together at room temperature for 4 h. The silver(I) oxide was filtered off and the solvent evaporated under reduced pressure. The residue obtained was chromatographed (eluant methylene dichloride-methanol (9.5:0.5)) to afford the **quinone** (**128**) (9.3 mg, 93%) as orange needles, m.p. 264°C (chloroform-ether). Its physical and spectroscopic properties as well as chromatographic behaviour were identical to a sample kindly provided by Kjær.[2a]

3,6,7,8,10,11-Hexamethoxy-1- methylbenzo[b]xanthen-12-one (**31**).- The hydroquinone (**35**) (112 mg, 0.27 mmol) was dissolved in dry acetone (100 ml). Dry potassium carbonate (374 mg, 2.7 mmol) and dimethyl sulphate (0.26 ml, 2.7 mmol) were added and the mixture boiled for 16 h. The cooled reaction mixture was filtered and evaporated. The residue was dissolved in ether and washed with a 25% ammonia solution, followed by water, dilute hydrochloric acid and finally water. The organic layer was dried and evaporated. The residue obtained was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **product** (**31**) (99 mg, 83%) as yellow needles, m.p. 204-205°C (2-propanol)(Found: C, 65.5; H, 5.25. $C_{24}H_{24}O_8$ requires C, 65.45; H, 5.45%); UV $\lambda_{max.}^{CHCl_3}$ nm (log *E*) 267 (4.78), 297 (4.77), and 414 (4.08); $\nu_{max.}$ 1652 (C=O) cm^{-1}; δ (200MHz) 2.86 (3H, d, *J* 0.5Hz, Ar-CH_3), 3.88, 3.90, 3.99, and 4.03 (each 3H, s, OCH_3), 4.01 (6H, s, 2 x OCH_3), 6.64 (1H, dq, *J* 2 and 0.5Hz, 2-H),

6.67 (1H, s, 9-H), and 6.80 (1H, d, *J* 2Hz, 4-H); *m/z* 440 (M^+, 100%), 425 (96), and 393 (15).

1:2,3:4-trans-Diepoxy-2-(2'-hydroxy-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxy-1,2,3,4-tetrahydronaphthalene (**139**) and *1:2,3:4-cis-Diepoxy-2-(2'-hydroxy-4'-methoxy-6'-methylbenzoyl)-1,4,5,6,8-pentamethoxy-1,2,3,4-tetrahydronaphthalene* (**140**).-

The naphthol (**32**) (69 mg, 0.16 mmol) was dissolved in dry benzene in a pyrex flask, and irradiated with ultraviolet light while oxygen was bubbled through the solution for 25 min. After evaporation of the solvent under reduced pressure the resulting residue was subjected to p.l.c. (eluant 10% ethyl acetate-light petroleum) to afford firstly, the major **product (139)*** (41 mg, 59%) as white needles, m.p. 154-155°C (light petroleum/methylene dichloride)(Found: C, 60.75; H, 5.5. $C_{24}H_{26}O_{10}$ requires C, 60.75; H, 5.5%); UV $\lambda_{max.}^{CHCl_3}$ nm (log *E*) 248 (4.63), 295 (4.15), and 342 (4.05) shoulder; $\nu_{max.}$ 1740 and 1716 cm^{-1}; δ(200MHz) 2.00 (3H, s, Ar-CH_3), 3.55, 3.56, 3.78, 3.81, 3.82, and 3.83 (each 3H, s, OCH_3), 5.36 (1H, s, 3-H), 6.24 (1H, d, *J* 2.5Hz, 5'-H), 6.35 (1H, d, *J* 2.5Hz, 3'-H), and 6.89 (1H, s, 7-H); *m/z* 474.1471 (M^+, 9%), 443.1350 (96), 411.1054 (100), 383 (50), and 165 (33). The second fraction afforded the minor **product (140)*** (11 mg, 16%) as an oil which crystallised on standing, m.p. 54-55°C (Found M^+-OCH_3, 443.1346. $C_{24}H_{26}O_{10}$ requires M-OCH_3, 443.1342); $\nu_{max.}$ 1740 and 1717 cm^{-1}; δ(200MHz) 1.89 (3H, s, Ar-CH_3), 3.68, 3.70, 3.72, 3.82, 3.83, and 3.85 (each 3H, s, OCH_3), 5.00 (1H, s, 3-H), 6.22 (1H, d,

*J*2.5Hz, 5'-H), 6.38 (1H, d, *J*2.5Hz, 3'-H), 6.73 (1H, s, 7-H); *m/z* 474.1471 (M^+, 11%), 443.1346 (84), 412.1148 (100), 383 (63), 165 (45), and 88 (42). *(At this stage in the work both are interchangeable).

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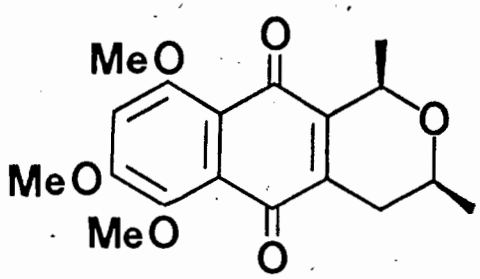
CHAPTER 3

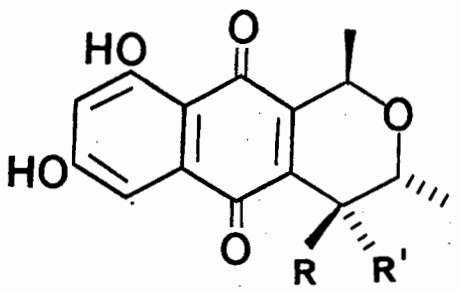
SYNTHESIS OF SEVERAL VENTILOQUINONES AND THEIR C-3 EPIMERS

INTRODUCTION

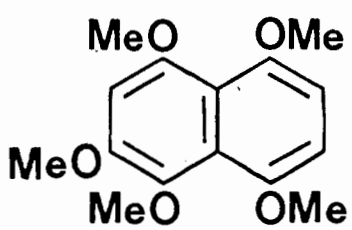
The benzisochromanquinones (for example (1)), recently isolated from *Ventilago maderspatana* and *V. calyculata* [1] were of synthetic interest to us as work in our laboratory[2] had lead, *via* a novel cyclisation, to the synthesis of quinone A (2) and its epimer quinone A' (3), which contain the related fused dihydro-1,3-dimethylnaphtho [2,3-*c*] pyran ring system. In addition, since the benzisochromanquinones have the same oxygenation pattern as that of the pentamethoxynaphthalene (4) which was also recently synthesised in our laboratory, and converted into bikaverin,[3] it was thought that by using this naphthalene (4) and our previously developed methodology for cyclisation, a number of these benzisochromanquinones could be assembled.



(1)



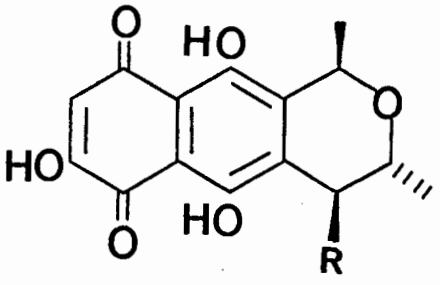
R = OH R' = H (2)
R = H R' = OH (3)



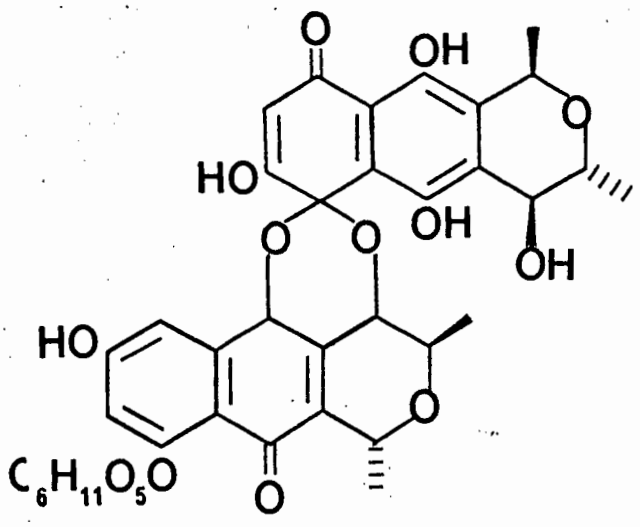
(4)

It appears that the benzisochromanquinones are similar in structure to one of the chemical degradation products (5) of the protodactynaphins (6).[4]

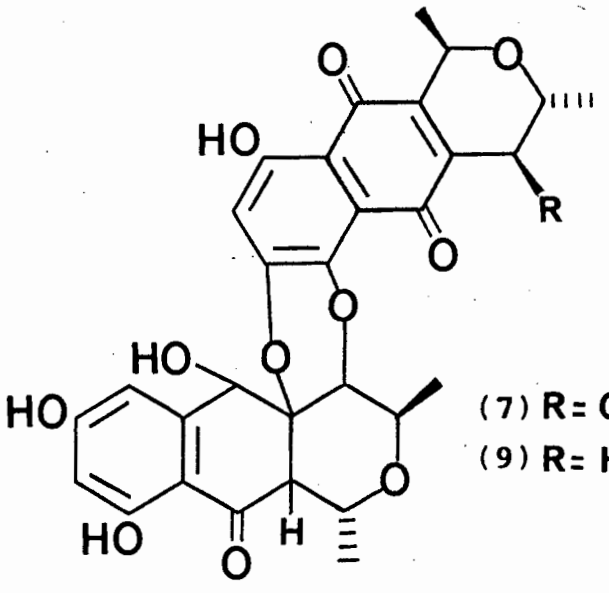
The protodactynaphins are glycosides which can be converted by acid treatment into isomeric interconvertible rhodo- and xanthodactynaphins- *jc-1* (7) and (8) respectively, as well as small amounts of rhodo- and xanthodactynaphins- *jc-2* (9) and (10) respectively.



R = H (11)
R = OH (5)

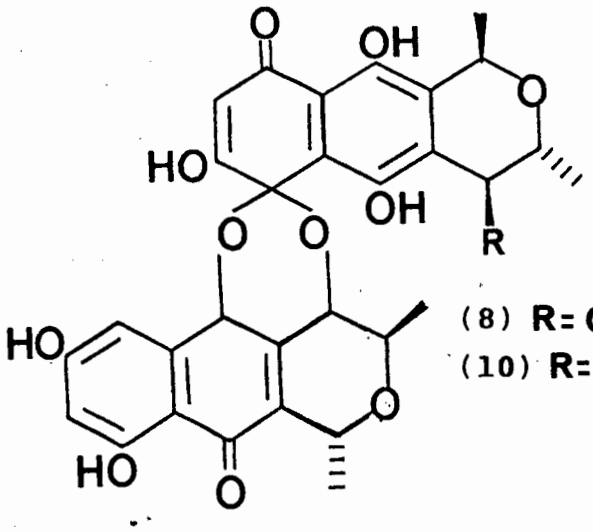


(6)

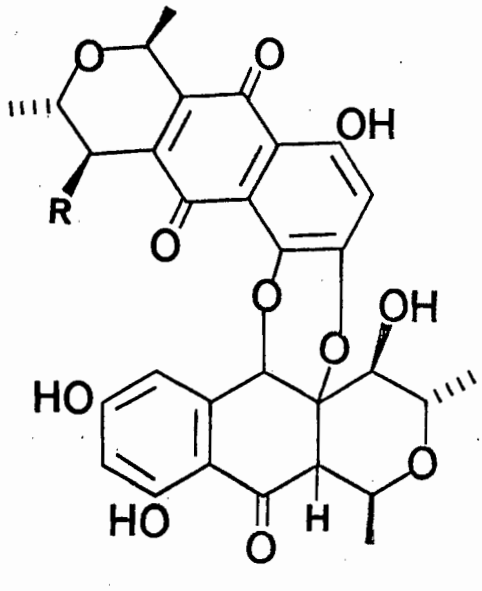


(7) R= OH
(9) R= H

or



(8) R= OH
(10) R= H



Alkaline treatment of the rhodo- and xanthodactynaphins-*jc-1* , (**7**) and (**8**), in an inert atmosphere affords two quinones: quinone A (**2**) and the quinone of interest (**5**) similar to the benzisochromanquinones, but possessing a hydroxyl in position 4.

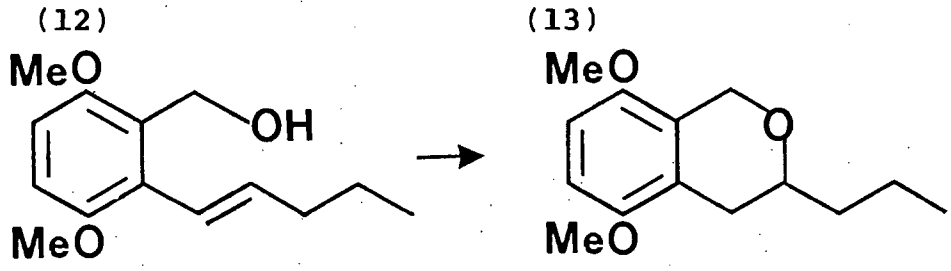
Alternatively, treatment of rhodo- and xanthodactynaphin-*jc-2* (**9**) and (**10**) with alkali in the absence of air affords quinone A (**2**) and quinone (**11**), the latter of which lacks the benzylic hydroxy group. The only difference between this quinone (**11**) and the general benzisochromanquinone structure isolated by Thomson[1] is the relative stereochemistry of the methyl groups of the pyran ring.

It was anticipated that it would be difficult to obtain a product with only the 1,3-*cis*-stereochemical configuration of the pyran ring (as in Thomson's natural products), since with our novel cyclisation[2] procedure the *trans*- stereochemistry was obtained exclusively, or by prolonging the reaction, some of the alternative *cis*-compound could also be formed together with the *trans*. However, other methods were also available for obtaining mixtures of *cis*- and *trans*-isomers, and it was therefore decided to try and synthesise the natural 1,3-*cis*-dimethyl products as well as their *trans*-isomers.

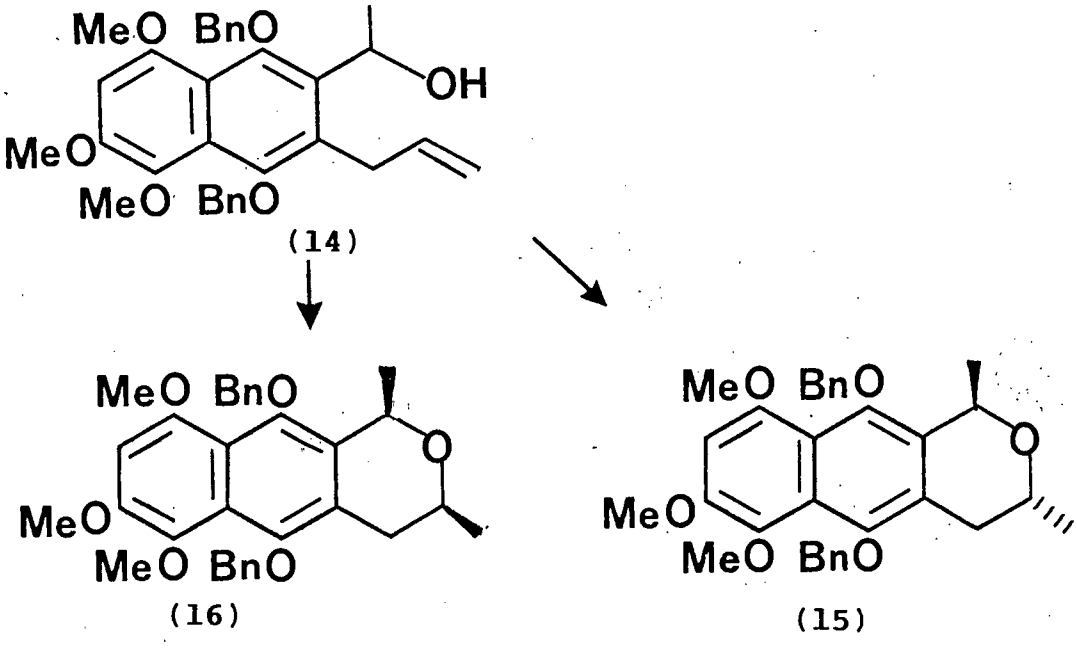
In addition, studies described earlier in this thesis had shown that the pentamethoxynaphthalene (**4**) could be regiospecifically acylated, and those results might now be used for the regiochemically correct assembly of some of the

unsymmetrically substituted ventiloquinones (e.g. (1)) described by Thomson.[1]

Previous work from our laboratory[5] has shown that reaction of aromatic benzyl alcohols, possessing an *ortho*-alkenyl function such as (12) readily undergo cyclisation by stirring with potassium *t*-butoxide in dimethylformamide at 60° under nitrogen to yield the pyran (13).

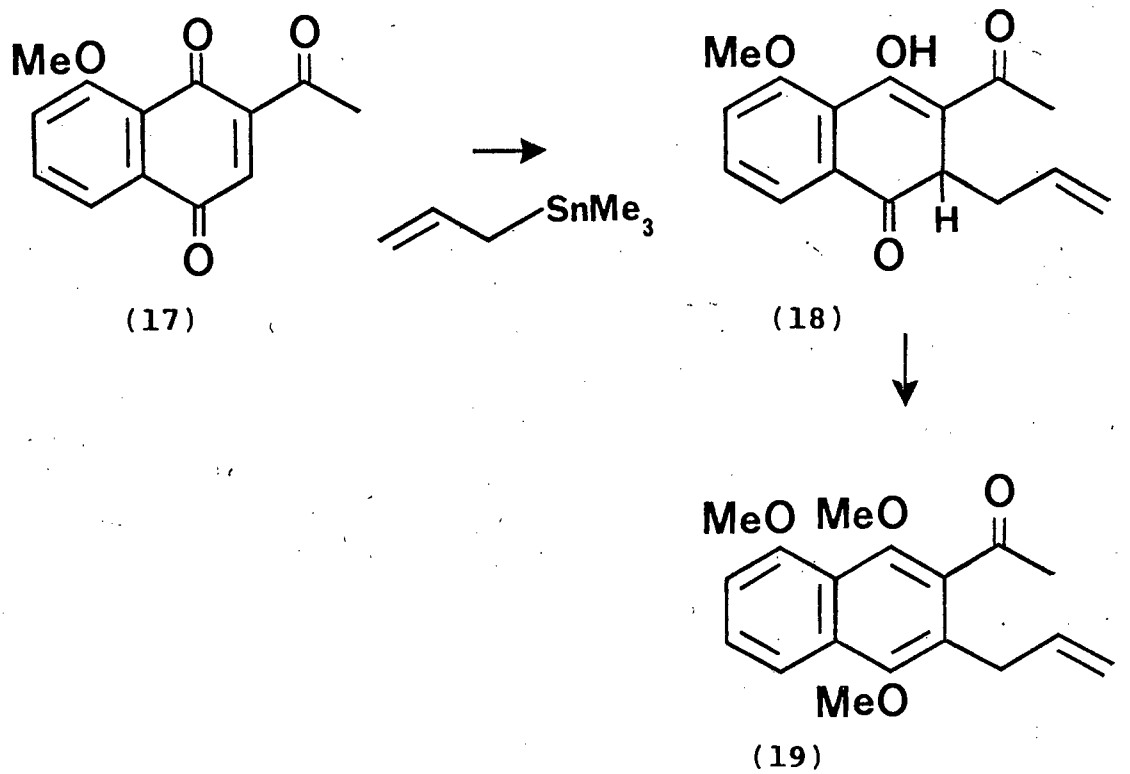


It was our aim to synthesise the alcohol (14), which it was hoped, would also readily undergo cyclisation to afford a mixture of the 1,3-*trans*- and 1,3-*cis*-naphtho[2,3-*c*]pyrans (15) and (16) respectively.



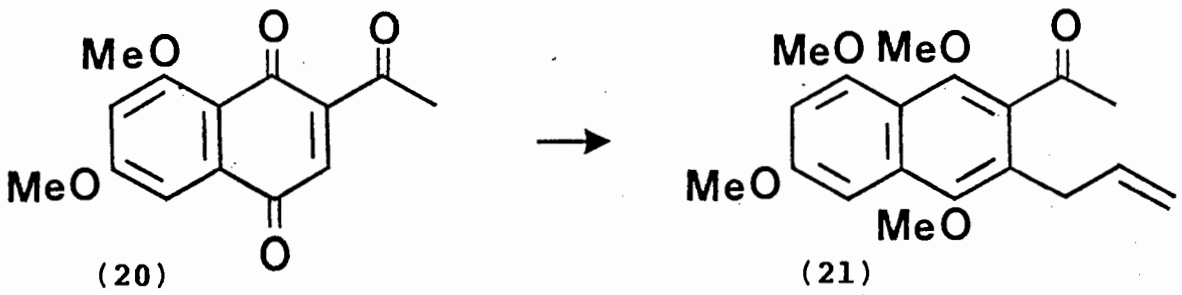
Selective removal of the benzyl groups of both of these precursors, followed by oxidation would then afford ventiloquinone E (1) and its C-3 epimer.

Maruyama[6] has synthesised the allyl derivative (19) of 2-acetyl-8-methoxy-1,4-naphthoquinone (17) by nucleophilic addition to (17) of allyltrimethylstannane in the presence of boron trifluoride etherate to afford product (18), which was methylated to give the corresponding hydroquinone dimethyl ether (19).



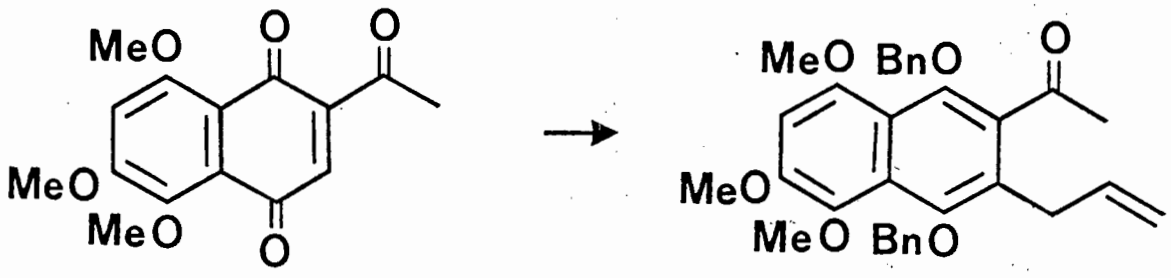
(17) (18) (19)

Giles *et al*.[2] have also recently shown that the ketone (21) could be synthesised from quinone (20) by employing allyltrimethylstannane.



(20) (21)

It was envisaged that reaction of the quinone (**22**) with allyltrimethylstannane, followed by benzylation, would yield the desired ketone (**23**), reduction of which with lithium aluminium hydride would afford the target alcohol (**14**).



(22) (23)

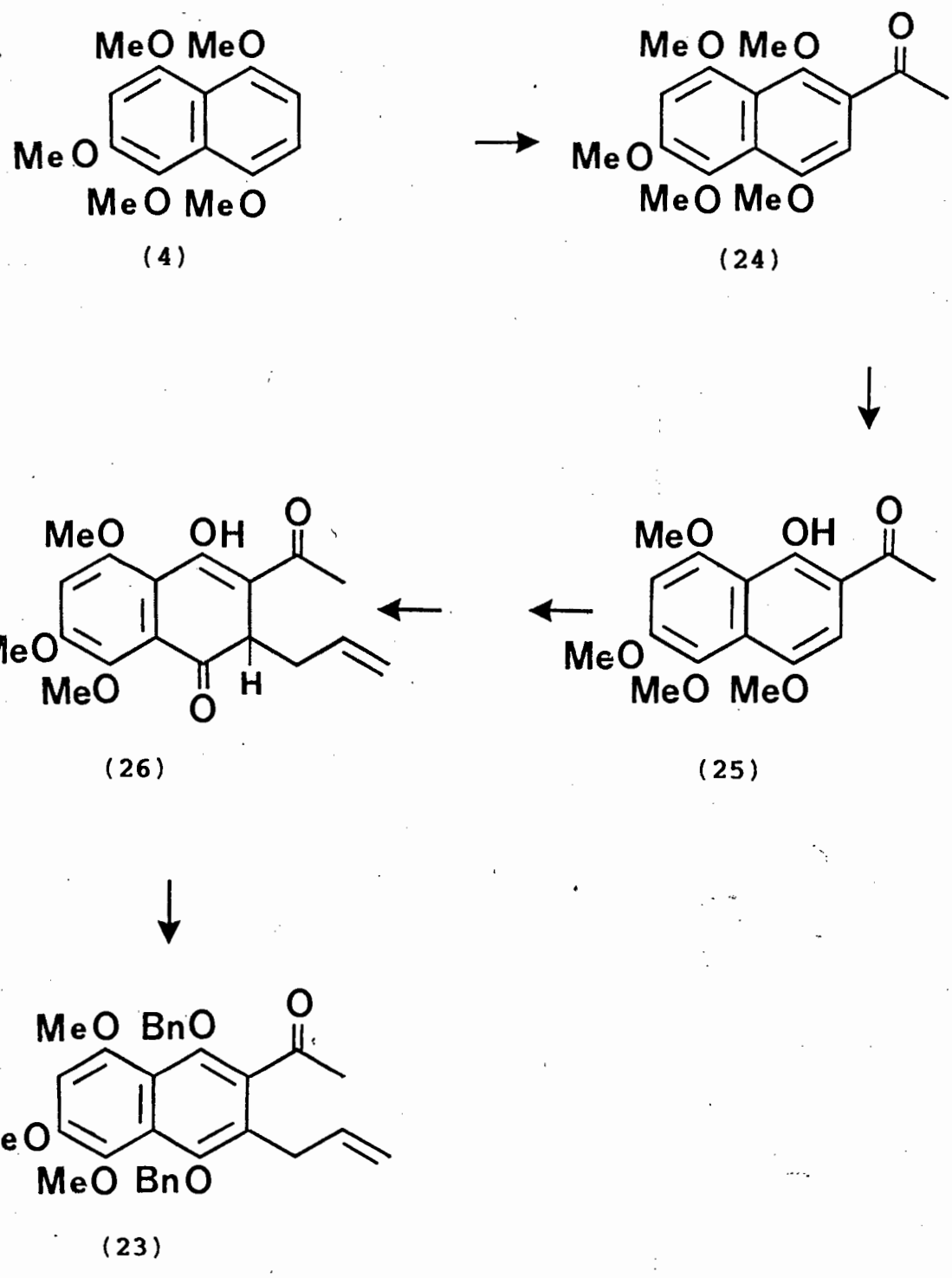
RESULTS AND DISCUSSION

As discussed in the previous chapter 2-acetyl-1,4,5,6,8-pentamethoxynaphthalene (**24**) was readily synthesised from pentamethoxynaphthalene (**4**) by acetylation. Since the present strategy for the synthesis of the benzisochromanquinones required the oxidation of the aromatic ring containing the acetyl group in compound (**24**), and, as previous experience[3] had shown that oxidation would preferentially take place in the more electron rich ring i.e. the aromatic ring containing three methoxy groups, an alternative route was devised to synthesise quinone (**22**).

Treatment of naphthalene (**24**) with 1.5 molar equivalents of boron trichloride resulted in the selective removal of the methyl group *ortho*-to the acetyl function, to afford the naphthol (**25**). The structure (**25**) was confirmed by its ^{1}H n.m.r. spectrum which showed a hydrogen bonded proton at δ14.08.

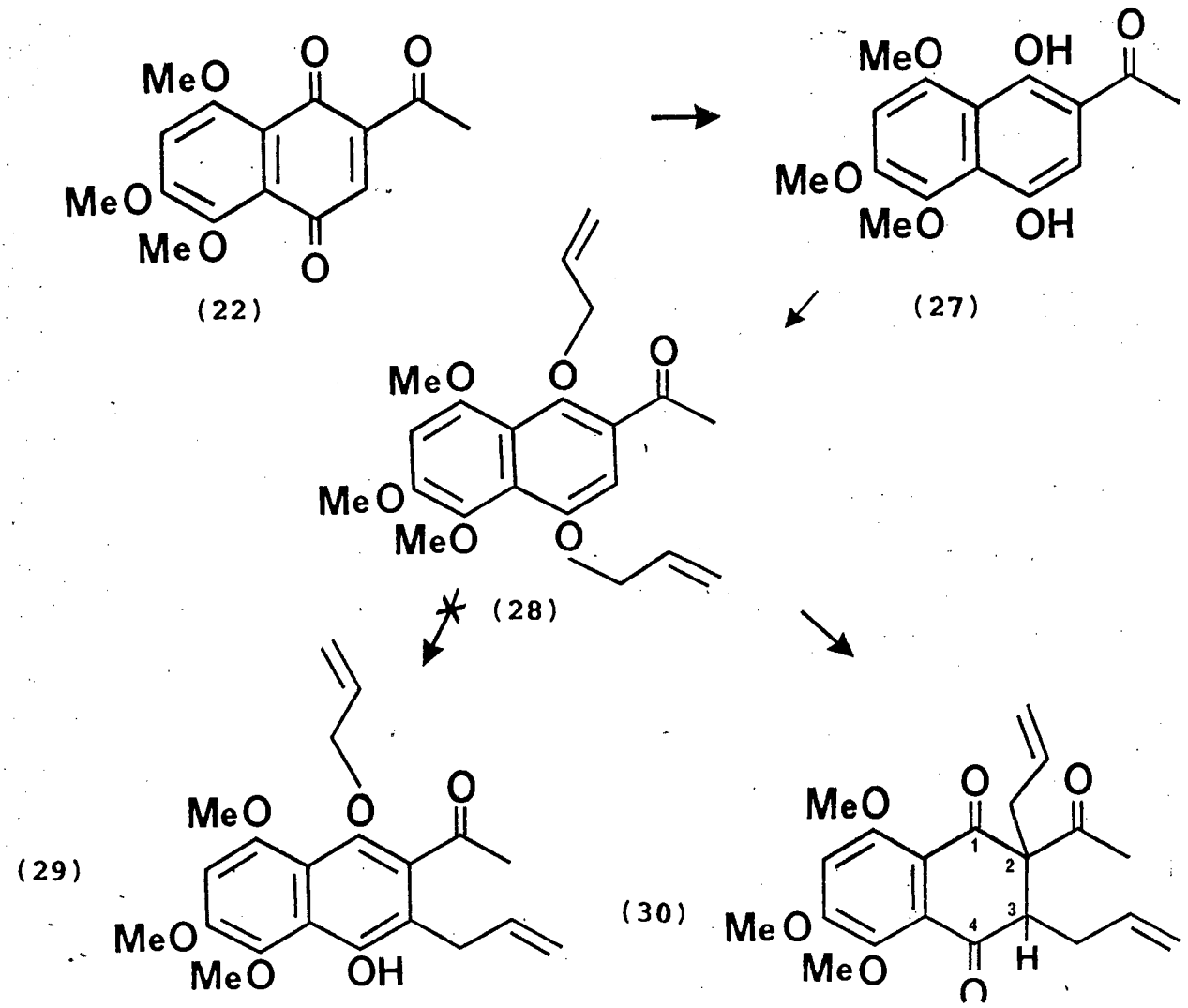
Treatment of the naphthol (**25**) with cerium(IV) ammonium nitrate furnished quinone (**22**) which was unstable, since evaporation of the solvent under reduced pressure led to its decomposition into dark red material. Fortunately, however, this did not seem to affect the subsequent reactions, provided these were carried out without delay.

Reaction of allyltrimethylstannane with the quinone (**22**) afforded the addition product (**26**), which, upon base catalysed benzylation, yielded the dibenzyl ether (**23**).



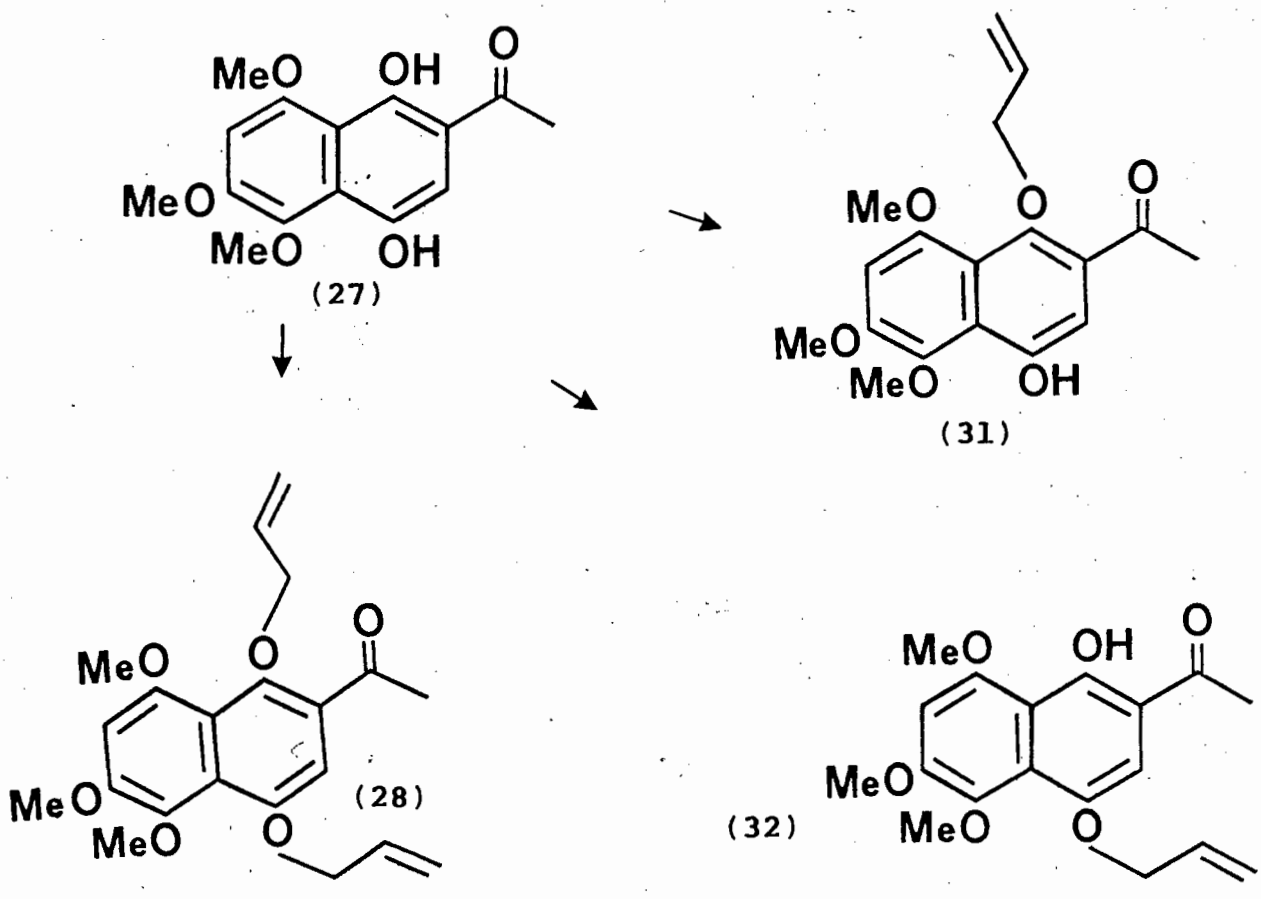
Evidence for its structure included a broad doublet at 3.61 with a coupling constant of 5Hz for the allyl methylene protons in the ^{1}H n.m.r. spectrum and a characteristic high field aromatic singlet at δ 6.75 for H-7. The assignment was corroborated by a molecular ion of *m/z* 512 in the mass spectrum and a carbonyl absorption in the infrared spectrum at 1696 cm^{-1}.

Alternatively, it might be possible to introduce the allyl substituent *via* a Claisen rearrangement. Initially, quinone (22) was converted into the hydroquinone (27) and by treating this with allyl bromide and potassium carbonate, the diallyl ether (28) was produced. However, Claisen rearrangement of this product (28) did not yield the desired compound (29), but instead it was found that both allyl moieties had migrated to yield the two possible stereoisomers of compound (30), which were separated chromatographically. Evidence that the allyl group at C-1 had migrated to C-2 was provided by the chemical shift change in the ^{1}H n.m.r. spectrum of the acetyl methyl protons which had moved from δ 2.73 in the starting material (28) to δ 2.05 and δ 2.10 for each of the geometrical isomers of (30).



It could also be seen from the ^{1}H n.m.r. spectrum that neither of the allyl groups were present in an ether linkage, as the characteristic methylene protons of the ether link in the region of δ4.5 were absent and now appeared around δ 3 typical of C-allylation.

Therefore monoallylation of the hydroquinone (**27**) was attempted by using one molar equivalent of allyl bromide.[15] This resulted in the formation of three products which were allylated in either position 1 (**31**), position 4 (**32**), or positions 1 and 4 (**28**). All three products had similar R_f values on subjection to silica gel chromatography using a variety of solvent systems, and therefore could not be separated easily.



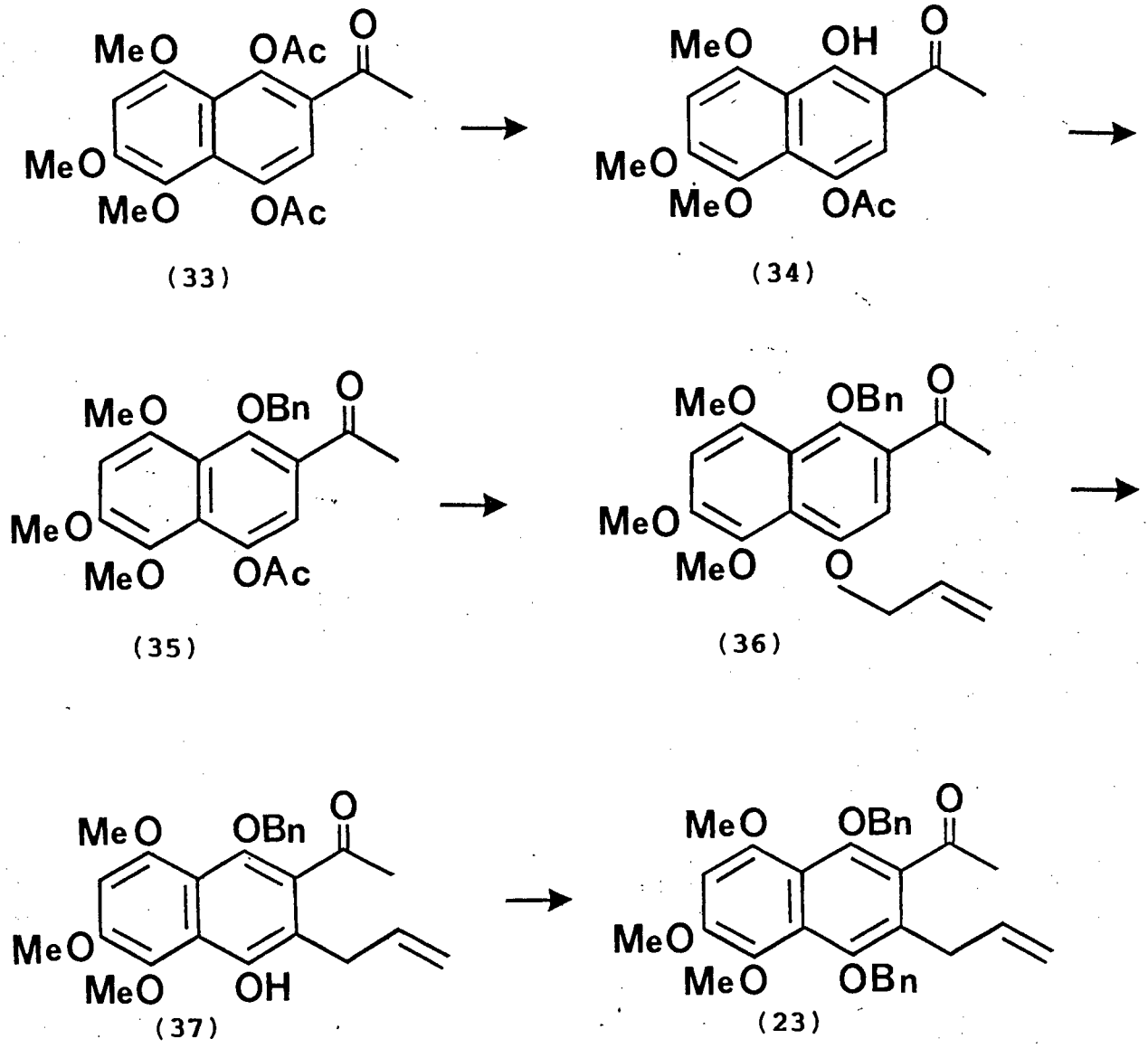
As this strategy was not successful, the hydroquinone (**27**) was acetylated to afford the diacetate (**33**) (69% yield from the naphthol (**25**)) which exhibited *inter alia*, the three proton acetyl singlets at δ 2.34, δ 2.39 and δ 2.57 respectively in the ^{1}H n.m.r. spectrum. In addition, two acetoxy stretching bands were observed in the infrared spectrum at 1763 and 1754 cm^{-1}, and the acetyl carbonyl at 1680 cm^{-1}. The ^{13}C n.m.r. spectrum also showed the three methyl carbons attached to the carbonyl carbon at δ 20.60, δ 21.38 and δ 30.74 respectively, as well as the two ester carbons at 169.38 and the carbonyl carbon at δ 195.95.

Treatment of the acetate (**33**) with 1.2 molar equivalents of potassium hydroxide in a dilute methanolic solution at room temperature furnished the naphthol (**34**), which was immediately reacted with benzyl bromide in the presence of potassium carbonate to afford the monoacetate (**35**).

Evidence that the ester group *ortho*- to the carbonyl at C-2 had been hydrolysed was provided after the Claisen rearrangement was performed on the allylated compound (**36**).

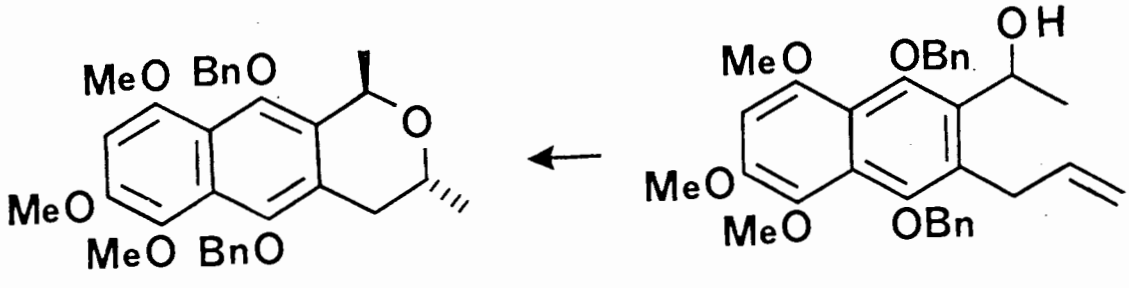
The acetate (**35**) was hydrolysed with base and the resulting naphthol immediately allylated with allyl bromide and potassium carbonate to afford the ether (**36**) in high yield. The ^{1}H n.m.r. spectrum indicated that O-allylation had taken place showing *inter alia*, a characteristic broad doublet at δ 4.72 for the methylene protons linked to the oxygen atom at C-4.

This allyl ether was pyrolysed under nitrogen for twenty four hours to furnished the naphthol (37). This was immediately converted into the dibenzyl ether (23) identical to the substance obtained earlier *via* the Michael addition of allyltrimethylstannane to (22).



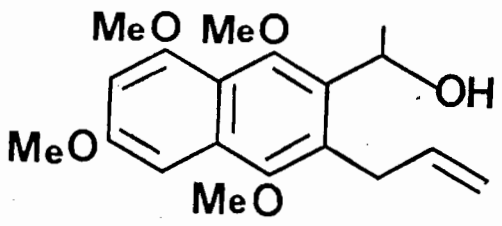
Although this method appears to be more involved than the former direct allylation procedure and its overall yield slightly lower (43% vs 51%), it obviated the use of the highly toxic and expensive chemical, trimethyltin chloride, from which the allyltrimethylstannane was produced. Additionally all the reaction steps involved in this synthetic scheme were quick and easy to perform. Most important of all, however, it allowed a distinction to be made between the protecting groups on oxygen at C-1 and C-4, which will subsequently be shown to be necessary in the synthesis of the pyrans (1) (ventiloquinone E) and the isomer (51) of ventiloquinone J (52).

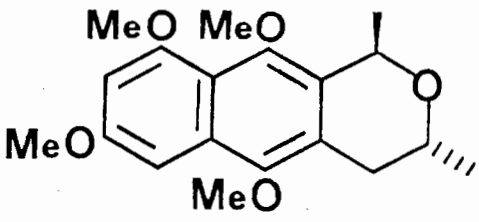
Ketone (23) was then reduced in high yield to the corresponding alcohol (14) with lithium aluminium hydride. Treatment of the alcohol (14) with potassium *t*-butoxide in dry dimethylformamide under nitrogen gave 1,3-*trans*-dimethylnaphthopyran (15) in high yield (92%) as the sole product.



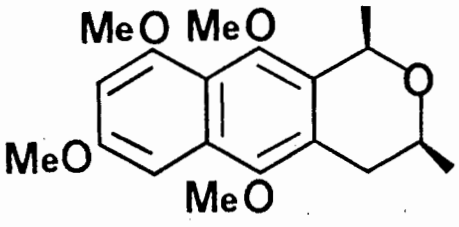
(15) (14)

Previous work from our laboratory[2] had resulted in the formation of both the 1,3-*trans*-(38) and 1,3-*cis*-naphtho[2,3-c]pyrans (39) as shown in the following scheme.

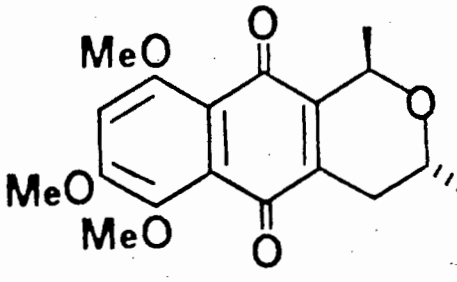




(38)



(39)



(40)

Comparison of the ^{1}H n.m.r. spectra showed the stereochemistry of our product (15) to be 1,3-*trans*. A striking difference between the 1,3-*trans*- (38) and the 1,3-*cis*-compound (39) was the value of the chemical shifts of the single protons at C-1 and C-3 of the pyran ring. For the *cis*-isomer (39), the proton at C-1 appeared at δ5.21 (quartet J6.5Hz), and the proton at C-3 at δ3.5-3.9 (multiplet), while the *trans*-isomer (38) displayed the proton at C-1 at δ5.31 (quartet J7Hz) and the proton at C-3 between δ 3.9-4.3 (multiplet). Examination of the ^{1}H n.m.r. spectrum of the naphthopyran (15) showed the proton at C-1 to be at δ 5.34 (quartet J6.6Hz) and the proton at C-3 between δ4.0-4.2 (multiplet), which suggested that our product (15) had the 1,3-*trans*-dimethylpyran configuration. This means that the methyl group at C-1 would occupy a *pseudo*-axial position while the hydrogen at C-1 would occupy a *pseudo*-equatorial position. Additionally, the methyl at C-3 would be equatorial and the hydrogen at C-3

would be axial. It seemed reasonable that the pyran ring would adopt this configuration as there was a large benzyl group *peri*- to the methyl at C-1. This based-induced cyclisation provided a further example of the exclusive formation by this method of the 1,3-*trans*-dimethylpyran ring which is found extensively in nature.[9-14] Most other synthetic methods for generating this pyran ring yield a mixture of the *cis*- and *trans*- products.[6,8,16-22] Unfortunately, however, Thomson's naturally occurring benzisochromanquinones all possess 1,3-*cis*-dimethyl stereochemistry in the pyran ring. Our procedure, however, furnished an attractive route for the preparation of the epimer of benzisochromanquinone E, since on selective removal of the benzyl moieties at C-5 and C-10 of the precursor (**15**) followed by air oxidation the epimer (**40**) was afforded. This was useful for providing spectroscopic comparisons with those data obtained from the corresponding *cis*-dimethyl compounds. Equally important was the fact that precursor (**15**) or its analogues might well be used to synthesise the aphin-derived quinones (**5**) and (**11**).

The ^{1}H n.m.r. spectrum of compound (**40**) (Figure 7) showed considerable fine structure for the two non-equivalent protons at H-4 and the two methine protons (H-1 and H-3), since geminal, vicinal and long range coupling was apparent. The *pseudo*-axial proton at H-4 appeared at δ 2.19 with a geminal coupling constant of 18.9Hz, vicinal coupling constant of 10.1Hz and long-range coupling constant of 1.85Hz (coupling with H-1) while the *pseudo*- equatorial proton H-4 appeared

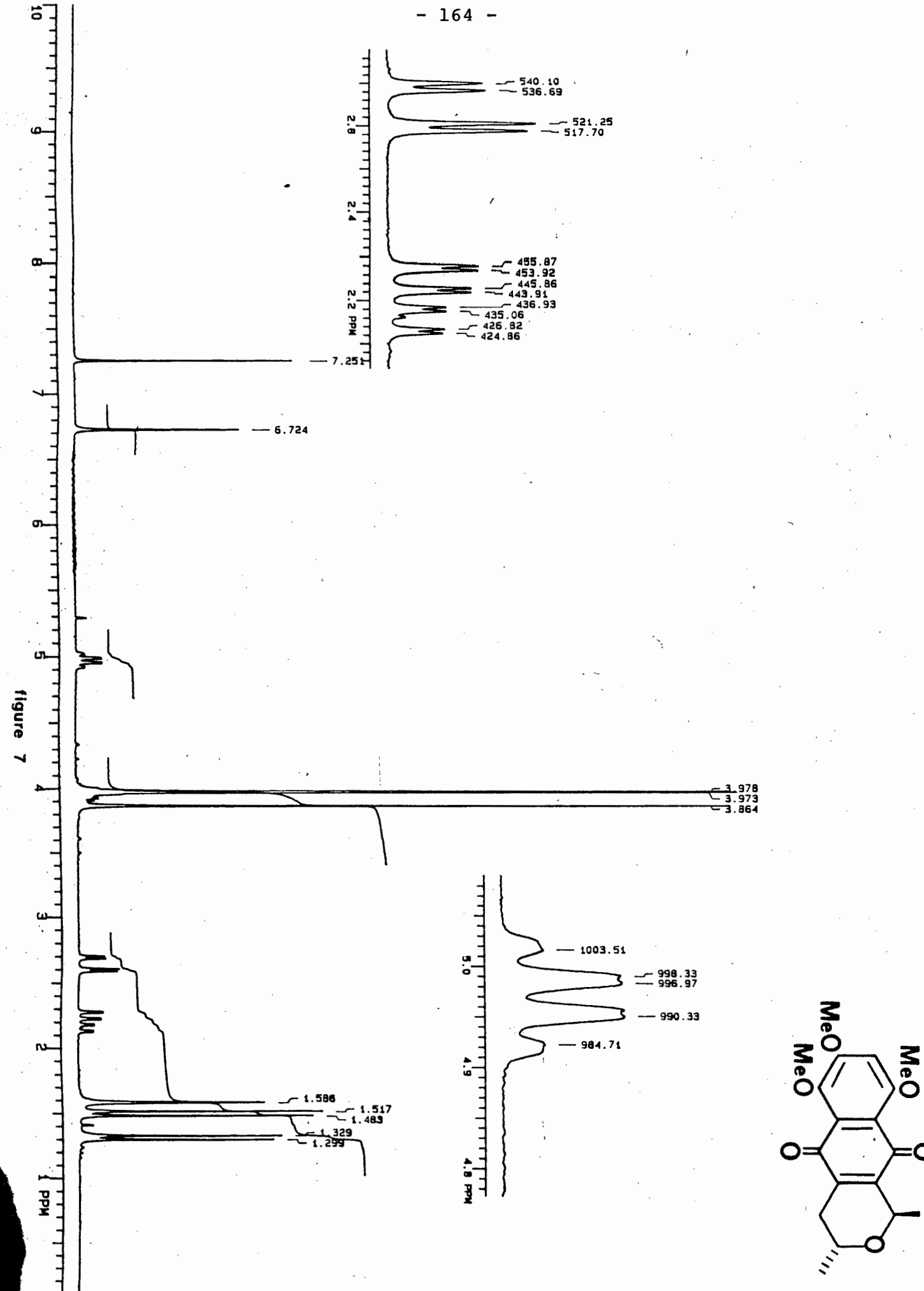

10
9
8
7
6
5
4
3
2
1 PPM
7.251
6.724
3.978
3.973
3.864
1.586
1.517
1.483
1.329
1.299
2.8
2.4
2.2 PPM
540.10
536.69
521.25
517.70
455.87
453.92
445.86
443.91
436.93
435.06
426.82
424.86
5.0
4.9
4.8 PPM
1003.51
998.33
996.97
990.33
984.71
MeO
MeO
MeO
O
O

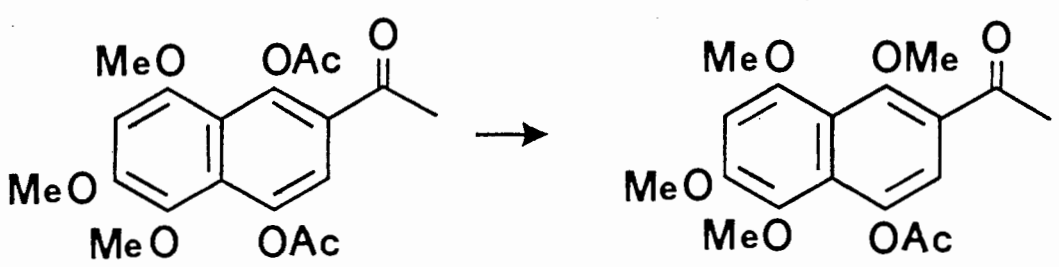
figure 7

as a doublet of doublets at δ 2.64 with a similar geminal coupling constant but had a vicinal coupling constant to H-3 of 3.5Hz and no long range coupling. This accounts for the observed multiplicity of the signal as a doublet of doublets in comparison to the signal for the *pseudo*-equatorial H-4 of the 1,3-*cis*-dimethyl isomer which appeared as a doublet of doublet of doublets. The methine proton at H-3 appeared as a multiplet at δ 3.9-4.0 obscured by the presence of the three methoxy groups, which seemed to be consistent with a 1,3-*trans*-dimethylpyran structure. Additionally the methine proton at H-1 appeared as a doublet of quartets at δ 4.96 (*J*6.8 and 1.85Hz), which further confirmed the assignment. The small coupling again being due to long range coupling to *pseudo*-axial H-4.

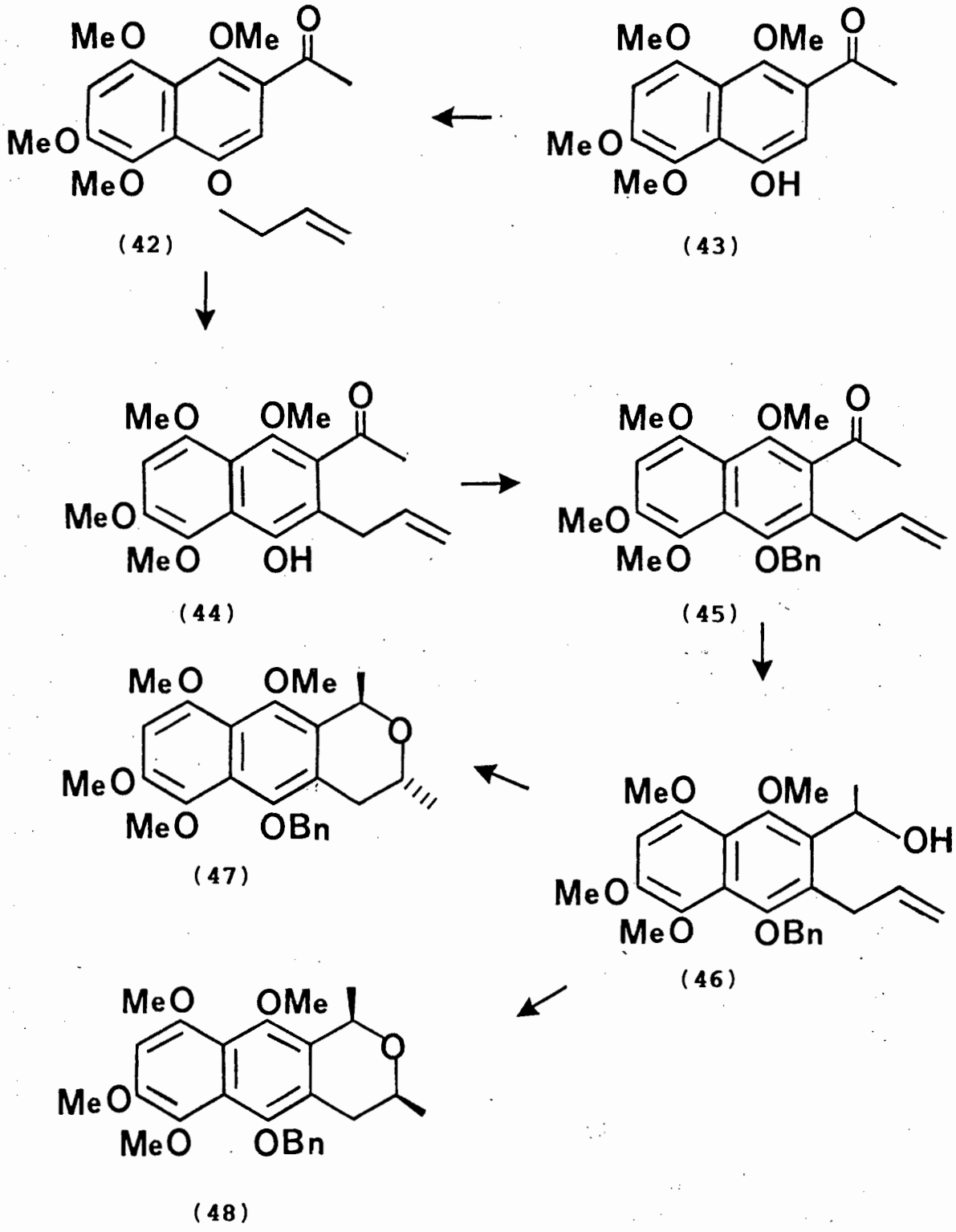
Attempts to partially convert the *trans*-isomer (**40**) with phosphoric acid[7] into the *cis*-isomer (**1**) were not successful. Additionally, utilising Yoshii's[8] method developed for ring closures using mercuric(11) acetate and sodium borohydride, which gave a 50:50 mixture of *trans*- to *cis*-pyrans in their case, the *trans*-isomer (**15**) was the only product obtained using our alcohol (**14**). This difference in behaviour on cyclisation of (**14**) to (**15**) was ascribed to the increased bulk of the benzyl substituent over that of the methyl, which in our case required that the C-1 methyl group adopt the less sterically demanding *pseudo*-axial configuration. It seemed therefore logical to try and replace the benzyl group at C-10 in compound (**14**) with a smaller moiety. It was however still imperative that the aromatic ring fused

to the pyran ring could subsequently be selectively oxidised to the quinone level. This meant that a selectively removable group would have to be introduced onto the oxygen atoms at C-5 and C-10. The solution seemed to be embodied in the synthesis of alcohol (**46**) containing a methoxy group at C-8 and a benzyloxy group at C-5.

This was accomplished by the following series of reactions. Selective hydrolysis of the acetate ester *ortho*-to the acetyl group of compound (**33**), followed by methylation gave the compound (**41**). Hydrolysis of the second acetate group gave the naphthol (**42**) which was immediately O-allylated to furnish ether (**43**). Claisen rearrangement of allyl ether (**43**) followed by benzylation of the resulting naphthol (**44**) afforded the ketone (**45**) in a total yield of 66% calculated from the diacetate ester (**33**). Reduction of the ketone gave the alcohol (**46**) in 93% yield which showed *inter alia*, the benzylic methyl as a doublet at δ 1.62 (J 6.6Hz) and the single benzylic proton at δ 5.16 as a quartet (J 6.6Hz) in the ^{1}H n.m.r. spectrum. A molecular ion of *m/z* 438 was seen in the mass spectrum.

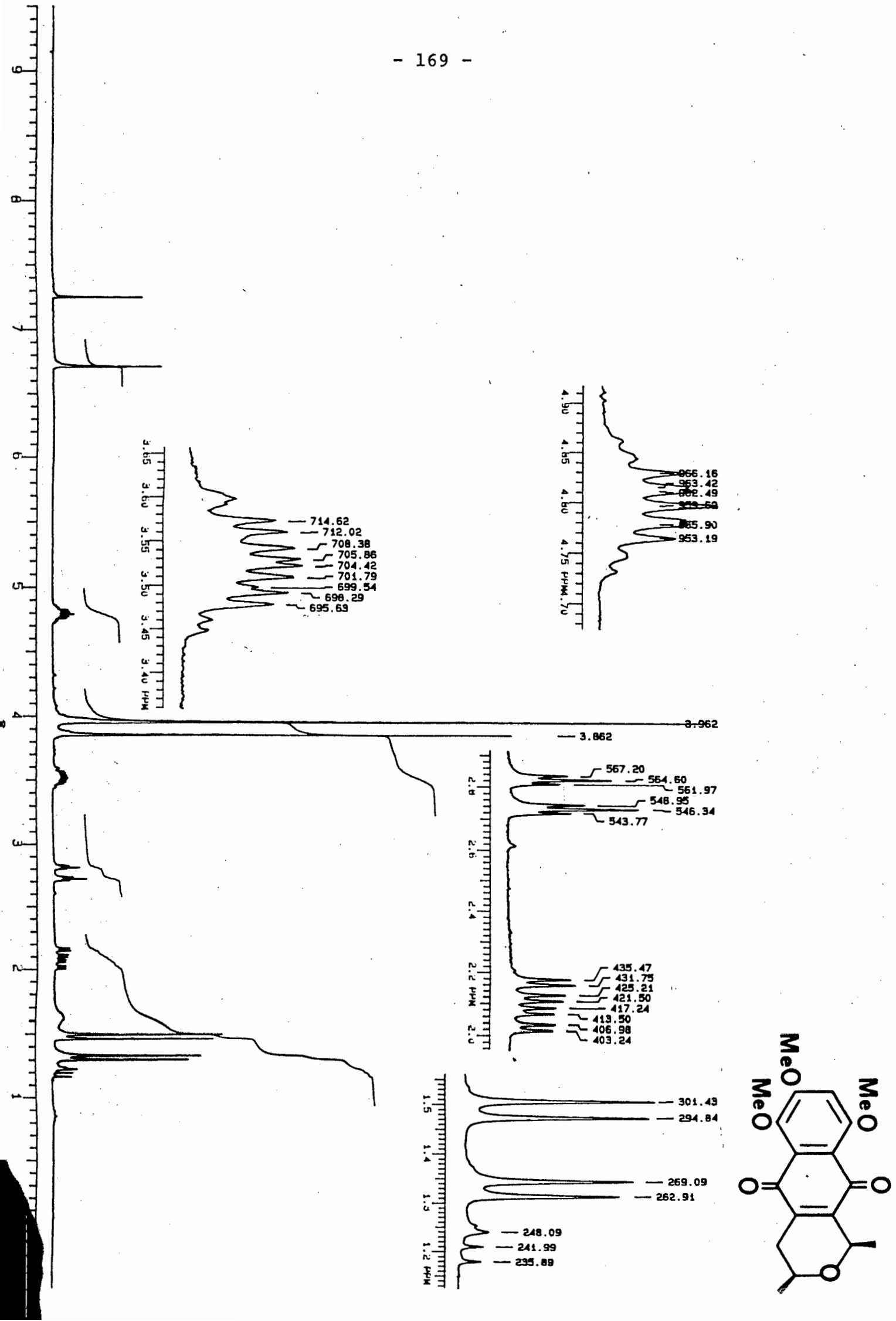


(33) (41)


MeO
OMe
O
MeO
MeO
O
(42)
MeO
OMe
O
MeO
MeO
OH
(43)
MeO
OMe
O
MeO
MeO
OH
(44)
MeO
OMe
O
MeO
MeO
OBn
(45)
MeO
OMe
OH
MeO
MeO
OBn
(46)
MeO
OMe
O
MeO
MeO
OBn
(47)
MeO
OMe
O
MeO
MeO
OBn
(48)

Ring closure of the alcohol (**46**) employing potassium *t*-butoxide still afforded entirely the 1,3-*trans*-dimethylpyran (**47**). However, on using the method developed for ring closure by Yoshii,[8] consisting of intramolecular acetoxymercuration and subsequent reduction using sodium borohydride, a mixture (1:1) of the two isomeric, naphthopyrans (**47**) and (**48**) respectively (total yield 56%) was furnished. Separation of the two isomers was achieved by preparative thin layer chromatography. The ^{1}H n.m.r. spectra of both the *trans*- product (**47**) and the *cis*- product (**48**) showed the expected differences. Most noticeable was the difference in chemical shift of the H-3 proton of the pyran ring, appearing as a doublet of doublet of quartets at δ 3.60 for the *cis*- product (**48**)and in the region between δ 3.9-4.15 for the *trans*- product (**47**) (slightly obscured by the methoxy protons).

The benzyl group of the *cis*- product (**48**) was selectively removed to afford the naphthol (**49**) oxidation of which with cerium(IV) ammonium nitrate gave the desired naturally occurring quinone, ventiloquinone E (**1**). Comparison of spectroscopic (^{1}H n.m.r. spectrum Figure 8) and physical properties of a sample of natural origin kindly provided by Professor Thomson with the synthetic sample proved them to be identical. This synthesis of ventiloquinone E (**1**) therefore confirmed the structural assignment made by Thomson and co-workers, both in respect of the pyran ring stereochemistry, where the natural material could be compared with both the *cis*- compound (**1**) and also the *trans*- isomer (**40**), and also in respect of the aromatic methoxy group being attached


714.62
712.02
708.38
705.86
704.42
701.79
699.54
698.29
695.69
966.16
963.42
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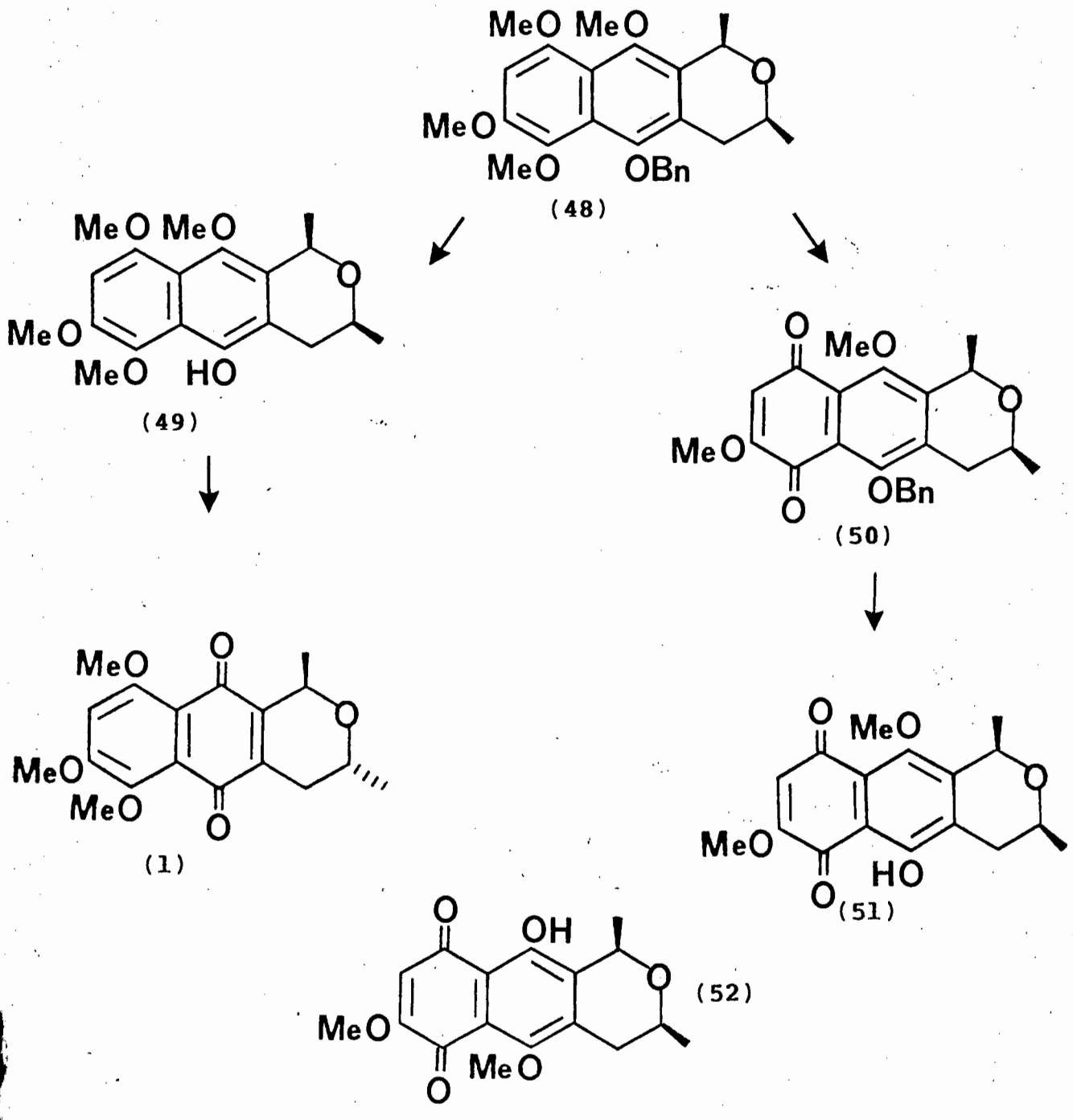
955.90
953.19
3.962
3.862
567.20
564.60
561.97
548.95
546.34
543.77
435.47
431.75
425.21
421.50
417.24
413.50
406.98
403.24
301.43
294.84
269.09
262.91
248.09
241.99
235.89
MeO
MeO
MeO
O
O

to C-7, rather than C-8, as originally proposed by Thomson on biogenetic grounds.

A survey was then made of the other ventiloquinones isolated by Thomson and co-workers with a view to confirming the structure of some of these by synthesis with the little material that remained. Of these, ventiloquinone J seemed a reasonable objective in view of the available precursors. Ventiloquinone J (either (51) or (52)) was chosen as a target.



Oxidation of the *cis*- product (**48**) with silver(II) oxide and nitric acid gave the quinone (**50**). This quinone also showed long range coupling in the ^{1}H n.m.r. spectrum between H-1 and both H-4 protons. Long range coupling is well known to occur in the pyran ring of a naphtho 2,3-*c* pyran ring system if the pyran is directly fused to a quinone ring (for example ventiloquinone E (**1**). In the case of compound (**50**) the *pseudo*-axial proton at C-4 appeared as a doublet of doublet of doublets at δ 2.32 (J17.0, 10.6, and 1.8Hz), with the long range coupling being 1.8Hz. The *pseudo*-equatorial proton at C-4 (δ2.87) appeared as a doublet of doublet of doublets (with J17.0, 2.0, and 1.5Hz) indicating that the long range coupling between the *pseudo*-equatorial proton at C-4 and the *pseudo*-axial proton at C-1 is 1.5Hz and the vicinal coupling between the same proton at C-4 and the axial proton at C-3 is 2.0Hz. As the latter two coupling constants were very similar, at first glance the signal appears to be a doublet of triplets. The proton at C-1 also showed long range coupling with both of the protons at C-4 as the signal appeared as a doublet of doublet of quartets. (J6.4, 1.8 and 1.5Hz).

Selective removal of the benzyl group of compound (**50**) afforded the quinone (**51**). Comparison of spectroscopic properties of this quinone with ventiloquinone J (**52**)[1] showed unequivocally that they were different. Whereas the ^{1}H n.m.r. data reported by Thomson[1] for natural ventiloquinone E were precisely the same as those of the substance obtained in our synthesis, there were notable differences in chemical shifts

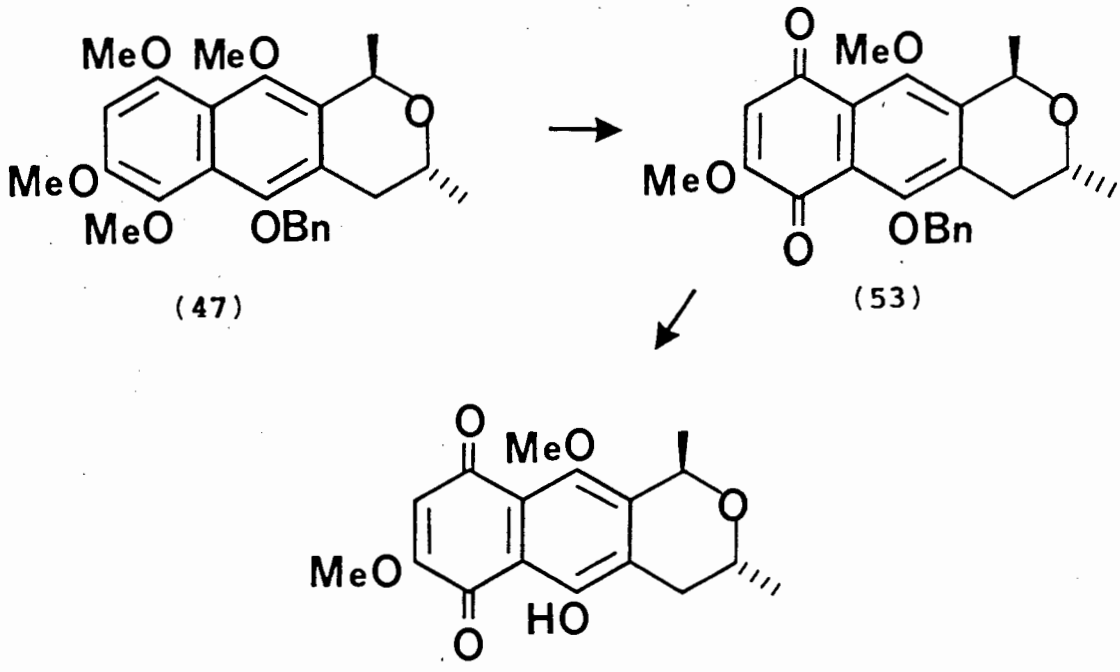
for many of the n.m.r. spectrum signals quoted by Thomson[1] of natural ventiloquinone J (**52**) and our synthetic compound (**51**) (Figure 9). Of significant difference was the chemical shift of the two methoxy three-proton singlets appearing at δ3.76 and δ3.85 in our product (**51**) and at δ3.84 and δ3.90 for ventiloquinone J (**52**). This provided negative evidence that ventiloquinone J (**52**) possessed a methyl group on the oxygen at C-5, and not one in position 10, which up until now has not been certain.[1]

As a sample of the naturally occurring ventiloquinone J (**52**) was not available it was not possible to compare physical and chromatographic properties, nor was it possible to compare the fingerprint regions of both infrared spectra.

Oxidation of the *trans*-product (**47**) with silver(II) oxide and nitric acid afforded the quinone (**53**). The ^{1}H n.m.r. spectrum of compound (**53**) displayed, *inter alia*, a doublet of doublet of doublets at δ2.30 (*J* 17.8, 10.8 and 0.8Hz) for the *pseudo*-axial proton at C-4, while the *pseudo*-equatorial proton appeared at δ2.89 as a doublet of doublets (*J* 17.8 and 3.4Hz).

Selective removal of the benzyl group afforded the quinone (**54**) which displayed a hydrogen bonded proton in the ^{1}H n.m.r. spectrum at δ12.83. Also observed was long range coupling between the *pseudo*-equatorial proton at C-1 and the *pseudo*-axial proton at C-4 (*J* 0.9Hz). Further evidence for its structure was provided by the mass spectrum indicating a molecular ion at *m/z* 318.

315.94
309.35
273.94
267.84
725.58
723.19
719.34
717.09
715.13
712.69
709.03
706.64
596.46
594.56
592.77
569.13
567.17
565.27
491.49
489.58
480.93
479.03
473.96
471.95
463.65
461.45
1.86
2.01
2.7
725.58
723.19
719.34
717.09
715.13
712.69
709.03
706.64
1005.61
1004.40
1002.07
997.32
995.97
993.47
991.53
989.75
986.93
985.17
3.845
3.758
MeO
O
O
MeO
HO
PPM



(47) (53) (54)

Thus the structure of ventiloquinone J had been confirmed to be that of compound (52) by synthesis of a structural isomer (51) of (52) possessing an *O*-methyl in position 10 instead of position 5, as well as its epimer (54).

Since no more material was available, work for the purposes of this thesis was terminated at this stage. However, it is clear that further work can be undertaken in the area of ventiloquinone synthesis, as well as the synthesis of the aphin derived *trans*-dimethylnaphthopyrans (5) and (11).

EXPERIMENTAL

Procedures, equipment and abbreviations are identical to those described in chapter **1**, except all ^{1}H n.m.r. were recorded on a Varian VXR-200 at 200MHz, while all ^{13}C n.m.r. were recorded on the same instrument at 50.1MHz.

2-Acetyl-4,5,6,8-tetramethoxy-1-naphthol (**25**).-

The naphthalene (**24**) (1.099 g, 3.43 mmol) in dry methylene dichloride (50 ml) was treated at -78°C with boron trichloride (0.403 g, 3.43 mmol) in the same solvent (8 ml). After 30 min the solution was allowed to warm to room temperature and then hydrolysed with an excess of water. The organic material was extracted into methylene dichloride (200 ml). The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) to afford the **naphthol** (**25**) (0.920 g, 88%) as off-yellow needles, m.p. 157-158°C (2-propanol) (Found: C, 62.55; H, 5.95. $C_{16}H_{18}O_6$ requires C, 62.75; H, 5.9%); $\nu_{max.}$ 1688(2C=0) and 1616(C=C) cm^{-1}; δ 2.62 (3H, s, $COCH_3$), 3.77, 3.88, 3.97, and 3.99 (each 3H, s, OCH_3), 6.67 (1H, s, 7-H), 6.96 (1H, s, 3-H), and 14.08 (1H, s, OH, D_2O exchangeable); *m/z* 306 (M^+, 100%), 291 (40), 277 (9), 262 (12), and 43 (25).

2-Acetyl-1,4-dibenzyloxy-5,6,8-trimethoxy-3-prop-2'-enylnaphthalene (**23**).-

The naphthol (**25**) (500 mg 1.63 mmol) in acetonitrile (120 ml) and water (50 ml) was treated with cerium(IV) ammonium nitrate (2.33 g, 4.24 mmol) in water (20 ml) during 8 min,

and stirring was continued for a further 15 min. The mixture was thrown into water, extracted with methylene dichloride, and the solution evaporated under reduced pressure to afford a residue. To this was added dry methylene dichloride (100 ml) and then cooled to -78°C and the flask flushed with nitrogen. Boron trifluoride etherate (0.22 ml, 1.63 mmol) was added, whereupon the solution turned dark brown. Allyltrimethylstannane (880 mg, 2.45 mmol) was added, and the reaction mixture stirred for 1 h at -78°C and then warmed to room temperature. Water (100 ml) was then rapidly added and the organic product extracted with methylene dichloride (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 (2.25 g, 16.3 mmol) and benzyl bromide (2.80 g, 1.94 ml, 16.3 mmol). The mixture was boiled with vigorous stirring for 12 h. The mixture was cooled, filtered, the solvent evaporated and the residue chromatographed (eluant 10%-20% ethylacetate-light petroleum) to yield the **product** (**23**) (427 mg, 51%), identical in all spectroscopic aspects with the material synthesised later.

1,4-Diacetoxy-2-acetyl-5,6,8-trimethoxynaphthalene (**33**).-

A solution of cerium(IV) ammonium nitrate (3.84 g) in water (70 ml) was added dropwise with stirring over a period of 15 min to a solution of the naphthol (**25**) (0.82 g, 2.68 mmol) in acetonitrile (100 ml) and water (30 ml). The solution was stirred for a further 15 min and then poured into water (200 ml). This was extracted twice with methylene

dichloride (200 ml x 2). The organic layer was separated and then shaken with an aqueous solution (200 ml) containing sodium dithionite (5 g, an excess) in a separating funnel. The residue obtained upon work-up of the fluorescent green organic phase was immediately dissolved in dry pyridine (50 ml), and acetic anhydride (5 ml) was added. The mixture was heated at 80°C for 2 h. The cooled reaction mixture was added to an excess of water. The organic material was then extracted with methylene dichloride keeping the pyridine in the aqueous layer by carefully acidifying with dilute hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **acetate** (**33**) (695 mg, 69%) as pale yellow rectangles, m.p. 170-171°C (light petroleum/methylene dichloride) (Found: C, 60.55; H, 5.35. $C_{19}H_{20}O_8$ requires C, 60.65; H, 5.3%); $\nu_{max.}$ 1763 (OAc), 1754 (OAc), and 1680 (2C=O) cm^{-1}; ^1H n.m.r. δ 2.34 and 2.39 (each 3H, s, $OCOCH_3$), 2.57 (3H, s, $CCOCH_3$), 3.77, 3.90, and 3.95 (each 3H, s, OCH_3), 6.69 (1H, s, 7-H), and 7.43 (1H, s, 3-H); ^{13}C n.m.r. δ20.60, 21.38, and 30.74 (3 x CH_3CO), 56.09, 56.48, and 61.55 (3 x OCH_3), 97.32 (C-7), 115.37 (C-8a)[b], 119.85 (C-3), 124.73 (C-2)[a], 126.29 (C-4a)[b], 135.45 (C-1)[a], 142.47 (C-4)[a], 144.81 (C-6), 152.03 (C-5), 154.37 (C-8), 169.38 (2 x CO), and 195.95 (CO) (assignments with the same superscript may be interchanged); *m/z* 376 (M^+, 23%), 334 (35), 292 (80), 277 (100), and 43 (43)

4-Acetoxy-2-acetyl-1-benzyloxy-5,6,8-trimethoxynaphthalene (**35**).- The acetate (**33**) (181 mg, 0.48 mmol) was dissolved by warming in methanol (30 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (to give a 1% w/v solution, 0.58 mmol) and the solution was stirred for 10 min. To the reaction mixture was added water (50 ml) and methylene dichloride (100 ml) and the whole was then carefully acidified with dilute hydrochloric acid. The residue obtained upon work-up was flash chromatographed (50% ethyl acetate-light petroleum) to yield the naphthol (**34**) which was immediately dissolved in dry acetone (50 ml). Dry potassium carbonate (330 mg, 2.39 mmol) and benzyl bromide (410 mg, 2.40 mmol) were added, and the mixture was boiled with stirring for 1 h. The cooled reaction mixture was filtered and the solution was evaporated. The residue was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the **product** (**35**) (173 mg, 85%) as white grains, m.p. 147-148°C (2-propanol) (Found: C, 68.05; H, 5.8. $C_{24}H_{24}O_7$ requires C, 67.9; H, 5.65%); $\nu_{max.}$ 1754 (OAc) and 1662 (2C=O) cm^{-1}; ^1H n.m.r. δ 2.35 (3H, s, $OCOCH_3$), 2.62 (3H, s, $CCOCH_3$), 3.81, 3.84, and 3.99 (each 3H, s, OCH_3), 4.93 (2H, s, CH_2-Ph), 6.73 (1H, s, 7-H), 7.35 (1H, s, 3-H), and 7.34-7.47 (5H, m, **Ph**-CH_2); ^{13}C n.m.r. δ 20.61 and 31.41 (2 x CH_3C), 56.47, 56.69, and 61.86 (3 x OCH_3), 78.81 (CH_2Ph), 97.12 (C-7), 116.65 (C-8a)[b], 120.21 (C-3), 124.84 (C-4a)[b], 126.5-128.45 (C of Ph), 135.92 (C-2)[a], 137.03 (C-1)[a], 141.25 (C-4)[a], 152.08 (C-6), 154.93 (C-5), 155.01 (C-8), 169.79, and 199.39 (CO) (assignments with the same superscript may be interchanged); *m/z* 424 (M^+,

28%), 382 (17), 340 (23), 325 (12), 291 (100), 234 (18), 233 (12), 91 (69), and 43 (61)

2-Acetyl-1-benzyloxy-5,6,8-trimethoxy-4-prop-2'-enyloxynaphthalene (**36**).- Compound (**35**) (131 mg, 0.31 mmol) was dissolved by warming in methanol (30 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (to give a 5% w/v solution, 1.55 mmol) and the solution stirred for 10 min. To the reaction mixture was added water (50 ml) and methylene dichloride (100 ml) and then the whole was carefully acidified with dilute hydrochloric acid. The residue obtained upon work-up was dissolved in dry acetone (50 ml), and dry potassium carbonate (210 mg, 1.52 mmol) and allyl bromide (200 mg, 1.65 mmol) were added, and the mixture was boiled with stirring for 16 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 40% ethyl acetate-light petroleum to afford the **product** (**36**) (107 mg, 82%) as pale yellow parallelogram plates, m.p. 105-106°C (2-propanol) (Found: C, 71.2; H, 6.4. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.15%); $\nu_{max.}$ 1646 (2C=0) cm^{-1}; ^1H n.m.r. δ 2.72 (3H, s, $COCH_3$), 3.89, 3.92, and 4.08 (each 3H, s, OCH_3) 4.72br. (2H, d, *J*5.2Hz, allyl CH_2), 4.96 (2H, s, CH_2-Ph), 5.39 (1H, dd, *J*10.5 and 1.4Hz, vinyl CH_2), 5.64 (1H, dd, *J*17.2 and 1.7Hz, vinyl CH_2), 6.27 (1H, ddd, *J*17.2, 10.5, and 5.2Hz, vinyl CH), 6.85 (1H, s, 7-H), 7.18 (1H, s, 3-H), and 7.37-7.58 (5H, m, **Ph**-CH_2); ^{13}C n.m.r. δ 31.62 (CH_3C), 56.54, 56.80, and 61.96 (3 x OCH_3), 70.83 (OCH_2-) 78.57 (CH_2Ph), 97.60 (C-3), 107.72 (=CH), 116,70 (C-8a)[b], 117.48 ($=CH_2$), 126.53

(C-4a)[b], 127.49-128.40 (C of Ph), 133.27 (C-7), 137.30 (C-1)[a], 138.07 (C-2)[a], 150.82 (C-4)[c], 150.94 (C-6)[c], 152.11 (C-5), 154.26 (C-8), and 200.51 (CO). (assignments with the same superscript may be interchanged); *m/z* 422 (M^+, 22%), 331 (47), 282 (15), 272 (10), 91 (100), 65 (13), 43 (29), and 41 (26).

2-Acetyl-1,4-dibenzyloxy-5,6,8-trimethoxy-3-prop-2'-enylnaphthalene (**23**).- The allyl compound (**36**) (189 mg, 0.45 mmol) was heated under nitrogen at 125°C for 24 h. The Claisen rearranged product of slightly higher R_f value was immediately dissolved in dry acetone (50 ml), and dry potassium carbonate (330 mg, 2.39 mmol) and benzyl bromide (410 mg, 2.40 mmol) were added and the mixture boiled with stirring for 7 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (20% ethyl acetate-light petroleum) to afford the **product** (**23**) (190 mg, 83%) as white needles, m.p. 93-94°C (2-propanol) (Found: C, 75.1; H, 6.0. $C_{32}H_{32}O_6$ requires C, 75.0, H, 6.25%); $\nu_{max.}$ 1695(2C=O) cm^{-1}; ^1H n.m.r. δ 2.60 (3H, s, $COCH_3$), 3.61br. (2H, d, *J* 5.0Hz, $ArCH_2$), 3.73, 3.91, and 4.04 (each 3H, s, OCH_3), 4.87 and 4.95 (each 2H, s, OCH_2-Ph), 4.95-5.10 (2H, m, partly obscured by peak at δ 4.95, vinyl CH_2), 5.90-6.10 (1H, m, vinyl CH), 6.75 (1H, s, 7-H), and 7.34-7.61 (10H, m, **Ph**-CH_2); ^{13}C n.m.r. δ 30.69 (CH_3C), 33.40 (CH_2-CH=), 56.38, 56.68, and 62.25 (3 x OCH_3), 76.74, 78.38 (2 x CH_2-Ph), 96.48 (C-7), 115.81 (C-8a)[b], 116.03 (=CH_2), 126.04 (C-4a)[b], 127.45-128.21 (C of 2 x Ph), 133.15 (C-3), 136.62 (=CH), 137.24 (C-1)[b], 137.71 (C-2)[b], 147.83 (C-4)[c], 147.96 (C-6)[c], 150.60 (C-5),

153.34 (C-8), and 205.53 (CO). (assignments with the same superscript may be interchanged); *m/z* 512 (M^+, 5%), 421 (21), 330 (9), 280 (13), 91 (81), and 57 (95).

1,4-Dibenzyloxy-2-(1-hydroxyethyl)-5,6,8-trimethoxy-3-prop-2'-enylnaphthalene (**14**).- The ketone (**23**) (342 mg, 0.67 mmol) in dry ether (20 ml) was added to a stirred suspension of lithium aluminium hydride (38 mg, 1.0 mmol) in ether (20 ml). When t.l.c. showed that all the starting material had been converted into product (ca. 5 min), the reaction was worked up by the addition of saturated aqueous solution of ammonium chloride, followed by anhydrous magnesium sulphate. Work-up of the filtrate gave a residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the **product** (**14**) (342 mg, 99%), m.p. 124-125°C (cyclohexane/methylene dichloride) (Found: C, 74.65; H, 6.85. $C_{32}H_{34}O_6$ requires C, 74.7; H, 6.6%); $\nu_{max.}$ 3433(OH) and 1604 (C=C) cm^{-1}; ^1H n.m.r. δ 1.62 (3H, d, *J* 6.8Hz, $CH(OH)CH_3$), 3.5-3.7 (2H, m, $Ar-CH_2$), 3.72, 3.85, and 4.02 (each 3H, s, OCH_3), 4.92 (4H, s, OCH_2-Ph), 4.96 (1H, dd, *J* 17 and 1.7Hz, vinyl CH_2), 5.10 (1H, dd, *J* 10.1 and 1.7Hz, vinyl CH_2), 5.23 (1H, q, *J* 6.8Hz, $CH-CH_3$), 4.9-5.3 (1H, OH, D_2O exchangeable), 6.11 (1H, m, vinyl CH), 6.75 (1H, s, 7-H), and 7.3-7.6 (10H, m, Ph-CH_2); ^{13}C n.m.r. δ 29.75 (CH_3C), 30.50 (CH_2-CH=), 56.75, 57.00, and 62.75 (3 x OCH_3), 67.25 ($CHOHCH_3$), 76.5 and 77.5 (2 x OCH_2-Ph), 97.25 (C-7), 115.75 ($=CH_2$), 116.5 (C-8a)[a], 125.35 (C-4a)[a], 127.5-129.7 (C of 2 x Ph), 136.70 (C-2)[b], 132.50 (C-3), 137.5 (=CH), 138.20 (C-1)[b], 148.4 (C-4), 149.5 (C-6), 150.00 (C-5), and 153.00 (C-8),

(assignments with the same superscript may be interchanged); *m/z* 514 (M^+, 3%), 422 (15), 315 (22), 91 (100), and 28 (69).

trans-*5,10-Dibenzyloxy-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* (15).-

Compound (**14**) (121 mg 0.24 mmol) dissolved in dry dimethylformamide (10 ml) and dry nitrogen was passed through the solution for 10 min. Potassium *t*-butoxide (0.21 g, 1.92 mmol) was added and the mixture stirred under nitrogen at an oil bath temperature of 70°C for 2 h. The mixture was cooled, thrown into water, and extracted exhaustively with ether (4 x 30 ml). The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum to afford the **naphthopyran** (**15**) (111 mg, 92%) as white grains, m.p. 125-126°C (crystallised after subjection to p.l.c. and left to stand, then washed with cyclohexane) (Found: C, 74.4; H, 6.35. $C_{32}H_{34}O_6$ requires C, 74.7; H, 6.65%.); $\nu_{max.}$ 1616 (C=C) and 1595 (C=C) cm^{-1}; ^1H n.m.r. δ1.35 (3H, d, *J* 6.0Hz 3-CH_3), 1.64 (3H, d, *J*6.6Hz, 1-CH_3), 2.57 (1H, dd, *J*17.0 and 11.0 Hz, *pseudo*-axial 4-H), 3.13 (1H, dd, *J*17.0 and 3.3Hz, *pseudo*-equatorial 4-H), 3.74, 3.87, and 4.02 (each 3H, s, OCH_3), 4.0-4.2 (1H, m, partly obscured by OCH_3 protons, 3-H), 4.75 and 4.80 (each 1H, d, *J*20.3Hz, CH_2-Ph) 5.00 and 5.05 (each 1H, d, *J*14.1Hz, CH_2-Ph), 5.34 (1H, q, *J*6.6Hz 1-H), 6.70 (1H, s, 8-H), 7.3-7.7 (10H, m, Ph-CH_2); ^{13}C n.m.r δ20.75 (C-3a), 22.05 (C-1a), 30.94 (C-4), 56.57, 56.80, 62.17 (3 x OCH_3), 62.54 (C-3), 68.77 (C-1), 75.50 and 76.26 (2 x CH_2-Ph), 96.41 (C-8),

116.11 (C-9a)[a], 124.70 (C-4a)[b], 126.78 (C-5a)[a], 127.42-128.39 (C of **Ph** x 2), 138.05 (C-10a)[b], 138.10 (C-10)[b], 146.69 (C-7)[c], 146.83 (C-5)[c], 149.36 (C-6), and 153.05 (C-9) (assignments with the same superscript may be interchanged); *m/z* 514 (M^+, 5%), 423 (13), 331 (17), 285 (10), 91 (100), and 43 (45).

trans-3,4-Dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (**40**).-

The pyran (**15**) (49 mg, 0.095 mmol) in ethyl acetate (10 ml) was stirred together with 10% Pd/C (100 mg) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 1 h. After filtration and evaporation of the solvent under reduced pressure the residue was chromatographed (eluant 50% ethyl acetate-light petroleum) to yield the **product** (**40**) (28 mg, 87%) as pale orange needles, m.p. 177.5-178.5°C (cyclohexane/methylene dichloride) (Found: C, 64.9; H, 6.0. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.0%); $\nu_{max.}$ 1651 (C=O), 1636 (C=O), 1579 (C=C), and 1551 cm^{-1}; ^1H n.m.r. δ 1.31 (3H, d, *J*6.0Hz, 3-CH_3), 1.50 (3H,d, *J*6.8Hz, 1-CH_3), 2.19 (1H, ddd, *J*18.9, 10.1, and 1.85Hz, *pseudo*-axial 4-H), 2.64 (1H, dd, *J*18.9 and 3.5Hz, *pseudo*-equatorial 4-H), 3.9-4.0 (1H, m, partly obscured by OCH_3 protons, 3-H), 4.96 (1H, dq, *J*6.8 and 1.85Hz, 1-H), and 6.72 (1H, s, 8-H); ^{13}C n.m.r. δ 19.62 (C-3a), 21.47 (C-1a), 29.50 (C-4), 56.17, 56.63, and 61.23 (3 x OCH_3), 62.51 (C-3), 67.16 (C-1), 101.15 (C-8), 112.93 (C-5a)[a], 126.41 (C-9a)[a], 140.73 (C-10a)[b], 143.41 (C-4a)[b], 146.65 (C-7), 158.03 (C-6), 159.55 (C-9), and 181.56 and 184.08 (2 x CO) (assignments with the same superscript may be

interchanged); *m/z* 332 (M^+, 100%), 317 (86), 302 (32), 289 (19), 259 (21), 137 (10), 115 (12), 65 (10), and 43 (36).

4-Acetoxy-2-acetyl-1,5,6,8-tetramethoxynaphthalene (**41**).- The acetate (**33**) (684 mg, 1.82 mmol) was dissolved by warming in methanol (70 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (to give a 1% w/v solution, 2.18 mmol) and the solution was stirred at room temperature for 10 min. To the reaction mixture was added water (100 ml) and methylene dichloride (150 ml) and the whole was then carefully acidified with dilute hydrochloric acid. The residue obtained upon work-up was immediately dissolved in dry acetone (150 ml), and dry potassium carbonate (1.25 g, 9.06 mmol) and dimethyl sulphate (1.15 g, 9.06 mmol) were added, and the mixture boiled with stirring for 3 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **product** (**41**) (551 mg, 87%) as dull orange hexagon layers, m.p. 158-160°C (2-propanol) (Found: C, 62.15; H, 5.7. $C_{18}H_{20}O_7$ requires C, 62.1; H, 5.8%); $\nu_{max.}$ 1758 (OAc) and 1646 (2C=O) cm^{-1}; ^1H n.m.r. δ 2.21 (3H, s, $OCOCH_3$), 2.61 (3H, s, $COCH_3$), 3.67, 3.71, 3.87, and 3.90 (each 3H, s, OCH_3), 6.64 (1H, s, 3-H), and 7.27 (1H, s, 7-H); ^{13}C n.m.r. δ 20.63 and 31.20 (CH_3C), 56.44, 56.73, 61.82, and 63.87 (4 x OCH_3), 96.96 (C-7), 116.30 (C-8a)[b], 120.18 (C-3), 126.53 (C-4a)[b], 126.73 (C-2)[b], 135.5 (C-1), 140.97 (C-4), 152.06 (C-6), 154.72 (C-5), 156.81 (C-8), 169.64 (CO), and 198.70 (CO) (assignments with the same superscript

may be interchanged); *m/z* 348 (M^+, 35%), 306 (53), 291 (100), 263 (12), 42 (43), and 28 (79).

2-Acetyl-1,5,6,8-tetramethoxy-4-prop-2'-enyloxynaphthalene (**42**).- Compound (**41**) (551 mg, 1.04 mmol) was dissolved by warming in methanol (100 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (to give a 5% w/v solution, 5.20 mmol) and the solution was stirred for 10 min. To the reaction mixture was added water (70 ml) and methylene dichloride (100 ml) and the whole was then carefully acidified with dilute hydrochloric acid. The residue obtained upon work-up was dissolved in dry acetone (100 ml), and dry potassium carbonate (1.1 g, 8.0 mmol) and allyl bromide (0.96 g, 7.9 mmol) were added and the mixture was boiled with stirring for 16 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the **product** (**42**) (507 mg, 92%) m.p. 85.5-86.5°C (cyclohexane) (Found: C, 66.25; H, 6.3. $C_{19}H_{22}O_6$ requires C, 65.90; H, 6.35%); $\nu_{max.}$ 1657 (2C=O) cm^{-1}; δ 2.73 (3H, s, $COCH_3$), 3.77, 3.78, 4.00, and 4.01 (each 3H, s, OCH_3), 4.62 (2H, dt, *J*5.3 and 1.4Hz, $ArCH_2$), 5.29 (1H, ddd, *J*10.5, 3.2, and 1.4Hz, vinyl CH_2), 5.53 (1H, ddd, *J*17.3, 3.2, and 1.7Hz, vinyl CH_2), 6.16 (1H, ddd, *J* 17.3, 10.5, and 5.3Hz, vinyl CH), 6.74 (1H, s, 3-H), 7.09 (1H, s, 7-H); ^{13}C n.m.r. δ31.32 (CH_3C), 56.71, 56.78, 61.93, and 63.64 (4 x OCH_3), 70.82 (OCH_2), 97.56 (C-7), 107.84 (=CH), 116.51 (C-8a)[b], 117.44 ($=CH_2$), 126.59 (C-4a)[b], 126.67 (C-1)[b], 133.27 (C-3), 138.03 (C-2), 150.66 (C-4)[a], 152.21

(C-6)[a], 153.02 (C-5), 154.20 (C-8), and 200.05 (CO) (assignments with the same superscript may be interchanged); *m/z* 346 (M^+, 75%), 305 (100), 289 (36), 275 (20), 270 (12), 245 (17), 43 (56), and 41 (58).

2-Acetyl-4-benzyloxy-1,5,6,8-tetramethoxy-3-prop-2'-enylnaphthalene (**45**).- Compound (**43**) (507 mg, 1.47 mmol) was heated under nitrogen at 125°C for 24 h. The product was immediately dissolved in dry acetone (50 ml) and dry potassium carbonate (1.00 g, 7.35 mmol) and benzyl bromide (1.25 g, 0.87 ml, 7.35 mmol) were added and the mixture was boiled with stirring for 27 h. The cooled reaction mixture was filtered and evaporated. The residue was chromatographed (eluant 5-30% ethyl acetate-light petroleum) to afford the **product** (**45**) (525 mg, 82%) as a pale yellow oil, (Found: M^+, 436.1877. $C_{26}H_{28}O_6$ requires M, 436.1886); $\nu_{max.}$ (film) 1696 (2C=O) cm^{-1}; δ 2.58 (3H, s, $COCH_3$), 3.57br. (2H, d, J5.9Hz, $ArCH_2$), 3.68 and 3.74 (each 3H, s, OCH_3), 4.02 (6H, s, 2 x OCH_3), 4.89 (2H, s, CH_2-Ph), 4.95 (1H, dd, J16.4 and 1.7Hz, vinyl CH_2); 5.03 (1H, dd, J10.4 and 1.5Hz, vinyl CH_2), 5.95 (1H, ddt, J16.4, 10.4 and 6.1Hz, vinyl CH), 6.74 (1H, s, 7-H) 7.3-7.6 (5H, m, **Ph**-CH_2); *m/z* 436 (M^+, 7%), 345 (100), 314 (23), 286 (13), 91 (47), 49 (23), and 28 (17).

4-Benzyloxy-2-(1-hydroxyethyl)-1,5,6,8-tetramethoxy-3-prop-2'-enylnaphthalene (**46**).-

The ketone (**45**) (172 mg, 0.39 mmol) in dry ether (15 ml) was added to a stirred suspension of lithium aluminium

hydride (23 mg, 0.61 mmol) in ether (10 ml). When t.l.c. showed that all the starting material had been converted into product (ca. 5 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** (**46**) (160 mg, 93%) as a pale brown oil, (Found: M^+, 438.207. $C_{26}H_{30}O_6$ requires M, 438.204); $\nu_{max.}$(film) 3468 (OH), 1604 (C=C), and 1585 (C=C) cm^{-1}; ^1H n.m.r. δ 1.62 (3H, d, *J* 6.6Hz, CH_3(OH)CH), 3.40-3.59 (2H, m, CH_2-CH=), 3.68, 3.87, 3.99, and 4.01 (each 3H, s, OCH_3), 4.83 and 4.86 (each 1H, d, *J* 10.3Hz, CH_2-Ph), 4.95 (1H, dd, *J*17.3, 1.7Hz, vinyl CH_2), 5.08 (1H, dd, *J*10.3 and 1.6Hz, vinyl CH_2), 5.16br. (1H, q, *J*6.6Hz, $CHCH_3$), 6.07 (1H, ddd, *J*17.3, 10.3, and 5.2Hz, vinyl CH), 6.74 (1H, s, 7-H), and 7.30-7.56 (5H, m, **Ph**-CH_2); ^{13}C n.m.r. δ 25.46 (CH_3-C), 30.45 (CH_2-C=), 56.92, 57.02, 62.36, and 63.70 (4 x OCH_3), 67.58 (CH), 76.66 (CH_2-Ph), 97.27 (C-7), 115.83 (=CH_2), 116.12 (C-8a)[a], 125.35 (C-4a)[a], 127.6-129.25 (C of Ph), 132.36 (C-3), 136.68 (C-2)[b], 137.38 (=CH), 138.21 (C-1)[b], 147.71 (C-4), 149.96 (C-6), 151.37 (C-5), and 152.75 (C-8) (assignments with the same superscript may be interchanged); *m/z* 438 (M^+, 11%), 347 (100), 329 (24), 298 (15), and 91 (37).

trans-*3,4-Dihydro-5-benzyloxy-6,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* (**47**) and cis-*3,4-Dihydro-5-benzyloxy-6,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* (**48**).-

A mixture of the alcohol (**46**) (160 mg, 0.37 mmol) and

mercury(11) acetate (134 mg, 0.37 mmol) in tetrahydrofuran (5 ml) and water 5 ml) was stirred for 1 h. Sodium hydroxide (3M, 3.0 ml) was added and the mixture stirred for 1 h, after which sodium borohydride (3M solution in 3M aqueous sodium hydroxide, 3.0 ml) was added. The mixture was stirred at room temperature for 40 min, then diluted with water and extracted with ethyl acetate (3 times). The residue obtained upon work-up was flash chromatographed (eluant 50% ethyl acetate-light petroleum), and the resulting residue was subjected to p.l.c. (eluant 7% ethyl acetate-light petroleum) to give firstly the ***cis*-compound (48)** (45 mg, 28%) as an oil. (Found: M^+, 438.2052. $C_{26}H_{30}O_6$ requires M, 438.2042); $\nu_{max.}$(film) 1606 (C=C) and 1590 (C=C) cm^{-1}; δ 1.35 (3H, d, *J*6.1Hz, 3-CH_3), 1.64 (3H, d, *J*6.3Hz, 1-CH_3), 2.49 (1H, dd, *J*16.2 and 10.7Hz, *pseudo*-axial 4-H), 3.10 (1H, dd, *J*16.2, 1.4Hz, *pseudo*-equatorial 4-H), 3.60 (1H, ddq, *J*10.7, 6.1, and 1.4Hz, 3-H), 3.72, 3.74, 4.00, and 4.01 (each 3H, s, OCH_3), 4.86 and 4.94 (each 1H, d, *J*10.4Hz, CH_2-Ph), 5.20 (1H, q, *J* 6.3Hz, 1-H), 6.69 (1H, s, 8-H), and 7.3-7.6 (5H, m, Ph); *m/z* 438 (M^+, 11%), 347 (100), 303 (87), 91 (68), 49 (19), and 28 (13). The second fraction afforded the ***trans*-compound (47)** (45 mg, 28%) as opaque quartz clusters, m.p. 139-140.5°C (light petroleum) (Found: C, 71.05; H, 7.2. $C_{26}H_{30}O_6$ requires C, 71.25; H, 6.9%); $\nu_{max.}$ 1609 (C=C) and 1591 (C=C) cm^{-1}; δ 1.33 (3H, d, *J*6.3Hz, 3-CH_3), 1.60 (3H, d, *J*6.6Hz, 1-CH_3), 2.53 (1H, dd, *J*17.3 and 11.2Hz, *pseudo*-axial 4-H), 3.10 (1H, dd, *J*17.3 and 3.4Hz, *pseudo*-equatorial 4-H), 3.71 and 3.76 (each 3H, s, OCH_3), 4.00 (6H, s, 2 x OCH_3), 3.9-4.15 (1H, m, obscured

by OCH_3 peaks, 3-H), 4.79 and 4.94 (each 1H, d, *J*10.0Hz, CH_2-Ph), 5.29 (1H, q, *J* 6.6Hz, 1-H), 6.68 (1H, s, 8-H), and 7.3-7.6 (5H, m, Ph); *m/z* 438 (M^+, 9%), 374 (100), 303 (67), 91 (58), 43 (23), and 28 (19).

cis-3,4-Dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (1).-

Compound (**48**) (22 mg, 0.05 mmol) in ethyl acetate (10 ml) was stirred together with 10% Pd/C (20 mg) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 30 min. After filtration and evaporation of the solvent under reduced pressure the residue was flash chromatographed (eluant ethyl acetate) to afford the naphthol (**49**), which was immediately dissolved in a mixture of acetonitrile (5 ml) and water (2 ml). A solution of cerium(IV) ammonium nitrate (70 mg, 1.28 mmol) in water (5 ml) was added dropwise with stirring over a period of 10 min. The solution was stirred for a further 15 min and then poured into water (20 ml). This was extracted with methylene dichloride (2 x 40 ml). The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the **quinone** (1) (13 mg, 78%) as orange crystals, which proved to be identical in spectroscopic and physical properties with a sample of natural origin m.p. 129-130°C (sample of natural origin m.p. 130°-130.5°C) (Found: M^+, 332.1278. $C_{18}H_{20}O_6$ requires M, 332.1260); Spectroscopic and thin layer chromatographic comparison of the synthetic with the naturally derived sample of ventiloquinone E showed them to be identical.

cis-5-Benzyloxy-3,4-dihydro-7,10-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-quinone (**50**).-

The naphthalene (**48**) (31 mg, 0.071 mmol), silver(II) oxide (45 mg, 0.36 mmol), and dioxane (5 ml) were stirred together at room temperature. Nitric acid (6M, 0.4 ml) was added and the reaction mixture stirred for 5 min. A mixture of methylene dichloride (10 ml) and water (3 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **quinone** (**50**) (25 mg, 87%) as orange needles, m.p. 180-182°C (methanol) (Found: C, 70.2; H, 5.8. $C_{24}H_{24}O_6$ requires C, 70.55; H, 5.9%); $\nu_{max.}$ 1676 (C=O) 1636 (C=C), and 1623 (C=C) cm^{-1}; δ 1.29 (3H, d, *J* 6.2Hz 3-CH_3), 1.57 (3H, d, *J*6.4Hz, 1-CH_3), 2.32 (1H, ddd, *J*17.0, 10.6, and 1.8Hz, *pseudo*-axial 4-H), 2.87 (1H, ddd, *J*17.0, 2.0, and 1.5Hz, *pseudo*-equatorial 4-H), 3.47 (1H, ddq, *J*10.6, 6.2, and 2.0 Hz, 3-H) 3.79, 3.85 (each 3H, s, OCH_3), 4.84 and 4.96 (each 1H, d, *J*10.2Hz, CH_2-Ph), 5.02 (1H, ddq, *J*6.4, 1.8, and 1.5Hz, 1-H), 6.05 (1H, s, 8-H), and 7.3-7.6 (5H, m, **Ph**-CH_2); *m/z* 408 (M^+, 17%), 317 (7), 273 (23), and 91 (100).

cis-3,4-Dihydro-5-hydroxy-7,10-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-quinone (**51**).-

The naphthalene (**50**) (14 mg 0.034 mmol) in ethyl acetate (7 ml) was stirred together with 10% Pd/C (15 mg) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 1 h. After filtration and evaporation of the solvent under reduced pressure the

residue was flash chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **naphthol** (51) (9 mg, 82%) as orange needles, m.p. 163-164°C (light petroleum) (Found: M^+, 318.1108. $C_{17}H_{18}O_6$ requires M, 318.1103); $\nu_{max.}$ 3394 (OH), 1646 (C=O), and 1638 (C=O) cm^{-1}; δ 1.35 (3H, d, *J* 6.1Hz, 3-CH_3), 1.56 (3H, d, *J* 6.4Hz, 1-CH_3), 2.38 (1H, ddd, *J* 17.5, 10.5, and 1.9Hz, *pseudo*-axial, 4-H), 2.88 (1H, ddd, *J* 17.5, 1.9, and 1.9Hz, *pseudo*-equatorial, 4-H) 3.58 (1H, ddq, *J* 10.5, 6.1, and 1.9Hz, 3-H), 3.76 and 3.85 (each 3H, s, OCH_3), 4.97 (1H, qt, *J* 6.4 and 1.9Hz, 1-H), 6.02 (1H, s, 8-H), and 12.79 (1H, s, OH, D_2O exchangeable); *m/z* 318 (M^+, 100%), 303 (77), 288 (50), 273 (29), 258 (50), 245 (25), 231 (19), 167 (15), 115 (23), 69 (40), 43 (76), and 28 (35).

trans-*5-Benzyloxy-3,4-dihydro-7,10-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c] pyran-6,9-quinone* (53).-

The naphthalene (**47**) (31 mg, 0.071 mmol), silver(II) oxide (45 mg, 0.36 mmol), and dioxane (5 ml) were stirred together at room temperature, nitric acid (6M, 0.4 ml) was added and the reaction mixture stirred for 5 min after which a mixture of methylene dichloride (10 ml) and water (3 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **quinone** (53) (22 mg, 76%) as yellow needles, m.p. 128.5-129.5°C (methanol) (Found: M^+, 408.1592. $C_{24}H_{24}O_6$ requires M, 408.1573); $\nu_{max.}$ 1676 (C=O), 1637 (C=O), and 1628 (C=C) cm^{-1}; δ 1.27 (3H, d, *J* 6.1Hz, 3-CH_3), 1.53 (3H,

d, *J*6.6Hz, 1-CH_3), 2.30 (1H, ddd, *J* 17.8, 10.8 and 0.8Hz, *pseudo*-axial, 4-H), 2.89 (1H, dd, *J*17.8 and 3.4Hz, *pseudo*-equatorial, 4-H), 3.85, 3.85 (each 3H, s, OCH_3), 3.75-4.05 (1H, m, partly obscured by OCH_3 peaks, 3-H), 4.80 and 4.98 (each 1H, d, *J*10.2Hz, CH_2-Ph), 5.13br. (1H, q, *J*6.6Hz, 1-H), 6.03 (1H, s, 8-H), and 7.3-7.6 (5H, m, **Ph**-CH_2); *m/z* 408 (M^+, 9%), 317 (5), 273 (12), 91 (100), 57 (55), and 28 (69).

trans-3,4-Dihydro-5-hydroxy-7,10-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-quinone 54).-

The quinone (53) (21 mg, 0.05 mmol) in ethyl acetate (10 ml) was stirred together with 10% Pd/C (20 mg) and a drop of concentrated hydrochloric acid at room temperature under an atmosphere of hydrogen for 1 h. After filtration and evaporation of the solvent under reduced pressure, the residue was flash chromatographed (eluant 50% ethyl acetate-light petroleum) to afford the **naphthol** (54) (15 mg, 92%) as orange needle clusters, m.p. 219-220°C (light petroleum) (Found: C, 63.85, H, 5.35. $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.65%); $\nu_{max.}$ 3368 (OH), 1634 (C=O), and 1611 (C=O) cm^{-1}; δ 1.38 (3H, d, *J*6.2Hz, 3-CH_3), 1.58 (3H, d, *J*6.6Hz, 1-CH_3), 2.39 (1H, ddd, *J*18.3, 10.7, and 0.9Hz, *pseudo*-axial 4-H), 2.89 (1H, dd, *J*18.3 and 3.6Hz, *pseudo*-equatorial, 4-H), 3.82 and 3.88 (each 3H, s, OCH_3), 4.07 (1H, ddq, *J* 10.7, 6.2, and 3.6Hz, 3-H), 5.12br. (1H, q, *J*6.6Hz, 1-H), 6.06 (1H, s, 8-H), and 12.83 (1H, s, OH, D_2O exchangeable); *m/z* 318 (M^+, 100%), 303 (97), 288 (70), 259 (35), 245 (27), 231 (16), 167 (13), 115 (15), 69 (20), 43 (31), and 28 (100).

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