The synthesis of some Naphtho[2,3-c]pyrans

by

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TO LESLEY-ANNE

Contents

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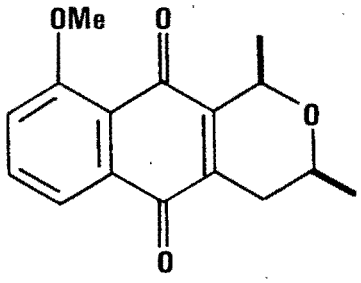
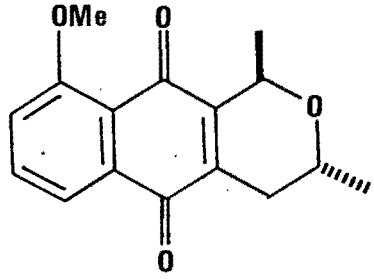
Introduction

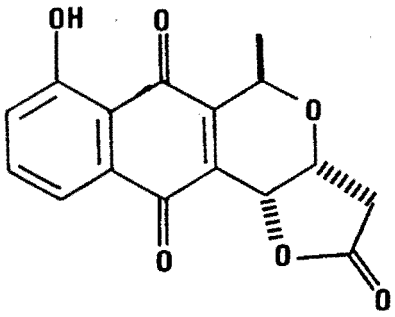
Many quinones present in nature contain the naphtho[2,3-c]pyran ring system as part of their structures. These naturally occurring compounds include the eleutherins[1,2,3](1) and (2), kalafungin[4](3), the nanaomycins[5,6](4) to (7) and ɣ-napththocyclinone[7](8).



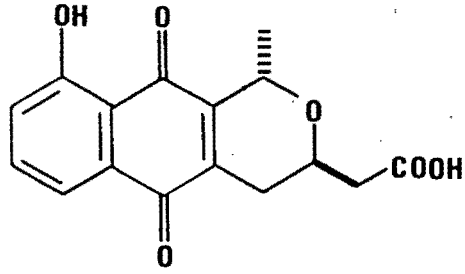
(+) - Eleutherin 1



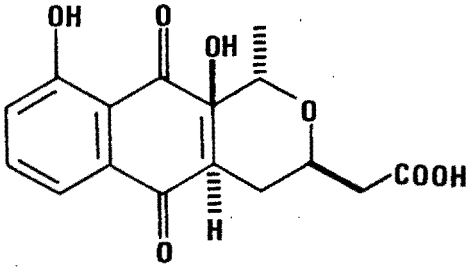
(-) - Isoeleutherin 2



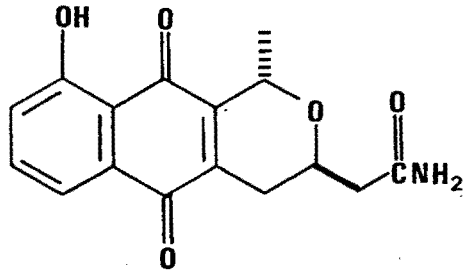
Kalafungin 3



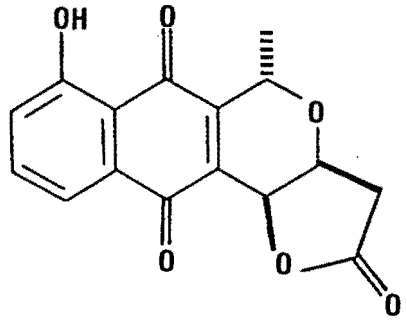
Nanaomycin A 4



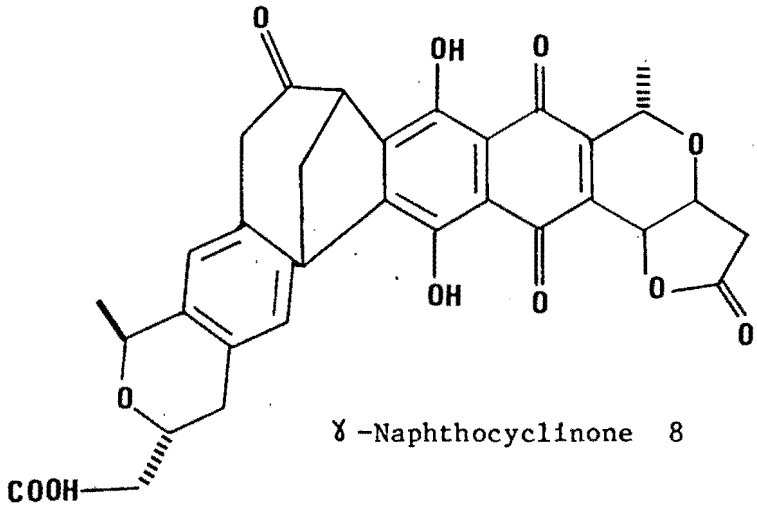
Nanaomycin B 5



Nanaomycin C 6

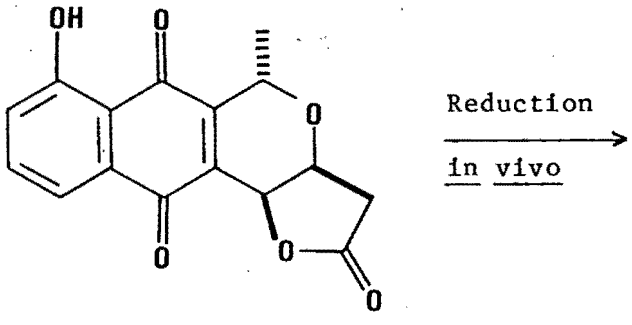


Nanaomycin D 7



ϒ-Naphthocyclinone 8

Moore[8] has reviewed numerous compounds that can act as bioreductive alkylating agents some of which have or can be predicted to have antineoplastic activity. Thus a compound that is biologically inactive can be transformed by a reduction <u>in vivo</u> to potent alkylating agents. One such compound reviewed is nanaomycin D (7) which contains the fused pyrano-ϒ-lactone moiety and which is ideally suited to act as a dialkylating agent by a bioreductive mechanism outlined below.



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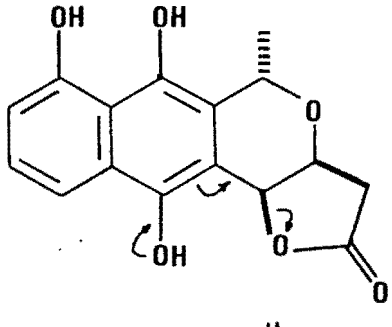
Reduction

<u>in vivo</u>



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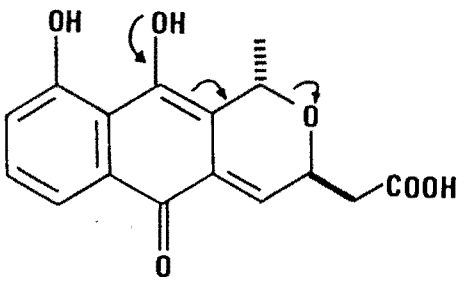

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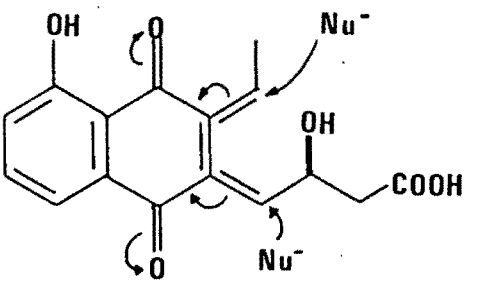

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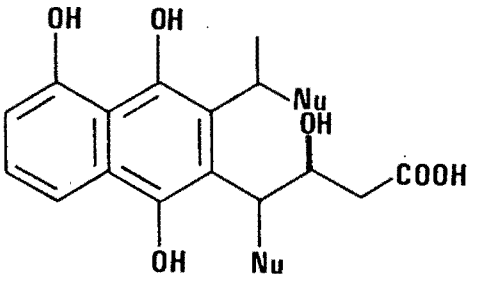

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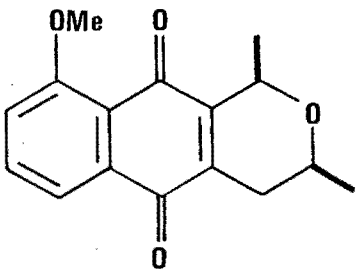
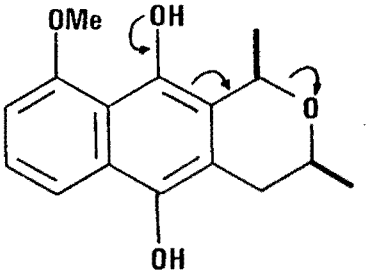
Thus the eleutherins (1) and (2) might also be able to act as bioreductive alkylating agents by the mechanism of quinone methide formation proposed above.



Eleutherin 1

Reduction

in vivo



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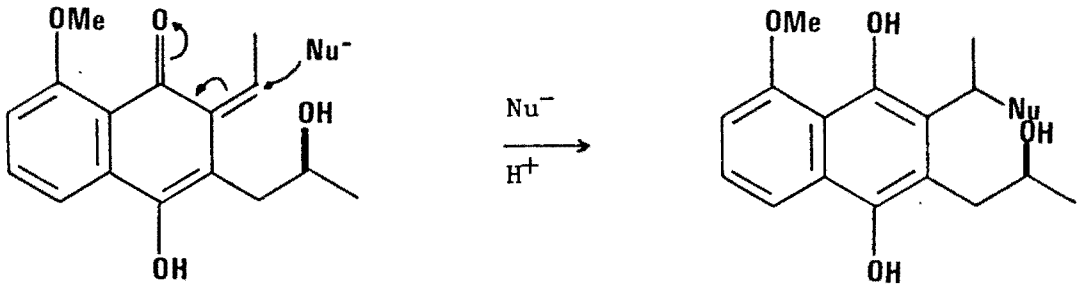
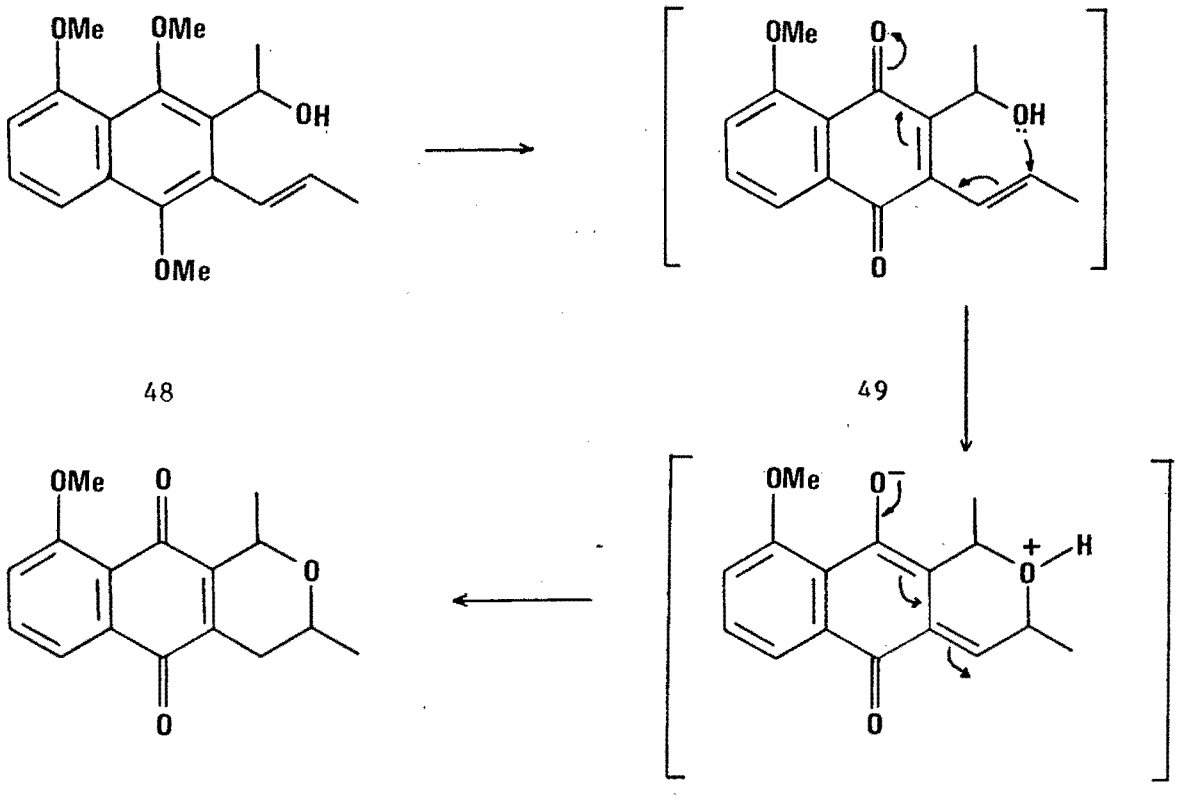


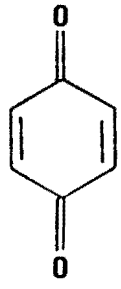
14 15

It can be seen by inspection that all the compounds discussed so far contain the naphtho[2,3-c]pyran ring structure and thus our interest was to find a satisfactory synthetic method for the formation of this fused ring system, which could be developed later to provide a route to more complex molecules with different substituents on the pyran ring.

This project initially aimed at synthesizing the eleutherins (1) and (2) by the following chemical transformations:



We thus proposed that the intermediate (49) might be sufficiently reactive to undergo spontaneous cyclization by an intramolecular nucleophilic attack by the hydroxyl group on the β carbon of the α,β unsaturated quinonoid system. p-Benzoquinone (19) has been shown to undergo a not unrelated intermolecular nucleophilic reaction with methanol in the presence of zinc chloride, to form the dimethoxy species (20).



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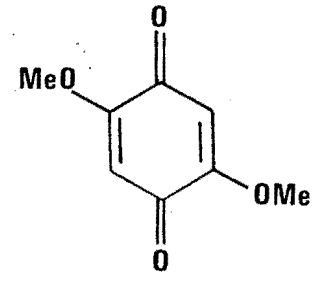

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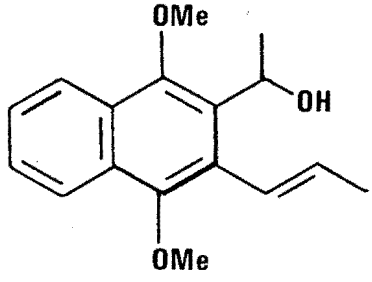
In practice when this procedure was applied to the model compound (21), the required cyclized product (22) was not formed spontaneously.



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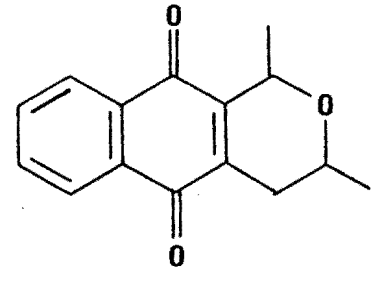
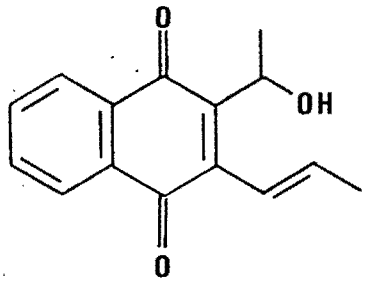
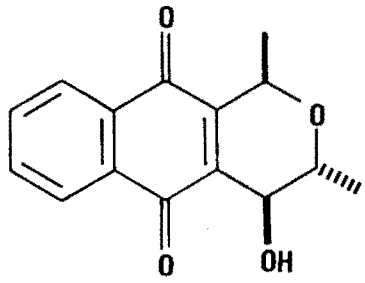


22

The only reaction product isolated with the reagent silver(II) oxide was the corresponding quinone (72). However under different reaction conditions, namely with the alternative demethylative oxidant ceric ammonium nitrate, cyclization of naphthalene (21) was observed to give quinones (24) and (25).



72



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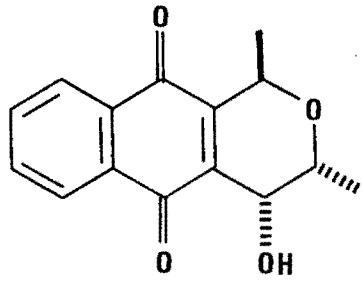
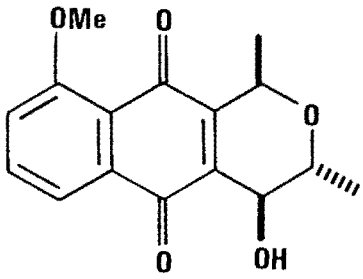


25

In view of this fact it was decided to abandon the original aim of synthesizing the eleutherins (1) and (2) since it was expected that on oxidative demethylation (48) would yield similar products to (24) and (25), that is (26) and (27).



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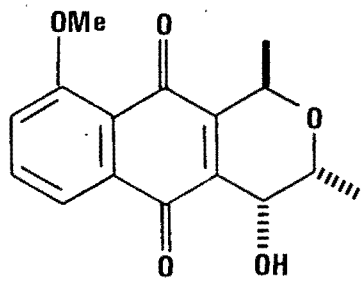
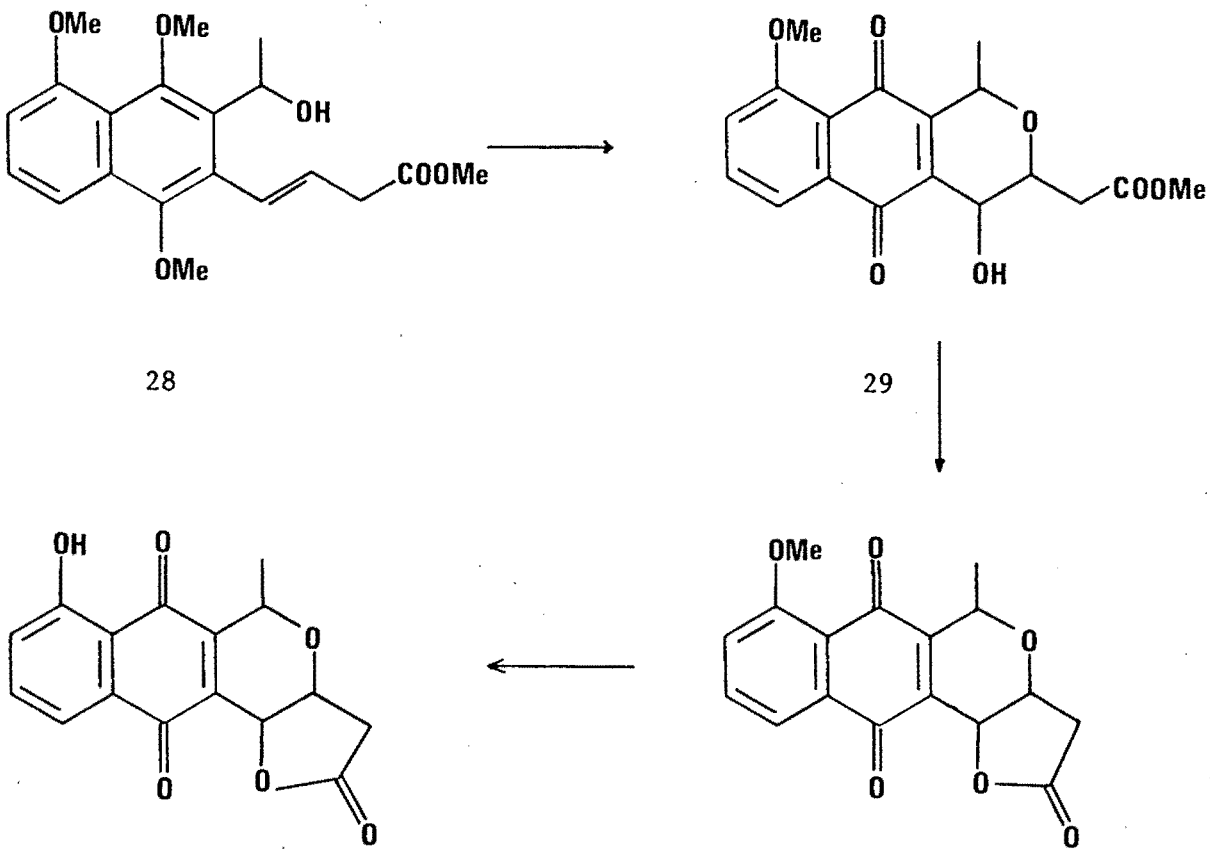


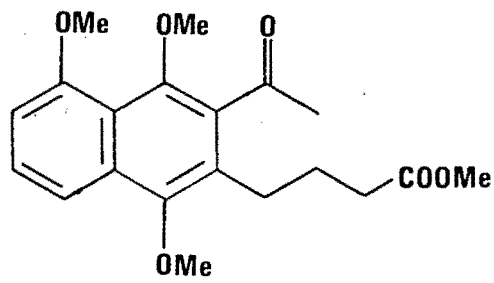
27

However by modifying the alkenyl side chain in (48) this type of cyclized reaction product could be used to our advantage. Thus by preparing (28)

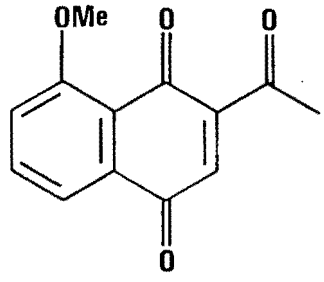
we would have a direct route to the nanaomycins (4) to (7) and specifically to nanaomycin D (7), as shown below.



Unfortunately the method employed to introduce the double bond in the carbomethoxypropyl side chain in (78) was not successful and further research into this reaction has been proposed. Thus in essence we had developed a highly attractive route to synthesize a large number of natural products containing the fused pyrano-γ-lactone system.

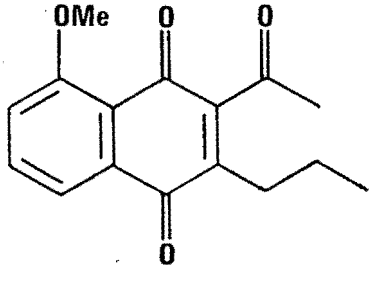


In our reaction scheme we required a high yield route to the synthetic intermediate (42),



42

which has been synthesized before by Eugster[9] but his yield was low (see page 16). This intermediate (42) was successfully synthesized in high yield and thus we had established a route to the alkylated quinones (31) and (33). We were able to make both these compounds as well as the analogue (34) since Torssell[10,11] has previously reported an efficient method of alkylating quinones.



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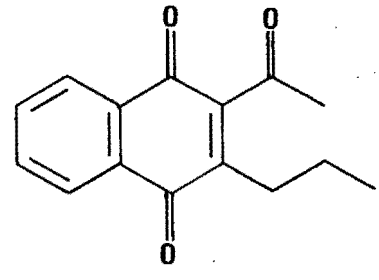

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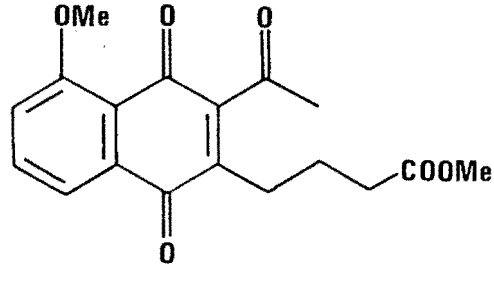
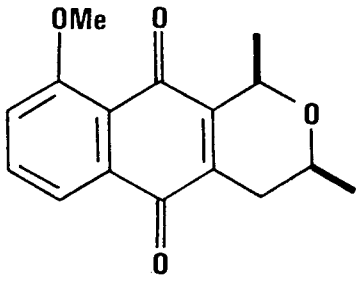


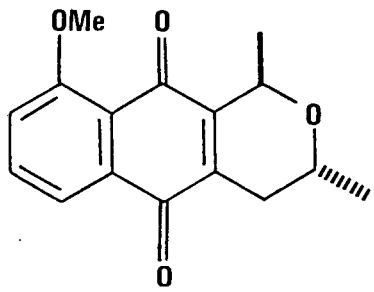
31

Discussion

This project initially aimed at synthesizing the eleutherins [1,2] (1) and (2) as their racemates.



(+) - Eleutherin 1

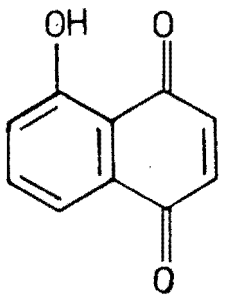


(-) - Isoeleutherin 2

These compounds have previously been synthesized by Eisenhuth and Schmid[3], and were isolated from the tubers of Eleutherine bulbosa (MILL.) URB. (Iridaceae)[1,2].

The proposed synthetic sequence is shown in scheme I. The starting material used was 5-hydroxy-1,4-naphthoquinone (juglone) (35) which is available from a number of routes. Thus juglone (35) was methylated to (36) with methyl iodide in a yield of 84%. In this reaction it was found that it did not proceed to completion even though an excess of methyl iodide was used and the mixture stirred for an extended time. Thus a quantity of juglone (35; 11%) was isolated from the reaction mixture. Reduction of juglone methyl ether (36) to the corresponding hydroquinone (37) proceeded smoothly with aqueous sodium dithionite[12], but this hydroquinone was neither isolated nor characterized due to its facile aerial oxidation. In its methylation to (39), only mono-methylation was observed under the conditions employed even though an excess of dimethyl sulphate was used. This can be explained by the ideal situation that arises for a six-membered hydrogen bonded ring structure (39), and also,

Scheme I



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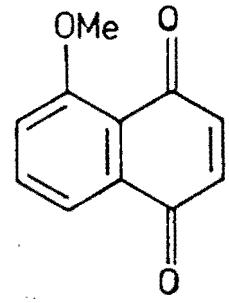

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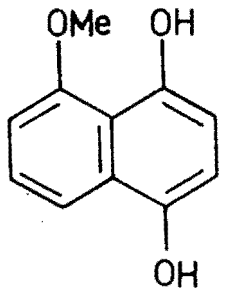

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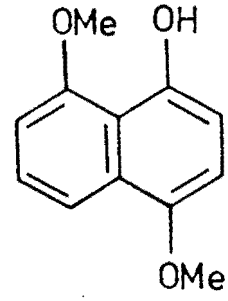

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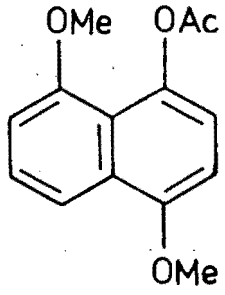

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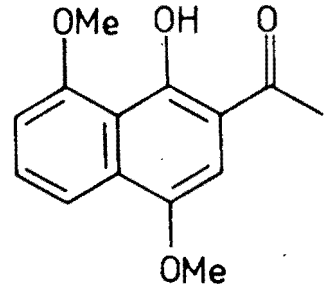

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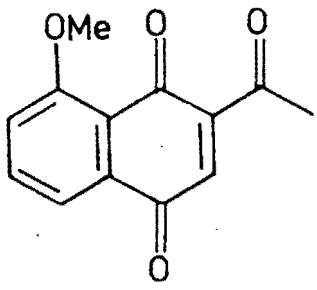

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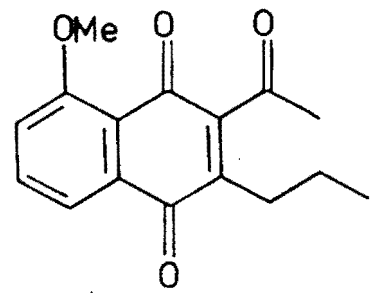
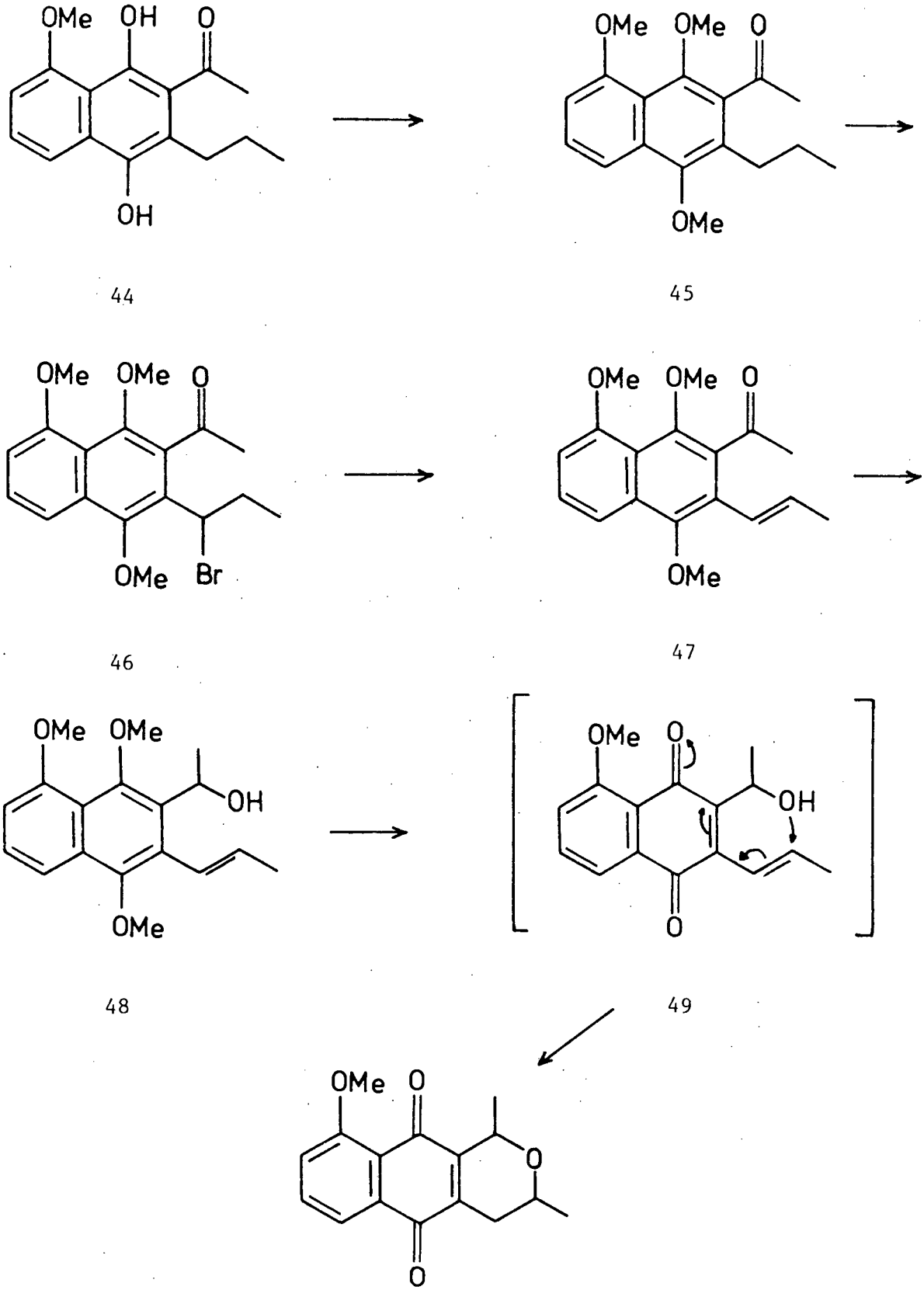


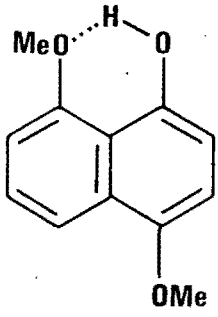
43

Scheme I (continued)



44 45 46 47 48 49 50

no doubt, because the hydroxyl in (39) is cryptophenolic.



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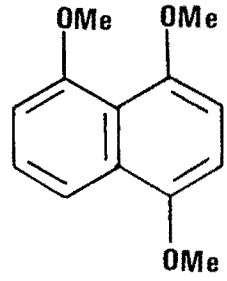


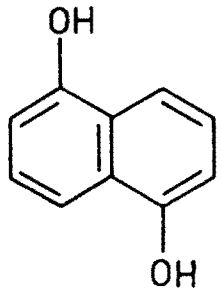
88

In fact if the trimethoxy species (88) is required, the reaction mixture needs extended heating under reflux, whereas the dimethoxy species (39) is produced in five hours under reflux, with a twofold excess of dimethyl sulphate.

As an alternative route, (39) was synthesized by the method of Rapoport[13] and this route is depicted in scheme II. This method is superior to the one depicted in scheme I for it avoids the necessity of using juglone (35) as starting material which is not as readily available as 1,5-dihydroxynaphthalene (52).

It is interesting to note, however, that the acetylation of 1,5-dimethoxy-4-naphthol (39) was achieved with relative ease to produce 4-acetoxy-1,5-dimethoxynaphthalene (40) in a yield of 96%, the reaction being complete after two hours. The greater ease of the acetylation reaction may be influenced by various other factors, including a higher reaction temperature. The Fries rearrangement of (40) to produce 3-acetyl-1,5-dimethoxy-4-naphthol however proved to be more difficult. In the literature[14] boron trifluoride etherate has been used in the

Scheme II



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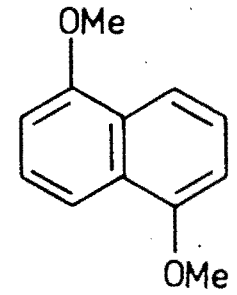

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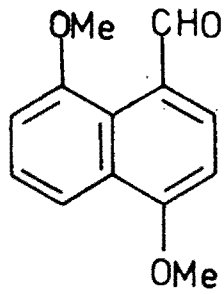
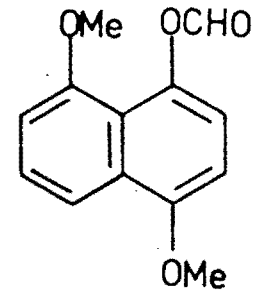


54



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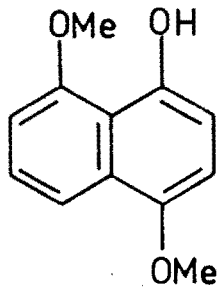
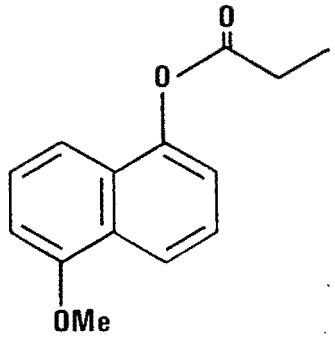


39

following conversion, in an 80% yield.



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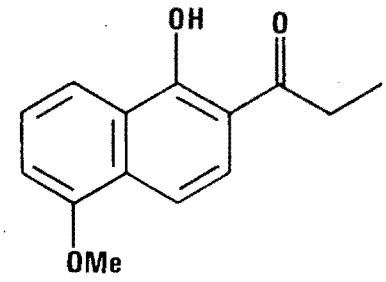
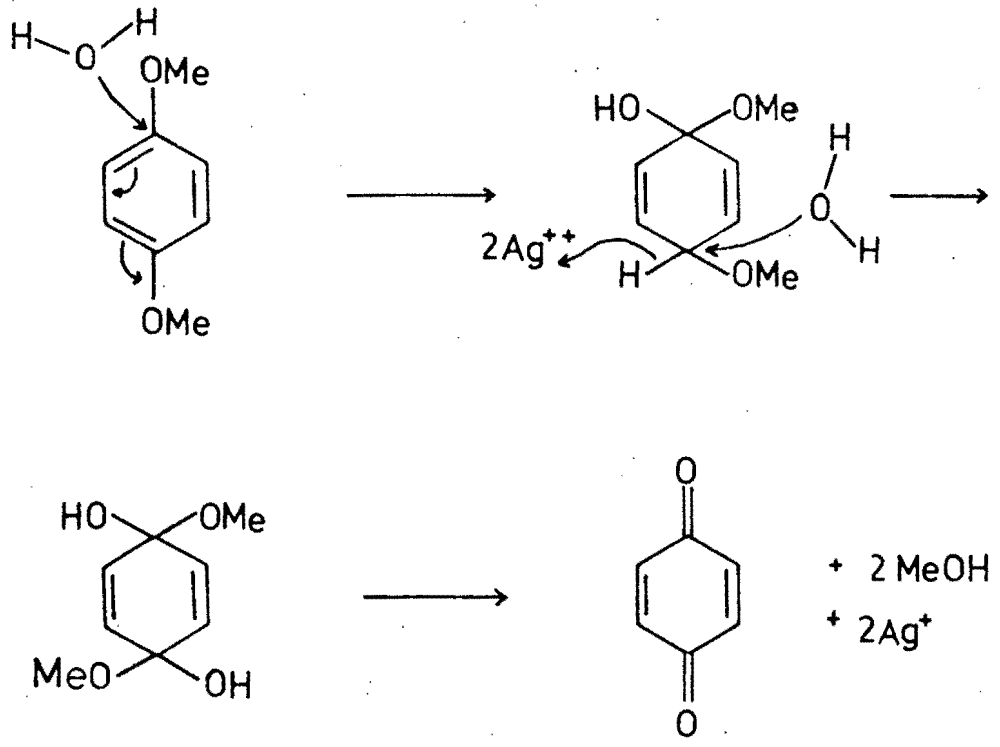


57

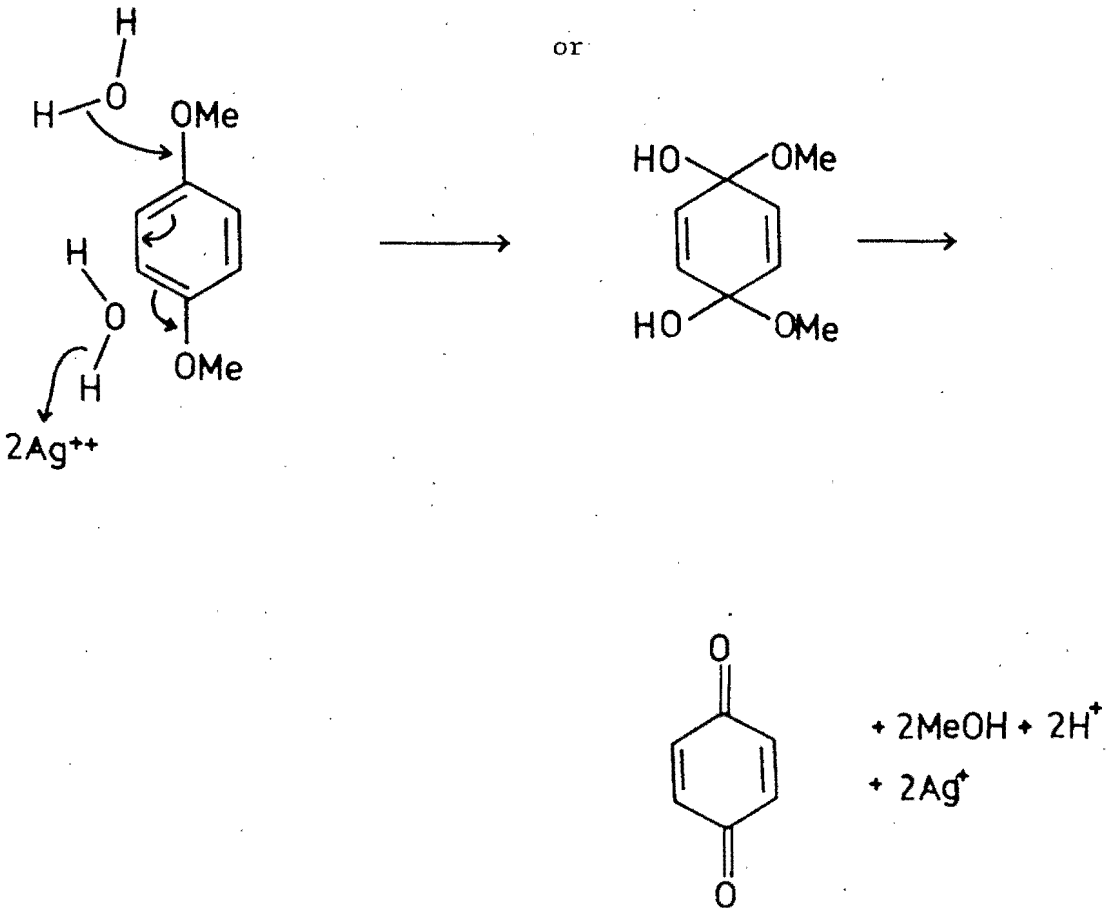
However, when these conditions were applied to compound (40) significant decomposition occurred but the desired product was produced in low yields (19%). It was thus obvious that this compound (40) was much more sensitive to the reaction conditions than (56). By lowering the reaction temperature to 60°C and the reaction time to thirty minutes, a 70% yield of (41) was achieved. Also isolated from the reaction mixture was 1,5-dimethoxy-4-naphthol (39) in a 24% yield. Thus by recycling this product formed, very high yields were obtained.

Silver(II) oxide[15] has been shown to be useful in demethylating naphthalene-1,2- and 1,4-dimethyl ethers, but has not been applied to compounds containing a phenol and a methoxy group. However from a mechanistic point of view there seemed no reason why it should not work on this system in compound (41). A mechanism that has been proposed by Snyder and Rapoport[15] is outlined overleaf.

In this paper it has also been shown that the demethylation involves aryl-oxygen bond fission by the use of ^{18}O in mechanistic studies.


H
O
H
OMe
OMe
HO
OMe
H
O
H
2Ag++
H
OMe
HO
OMe
MeO
OH
O
O
+ 2 MeOH + 2H+
+ 2Ag+

or

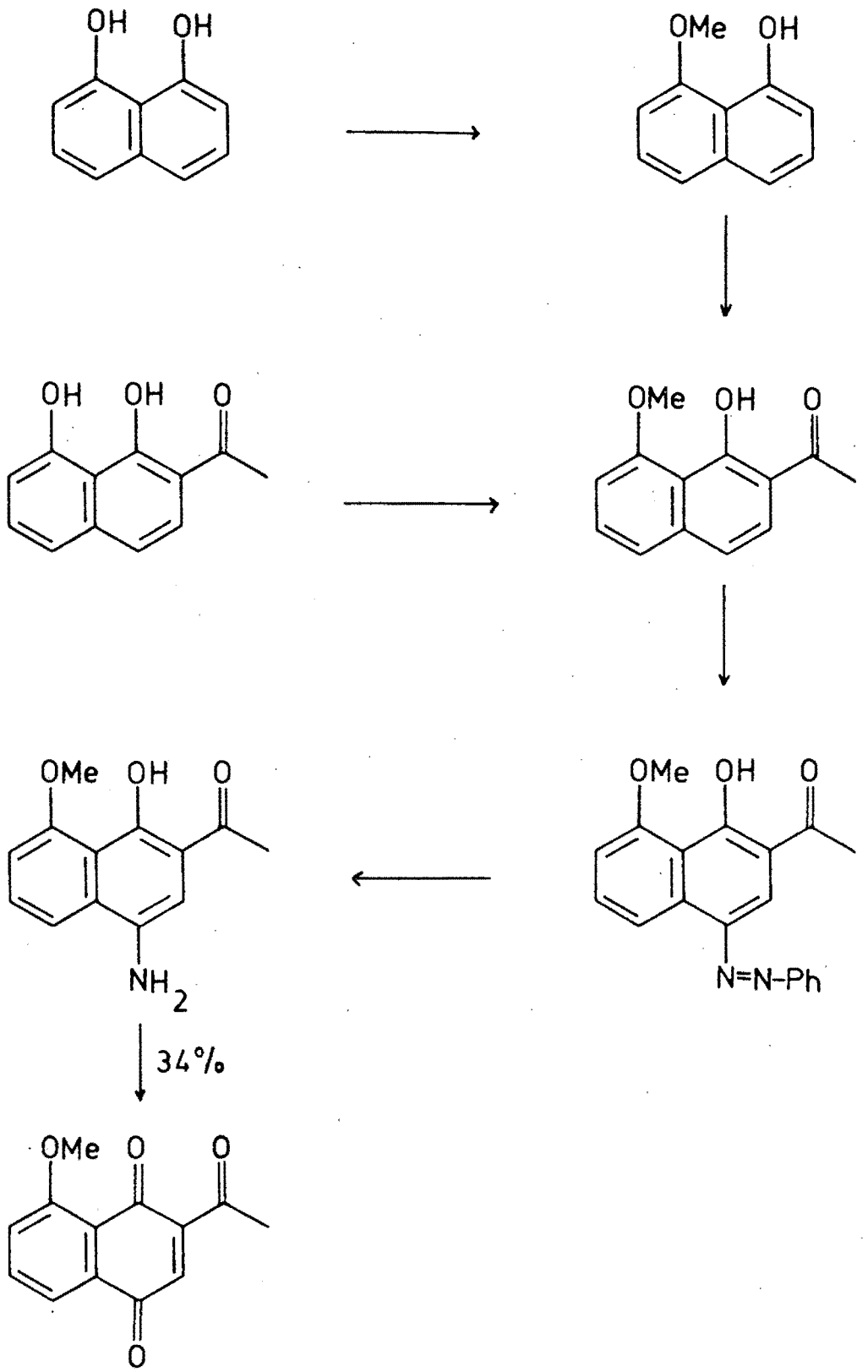

H
O
H
OMe
H
O
H
OMe
2Ag++
HO
OMe
HO
OMe
O
O
+ 2MeOH + 2H+
+ 2Ag+

Ceric ammonium nitrate[16] has also been shown to be useful for the same oxidative demethylations as silver(II) oxide is. Silver(II) oxide requires a strongly acidic medium for the reaction to work, whereas ceric ammonium nitrate can be used in the absence of a strong acid, thus it is claimed[16] to be highly suitable for acid sensitive compounds. However, we note that as the reaction proceeds the reaction mixture becomes acidic.

In the oxidation of (41) to 3-acetyl-5-methoxy-1,4-naphthoquinone (42) both silver(II) oxide and ceric ammonium nitrate were used with much the same result. Compound (42) was found to be particularly unstable, and hence was made as required and was not purified due to the fact that significant decomposition occurred when column chromatography was employed as a purification technique. In this way overall yields could be improved. Compound (42) has been synthesized before by Eugster[9] but this route was a low yield process and is outlined overleaf.

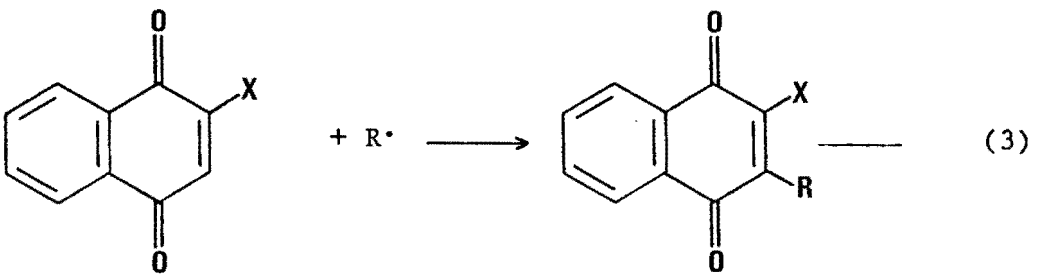
His low yield is probably due to the instability of (42) and the harsher conditions used in his last reaction than in the present case. When quantified the present reaction produced a yield of 64% of quinone (42).

Another difficult reaction was that of alkylating quinone (42) to give 3-acetyl-5-methoxy-2-propyl-1,4-naphthoquinone (43). Jacobson and Torssell[10,11] have developed a useful method of alkylating quinones by the generation of radicals from the decarboxylation of carboxylic acids with silver ions and peroxodisulphate [equations (1) - (4)].


OH
OH
OMe
OH
OH
OH
O
OMe
OH
O
OMe
OH
O
N=N-Ph
OMe
OH
O
NH2
34%
OMe
O
O
O

$$Ag^{+} + S_2O_8^{=} \longrightarrow Ag^{2+} + SO_4^{2-} + SO_4^{\cdot -} \qquad (1)$$

$$Ag^{2+} + RCOOH \longrightarrow Ag^{+} + CO_2 + H^{+} + R^{\cdot} \qquad (2)$$



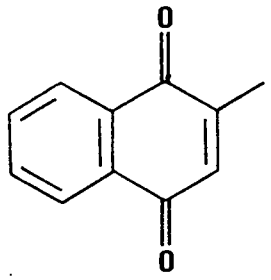
(3)

$$Ag^{+} + SO_4^{\cdot -} \longrightarrow SO_4^{2-} + Ag^{2+} \qquad (4)$$

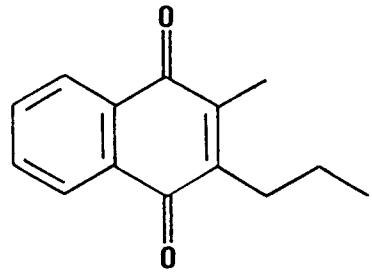
The yields of alkylated quinones reported in their papers vary from 40% to 84% and depend on the nature of the quinone and the acid used. Their general procedure was to add a solution of ammonium peroxodisulphate over one hour to a vigorously stirred water/acetonitrile solution of the quinone, carboxylic acid and silver nitrate at 60-65°C.

When this procedure was applied to the present system an overall yield of 6% of the alkylated quinone (43) was obtained from (41) with no other major component or starting material present. As was noted earlier, compound (42) was found to be particularly unstable so by lowering the temperature of the reaction to 60-65°C (external bath temperature) it was thought that this would have a favourable effect on the yield from the reaction. However when tried at a lower temperature, the major compound isolated was the starting material (42). Obviously the lower temperature inhibited the formation of radicals necessary for the success of the reaction. As a further variation the ammonium peroxodisulphate was substituted with potassium peroxodisulphate, the temperature still remaining at 60-65°C (external bath temperature) and in this case the yield was much improved to give the alkylated quinone (43) in a 50%

overall yield from (41). The effect in yield in changing from ammonium peroxodisulphate to potassium peroxodisulphate was however not observed when using both reagents for alkylations on the model compound (58) which in both cases produced the alkylated quinone (59) in the same yields (58%).



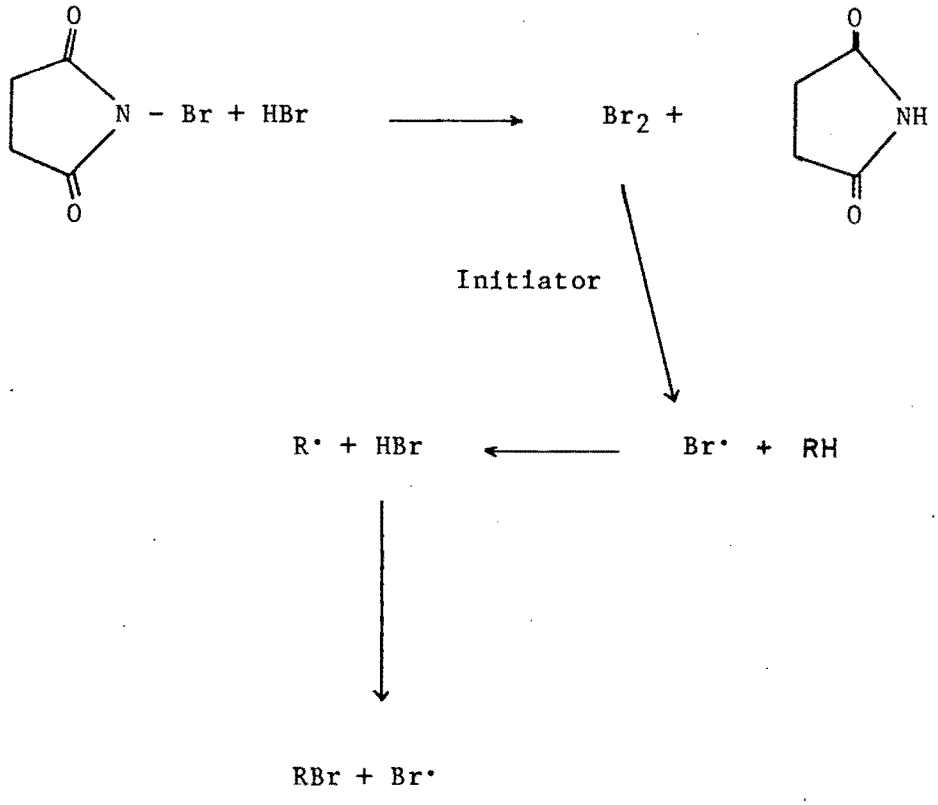
58



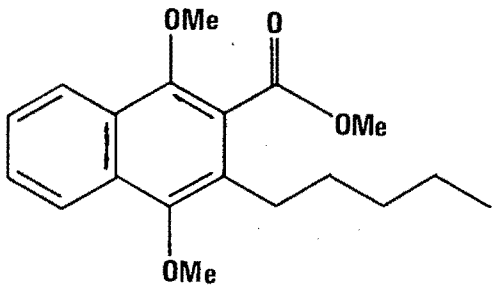
59

Reduction of the quinone (43) to the corresponding hydroquinone (44) proceeded smoothly with sodium dithionite. As before, the hydroquinone (44) was not isolated to prevent oxidation by the atmosphere and was methylated in high yield (95%) to the trimethoxy compound (45) with dimethyl sulphate. This product was an oil which later solidified on standing.

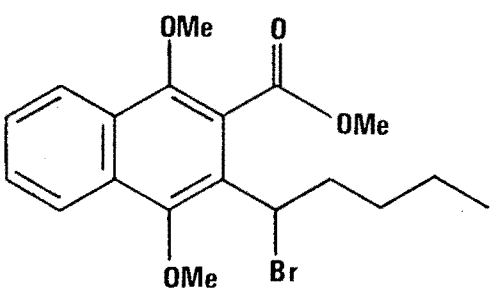
Allylic and benzylic brominations[17,18,19] have been extensively reviewed. A non-polar solvent (usually carbon tetrachloride) is used in which N-bromosuccinimide is insoluble. In fact a lack of solubility has been shown to be desirable[20]. The reaction operates from a pool of bromine that is generated initially from adventitious acid and later from generated acid. The following reactions are pertinent:



In the bromination of (45) it was envisaged that the reaction should be carried out under high dilution to promote benzylic bromination and to avoid the possibility of nuclear bromination. In practice it was found that no reaction occurred under high dilution. In order to avoid using compound (45) to establish conditions for the reaction, it was decided to use the far more accessible model ester (60), obtained by methylation of the corresponding acid[21].



60



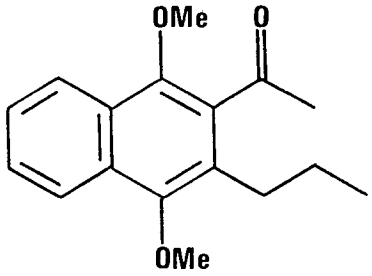
61

The reaction was carried out using 0,1g of (60) in 100ml of carbon tetrachloride for the complete conversion to the required bromo-compound

(61). However when using identical conditions (45) was not brominated to completion. In subsequent trial reactions it was found that the volume of carbon tetrachloride could be greatly reduced provided that the N-bromosuccinimide used was freshly recrystallized from water before use. In a typical reaction 0,1g of (45) was boiled in 10ml of carbon tetrachloride for three and a half hours to effect a complete conversion to the required bromo-compound (46). This bromo-compound was not isolated, nor purified due to its instability. In fact if it was left standing it became black. However the ^{1}Hn.m.r. spectrum of the crude product was found to be completely consistent with its proposed structure, showing inter alia a one-proton triplet at δ5,35 due to the remaining benzylic hydrogen. There were no signals in the spectrum due to the starting material, nor nuclear brominated material.

The next step in the synthesis was to dehydrobrominate (46) to the corresponding olefin (47). The best yield of this olefin achieved was 15%, using a variety of reagents and conditions which included boiling in 2,6-lutidine, boiling in acetone in the presence of butyl ammonium bromide and 2,6-lutidine, heating in dimethylsulphoxide in the presence of 2,6-lutidine and heating in tetrahydrofuran in the presence of potassium-t-butoxide. The product isolated was the trans olefin exclusively as shown by the large coupling constant (16Hz) of the olefinic protons.

Due to the fact that this was a long synthesis and we had run out of material to work on, it was decided rather to use the more readily available model compound (69) to prepare the demethoxy eleutherin (22) as a way to establish a general route to the naphthopyran quinones.



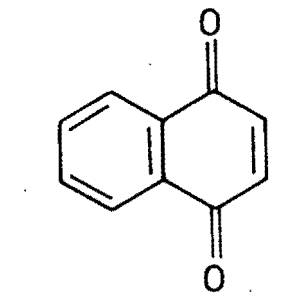
69

In scheme III the proposed synthetic sequence is outlined, which is basically the same as depicted in scheme I for the methoxy analogue. The reactions to obtain compound (69) will be described briefly for the sake of completeness.

Naphthoquinone (63) was reductively acetylated with zinc dust and acetic anhydride to yield 97% of the diacetate (64). This compound has been prepared before by Spruit[22]. The Fries rearrangement of 1,4-diacetoxynaphthalene (64) was carried out using zinc chloride as catalyst in an 85% yield. Acid hydrolosis of (65) proceeded quantitatively to yield 2-acetyl-1,4-dihydroxynaphthalene (66). The corresponding quinone (67) was produced by silver(I) oxide in a 74% yield. It is interesting to note that, although this quinone (67) is structurally similar to quinone (42), it is markedly more stable.

The alkylation of this quinone (67) was undertaken as described before for quinone (42) and yielded very similar results. When the alkylation was performed using ammonium peroxodisulphate as the source of radicals, only a 20% yield of the alkylated quinone (34) was obtained but when potassium peroxodisulphate was used, the yield was increased to 55%. Reductive methylation of this quinone (34) proceeded in quantitative yield to give (69).

Scheme III



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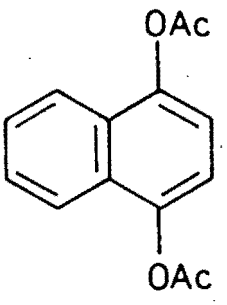
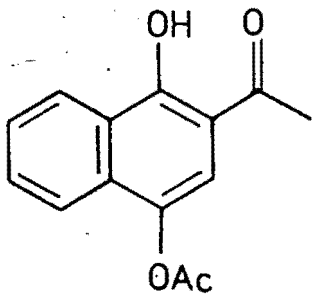
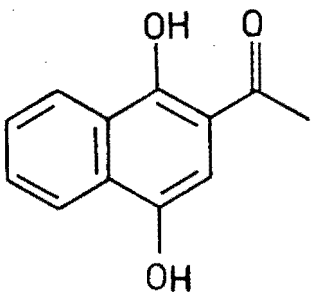


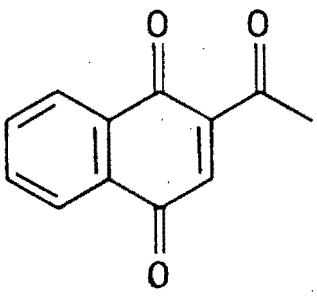
64



65



66



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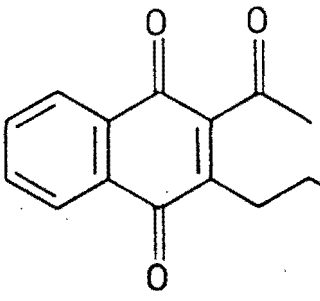

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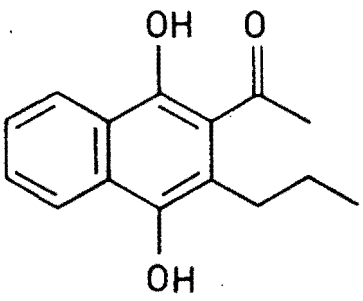
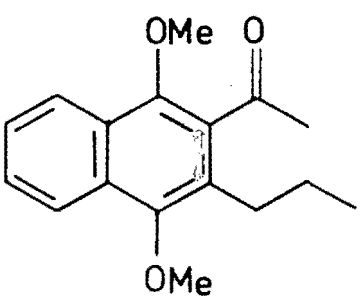
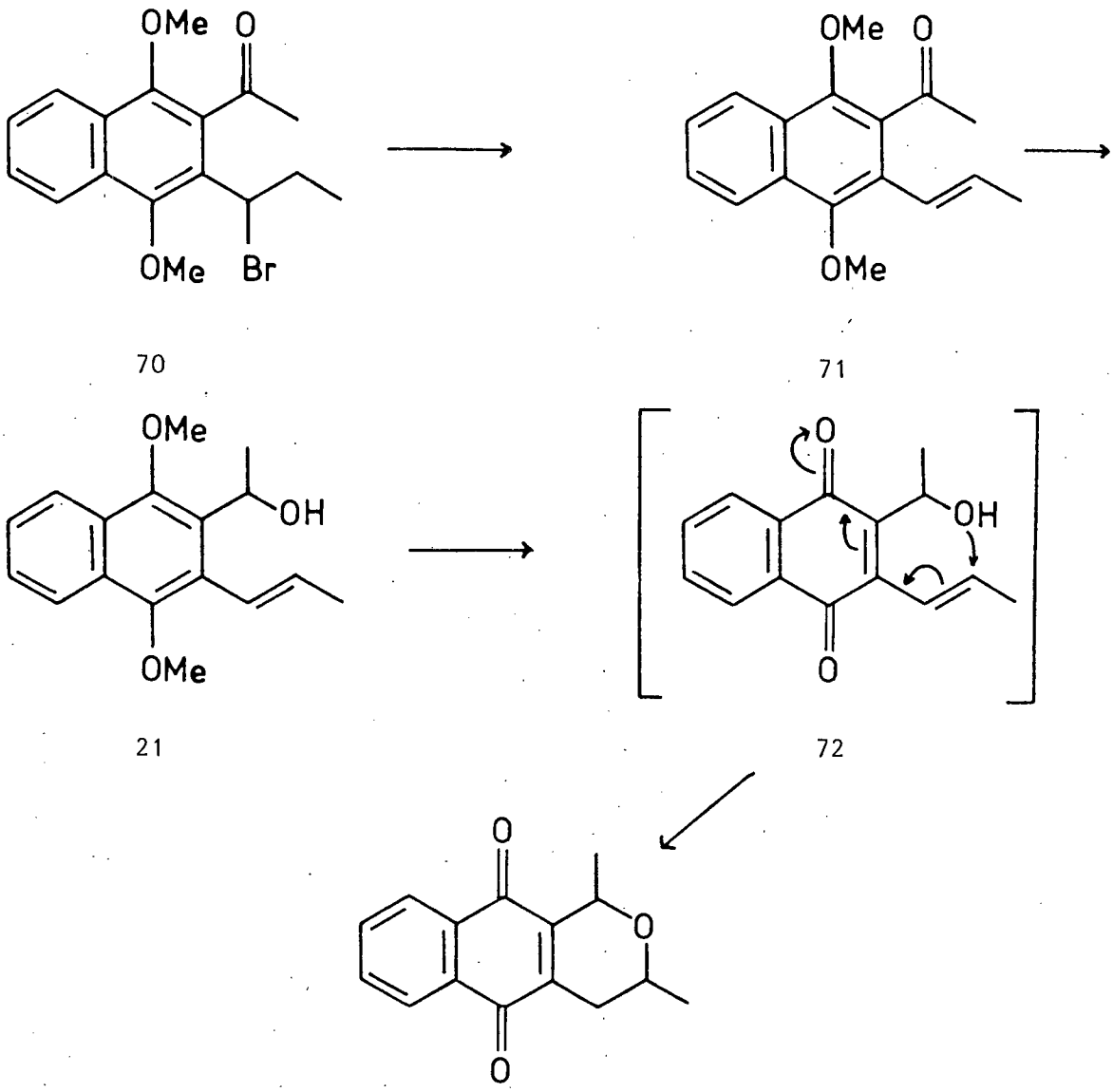


68



69

Scheme III (continued)



70 71

21 72

22

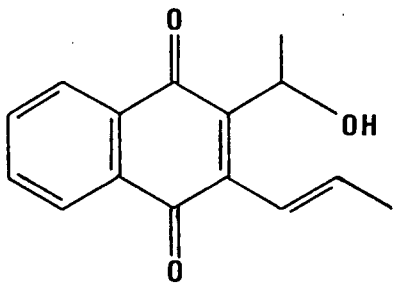
Bromination of (69) proceeded much more readily to afford the bromide (70), than was the case in the bromination of (45). A variety of reagents and conditions were used in the conversion of (70) to the trans olefin (71). The best procedure found was to heat the bromide (70) in dimethylformamide in the presence of 1,5-diazabicyclo[4,3,0]non-5-ene to yield 59% of the required olefin (71). Once again the trans olefin was produced exclusively as shown by the large coupling constant (16Hz) in its ^{1}Hn.m.r. spectrum.

Reduction of (71) to the corresponding alcohol (21) was achieved by extended stirring in absolute ethanol in the presence of an excess of sodium borohydride. Initially the reaction was tried in absolute methanol but no reduction took place. Feiser and Feiser[23] have pointed out that sodium borohydride reacts with methanol at an appreciable rate but only slowly with ethanol.

Thus if the reduction is "hard", ethanol is the preferred reaction medium. The yield of alcohol (21) was 93% after twelve hours stirring at room temperature. The slow reduction of the carbonyl group may be ascribed at least in part to its crowded environment, the aromatic ring to which it is attached being fully substituted.

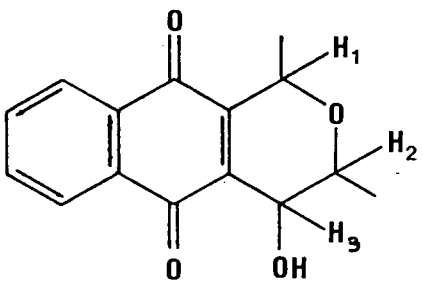
We were now in a position to test whether this alcohol (21) would cyclize spontaneously when treated with silver(II) oxide[15]. When (21) was treated with silver(II) oxide in acid medium the only isolatable product formed was (72; 60%). Thus the desired spontaneous cyclization had not taken place. Several attempts to effect cyclization of compound (72) were also unsuccessful. Thus compound (72) was treated with sodium hydride in tetrahydrofuran, yielding only starting material. Trifluroacetic acid was also used in an attempt to yield the desired

cyclized product (22) but this led to significant decomposition of the starting material.

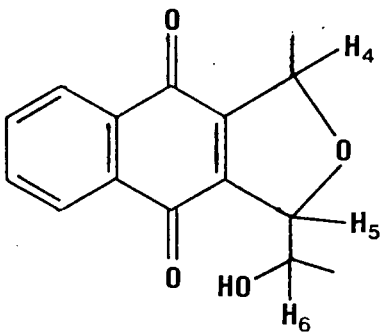


72

As pointed out earlier ceric ammonium nitrate[16] can also be used for oxidative demethylations. When compound (21) was treated with ceric ammonium nitrate, two compounds were isolated in yields of 33 and 65%. These two compounds were purified over silica (20% ethyl acetate/light petroleum). The front band eluted relatively easily whereas the back band was strongly adsorbed onto the silica. ^{1}Hn.m.r. spectra of both these bands proved to be very similar, probably indicating that both compounds had similar structures. Either of the two gross structures (73) and (74) could be proposed for these two compounds.



73



74

Elemental analysis of both compounds agreed with the proposed molecular formula. The strategy used to determine whether the pyran was a 5- or a 6-membered ring was to acetylate the free hydroxyl group and to observe

any shifts in the ^{1}Hn.m.r. spectra. This procedure was applied to both compounds. The spectrum of the band with lower R_F showed the three heterocyclic ring protons to have the following chemical shifts and appearances:

4,00 [1H, d x quartet, H_2 in (73), H_6 in (74)]

4,52 [1H, d, H_3 in (73), H_5 in (74)]

5,00 [1H, quartet, H_1 in (73), H_4 in (74)].

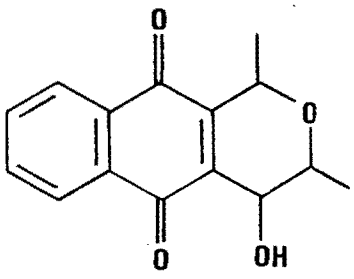
Thus on acetylation we should expect the doublet from H_3 to move to lower field if the proposed structure (73) was correct, or the doublet of quartets from H_6 to move to lower field if (74) was the correct structure. On acetylation the band of lower R_F showed the following spectrum for the heterocyclic ring protons:

4,09 (1H, d x quartet, H_2)

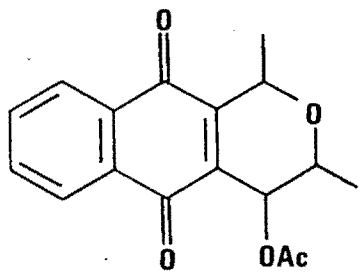
5,08 (1H, quartet, H_1)

5,97 (1H, d, H_3).

Thus, since it was the doublet that moved to lower field, the structure of this compound was (73) and that of the acetylated product (75).



73



75

Similarly the ^{1}Hn.m.r. spectrum of the band of higher R_F showed the

following chemical shifts and appearances for the three heterocyclic protons:

3,85 [1H, d x quartet, H_2 in (73), H_6 in (74)]

4,48 [1H, d x d, H_3 in (73), H_5 in (74)]

4,94 [1H, d x quartet, H_1 in (73), H_4 in (74)].

After acetylation the following pattern appeared:

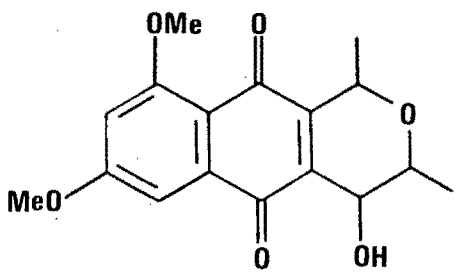
4,14 (1H, apparent quintet, H_2)

4,93 (1H, d x quartet, H_1)

5,78 (1H, d x d, H_3).

Thus, again since it was the doublet of doublets that moved to lower field, the compound of higher R_F also contained the 6-membered pyran ring system and both products were therefore stereoisomers. All that remained was to determine the stereochemistries of both compounds.

Cameron[24] has made a detailed study of the ^{1}Hn.m.r. spectra of the substituted naphthoquinone dimethyl ethers derived from protoaphin-fb and protoaphin-sl (76).



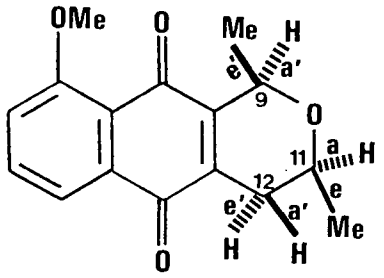
76

He used the analysis of the ^{1}Hn.m.r. spectra of eleutherin (1) and

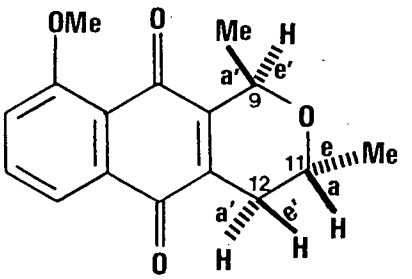
isoeleutherin (2) to deduce information about the configurations and conformations of the partially saturated rings in the naphthoquinone dimethyl ethers derived from protoaphin-fb and protoaphin-sl.

Since the structure of our two isolates (73) closely resemble (76), we were thus able to use similar arguments to deduce the stereochemistries of compounds (73). In order to deduce the stereochemistries it is first necessary to digress to discuss the analysis of the ^{1}Hn.m.r. spectra of eleutherin (1) and isoeleutherin (2).

Eleutherin (1) and isoeleutherin (2) have been shown by Schmid[2,3] and his co-workers to have the following stereochemical structures (1) and (2)*.



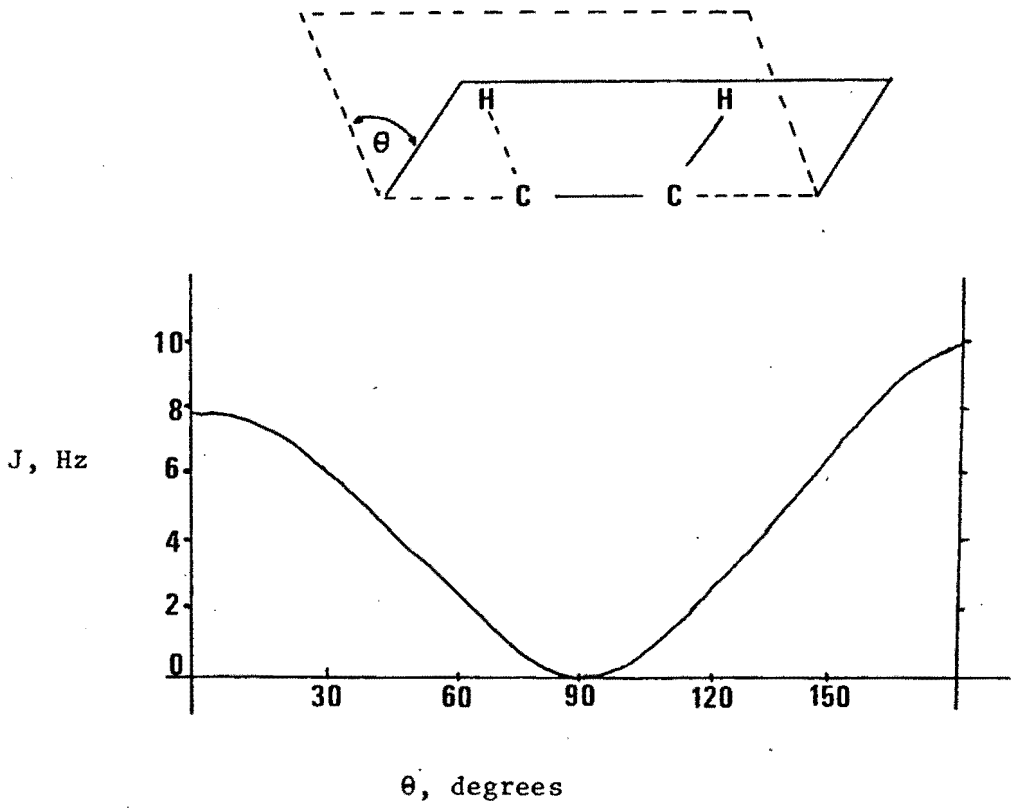
Eleutherin 1



Isoeleutherin 2

The symbols a' and e' denote pseudo-axial and pseudo-equatorial configurations of the bonds in question in the chair-like conformation of the partially unsaturated ring. A useful tool for determining the stereochemistries of protons on adjacent carbon atoms is to use the Karplus equation[25,26]. The dihedral angle θ between planes determines the coupling of protons on adjacent carbon atoms as shown in the figure overleaf.

* The numbering of this ring system in the discussion is that used in the earlier literature[24] for ease of comparison. However IUPAC nomenclature is used in the experimental.



Thus adjacent axial-axial protons, having a dihedral angle of 180° are strongly coupled (ca. 10Hz), whereas axial-equatorial and equatorial-axial protons, having a dihedral angle θ of about 60°, should only be moderately coupled.

Thus in the case of eleutherin (1) and isoeleutherin (2) we should observe a relatively large $J^{a'a}$ and a smaller $J^{e'a}$ vicinal coupling constant. Karplus[27] has also shown that long range proton-proton couplings in the CH-C=C-CH system should be greatest where the CH bonds are perpendicular to the plane of the double bond. Thus the pseudo-axial configuration (a') will give rise to a greater angle between the direction of the CH bond and the plane of the double bond than would the pseudo-equatorial (e') configuration. Thus the magnitudes of these coupling constants should be as follows for $J_{9,12}$: $J^{a'a'} > J^{a'e'} \approx J^{e'a'} > J^{e'e'}$. The following table lists the assignments of coupling constants for eleutherin (1) and isoeleutherin

(2) (taken from reference 24).

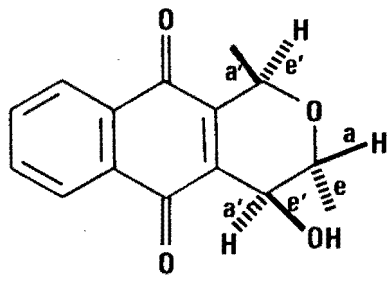
Coupling Constant (Hz)			
Eleutherin		Isoeleutherin	
$J^{gem}_{12,12}$	17,8	$J^{gem}_{12,12}$	18,8
$J^{a'a}_{12,11}$	9,2	$J^{a'a}_{12,11}$	8,8
$J^{e'a}_{12,11}$	2,9	$J^{e'a}_{12,11}$	4,5
$J^{a'a'}_{9,12}$	3,5	$J^{e'a'}_{9,12}$	2,0
$J^{a'e'}_{9,12}$	2,9	$J^{e'e'}_{9,12}$	1

Thus we are now in a position to assign stereochemistries to the two compounds (73) isolated.

We shall consider the compound with higher R_F first. The chemical shifts and coupling constants from its ^{1}Hn.m.r. spectrum are shown overleaf:

Grouping	Chemical shift (δ)	Coupling Constant (Hz)
$C-CH_3$ (11)	1,41 (d)	6,5
$C-CH_3$ (9)	1,59 (d)	7
CH-O (11)	3,85 (d x quartet)	8 and 6,5
CH (12)	4,47 (d x d)	8 and 2
CH-O (9)	4,92 (d x quartet)	7 and 2

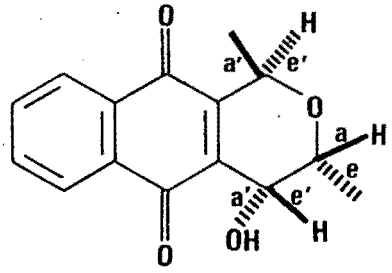
Assignments of the coupling constants are as follows : $J_{12,11}$ 8Hz, $J_{9,12}$ 2Hz. The large coupling constant of $J_{12,11}$ 8Hz indicates that these two vicinal CH bonds have essentially axial configurations. This thus fixes the hydroxyl group on C_{12} as pseudo-equatorial and the methyl group at C_{11} as [illegible] equatorial. The long range coupling constant $J_{9,12}$ 2Hz indicates that the CH bond on C_9 has the pseudo-equatorial position since the CH bond on C_{12} is pseudo-axial. Thus the stereochemistry of this front band is:



The chemical shifts and coupling constants from the ^{1}Hn.m.r. spectrum of the compound of lower R_F are shown below:

Grouping	Chemical shift (δ)	Coupling Constant (Hz)
C-CH_3 (11)	1,41 (d)	6,5
C-CH_3 (9)	1,52 (d)	7,5
CH-O (11)	4,00 (d X quartet)	6,5 and 2,5
CH (12)	4,52 (d)	2,5
CH-O (9)	5,00 (quartet)	7,5

In this spectrum there is a negligible coupling constant for $J_{9,12}$ suggesting that both CH bonds on C_9 and C_{12} have the pseudo-equatorial configurations. This thus fixes both the methyl group at C_9 and the hydroxyl group on C_{12} as pseudo-axial. The vicinal coupling constant $J_{12,11}$ 2,5Hz is consistent with H at C_{11} in the axial configuration, (since the H at C_{12} is pseudo-equatorial). Thus the detailed stereochemistry of the compound of lower R_F is:



The stereochemistries assigned for the hydroxyls in compounds (24) and (25) are supported by their relative R_F values. The compound with the pseudo-equatorial hydroxyl would possess a stronger intramolecular hydrogen bond with the peri quinonoid carbonyl, since models show the two substituents to be closer and this compound would therefore be expected to have a higher R_F. The converse would be expected for the compound with a pseudo-axial hydroxyl.

The steroeochemistries observed for the two compounds may be explained as follows. The methyl group at C_{11} adopts the less crowded equatorial position. The methyl at C_9 adopts a pseudo-axial configuration as this is less crowded, since in the pseudo-equatorial environment it would be subjected to greater interaction with the peri quinonoid carbonyl. The hydroxyl at C_{12} similarly prefers to adopt a pseudo-axial configuration for the same reason, but there are two reasons mitigating against it being exclusively pseudo-axial; firstly its steric volume is considerably less than that of the methyl group, and secondly, while pseudo-equatorial, the hydroxyl is better able to participate in hydrogen bonding with the neighbouring carbonyl, as mentioned earlier. Nevertheless, the relative propotions of (24) to (25) found in the reaction show that the hydroxyl has a preference for the pseudo-axial site.

As far as our initial aims were concerned, we had shown that quinone (72) did not undergo ready cylization to an 8-demethoxyeleutherin, and thus there seemed no point in returning to our previous synthesis of the eleutherins, since it would be expected that similar products would result if the above reaction sequence was followed. However, an important result arising out of the synthesis of (24) and (25) was the

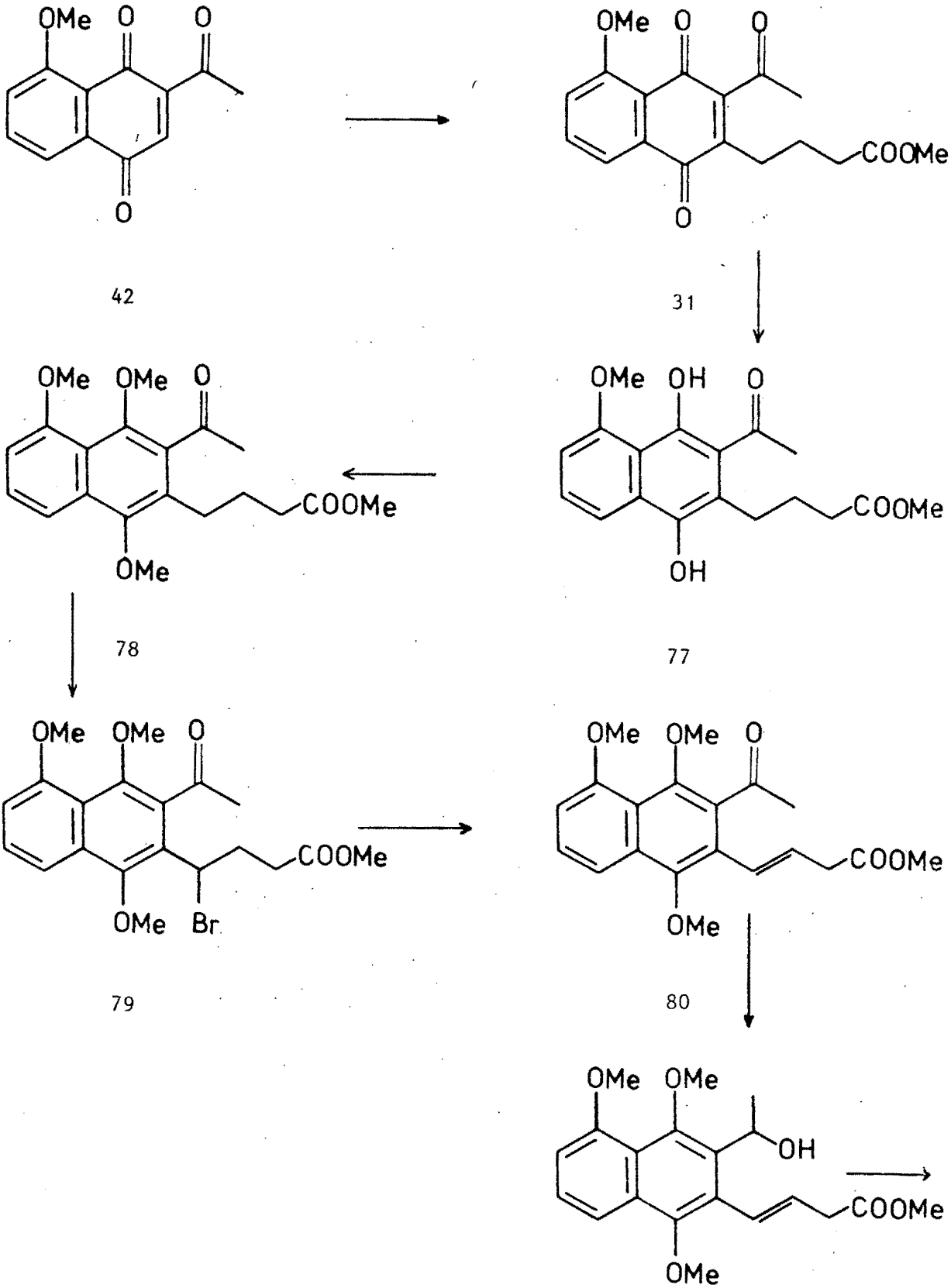
introduction of the hydroxyl group on C_{12}. By using the same sequence of reactions it would thus be possible to synthesize nanaomycin D (7) and a variety of other natural products possessing oxygen at this position. The proposed synthetic route to nanaomycin D is outlined in scheme IV.

Quinone (42) was successfully alkylated with monomethylglutarate in the presence of silver nitrate and potassium peroxodisulphate according to the procedure we adopted earlier to synthesize quinones (33) and (34). The overall yield of the alkylated quinone (31) was 55% from (41). The quinone (31) was reduced to the corresponding hydroquinone (77) with aqueous sodium dithionite. This was not isolated, to avoid aerial oxidation, but was methylated with dimethyl sulphate to the trimethyl ether (78) in an 88% yield.

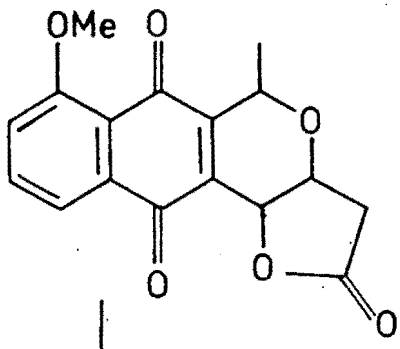
Benzylic bromination of (78) with N-bromosuccinimide was successful to form the bromo-derivative (79), but when this compound was subjected to identical conditions as were used to produce (71) from (70), no product (80) could be isolated from the reaction mixture. Changing the conditions of the reaction did not result in any improvement and thus the reaction pathway was abandoned.

It is interesting to note that similar difficulty was experienced with the dehydrobromination of (46). The failure of these reactions can best be explained by the higher electron density in the aromatic systems (79) and (46) which must lead to serious side reactions. A possible solution to this problem might be to decrease the electron density in the aromatic system by synthesizing (82) and to proceed as outlined in scheme IV.

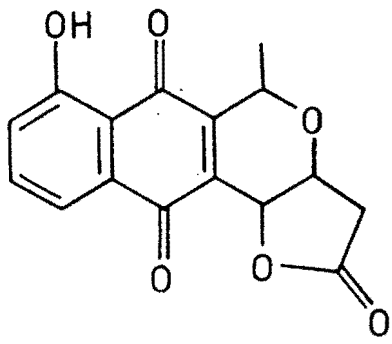
Scheme IV


OMe O O
O
COOMe
42
31
OMe OH O
OH
77
OMe OMe O
OMe
78
OMe OMe O
OMe Br
79
80
OH
28

Scheme IV (continued)

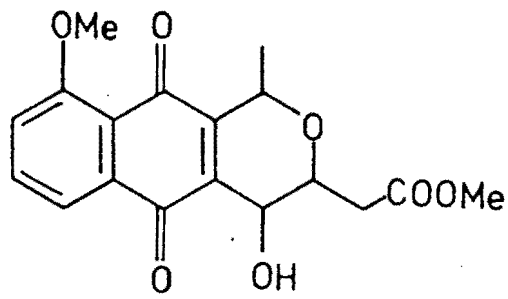


81

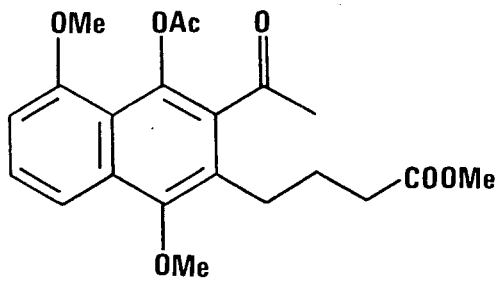


Nanaomycin D7

or

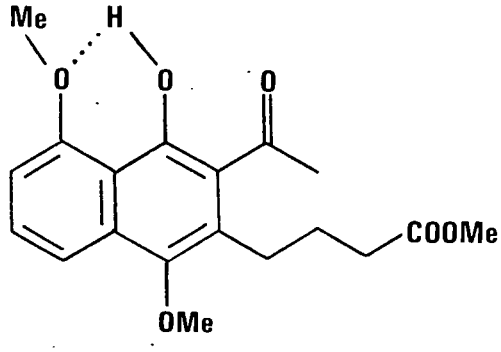


29



82

This compound (82) has subsequently been prepared by Professor Giles and Dr. Mitchell as follows. Boron trichloride demethylation of the trimethyl ether (78) cleanly afforded the dimethyl ether (83) which was acetylated with acetic anhydride and pyridine to give compound (82). Whether this compound will lend itself to bromination-dehydrobromination in the desired sense remains to be seen.



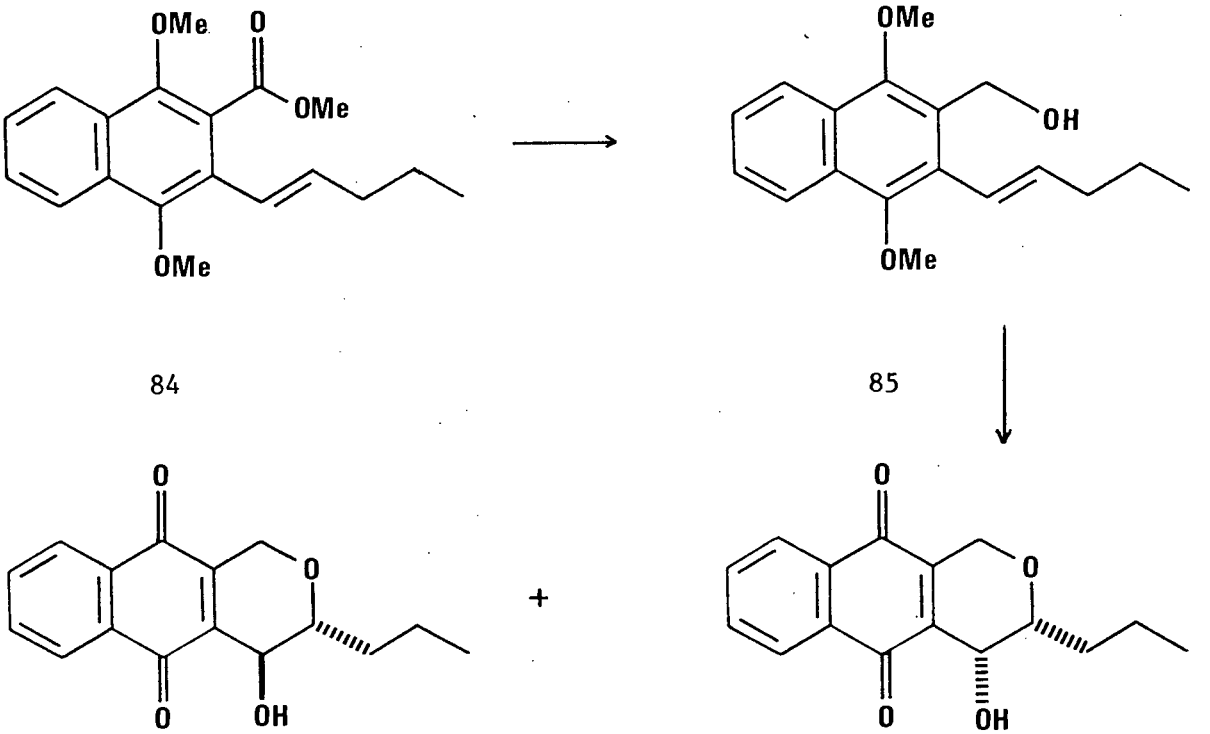
83

The n.m.r. spectrum of (83) showed the hydrogen bonded hydroxyl at δ 9,47 suggesting hydrogen bonding to the <u>peri</u> methoxyl rather than to the <u>ortho</u> acetyl [c.f. δ8,92 for the hydrogen bonded hydroxyl hydrogen in compound (39)]. This may be the result of steric crowding preventing the hydroxyl and the acetyl oxygen from being sufficiently close for hydrogen bonding between them. It is noteworthy that no low field hydrogen-bonded hydrogen was observed in the ^{1}Hn.m.r. spectrum of quinone (72), another crowded system which would otherwise be expected to show hydrogen

bonding. On the other hand, the proton under discussion in compound (83) can be contrasted with the very low field proton of the less crowded analogue (41) at δ 13,46.

Finally, Professor Giles and Dr. Green have since shown that the related primary alcohol (85) undergoes similar cyclization with ceric ammonium nitrate, to afford the stereoisomeric quinones (86) and (87). The alcohol (85) was obtained by dehydrobromination of the bromo ester (61) in boiling 2,6-lutidine to give the ester (84), followed by lithium aluminium hydride reduction, (Scheme V).

Scheme V



This indicates that the cyclization may provide a general route to

naphtho[2,3-c]pyran-5,10-quinones. In addition, removal of the 4-hydroxyl group from appropriately substituted systems would give rise to natural products such as the eleutherins (1) and (2) and nanaomycin A (4).

Experimental

1. Infrared spectra were measured for chloroform solutions on a Perkin-Elmer 237 Grating Infrared Spectrophotometer.

2. Nuclear magnetic resonance spectra were recorded for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference on a Varian XL-100, 100MHz spectrometer or on a Brüker WH-90 spectrometer.

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

4. Column chromatography was performed on dry columns using Merck Kieselgel 60 (70-230 mesh), the material to be separated being preadsorbed onto Merck Kieselgel 60 (35-70 mesh).

5. Light petroleum refers to the fraction of boiling point 60-80°C.

5-Methoxy-1,4-naphthoquinone, (juglone methyl ether): (36)

Juglone (35; 7,10g), silver(I) oxide (9,2g), dry magnesium sulphate (10,0g) and methyl iodide (12,0ml) in dichloromethane (150ml) were stirred at room temperature in the dark for two days. Further addition of methyl iodide did not result in complete reaction, so the reaction mixture was filtered and purified on a dry column, (eluant 5% ethyl acetate/light petroleum - 50% ethyl acetate/light petroleum). This yielded juglone (35; 0,14g) and juglone methyl ether (36; 6,42g; 84%). An analytical sample was recrystallized from light petroleum to yield fine yellow needles, m.p.177-179°C dec. (Lit.[13,28] 180-185 and 182-185°C). (Found: C, 70,1; H, 4,4. $C_{11}H_8O_3$ requires C, 70,2; H, 4,3%); $\nu_{max.}(CHCl_3)$ 1670, 1625 and 1600 cm^{-1}; $\delta(CDCl_3)$ 4,01 (3H, s, OCH_3), 6,87 (2H, s, quinonoid H), 7,31 (1H, dd, J 4 and 7Hz, 6-H decoupled to a singlet on irradiation of 7- and 8-H), and 7,71 (2H, m, 7- and 8-H).

1,5-Dimethoxy-4-naphthol: (39)

Juglone methyl ether (36; 6,34g) was dissolved in dichloromethane (150ml) and diethyl ether (200ml). This solution was shaken with an aqueous sodium dithionite solution (60g; 200ml) in a separatory funnel. The colourless organic phase was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed by a stream of nitrogen. The crude hydroquinone (37) was dissolved in dry acetone (300ml), dimethyl sulphate (12,6ml) and dry potassium carbonate (12,8g) were added and the

mixture was boiled for five hours under a positive pressure of nitrogen. The solution was cooled, filtered and the solvent removed. The excess of dimethyl sulphate was decomposed by the addition of aqueous ammonia solution. The solution was extracted with dichloromethane and washed successively with dilute aqueous hydrochloric acid and water and dried over anhydrous magnesium sulphate. The solution was filtered and the solvent evaporated to yield a white crystalline solid (39; 6,47g; 94%). An analytical sample was recrystallized from light petroleum, m.p.155,5-156,5°C. (Lit. [28,30] 155-156°C). (Found: C, 70,6; H, 5,8. $C_{12}H_{12}O_3$ requires C, 70,6; H, 5,9%); $\nu_{max.}$($CHCl_3$) 3420, 1643 and 1628cm^{-1}; δ($CDCl_3$) 3,92 (3H, s, OCH_3), 4,02 (3H, s, OCH_3), 6,77 (2H, s, 2- and 3-H), 6,81 (1H, d, J 8Hz, 6-H), 7,31 (1H, t, J 8Hz, 7-H), 7,85 (1H, d, J 8Hz, 8-H), and 8,92 (1H, s, OH, disappears in D_2O wash).

4-Acetoxy-1,5-dimethoxynaphthalene: (40)

1,5-Dimethoxy-4-naphthol (39; 3,67g), acetic anhydride (13ml) and pyridine (74ml) were heated under reflux for two hours, cooled, thrown onto ice and the white crystalline solid filtered, washed with water and vacuum dried to yield (40; 4,25g; 96%). An analytical sample was recrystallized from light petroleum m.p.119-120°C. (Found: C, 68,3; H, 5,8. $C_{14}H_{14}O_4$ requires C, 68,3; H, 5,7%); $\nu_{max.}$($CHCl_3$) 1760 and 1615 cm^{-1}; δ($CDCl_3$) 2,35 (3H, s, $COCH_3$), 3,91 (3H, s, OCH_3), 3,96 (3H, s, OCH_3), 6,74 (1H, d, J 8Hz, 2-H), 6,87 (1H, d, J 8Hz, 6-H), 6,96 (1H, d, J 8Hz, 3-H), 7,37 (1H, t, J 8Hz, 7-H), and 7,88 (1H, d, J 8Hz, 8-H).

3-Acetyl-1,5-dimethoxy-4-naphthol: (41)

4-Acetoxy-1,5-dimethoxynaphthalene (40; 1,39g) and boron trifluoride etherate (2,8ml) were heated in an oil bath maintained at 60°C for thirty minutes. The reaction mixture was thrown onto ice (20ml), extracted with dichloromethane, the organic phase separated and dried over anhydrous magnesium sulphate. The solution was filtered and chromatographed over silica (eluant 5% ethyl acetate/light petroleum - 15% ethyl acetate/light petroleum), to yield 1,5-dimethoxy-4-naphthol (39; 0,28g) and product (41; 0,96g, 69%). An analytical sample was recrystallized from light petroleum to yield dark green needles, m.p.132,5-133,5°C. (Found: C, 68,0; H, 5,65. $C_{14}H_{14}O_4$ requires C, 68,3; H, 5,70%); $\nu_{max.}$($CHCl_3$) 3365, 1635, 1618 and 1590 cm^{-1}; δ($CDCl_3$) 2,69 (3H, s, $COCH_3$), 3,95 (3H, s, OCH_3), 4,04 (3H, s, OCH_3), 6,95 (1H, d, J 8Hz, 6-H), 6,97 (1H, s, 2-H), 7,51 (1H, t, J 8Hz, 7-H), 7,85 (1H, d, J 8Hz, 8-H), and 13,46 (1H, s, OH, disappears in D_2O wash).

3-Acetyl-5-methoxy-1,4-naphthoquinone: (42)

3-Acetyl-1,5-dimethoxy-4-naphthol (41; 0,50g) was dissolved in dioxane (20ml) and to this solution was added silver(II) oxide (1,02g) and nitric acid (6M; 2,0ml). The mixture was stirred for one minute at room temperature, the reaction being terminated by the addition of dichloromethane/water (8:2; 20ml). The reaction mixture was extracted with dichloromethane, the organic phase separated and washed successively with water, aqueous sodium bicarbonate then water and dried over anhydrous magnesium sulphate. The solution was filtered and without purification was used in subsequent chemical reactions. However an

analytical sample was recrystallized from light petroleum to yield fine yellow needles, m.p.102-103,5°C (Lit.[9] 103,5-104,5°C). (Found: C, 67,7; H, 4,4. $C_{13}H_{10}O_4$ requires C, 67,8; H, 4,4%); $\nu_{max.}$($CHCl_3$) 1715, 1675 and 1600 cm^{-1}; δ($CDCl_3$) 2,62 (3H, s, $COCH_3$), 4,04 (3H, s, OCH_3), 7,00 (1H, s, quinonoid H), 7,39 (1H, dd, J 4Hz, 6-H), and 7,72 (2H, m, 6- and 7-H).

3-Acetyl-5-methoxy-2-propyl-1,4-naphthoquinone: (43)

3-Acetyl-5-methoxy-1,4-naphthoquinone (42), without purification, was dissolved in acetonitrile/water (10 : 6; 0,64ml) and to this solution was added silver nitrate (0,64g), butyric acid (0,45ml), and the mixture stirred at 65-70°C (external bath temperature). Potassium peroxodisulphate (2,12g) in water (20ml) was added dropwise over one hour. The mixture was heated for a further fifteen minutes, cooled, thrown into water and extracted with dichloromethane. The organic phase was separated and washed successively with water, aqueous sodium bicarbonate and water, and dried over anhydrous magnesium sulphate. The solution was filtered and chromatographed over silica (eluant 10% ethyl acetate/light petroleum) to yield 0,28g of product [51% from (41)]. An analytical sample was recrystallized from light petroleum to yield fine yellow needles m.p.130,5-131,5°C. (Found: C, 70,5; H, 5,8. $C_{16}H_{16}O_4$ requires C, 70,6; H, 5,9%); $\nu_{max.}$($CHCl_3$) 1715, 1675 and 1600 cm^{-1}; δ($CDCl_3$) 0,97 (3H, t, J 8Hz, 3'-CH_3), 1,55 (2H, sextet, J 8Hz, 2'-CH_2), 2,41 (2H, t, J 8Hz, 1'-CH_2), 2,49 (3H, s, $COCH_3$), 4,01 (3H, s, OCH_3), 7,24 (1H, dd, J 4 and 8Hz, 6-H), and 7,72 (2H, m, 7- and 8-H).

3-Acetyl-2-propyl-1,4,5-trimethoxynaphthalene: (45)

3-Acetyl-5-methoxy-2-propyl-1,4-naphthoquinone (43; 0,65g) was dissolved in dichloromethane (5ml) and diethyl ether (20ml) and shaken with an aqueous solution of sodium dithionite (6g in 50ml). The organic phase was separated, dried over anhydrous magnesium sulphate, filtered and the solvent removed by a stream of nitrogen. The crude hydroquinone (44) was dissolved in dry acetone (50ml) and to this solution was added dimethyl sulphate (0,9ml) and potassium carbonate (1,32g), the mixture being boiled for two hours under a positive pressure of nitrogen. The solution was cooled, filtered and the solvent removed and the excess of dimethyl sulphate decomposed by the addition of aqueous ammonia solution. The solution was extracted with dichloromethane, the organic phase separated and washed successively with water, dilute aqueous hydrochloric acid, water and finally dried over anhydrous magnesium sulphate. The solution was filtered and chromatographed over silica to yield 0,68g of product (95%). An analytical sample was recrystallized from light petroleum to yield colourless plates m.p.85-86°C. (Found: C, 71,3; H, 7,3. $C_{18}H_{22}O_4$ requires C, 71,5; H, 7,3%); $\nu_{max.}$($CHCl_3$) 1700, 1625 and 1600 cm^{-1}; δ($CDCl_3$) 0,98 (3H, t, J 8Hz, CH_3), 1,60 (2H, sextet, J 8Hz, 2'-CH_2), 2,62 (5H, s and t overlapped, 1'-CH_2 and $COCH_3$), 3,79 (3H, s, OCH_3), 3,88 (3H, s, OCH_3), 4,01 (3H, S, OCH_3), 6,87 (1H, d, J 8Hz, 6-H), 7,43 (1H, t, J 8Hz, 7-H) and 7,68 (1H, d, J 8Hz, 8-H).

3-Acetyl-2-(2'-bromopropyl)-1,4,5-trimethoxynaphthalene: (46)

3-Acetyl-2-propyl-1,4,5-trimethoxynaphthalene (45; 0,098g), N-bromosuccinimide (0,069g), di-t-butyl peroxide (4ml) and carbon

tetrachloride (20ml) were heated under reflux for three and a half hours. The mixture was cooled, the solvent removed and filtered. The product was not purified due to its inherent instability, but its ^{1}Hn.m.r. spectrum was completely consistent with the proposed structure. $\delta(CDCl_3)$ 1,00 (3H, t, J 7Hz, 3'-CH_3), 2,39 (2H, quintet, J 7Hz, 2'-CH_2), 2,74 (3H, s, $COCH_3$), 3,78 (3H, s, OCH_3), 4,02 (6H, s, 2 x OCH_3), 5,34 (1H, t, J 8Hz, 1'-CH), 6,93 (1H, d, J 8Hz, 6-H), 7,46 (1H, t, J 8Hz, 7-H), and 7,71 (1H, d, J 8Hz, 8-H).

trans 3-Acetyl-1,4,5-trimethoxy-2-(prop-1'-enyl)naphthalene: (47)

The foregoing bromo compound (46), was boiled with 2,6-lutidine (5ml) for half an hour. The mixture was cooled, and the excess of lutidine removed under vacuum. The residue was taken up in dichloromethane and washed with water, and chromatographed over silica (eluant 5% ethyl acetate/light petroleum - 10% ethyl acetate/light petroleum) to yield 0,0148g of the product (15%). The ^{1}Hn.m.r. spectrum of this compound was found to be consistent with its proposed structure. $\delta(CDCl_3)$, 1,92 (3H, d, J 6Hz, 3'-CH_3), 2,50 (3H, s,$COCH_3$), 3,82 (6H, s, 2 x OCH_3), 4,02 (3H, s, OCH_3), 6,13 (1H, d x quartet, J 6 and 16Hz, 2'-CH), 6,44 (1H, d, J 16Hz, 1'-CH), 6,88 (1H, d, J 8Hz, 6-H), 7,43 (1H, t, J 8Hz, 7-H), and 7,74 (1H, d, J 8Hz, 8-H).

1,5-Dimethoxynaphthalene: (53)

1,5-Dihydroxynaphthalene (52; 20,95g), potassium carbonate (10g) and dimethyl sulphate (28ml) were boiled in acetone (200ml) for two hours. The reaction mixture was cooled, filtered and the solvent removed. Excess dimethyl sulphate was decomposed by the addition of aqueous ammonia solution. The solution was extracted with dichloromethane, the organic phase separated, and washed successively with water, dilute aqueous hydrochloric acid and water and dried over anhydrous magnesium sulphate. The solution was filtered and the solvent removed to yield colourless crystals (23,5g; 95%) m.p.181,5-182°C (light petroleum).

1,5-Dimethoxy-4-naphthol: (39)

As an alternative route, this compound (39) was prepared by the method of Rapoport[13] from 1,5-dimethoxynaphthalene (53).

(a) 4,8-Dimethoxy-1-naphthalenecarboxaldehyde: (54)

Yield 94%, m.p.128,5-129,5°C (light petroleum). (Lit.[13,29] 125-126 and 124-126°C). (Found: C, 72,2; H, 5,6. $C_{13}H_{12}O_3$ requires C, 72,20; H, 5,60%); $\nu_{max.}$($CHCl_3$) 1677, 1625, 1600 and 1583 cm^{-1}; δ(C_6D_6) 3,23 (3H, s, OCH_3), 3,32 (3H, s, OCH_3), 6,33 (1H, d, J 8Hz, 7-H), 6,49 (1H, d, J 7Hz, 3-H), 7,18 (1H, t, J 7Hz, 6-H), 8,09 (1H, d, J 8Hz, 5-H), 8,26 (1H, d, J 8Hz, 2-H), and 11,27 (1H, s, CHO).

(b) Baeyer-Villager oxidation of (54): (55)

Yield 77%. (Found: C, 67,2; H, 5,2. $C_{13}H_{12}O_4$ requires C, 67,25; H, 5,20%); $\nu_{max.}$($CHCl_3$) 1740 and 1613 cm^{-1}; δ($CDCl_3$) 3,91 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 6,64 (1H, d, J 8Hz, 7-H), 6,89 (1H, d, J 8Hz, 3-H), 7,04 (1H, d, J 8Hz, 5-H), 7,39 (1H, t, J 8Hz, 6-H), 7,90 (1H, d, J 8Hz, 2-H), and 8,33 (1H, s, OCHO).

(c) 1,5-Dimethoxy-4-naphthol: (39)

Yield 73%, m.p.155-156°C (light petroleum) (Lit.[13,30] 155-156°C).

1,4-Diacetoxynaphthalene: (64)

1,4-Naphthoquinone (63; 55g), zinc dust (45g) and sodium acetate (10g) were added to acetic anhydride (350ml) and stirred vigorously while the temperature was raised to 90°C and maintained there for twelve hours. During this time the colour of the solution changed from yellow to almost colourless. Hot acetic acid (300ml) was then added, and the mixture brought to the boil and then rapidly filtered. The filtrate was poured onto ice, stirred and filtered, the filter cake was washed with water and dried to yield 78g (97%) of the diacetate (64). An analytical sample was recrystallized from ethanol m.p.127-128°C. (Lit.[31] 128-129°C).

4-Acetoxy-2-acetyl-1-naphthol: (65)

To a solution of crushed anhydrous zinc chloride (72g) in glacial acetic acid (160ml) was added 1,4-diacetoxynaphthalene (64; 72g) and the mixture was then rapidly heated to boiling for thirty minutes. The mixture was then cooled, thrown into an ice water mixture (5 litres) and stirred for fifteen minutes until crystallization was complete. The crystals were filtered, washed with aqueous cold ethanol (30% ethanol) and dried, yielding 85% product. An analytical sample was recrystallized from cyclohexane to afford yellow-green needles, m.p.96°C (Lit. [31,32] 103-104°C).

2-Acetyl-1,4-dihydroxynaphthalene: (66)

4-Acetoxy-2-acetyl-1-naphthol (65; 11,5g) was dissolved in ethanol (120ml) with heating. Concentrated hydrochloric acid (60ml) in water (40ml) at 60°C, was added to the ethanolic solution. The resulting mixture was heated under reflux for fifteen minutes, cooled, and poured into water and chilled for twelve hours, whereupon fine yellow crystals precipitated. There were filtered to yield (66) in quantitative yield, m.p.204-206°C (benzene) (Lit.[31,32] 206 and 206-208°C).

2-Acetyl-1,4-naphthoquinone: (67)

2-Acetyl-1,4-dihydroxynaphthalene (66; 10,5g) in ether (900ml) plus freshly prepared silver(I) oxide (36g) and sodium sulphate (43g) were

stirred at room temperature for twenty minutes, filtered and the solvent removed to yield a brown crystalline mass. This residue was extracted with boiling cyclohexane to yield long green-yellow flat needles (7,62g; 74%) m.p.82-83°C (cyclohexane) (Lit.[31,32] 84 and 83-84°C). $\nu_{max.}$($CHCl_3$) 1690, 1664, 1588 and 1237 cm^{-1}; δ($CDCl_3$) 2,64 (3H, s, $COCH_3$), 7,14 (1H, s, 3-H), 7,80 (2H, m, 6- and 7-H), and 8,10 (2H, m, 5- and 8-H).

2-Acetyl-3-propyl-1,4-naphthoquinone: (34)

2-Acetyl-1,4-naphthoquinone (67; 2,0g) and butyric acid (1,32g) were dissolved in acetonitrile (50ml). An aqueous solution of silver nitrate (1g in 1ml) was added and the mixture stirred at 65-70°C. Potassium peroxodisulphate (4,5g) in water (70ml) was added slowly over forty five minutes at constant temperature. The solution was cooled, filtered, thrown into water and extracted with chloroform. The organic phase was separated and washed with sodium bicarbonate and chromatographed over silica (eluant 20% ethyl acetate/light petroleum) to yield an oil (1,33g; 55%). (Found: C, 74,65; H, 5,7. $C_{15}H_{14}O_3$ requires C, 74,4; H, 5,8%); δ($CDCl_3$) 0,99 (3H, t, J 7Hz, 3'-CH_3), 1,58 (2H, sextet, J 7Hz, 2'-CH_2), 2,47 (2H, t, J 7Hz, 1'-CH_2), 2,51 (3H, s, $COCH_3$), 7,76 (2H, m, 6- and 7-H), and 8,11 (2H, m, 5- and 8-H).

2-Acetyl-3-propyl-1,4-dimethoxynaphthalene: (69)

2-Acetyl-3-propyl-1,4-naphthoquinone (34; 400mg) in ether (50ml) was

shaken with an aqueous solution of sodium dithionite (4g). The organic phase was separated and dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The quinol (68) was immediately dissolved in dry acetone (20ml) and treated with potassium carbonate (1,14g) and dimethyl sulphate (1,25g). The mixture was heated under reflux for eighteen hours, cooled, the solvent removed and the residue was thrown into water and extracted with chloroform. The chloroform extract was dried and chromatographed over silica (eluant 10% ethyl acetate/light petroleum), to yield 390mg (87%) of a viscous oil which later solidified, m.p.37,5-39°C. (Found: C, 74,95; H, 7,15. $C_{17}H_{20}O_3$ requires C, 75,00; H, 7,35); $\nu_{max.}$($CHCl_3$) 1705, 1695 and 1588 cm^{-1}; δ($CDCl_3$) 0,98 (3H, t, J 7Hz, 3'-CH_3), 1,63 (2H, quintet, J 7Hz, 2'-CH_2), 2,65 (3H, s, $COCH_3$), 3,69 (2H, t, J 7Hz, 1'-CH_2), 3,89 and 3,91 (3H each, s, OCH_3), 7,52 (2H, m, 6- and 7-H), and 8,06 (2H, m, 5- and 8-H).

2-Acetyl-3-(1'-bromopropyl)-1,4-dimethoxynaphthalene: (70)

2-Acetyl-3-propyl-1,4-dimethoxynaphthalene (69; 0,0583g), N-bromosuccinimide (0,465g), and di-t-butyl peroxide (10 drops) was boiled in carbon tetrachloride (10ml) for an hour and a half. The solution was cooled, the solvent removed and an n.m.r. spectrum run on the residue. δ($CDCl_3$) 1,02 (3H, t, J 8Hz, 3'-CH_3), 2,32 (2H, d x quartet, J 8Hz, 2'-CH_2), 2,76 (3H, s, $COCH_3$), 3,89 (3H, s, OCH_3), 4,04 (3H, s, OCH_3), 5,42 (1H, t, J 8Hz, 1'-CH), 7,59 (2H, m, 6- and 7-H), and 8,10 (2H, m, 5- and 8-H).

trans 2-Acetyl-3-(prop-1'-enyl)-1,4-dimethoxynaphthalene: (71)

The foregoing bromo compound (70) without purification, was heated with dry dimethylformamide (10ml) and 1,5-diazabicyclo[4,3,0]non-5-ene (0,3ml) at 45°C (external bath temperature) for ninety minutes. The solution was cooled, the solvent removed and the residue chromatographed over silica (eluant 5% ethyl acetate/light petroleum) to yield the product 0,0271g (59%) as an oil. (Found: M^+ 270,12562. $C_{17}H_{18}O_3$ requires M 270,12559); $\nu_{max.}(CHCl_3)$ 1710 and 1585 cm^{-1}; $\delta(CDCl_3)$ 1,93 (3H, d, J 6Hz, 3'-CH_3), 2,50 (3H, s, $COCH_3$), 3,85 (3H, s, OCH_3), 3,92 (3H, s, OCH_3), 6,20 (1H, d x quartet, J 6 and 16Hz, 2'-CH), 6,60 (1H, d, J 16Hz, 1'-CH), 7,53 (2H, m, 6- and 7-H), and 8,10 (2H, m, 5- and 8-H).

trans 2-(1'-Hydroxyethyl)-1,4-dimethoxy-3-prop-1'-enylnaphthalene: (21)

trans 2-Acetyl-3-prop-1'-enyl-1,4-dimethoxynaphthalene (71; 0,162g) was stirred with excess sodium borohydride in dry ethanol (20ml) for twelve hours at room temperature. The solvent was removed and the residue taken up in diethyl ether, washed with water and dried over anhydrous magnesium sulphate. The solution was filtered and chromatographed over silica (eluant 5% ethyl acetate/light petroleum) to yield 0,155g (95%) of a colourless oil. (Found: M^+ 272,14123. $C_{17}H_{20}O_3$ requires M 272,13761); $\nu_{max.}(CHCl_3)$ 3480 and 1585 cm^{-1}; $\delta(CDCl_3)$ 1,63 (3H, d, J 7Hz, 2'-CH_3), 1,97 (3H, d, J 6Hz, 3'-CH_3), 3,74 (1H, broad s, OH), 3,79 (3H, s, OCH_3), 4,03 (3H, s, OCH_3), 5,35 (1H, quartet, J 6Hz, 2'-CH), 6,06 (1H, d x quartet J 6 and 16Hz, 2'-CH), 6,60 (1H, d, J 16Hz, 1'-CH), 7,47 (2H, m, 6- and 7-H), and 8,05 (2H, m, 5- and 8-H).

trans 2-(1'-Hydroxyethyl)-3-prop-1'-enyl-1,4-naphthoquinone: (72)

trans 2-(1'-Hydroxyethyl)-1,4-dimethoxy-3-prop-1'-enylnaphthalene (21; 0,0245g) silver(II) oxide (0,0446g) and nitric acid (6M; 0,1ml) were stirred at room temperature for two minutes. Dichloromethane/water (8:2; 10ml) was then added to quench the reaction. The reaction mixture was extracted with dichloromethane, washed with aqueous sodium bicarbonate solution, water, dried over anhydrous magnesium sulphate and chromatographed over silica (eluant 20% ethyl acetate/light petroleum) to yield 0,0218g (59%) of an oily product. (Found: C, 74,05; H, 6,25. $C_{15}H_{14}O_3$ requires C, 74,35; H, 5,8%); $\delta(CDCl_3)$ 1,64 (3H, d, J 6Hz, 2'-CH_3), 2,00 (3H, d, J 5Hz, 3'-CH_3), 3,97 (1H, d, J 12Hz, OH), 5,07 (1H, quartet, J 6Hz, 1'-CH), 6,38 (2H, m, 1'- and 2'-CH), 7,73 (2H, m, 6- and 7-H), and 8,06 (2H, m, 5- and 8-H).

(1R, 3R, 4S)-4-Hydroxy-1,3-dimethylnaphtho[2,3-c]Pyran-5,10-quinone (24) and its Enantiomer, and

(1R, 3R, 4R)-4-Hydroxy-1,3-dimethylnaphtho[2,3-c]pyran-5,10-quinone (25) and its Enantiomer.

trans 2-(1'-Hydroxyethyl)-1,4-dimethoxy-3-prop-1'-enylnaphthalene (21; 0,10g) was dissolved in acetonitrile (10ml) and ceric ammonium nitrate (0,838g) in water (5ml) was added over five minutes with stirring, at room temperature. The mixture was stirred for an additional 5 minutes and then extracted with dichloromethane, washed with water, dried over anhydrous magnesium sulphate, filtered and chromatographed over silica (eluant 20% ethyl acetate/light petroleum) to yield two compounds:

(a) (24; 0,035g; 33%) m.p.131-132°C (hexane). (Found: C,69,65; H, 5,5. $C_{15}H_{14}O_4$ requires C, 69,75; H, 5,45%); $\delta(CDCl_3)$ 1,41 (3H, d, J 6,5Hz, 3-CH_3), 1,59 (3H, d, J 7Hz, 1-CH_3), 3,92 (1H, broad s, OH, overlapped), 3,85 (1H, d x quartet, J 8 and 6,5Hz, 3-CH), 4,47 (1H, d x d, J 8 and 2Hz, 4-CH), 4,92 (1H, d x quartet, J 7 and 2Hz, 1-CH), 7,73 (2H, m, 7 and 8-H), and 8,05 (2H, m, 6- and 9-H);

(b) (25; 0,068g; 65%) m.p.146-147°C (hexane). (Found: C, 69,55; H, 5,35. $C_{15}H_{14}O_4$ requires C, 69,75; H, 5,45%); $\delta(CDCl_3)$ 1,41 (3H, d, J 6,5Hz, 3-CH_3), 1,52 (3H, d, J 7,5Hz, 1-CH_3), 2,26 (1H, broad s, OH), 4,00 (1H, d x quartet J 6,5 and 2,5Hz, 3-CH), 4,52 (1H, d, J 2,5Hz, 4-CH), 5,00 (1H, quartet, J 7,5Hz, 1-CH), 7,72 (2H, m, 7- and 8-H), and 8,06 (2H, m, 6- and 9-H).

The foregoing quinones (24) and (25) were each acetylated with pyridine and acetic anhydride. The acetate of (24) gave $\delta(CDCl_3)$ 1,29 (3H, d, J 6Hz, 3-CH_3), 1,61 (3H, d, J 7Hz, 1-CH_3), 2,12 (3H, s, $COCH_3$), 4,13 (1H, apparent quintet, J 6Hz, 3-H), 4,93 (1H, d x quartet, J 7 and 2Hz, 1-H), 5,78 (1H, d, J 5 and 2Hz, 4-H), 7,75 (2H, m, 7- and 8-H), and 8,08 (2H, m, 6- and 9-H).

The acetate of (25) gave m.p.186,5-187,5°C (hexane). (Found: C, 67,65; H, 5,65. $C_{17}H_{16}O_5$ requires C, 68,0; H, 5,35%); $\delta(CDCl_3)$ 1,28 (3H, d, J 7Hz, 3-CH_3), 1,56 (3H, d, J 7,5Hz, 1-CH_3), 2,13 (3H, s, $COCH_3$), 4,10 (1H, d x quartet, J 7,5 and 2,5Hz, 3-CH), 5,09 (1H, quartet, J 7Hz, 1-CH), 5,98 (1H, d, J 2,5Hz, 4-CH), 7,72 (2H, m, 7- and 8-H), and 8,10 (2H, m, 6- and 9-H).

3-Acetyl-2-(3'-methoxycarbonylpropyl)-5-methoxy-1,4-naphthoquinone: (31)

3-Acetyl-1,5-dimethoxy-4-naphthol (41; 0,50g) was oxidatively demethylated to the corresponding quinone (42) with silver(II) oxide as described earlier. The crude quinone (42), without purification, was dissolved in acetonitrile/water (20:12; 64ml) and to this solution was added silver nitrate (1,65g), monomethylglutarate (0,31ml) and the mixture was stirred at 65-70°C (external bath temperature). Potassium peroxodisulphate (1,10g) in water (20ml) was added dropwise over one hour. The mixture was heated for a further fifteen minutes, cooled, thrown into water and extracted with dichloromethane. The organic phase was separated and washed successively with water, aqueous sodium bicarbonate solution, and water and dried over anhydrous magnesium sulphate. The solution was filtered and chromatographed over silica (eluant 30% ethyl acetate/light petroleum) to yield the product (0,37g; 55%) as fine yellow needles, m.p.126-127°C (hexane). (Found: C, 65,15; H, 5,4. $C_{18}H_{18}O_6$ requires C, 65,45; H 5,45%), $\nu_{max.}(CHCl_3)$ 1730, 1715, 1623 and 1595cm^{-1}; $\delta(CDCl_3)$ 1,89 (2H, quartet, J 7Hz, 2'-CH_2), 2,40 (2H, t, J 7Hz, 3'-CH_2), 2,48 (2H, t, J 7Hz, 1'-CH_2), 2,50 (3H, s, $COCH_3$), 3,67 (3H, s, $COOCH_3$), 4,01 (3H, s, OCH_3), 7,33 (1H, m, 6-H), and 7,72 (2H, m, 7- and 8-H).

3-Acetyl-2-(3'-methoxycarbonylpropyl)-1,4,5-trimethoxynaphthalene: (78)

3-Acetyl-2-(3'-methoxycarbonylpropyl)-5-methoxy-1,4-naphthoquinone (31; 2,7g) was reduced to the corresponding quinol (77) by shaking the ethereal solution of the quinone (31) with an excess of aqueous sodium dithionite solution. The organic phase was separated, dried over anhydrous

magnesium sulphate, filtered, and the solvent removed. The crude hydroquinone (77) was not isolated nor characterised due to the possibility of aerial oxidation, but was immediately dissolved in dry acetone (100ml) and heated with dimethyl sulphate (5,6ml) and potassium carbonate (5,2g) and heated under reflux for ten hours. The mixture was cooled, the solvent removed and the residue treated with aqueous ammonia solution to decompose any excess of dimethyl sulphate. The mixture was extracted with dichloromethane, washed successively with water, dilute hydrochloric acid, and water and finally dried over anhydrous magnesium sulphate. The mixture was filtered and chromatographed over silica (eluant 20% ethyl acetate/light petroleum) to yield the product (2,6g; 88%). An analytical sample was recrystallized from hexane/dichloromethane to yield colourless rhombi, m.p.82,5-83,5°C. (Found: C, 66,5; H, 6,7. $C_{20}H_{24}O_6$ requires C, 66,65; H, 6,65%); $\nu_{max.}(CHCl_3)$ 1730, 1700, 1625, 1600 and 1585 cm^{-1}; $\delta(CDCl_3)$ 1,96 (2H, quartet, J 7Hz, 2'-CH_2), 2,39 (2H, t, J 7Hz, 3'-CH_2), 2,64 (3H, s, $COCH_3$), 2,71 (2H, t, J 7Hz, 1'-CH_2), 3,67 (3H, s, $COOCH_3$), 3,78 (3H, s, OCH_3), 3,88 (3H, s, OCH_3), 4,02 (3H, s, OCH_3), 6,88 (1H, d, J 8Hz, 6-H), 7,43 (1H, t, J 8Hz, 7-H), and 7,66 (1H, d, J 8Hz, 8-H).

3-Acetyl-2-(3'-methoxycarbonyl-1'-bromopropyl)-1,4,5-trimethoxynaphthalene: (79)

3-Acetyl-2-(3'-methoxycarbonylpropyl)-1,4,5-trimethoxynaphthalene (78; 0,25g), N-bromosuccinimide (0,148g) and di-t-butyl peroxide (3ml) were heated under reflux in carbon tetrachloride (150ml) for three and a half hours. The solution was cooled, filtered and the solvent removed. No attempts were made at purifying the crude product (79), but an ^{1}Hn.m.r.

spectrum was run on the crude product which was found to be consistent with the proposed structure. $\delta(CDCl_3)$ 2,48 (4H, m, 2'- and 3'-CH_2), 2,72 (3H, s, $COCH_3$), 3,68 (3H, s, $COOCH_3$), 3,77 (3H, s, OCH_3), 4,01 (6H, s, 2 x OCH_3), 5,44 (1H, m, 1'-H), 6,95 (1H, d, J 8Hz, 6-H), 7,47 (1H, t, J 8Hz, 7-H), and 7,70 (1H, d, J 8Hz, 8-H).

2-Methyl-3-propyl-1,4-naphthoquinone: (59)

2-Methyl-1,4-naphthoquinone (58; 0,50g) was dissolved in acetonitrile/water (20:12; 64ml) and to this solution was added silver nitrate (0,40g) and butyric acid (0,27ml), the mixture being stirred at 80-85°C (external bath temperature). Potassium peroxodisulphate (1,61g) in water (20ml) or alternatively ammonium peroxodisulphate (1,36g) in water (20ml) was added dropwise over one hour to this mixture. The mixture was cooled, thrown into water and extracted with dichloromethane. The organic phase was separated and washed successively with water, sodium bicarbonate solution, and water and dried over anhydrous magnesium sulphate and chromatographed over silica (eluant 5% ethyl acetate/light petroleum) to yield (23; 0,58g; 58%) in both cases. An analytical sample was recrystallized from light petroleum, m.p.64-65°C. (Found: C, 78,45; H, 6,8. $C_{14}H_{14}O_2$ requires C, 78,50; H, 6,55%); $\nu_{max.}(CHCl_3)$ 1670, 1627 and 1610 cm^{-1}; $\delta(CDCl_3)$ 1,02 (3H, t, J 7Hz, 3'-CH_3), 1,54 (2H, sextet, J 7Hz, 2'-CH_2), 2,21 (3H, s, 2-CH_3), 2,64 (2H, t, J 7Hz, 1'-CH_2), 7,68 (2H, m, 6- and 7-H), and 8,08 (2H, m, 5- and 8-H).

2-Carbomethoxy-3-(1'-bromopentyl)-1,4-dimethoxynaphthalene: (61)

2-Carbomethoxy-3-pentyl-1,4-dimethoxynaphthalene (60; 0,093g) was dissolved in carbon tetrachloride (100ml) and to this solution was added N-bromosuccinimide (0,058g) and di-t-butyl peroxide (2ml). The resulting mixture was refluxed for forty five minutes, cooled, the solvent removed to 10ml, filtered and the residual solvent removed. The product was characterized only by its ^{1}Hn.m.r. spectrum due to the compound's inherent instability, but was found to be completely consistent with its proposed structure. $\delta(CDCl_3)$ 0,90 (3H, t, J 7Hz, 5'-CH_3), 1,34 (6H, m, 2'-, 3'- and 4'-CH_2), 3,99 (6H, s, $COOCH_3$ and OCH_3), 4,04 (3H, s, OCH_3), 5,49 (1H, t, J 7Hz, 1'-CH), 7,54 (2H, m, 6- and 7-H), and 8,08 (2H, m, 5- and 8-H).

References

1. H. Schmid, A. Ebnöther and Th. M. Meijer, Helv. Chim. Acta, 1950, 33, 1751.

2. H. Schmid, and A. Ebnöther, ibid., 1951, 34, 561.

3. W. Eisenhuth and H. Schmid, Helv. Chim. Acta, 1958, 41, 2021.

4. A Zeeck, H. Zahrer and M. Mardin, Annalen, 1974, 1101.

5. S. Ōmura, H. Tanaka, Y. Okada and H. Marumo, J. Chem. Soc., Chem. Comm., 1976, 320.

6. T. Li and R.H. Ellison, J. Amer. Chem. Soc., 1978, 100, 6263.

7. A. Zeeck and M. Mardin, Justus Liebigs Ann. Chem., 1974, 7, 1063.

8. H.W. Moore, Science, 1977, 197, 527.

9. P. Bosshard, S. Fumagalli, R. Good, W. Treub, W.V. Philipsborn and C.H. Eugster, Helv. Chim. Acta, 1964, 47, 769.

10. N. Jacobson and K. Torssell, Acta Chem. Scand., 1972, 27, 3211.

11. N. Jacobson and K. Torssell, Ann., 1972, 135, 763.

12. F. Feiser, "Organic Experiments", D.C. Heath and Co., Boston, 1964.

13. R.L. Hannan, R.B. Barber and H. Rapoport, J. Org. Chem., 1979, 44, 2153.

14. R.D. Gleim, S. Trenbeath, F. Suzuki and C.J. Sih, J. Chem. Soc., Chem. Comm., 1978, 242.

15. C.D. Snyder and H. Rapoport, J. Amer. Chem. Soc., 1972, 94, 227.

16. P. Jacob III, P.S. Callery, A.T. Shulgin and N. Castagnoli Jr., J. Org. Chem., 1976, 41, 3627.

17. C. Djerassi, Chem. Rev., 1948, 43, 271.

18. L. Horner, Angew. Chem., 1959, 71, 349.

19. R. Filler, Chem. Rev., 1963, 63, 21.

20. C. Walling, J. Amer. Chem. Soc., 1963, 85, 3129.

21. R.G.F. Giles, M.K. Reuben, and G.H.P. Roos, S. Afr. J. Chem., 1979, 32, 127.

22. C.J.P. Spruit, Rec. Trav. Chim., 1947, 66, 655.

23. L.F. Feiser and M. Feiser, Reagents for Organic Synthesis, 1967, 1050.

24. D.W. Cameron, D.G.I. Kingston, N. Sheppard and Lord Todd, J. Chem. Soc., 1964, 98.

25. M. Karplus and D.H. Anderson, J. Chem. Phys., 1959, 30, 6.

26. M. Karplus, J. Chem. Phys., 1959, 30, 11.

27. M. Karplus, J. Chem. Phys., 1960, 33, 1842.

28. R.H. Thomson, E. Race and F.M. Rowe, J. Chem. Soc., 1947, 350.

29. N.P. Buu-Hoi and D. Lavit, J. Org. Chem., 1955, 20, 1191.

30. H. Suzuki and H. Lida, Logyo Kagaku Zasshi, 1965, 68, 1241.

31. C.J.P. Spruit, Rec. Trav. Chim., 1947, 66, 655.

32. E. Kurosawa, Bull. Chem. Soc. Japan, 1961, 34, 300.