SYNTHESES OF NAPHTHO[2,3-c]PYRANS

INCLUDING THE APHIN-DERIVED QUINONE A'

A thesis submitted to the

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in fulfillment of the requirements for the degree of

MASTER OF SCIENCE

by

JURGEN ERNST RAMDOHR

B.Sc.(Hons.)(U.C.T)

Department of Organic Chemistry

University of Cape Town

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Für meine Eltern

In der Wissenschaft gibt es wohl glückhafte Zufälle, die erhoffte Entdeckungen erleichtern, aber es gibt nichts, das dem Forscher unverdient zufällt.

Hellmuth Unger

CONTENTS

ACKNOWLEDGEMENTS

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Thanks also to all my friends in the department who provided those many light-hearted moments during the last few years.

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SUMMARY

Compounds which can be structurally defined as bioreductive alkylating agents have considerable potential as antineoplastic agents, according to H.W. Moore (Science 1977).
This thesis deals with studies directed towards the synthesis of some quinones of potential medicinal interest.

Chapter One describes the synthesis of a trifluoroethylnaphtho-1,4-quinone *via* a regiospecific trifluoroacetylation of a appropriately substituted naphthalene.

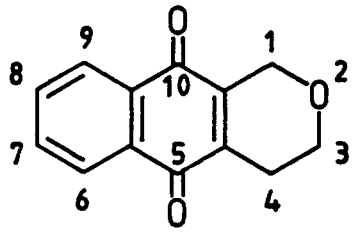
Chapter Two describes the synthesis of the methyl ethers of the naturally occuring quinones A and deoxyquinone A for evaluation of their "anti-cancer" activity by the National Institutes of Health.

In Chapter Three the final few steps of the synthesis of the aphid-derived quinone A' are described. This was made possible by the development of an efficient route for the conversion of a precursor to quinone A' *via* the corresponding chloro-derivative.

Introduction

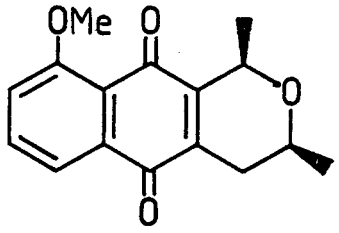
Natural quinones are widely distributed, and exist in large numbers and great structural variety.[1] In the animal kingdom they are most evident in sea urchins and related marine animals, bacteria, arthropods, echinoderms and plant aphids. In plants they occur in certain fungi and lichens as well as in higher plants.

Naphthoquinones form the vast majority of naphthalene derivatives found in nature and a common feature is an oxygen heterocycle fused to the quinonoid ring such as the naphtho[2,3-c]pyran ring system shown below.

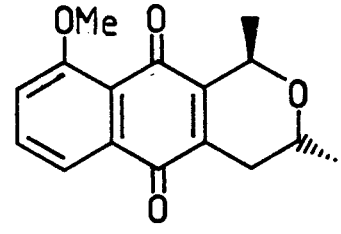


The distribution of naphthoquinones is sporadic. Nearly half of them occur in various parts of higher plants, while in animals many have been found in echinoderms, chiefly sea urchins with occasional examples in brittle stars, sea stars and starfish. Two complex stereo-isomeric naphthoquinones with the above skeleton occur in many plant aphid species and give rise, postmortem, to a series of pigments which will be discussed later.

Eleutherin (1) and isoeleutherin (2) are the simplest examples of the naturally occurring 5,10-quinones of this ring system and are found in Eleutherin bulbosa[2], whereas ventilagone (3)[3] from

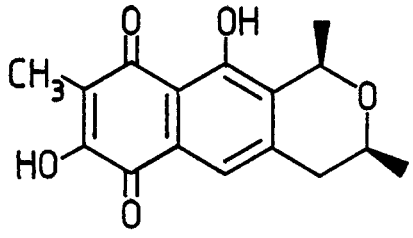


(1)



(2)

the root bark of Ventilago vimilis and fusarubin (4)[4] belong to the group of compounds having the 6,9-quinonoid skeleton.



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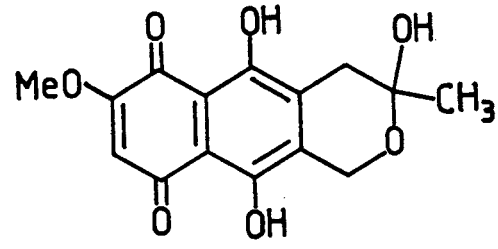

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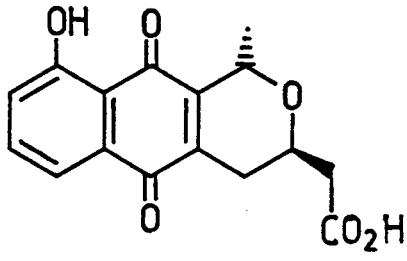
Other naturally occurring quinones containing the 5,10-quinone moiety of the eleutherins are the nanaomycins A (5) and C (6)[5] and griseusin B (7).[6]



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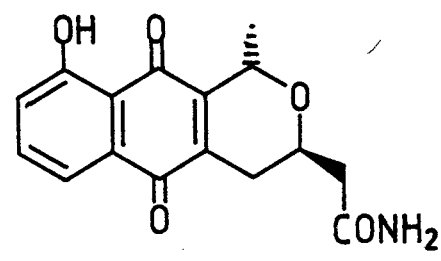

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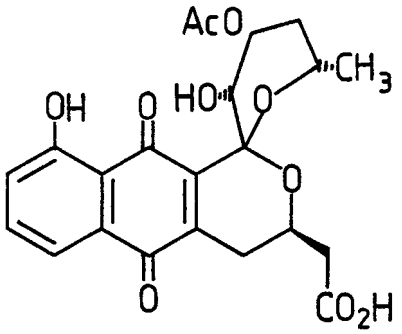
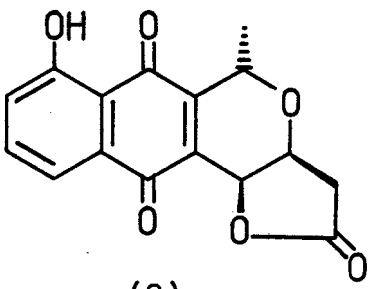


(7)

A number of these naturally occurring quinones contain the fused pyrano-lactone skeleton such as that found in the antibiotic nanaomycin D (8).[5] Another two examples are griseusin A (9)[6] and γ-naphthocyclinone (10).[7]



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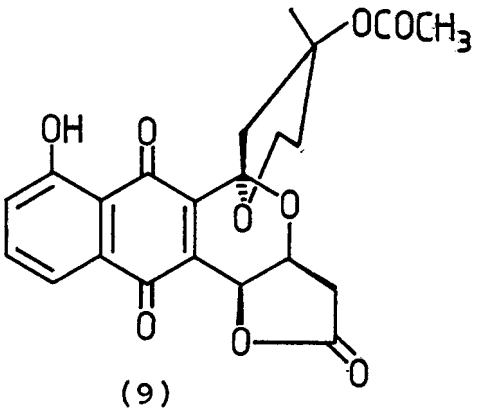

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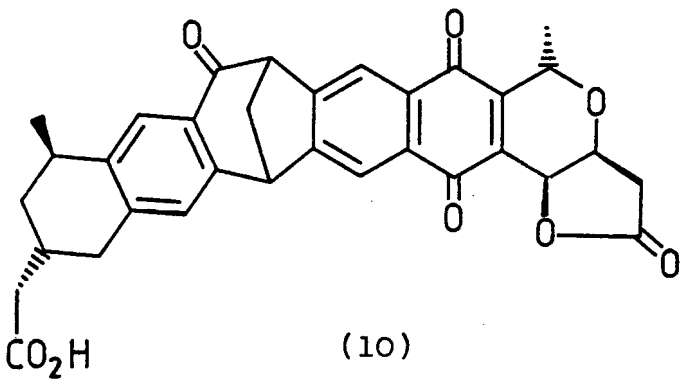
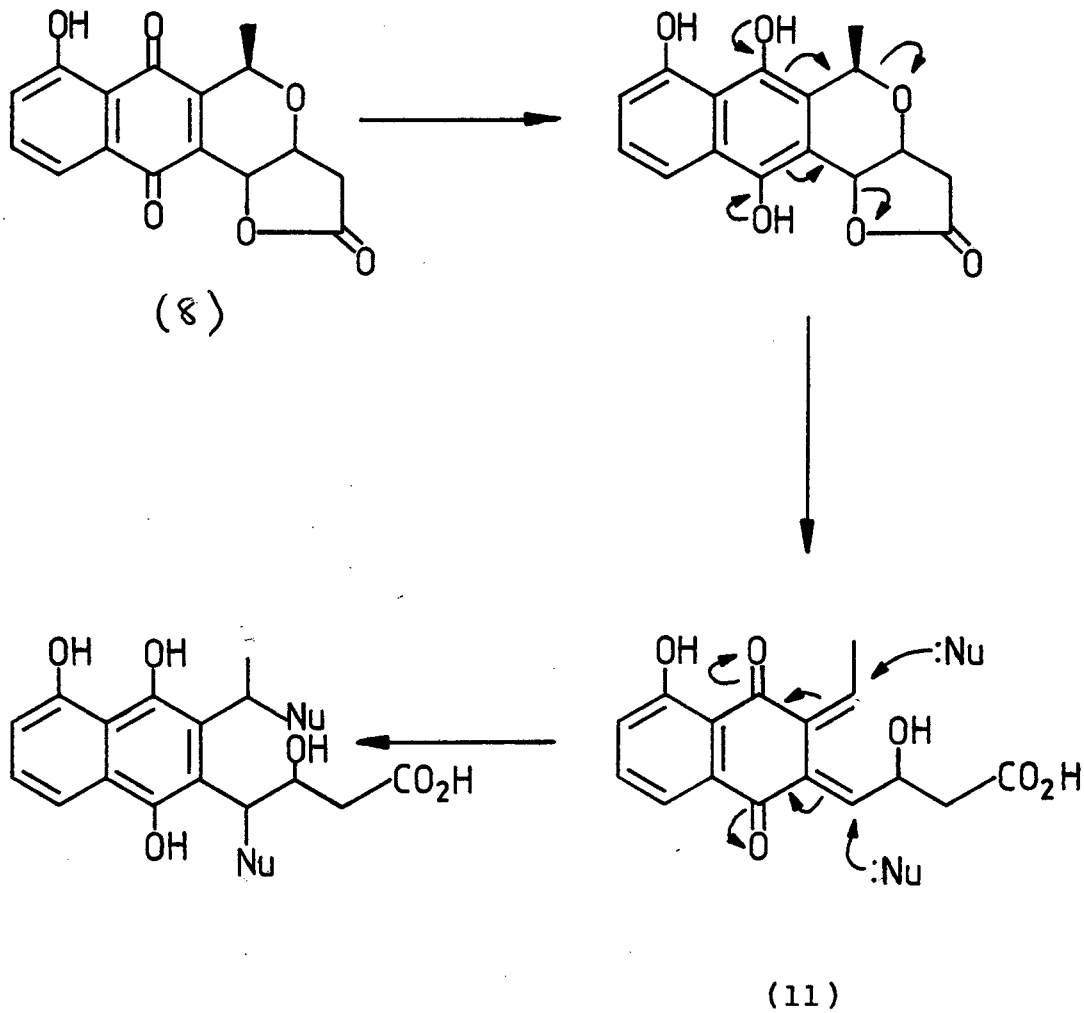


(10)

All these compounds have been listed in a paper by H.W. Moore[8] as compounds that, from a structural point of view, can function as bioreductive alkylating agents. Such compounds could be expected to have antineoplastic, or so-called anti-cancer activity.

A proposed mechanism[8] of action for these quinones is illustrated in Scheme 1 using nanaomycin D (8) as an example.

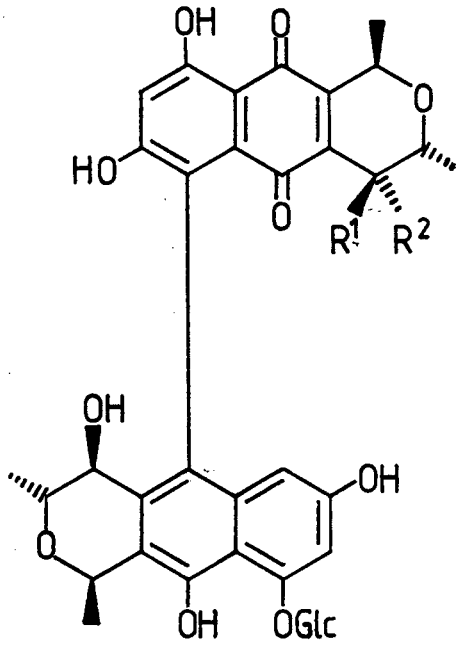


Scheme 1

It is believed that the quinone is first reduced in vivo to the corresponding hydroquinone which then undergoes two ring opening reactions. The resulting quinone methide (11) could then act as

the key dialkylating agent which, as a reactive Michael acceptor, would crosslink DNA non-specifically. It is however also possible that some of these drugs intercalate into DNA, thus inhibiting transcription and translation.

In the work to be described in this thesis, the possibility was considered that either the protoaphin pigments (12), (13) and (14), or their derivatives, quinone A (16), quinone A' (17) and deoxyquinone A (18), might conceivably show activity by means of the same bioreductive alkylation mechanism.



(12) R^1 = OH ; R^2 = H

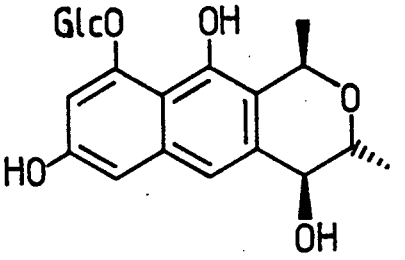
(13) R^1 = H ; R^2 = OH

(14) R^1 = R^2 = H

Protoaphins are brownish-yellow, hygroscopic and acidic compounds. Protoaphin-fb (12) was first isolated from the haemolymph of the broad bean aphid Aphis fabae Scop, while the isomeric protoaphin-sl (13) was obtained from the willow aphid, Tuberolachnus salignus Gmelin. More recently Cameron and Banks [9] obtained deoxyprotoaphin (14) from the aphid Dactynotus cirsii. (14) is identical to (12) and (13), lacking only the hydroxyl

group at C-4 on the quinonoid moiety of the binaphthyl system.

On mild reduction, either with sodium dithionite[10] or by catalytic hydrogenation[11], followed by reoxidation, the protoaphins were cleaved into an acidic quinone and a naphthalenic glucoside. Both protoaphin-fb (12) and protoaphin-sl (13) gave the same glucoside B (15), but the quinonoid fragment, quinone A, obtained from protoaphin-fb was shown to be compound (16), which differed from quinone A' (17), obtained from protoaphin-sl, in the stereochemistry of the C-4 hydroxyl group. Quinone A and A' are therefore epimeric at C-4. Deoxyprotoaphin (14) similarly gave glucoside B (15) and deoxyquinone A (18), the latter lacking the C-4 hydroxyl group found in quinones A and A'.



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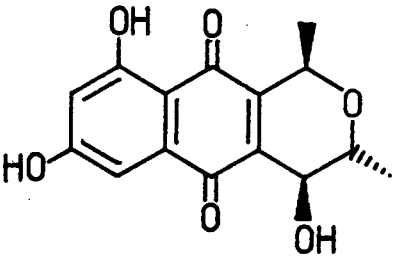

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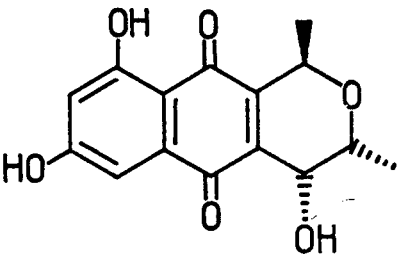

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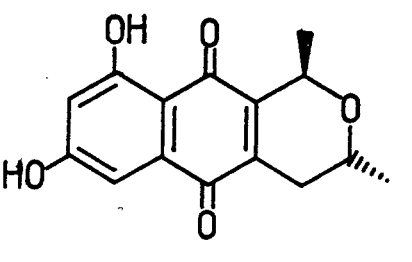
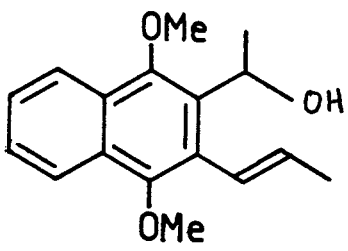


(18)

The stereochemistry of the pyran ring system of quinone A (16), quinone A' (17), and deoxyquinone A (18) at C-1 and C-3 is identical to that of isoeleutherin (2). The C-1 methyl group is pseudo-axial, while the methyl group at C-3 is equatorial. In quinone A (16) and quinone A' (17) the hydroxyl group is pseudo-equatorial for the former and pseudo-axial for quinone A'.

The first contruction of this naphtho[2,3-c]pyran ring was reported in 1958 by Schmid and Eisenhuth [12] who synthesised eleutherin (1) and isoeleutherin (2).

Professor Giles and colleagues at the University of Cape Town were the first to synthesise C-4 hydroxylated naphtho[2,3-c]-pyran-5,10-quinones. They reported the oxidative cyclisation of the naphthalene (19) with cerium(IV) ammonium nitrate to the 7,9-dideoxy quinones (21) and (22), analogues of quinone A (16) and A' (17) respectively, in which the correct stereochemistry about the pyran ring was achieved.



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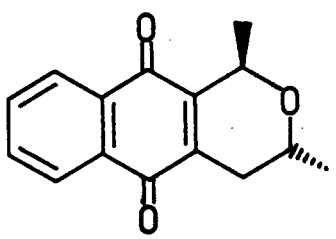

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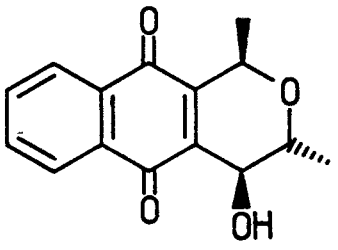

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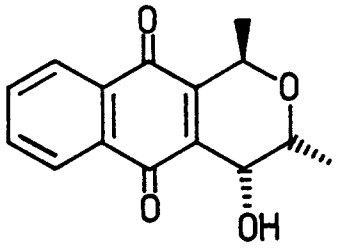
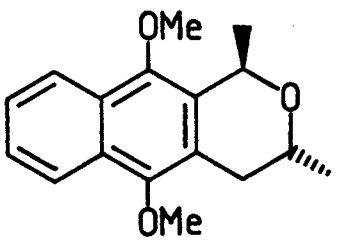


(22)

This reaction was shown to proceed via the 4-hydroxynaphthopyrans (24) and (25) which are also obtained from the aerobic base-catalysed cyclisation of compound (26), a reaction also pioneered in these laboratories.[14]



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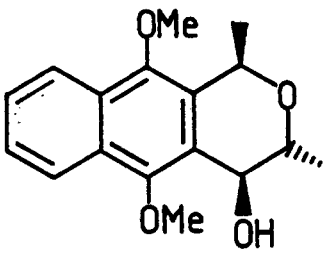

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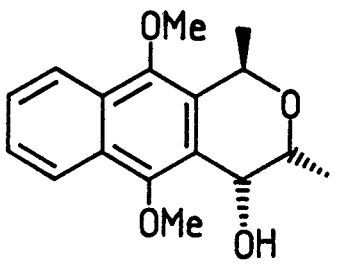

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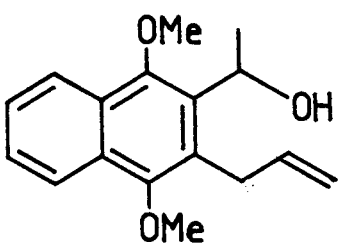
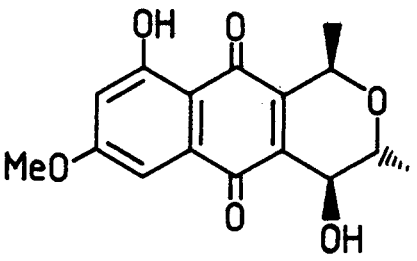


(26)

However, treatment of the unconjugated alcohol (26) with potassium t-butoxide under nitrogen afforded the 4-deoxynaphthopyran (23) which can, like compounds (24) and (25), be oxidised with cerium(IV) ammonium nitrate or silver(II) oxide to their respective quinones (20) - (22).

The aim of this project was to synthesise the 7-O-methyl ethers of quinone A and deoxyquinone A (27) and (28), respectively. The third target molecule was the 1,4-naphthoquinone (29).



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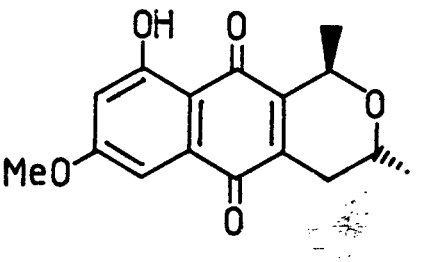

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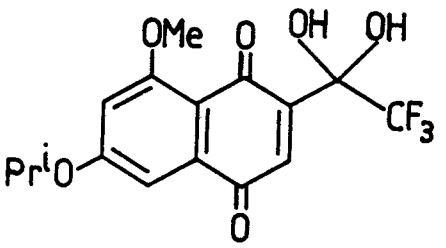
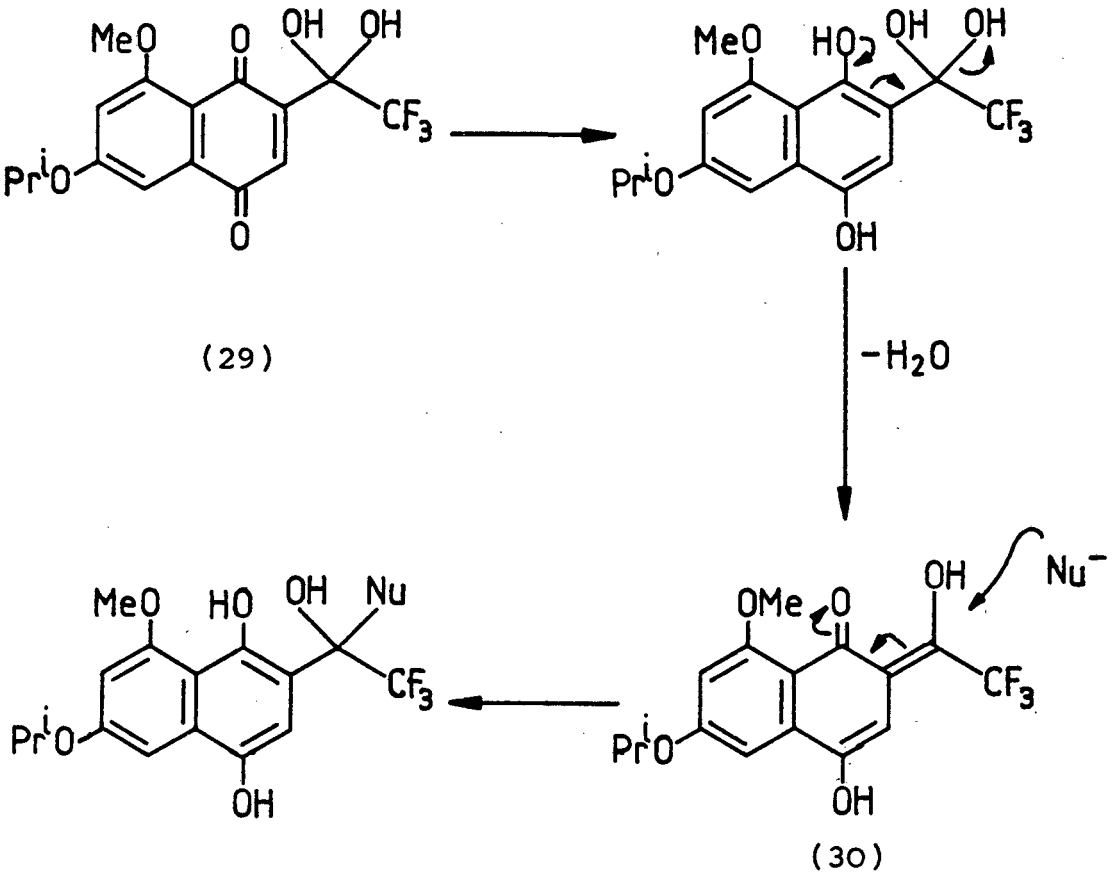


(29)

The aphid quinone analogues (20) - (22) have been screened as antineoplastic agents by the National Institutes of Health and sufficient quantities of (27) and (28) had to be prepared to have them evaluated for comparison.

Since the quinone (29), also synthesized in these laboratories,[19] meets the structural requirements for the formation of the quinone methide (30) which is required by the proposed mechanism for the bioreductive alkylation[8] as illustrated in Scheme 2, it was decided to have its activity evaluated as well.



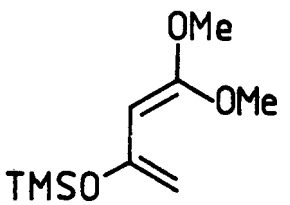
Scheme 2

This decision was made in response to a request by the National Institutes of Health that this compound should be prepared for them to screen.

Chapter One

THE SYNTHESIS OF A DIHYDROXYTRIFLUOROETHYL-1,4-NAPHTHOQUINONE OF POTENTIAL MEDICINAL INTEREST

The construction of the 1,4,5,7-tetraoxygenated naphthalene nucleus of the title compound (29) was achieved by the Diels-Alder addition of Brassard's diene (31)[16,17] to 1,4-benzoquinone in dry boiling benzene under reflux. This afforded the intermediate adduct (32) which was not further purified beyond evaporation of the solvent.



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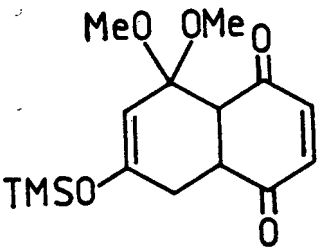
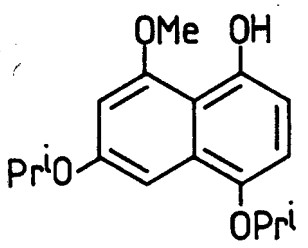


(32)

It was immediately alkylated with isopropyl bromide and anhydrous potassium carbonate in dimethylformamide at 60°C for 9 hours to afford the naphthol (33).



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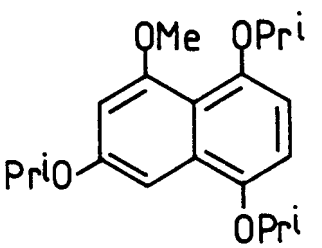
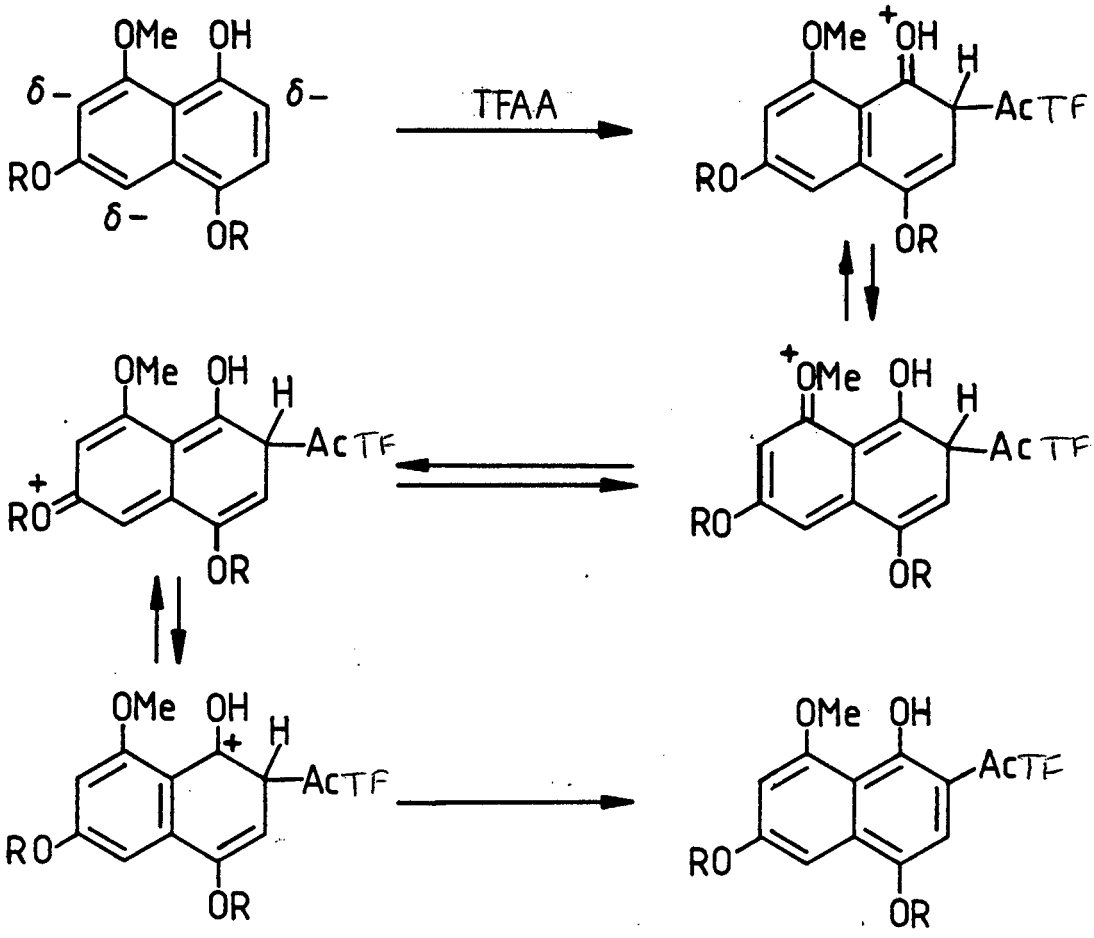


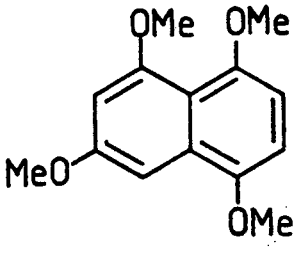
(34)

The more hindered and hydrogen-bonded 4-hydroxyl group remained unprotected as was indicated by its ^1H n.m.r. spectrum which showed a sharp singlet at δ 8.83. Longer reaction times or a higher reaction temperature led to the fully protected tetraalkyloxynaphthalene (34).

Regiospecific C-3 trifluoroacylation to give the title compound (29), however, requires the C-4 hydroxyl substituent to remain unprotected. The reason for this is the smaller steric hindrance as well as the stronger electron donating effect[18] of the hydroxyl group, both of which direct the electrophilic attack towards the C-3 position. The C-5 and C-7 alkoxy groups[9] activate the nucleus even further towards a electrophilic substitution at C-3 and stabilize the intermediate arenium ion, as outlined below.



This is supported by selective acylation experiments of oxygenated naphthalenes[19,20] conducted by Professor Giles and his group. Acylation of the tetramethoxynaphthalene (35) with trifluoroacetic anhydride readily afforded only the 8-trifluoroacetyl derivative (36), whereas reaction of the 1,4,5-trimethoxynaphthalene (37) with trifluoroacetic anhydride slowly formed the two isomeric C-8 and C-3 trifluoroacylated naphthalenes (38) and (39) respectively, with the former predominating. No reaction was observed with 1,4-dimethoxynaphthalene (40).



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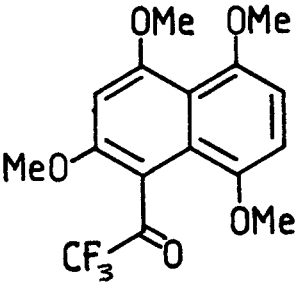

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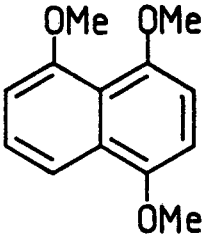

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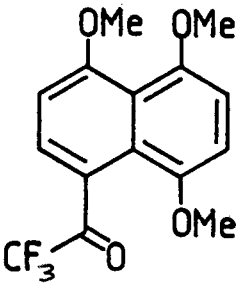

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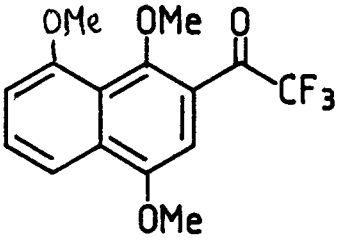
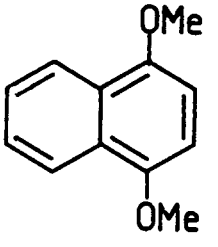
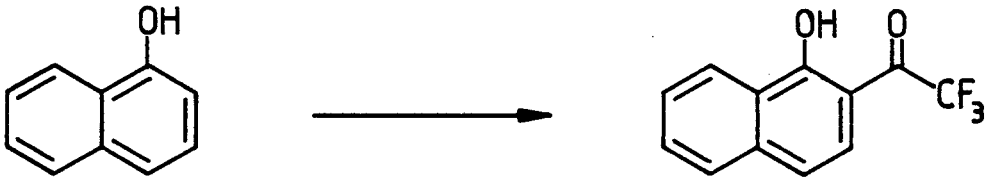


(39)

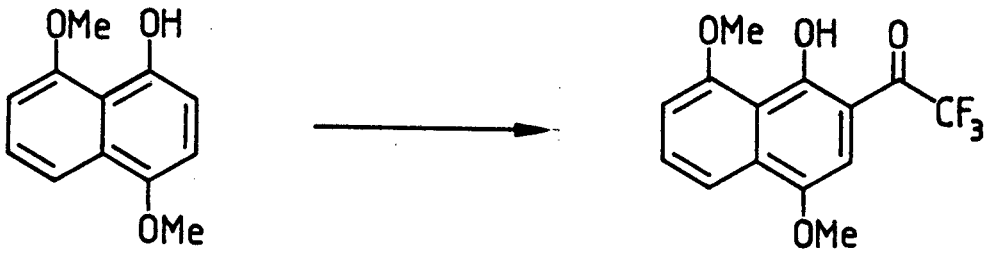


(40)

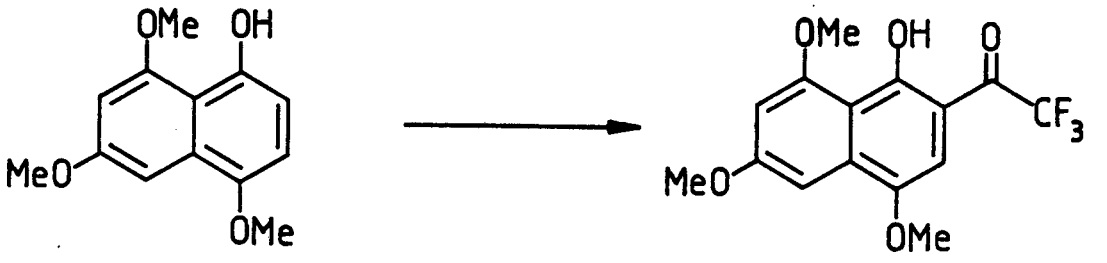
In comparison, the 1-naphthols (41) - (43) all afforded only the ortho-trifluoroacetylnaphthols (44) - (46) respectively. The lowfield signal (approximately δ 13) for a hydrogen-bonded hydroxyl group supported the structural assignment of the products.



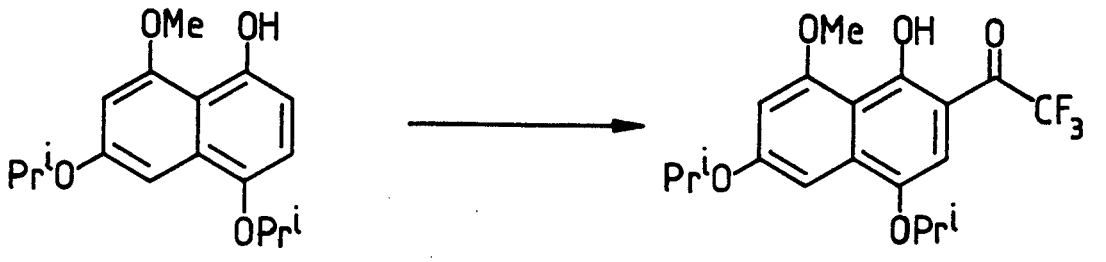
(41) (44)



(42) (45)



(43) (46)



(33) (47)

Thus compound (33) reacted with trifluoroacetic anhydride in dichloromethane at room temperature to afford the naphthol (47) in high yield (80%). The structure was confirmed, inter alia, by the ^{1}H n.m.r. spectrum, which showed the appropriate alkoxy substituents and, in addition to two meta-coupled aromatic protons, a one-proton quartet (J 2.5 Hz) for the single aromatic proton ortho to the trifluoroacetyl substituent. This splitting pattern arose through long-range coupling of the 2-H proton to the three fluorine nuclei of the neighbouring trifluoroacetyl group. The naphthol was then oxidised with two moles of cerium(IV) ammonium nitrate in water to the corresponding 1,4-naphthoquinone in a yield of 80%. This reaction afforded the simultaneous hydration of the trifluoroacetyl carbonyl group, due to the strong electron withdrawing properties of both the quinonoid system and the trifluoromethyl group, forming the title compound (29) in one step. After recrystallisation from dichloromethane - light petroleum, a crystal structure determination was performed which confirmed the structure as (29).[19]

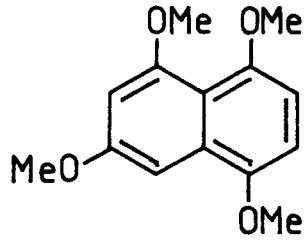
Chapter Two

THE SYNTHESIS OF (±)-7-O-METHYL QUINONE A (27) AND (±)-7-O-METHYL DEOXYQUINONE A (28)

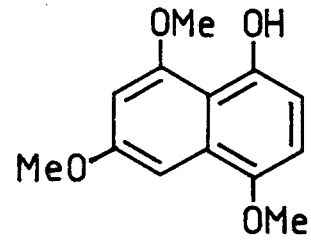
As in the synthesis of the eleutherins (1) and (2) by Schmid and Eisenhuth[7] or that of 7-methoxy-eleutherin and deoxyquinone A dimethyl ether by Cameron et al[15], the synthesis of a suitably substituted naphthalenic precursor was used as the entry to the two title compounds (27) and (28).

An important point about the synthesis to be described is that, while much of the work had been done previously in this Department[22], sufficient material had to be synthesised to provide gram quantities of the final products for screening by the National Institutes of Health. This synthesis, therefore, had to be performed on a large scale.

The crude Diels-Alder adduct (32) of Brassard's diene (31)[16,17] and 1,4-benzoquinone was dissolved directly in dry acetone and alkylated with dimethyl sulphate and potassium carbonate under reflux for 2.5 hours to afford the trimethoxy-4-naphthol (43) in a high yield. The ^1H n.m.r. spectrum of the product showed a sharp, lowfield, D_2O exchangeable singlet at δ 8.69 for the hydrogen bonded 4-hydroxy proton. Three three-proton singlets in the δ 4 region confirmed the presence of three methoxy groups and the aromatic region of the spectrum indicated the presence of two meta-coupled protons (J 2 Hz) and two ortho-coupled protons (J 8 Hz).

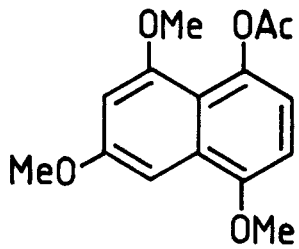


(35)

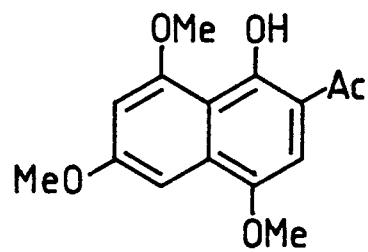


(43)

This napthol (43) was converted into the corresponding white crystalline acetate (48) with acetic anhydride in pyridine at 110°C. The structure of this new product was confirmed by the presence of a sharp three-proton singlet at δ 2.33, which replaced the napthol proton in its precursor, other signals remaining by and large unaltered. The mass spectrum afforded a molecular ion at 42 mass units higher than that of its precursor (43), in line with expectation. An infrared absorption at 1750 cm^{-1} was also consistent with the presence of an aromatic acetate.



(48)

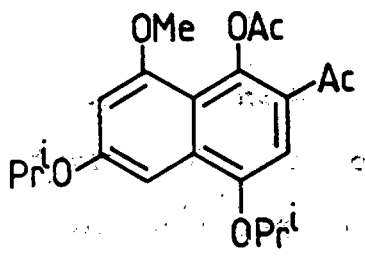


(49)

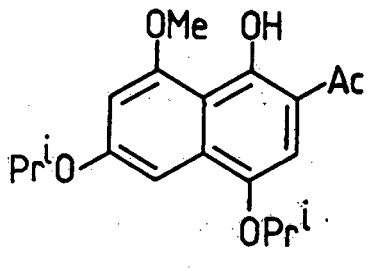
The acetate (48) was subjected to a Fries rearrangement with borontrifluoride-diethyl ether at 60°C for 30 minutes. This gave the isomeric ortho-acetylnaphthol (49) together with some deacetylated napthol (43). The structural assignment of compound (49) was supported by its ^1H n.m.r. spectrum which showed a sharp

singlet at δ 14.01 for the strongly hydrogen-bonded 4-hydroxyl proton. In addition, the two doublets at δ 6.70 and 6.87 (J 8 Hz) for the ortho-coupled H-2 and H-3 protons of starting material (48) were replaced by a somewhat more deshielded singlet at 7.49 for the H-2 in the ^{1}H n.m.r. spectrum of the product (49). Furthermore, the three-proton acetate methyl signal at δ 2.33 in starting material (48) was deshielded to a value (δ 2.63) consistent with an aryl acetyl signal. This was supported in the infrared spectrum by an absorbtion at 1600 cm^{-1} anticipated for an ortho-acetylnapthol. The molecular ion showed the product (49) to be isomeric with starting material (48).

An alternative route to compound (49) might have been the direct acetylation of (43) with premixed glacial acetic acid and trifluoroacetic anhydride ; it was shown in these laboratories[20] that treatment of the 5-methoxy-1,7-diisopropoxy-4-naphthol (33) with this mixture gave the acetyl acetate (50) in a 70% yield, with C-acylation as required at C-3.

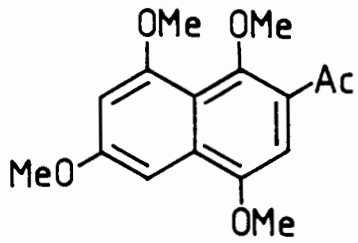


(50)

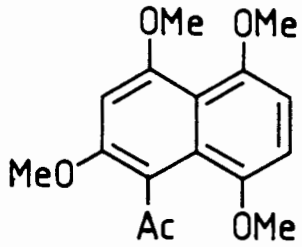


(51)

Mild base hydrolysis provided the ortho-acetylnaphthol (51). On the other hand, similar acetylation of 1,4,5,7-tetramethyoxynaphthalene (35) with glacial acetic acid and trifluoroacetic anhydride resulted only in the slow formation of the two isomeric acetates (52) and (53) in a 1 : 3 ratio.[20]

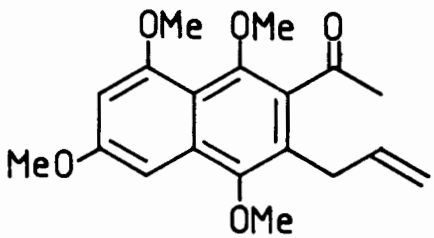


(52)

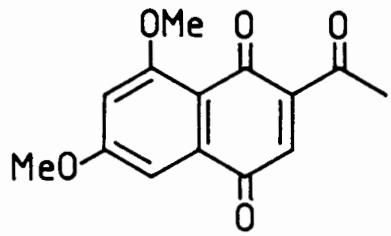


(53)

The naphthyl ketone (54) is available from the 3-acetyl-1,5,7-trimethoxy-4-naphthol (49) by two routes, both of which require the oxidation of naphthol (49) to the quinone (55) with cerium(IV) ammonium nitrate in acetonitrile-water prior to the allylation.

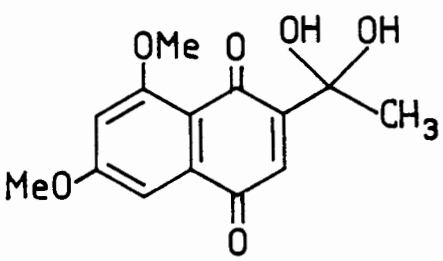


(54)

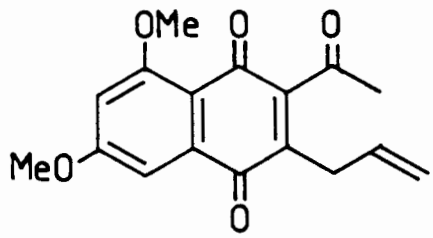


(55)

It is interesting to note that this oxidation does not give the hydrated quinone (56), analogous to the title compound (29) which was obtained by an identical oxidation from the naphthol (47) as described in chapter 1.



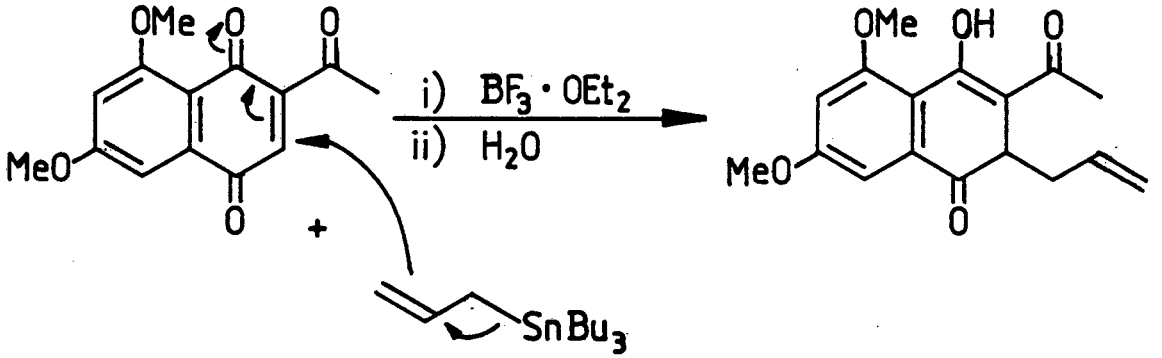
(56)



(57)

Obviously the greater electronegativity of fluorine over hydrogen encourages formation of the hydrate in the case of quinone (29), much as the simpler molecule chloral undergoes hydration to give chloral hydrate, whereas acetaldehyde has no such marked tendency.

The first route to (54) involved an allylation[22] of (55) with vinylacetic acid to afford the allylquinone (57) which was then reductively methylated to the stable naphthyl ketone (54). The second method, which was used in this synthesis because of the higher yields obtainable, was developed by Maruyama et al[23] for yet another synthesis of the eleutherins (1) and (2). The acetyl quinone (55) was regioselectively allylated with allyltributyl-stannane (58) and borontrifluoride-diethyl ether as a Lewis acid to the conjugate adduct (59)[23], which was methylated without purification to the naphthyl ketone (54).

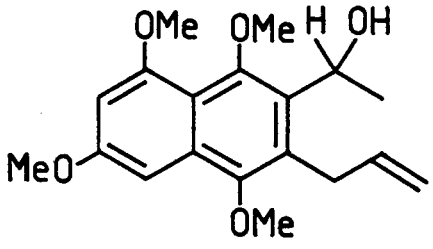


(55) (58) (59)

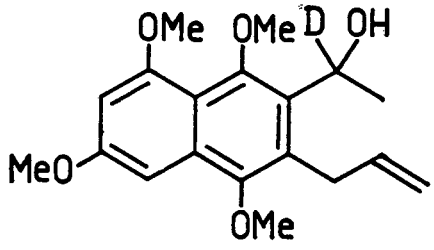
Its ^1H n.m.r. spectrum showed, in addition to four three-proton singlets in the region δ 3.7 to 4.0 for the methoxy methyl groups and the three-proton acetyl singlet at δ 2.61, a doublet of doublets (J 2Hz and 6Hz) at δ 3.56 for the two aliphatic propenyl protons and two multiplets centred at δ 4.9 and δ 6.0

for the vinyl CH_2 and CH protons, respectively. Both the 2-H singlet at δ 7.49 and the D_2O exchangeable signal for the hydrogen bonded C-4 hydroxy proton of the naphthol (49) had disappeared. In the aromatic region only a pair of one-proton meta-coupled doublets (J 2 Hz) remained.

The ketone (54) was then readily reduced with lithium aluminium hydride to the corresponding benzylic alcohol (60).



(60)

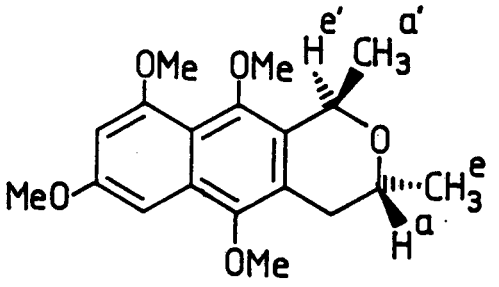


(61)

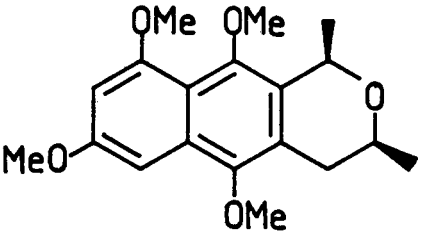
Its ^1H n.m.r. spectrum showed instead of the three-proton acetyl singlet at δ 2.61, a doublet at δ 1.63 (3H, J 7 Hz), a broad singlet centred at δ 4.10 and a broad multiplet at δ 5.26 for the $CH(OH)C\underline{H}_3$, $CH(O\underline{H})CH_3$ and $C\underline{H}(OH)CH_3$ protons respectively.
A small amount of the ketone (54) was reduced with $LiAlD_4$ to the deuterated alcohol (61). The position of the deuterium was confirmed by the ^1H n.m.r. spectrum of the product in which the methyl doublet had collapsed into a three-proton singlet at δ 1.62 while the $C\underline{H}(OH)CH_3$ signal at δ 5.26 had disappeared altogether. The mass spectrum of compound (61) showed the molecular ion and other relevant signals at one mass unit higher than in its non-deuterated analogue (60). The formation of compound (61) is in accordance with the known mechanism of ketone reduction. This deuterated alcohol was prepared to investigate

the mechanism of the cyclisation to be discussed.

Brief treatment of the alcohol (60) with potassium t-butoxide in dimethylformamide under nitrogen afforded the naphthopyran (62) in a yield of 88%. None of the isomeric cis-dimethyl naphthopyran (63) was observed under these conditions, although prolonged treatment did afford some of the latter stereoisomer.

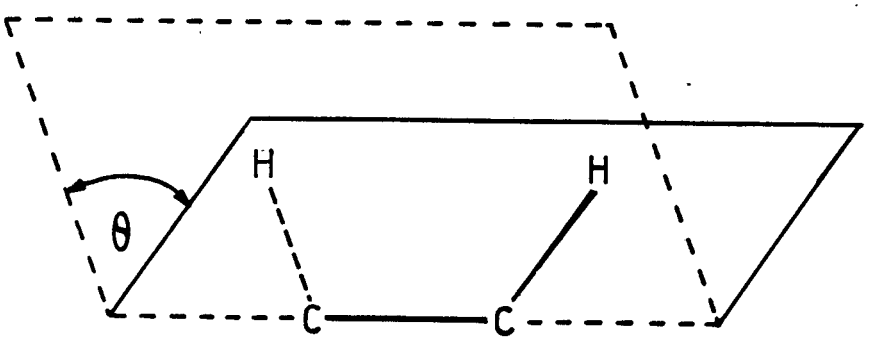


(62)



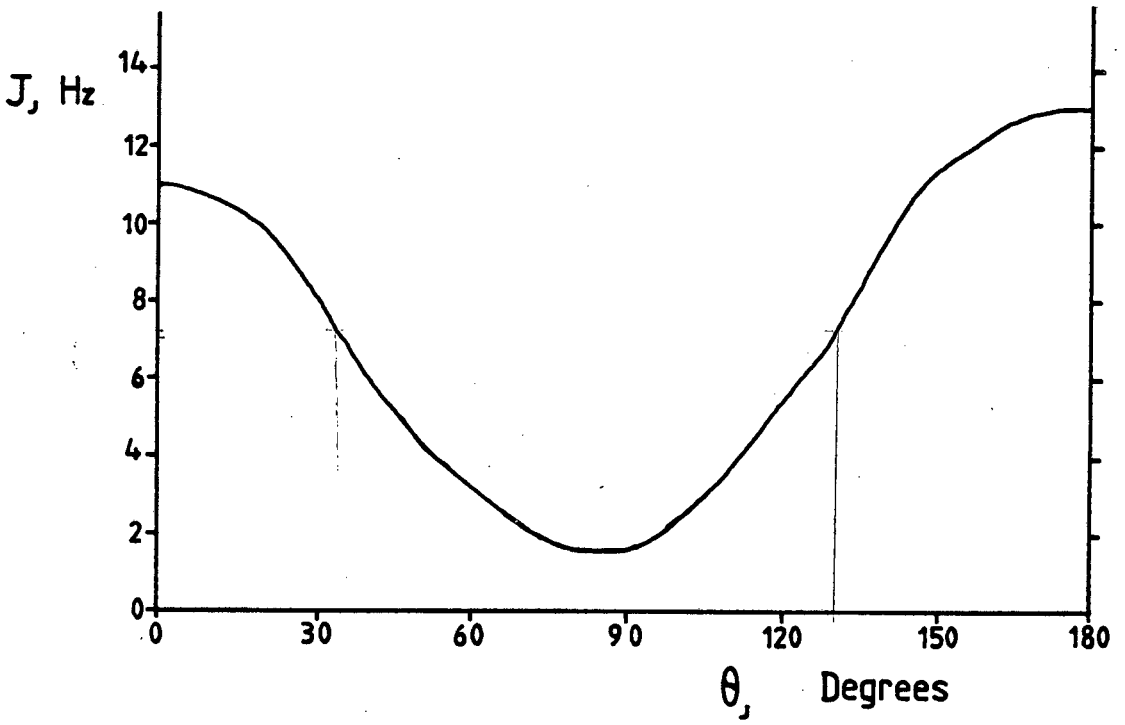
(63)

The vicinal coupling constant through carbon depends on the dihedral angle, θ , between the C-H bonds, as expressed in the Karplus equation[24,25], and illustrated below. The coupling constants can therefore be used to determine the stereochemistry around the pyran ring system.

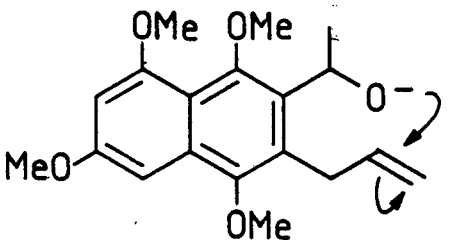


The ^1H n.m.r. spectrum of compound (62) showed two doublets for the C-1 and C-3 methyl groups, a quartet for 1-H and a multiplet for the axial 3-H which is coupled to both the pseudo-axial and pseudo-equatorial 4-H. The pseudo-axial 4-H appeared as a

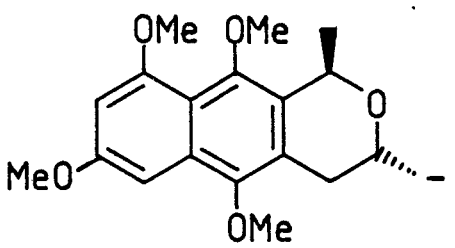
doublet of doublets with coupling constants of 10 and 16.7Hz, the former due to coupling to the pseudo-axial 3-H and the latter due to geminal coupling. The pseudo-equatorial 4-H also appeared as a doublet of doublets, coupling to the axial 3-H (3.5 Hz) and geminal coupling (16.7 Hz) to the pseudo-axial 4-H.



A possible mechanism[26] for this base-induced cyclisation would involve the deprotonation of the alcohol (60) to the alkoxide (64). This then undergoes cyclisation to the trans-dimethyl pyran carbanion (65), favoured kinetically because the methylene anion at C-3 prefers the less crowded equatorial position, while the methyl group at C-1 goes pseudo-axial to minimise steric



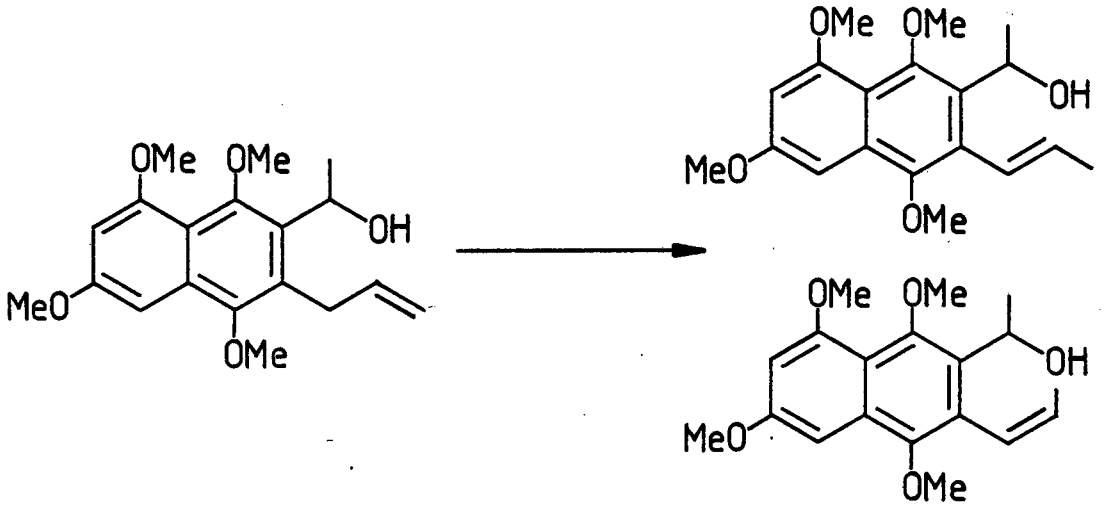
(64)



(65)

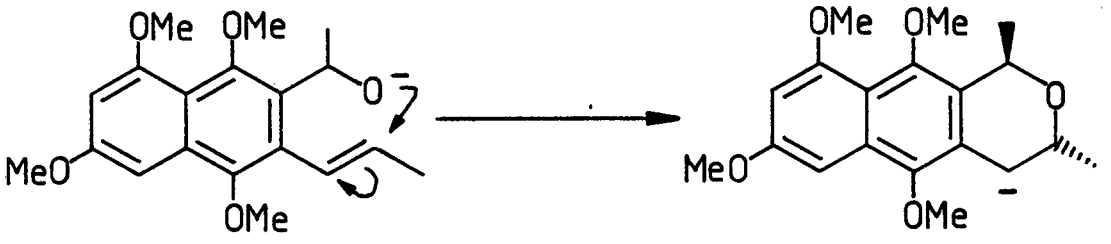
interaction with the neighbouring methoxy group on the naphthalene ring. The carbanion (65) then abstracts a proton from the reaction mixture [from the t-butyl alcohol produced as a by-product in the formation of the alkoxide (64)] to yield the observed product (62).

Perhaps a more likely mechanism would involve initial conjugation of the allyl double bond to afford the corresponding styryl compound. Evidence for this postulate was obtained by quenching the reaction during the conversion of alcohol (60) to naphthopyran (62). After purification by chromatography of product (62) a ^{1}H n.m.r. investigation of the remaining alcohol showed it to be a mixture of the E- and Z- styrene derivatives and not the original alcohol (60).



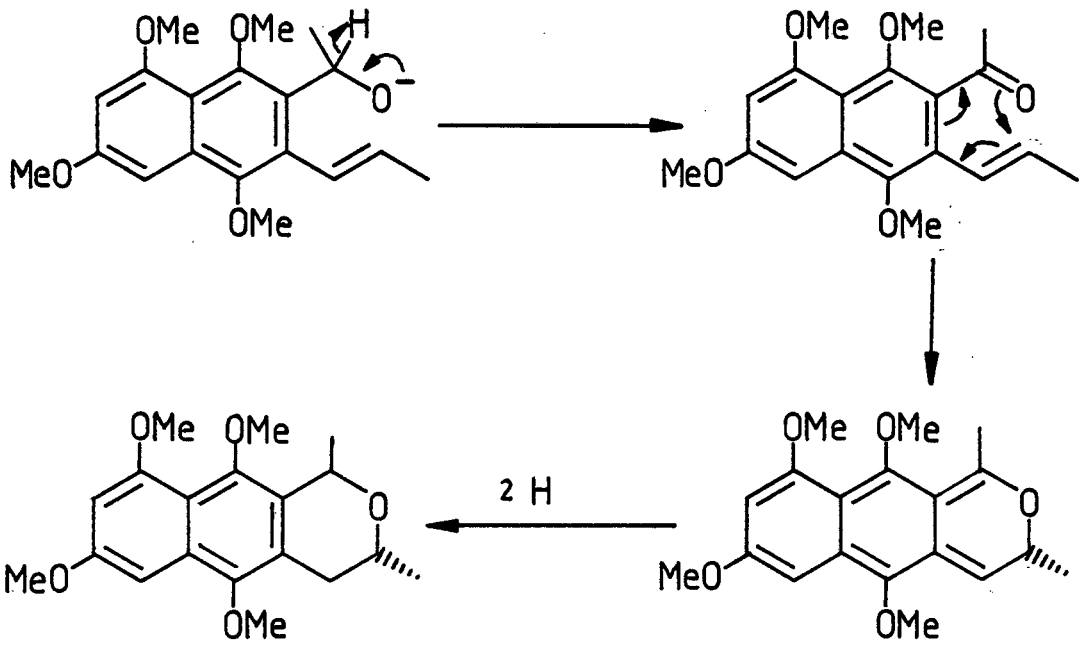
(60)

Resubjection of this stereochemical mixture to the reaction conditions afforded the naphthopyran (62). Subsequent intramolecular attack by alkoxide would then give the benzylic carbanion (72), isomeric with (65), which would then be protonated as before.



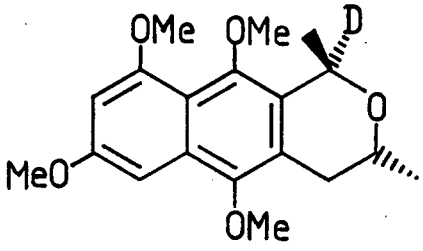
(72)

The addition of nucleophiles to carbon-carbon double bonds, whether in conjugation with an aromatic system or not, can hardly be described as a regular reaction pathway; it has, however, been accepted by a number of internationally eminent chemists for this particular reaction developed in the Department. Others have however put forward a number of different possibilities, one of which has been proposed independently by various chemists of note, and is shown in Scheme 3.



Scheme 3

The basis of this alternative proposal is that the initially derived conjugated alcohol is deprotonated to the corresponding alkoxide which consequently ejects a hydride ion to the reaction mixture, perhaps to the solvent dimethylformamide. The derived ketone is then well equipped to undergo a concerted electrocyclic ring closure to form the naphthopyran shown. This would in turn have to recover the two hydrogens (a proton and a hydride species) to generate the final dihydronaphthopyran (62). Unless the recovery of these hydrogens proceeded specifically with C-1 of the naphthopyran recovering hydride and the proton attaching at C-4, subjection of the deutero-alcohol (61) to the same cyclisation would lead to scrambling of the deuterium label.
Thus, when the deutero-alcohol (61) was reacted with potassium t-butoxide in dimethylformamide under anaerobic conditions the 1-D-naphthopyran (66) was obtained as the sole product in high yield.

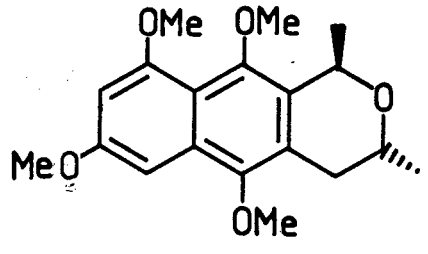


(66)

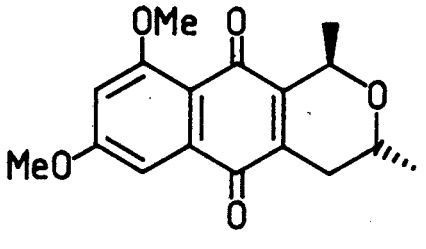
Its ^{1}H n.m.r spectrum showed, inter alia, a three-proton singlet for the C-1 methyl group instead of the doublet of compound (62) while the 1-H quartet at δ 5.31 had disappeared altogether, thus suggesting that the C-1 carbon-hydrogen bond is not broken during the formation of the pyran ring system. This finding therefore supports the proposal that cyclisation does proceed by addition of alkoxide to the conjugated olefin. The possibility that

deuterium is lost from and returns to the same carbon by a Meerwein-Ponndorf-like mechanism cannot be excluded, but seems unlikely.

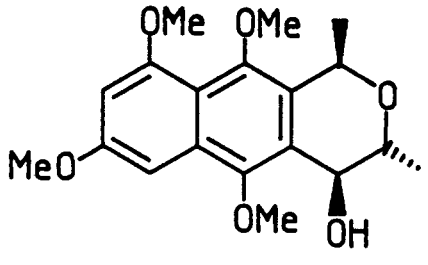
The synthesis of quinone A monomethyl ether (27) required the hydroxylation of the naphthopyran (62) at C-4 of the ring before oxidation to the quinone (70) and deprotection to (27). Using the literature method[22] developed in these laboratories, the reaction yielded 28% of compound (67) and 10% of compound (68).



(62)



(69)



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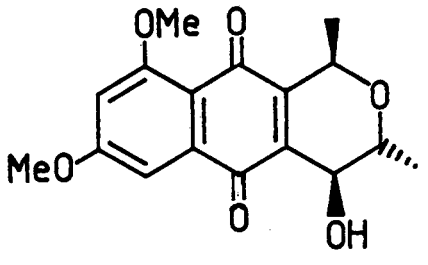
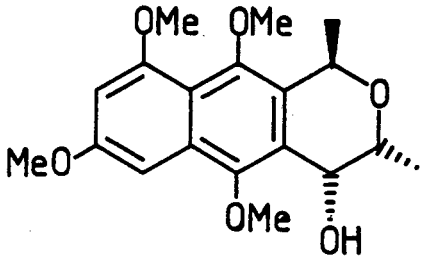


(70)



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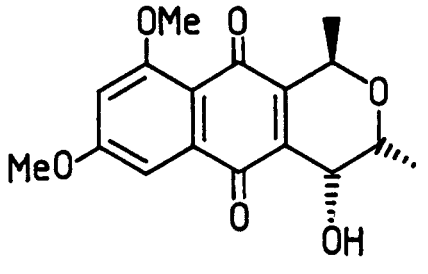
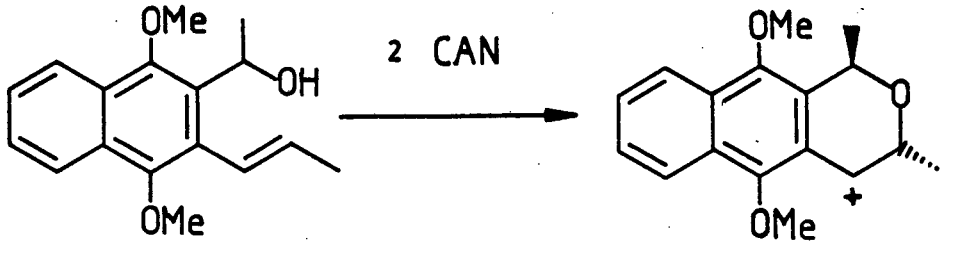


(71)

This involved treating the naphthopyran (62) with potassium t-butoxide in dimethylformamide at 60°C in the presence of dry air for three hours.

The coupling constant of 8 Hz between 3-H and 4-H for compound (67) predicts a dihedral angle, θ, of about 130° between the C^3-H and C^4-H bonds. This confirms 3-H as axial and 4-H as pseudo-axial. The hydroxyl group is therefore in the pseudo-equatorial position. For (68) the smaller coupling constant of 2 Hz indicated a smaller dihedral angle of about 70° which, with 3-H again axial, required 4-H pseudo-equatorial and the OH group pseudo-axial.

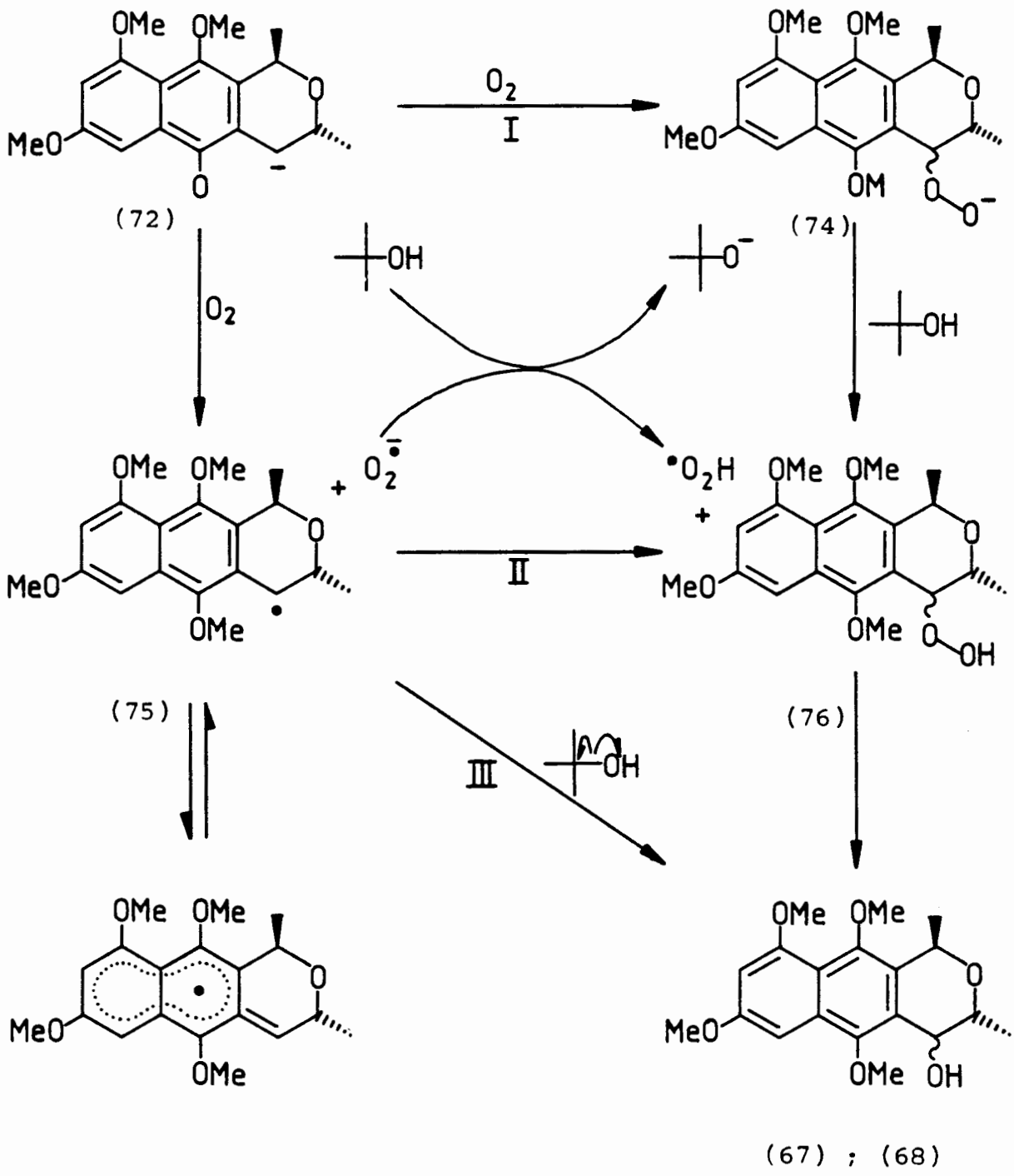
A mechanism for the oxygenation of the pyran ring has been suggested[26], but can only be speculative at this stage and warrants further investigation. Under the strongly basic conditions generated by butoxide in the dipolar aprotic solvent, the anion (72), regenerated from the pyran (62), can undergo oxidation to the corresponding carbonium ion, stabilized by the highly polar environment, followed by reaction with water to form the products (Scheme 4). This mechanism seems to be unlikely, however, in view of the fact that the reaction of the conjugated alcohol (19) with 2 moles cerium(IV) ammonium nitrate yields the two epimeric 4-hydroxy naphthopyrans (24) and (25)[13] via a postulated carbonium ion (73).



(19) (73)

In this reaction the pyran (25) with the 4-hydroxyl group in the less crowded pseudo-axial configuration predominated, the opposite being true in this base-catalysed reaction. Alternatively the anion (72) can either react with molecular oxygen directly to the peroxide anion (74) or it can be oxidised by oxygen to the corresponding radical (75) and the superoxide radical ion $O_2^{\bullet -}$, which has a significant lifetime in aprotic and even alkaline aqueous solutions.[27] The t-butyl alcohol could then react directly with the pyran radical (75) to form the final products (67) and (68) and a t-butyl radical, which would be too bulky to react with another pyran radical, or it could lose a proton to the superoxide radical ion producing the peroxide radical which in turn combines with a pyranyl radical (75) to form the pyranyl peroxide (76) and eventually the products (67) and (68).

On attachment, the C-4 hydroxyl group shows preference for the pseudo-equatorial configuration [see relative yields of (67) and (68)], unlike the considerably larger C-1 methyl group which goes exclusively pseudo-axial during the cyclisation to minimise steric interaction with the neighbouring methoxy group. The reason for this is presumably that the hydroxyl group in the pseudo-equatorial position, being closer to the peri-oxygen, can more effectively intramolecularly hydrogen-bond with it, which is supported by compounds (21), (24) and (67) having higher R_f values than their C-4 epimers (22), (25) and (68).



Scheme 4

Various reaction conditions were attempted to increase the yields of these oxygenation reactions. When the solvent was changed to dimethyl sulfoxide while keeping all other reaction conditions the same, the C-4 hydroxy derivatives (67) and (68) were obtained in yields of 12% and 7% respectively, while 74% starting material (62) was recovered. Dry oxygen was then used in place of air which enabled milder reaction conditions to be employed while at the same time improving the yields notably. Treatment of compound (62) with base in dimethylformamide at room temperature under a stream of dried oxygen for 30 minutes, before quenching the reaction with water, gave the two hydroxy compounds (67) and (68) in yields of 48% and 15%, respectively. No starting material was recovered. The use of dimethyl sulphoxide under the same conditions afforded 63% of compound (67) and 23% of compound (68), which made it the method of choice.

This considerable improvement in the yields of the products of oxygenation of naphthopyran (62) to afford the epimeric alcohols (67) and (68) was the result of research work undertaken by the author of this thesis. It represented a major breakthrough in the synthesis of the racemates of dimethyl ethers of the quinones A and A', since it doubled the yields of the reaction products previously obtained, and therefore doubled the overall yields of the target quinones.

As will be seen in chapter 3 of this thesis, it also led to a doubling (at least) of the overall yields of quinone A' relative to that previously obtained. (Quinone A' had not been prepared in the laboratory prior to the work described in chapter 3).

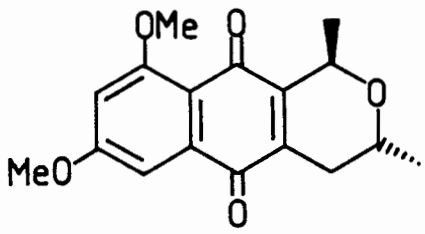
The naphthopyrans (62), (67) and (68) were readily oxidised with silver(II) oxide to the corresponding 5,10-quinones (69), (70) and (71) in good yields. Confirmation of the stereochemical assignments for the pyran ring system were obtained from their respective ^{1}H n.m.r. spectra.

Karplus has shown[28] that long-range proton-proton coupling in a CH-C=C-CH system should be greatest where the C-H bonds are perpendicular to the plane of the double bond. Thus the magnitudes of the coupling constants between 1-H and 4-H, $J_{1,4}$, of compounds (70) and (71) should be greatest if both protons are in the pseudo-axial configuration and smallest if they are both in the pseudo-equatorial position. If one of the protons is pseudo-equatorial and the other pseudo-axial, $J_{1,4}$ will be of intermediate magnitude.

The large coupling constant of 8 Hz between H-4 and axial H-3 in the n.m.r. spectrum of quinone (70) indicates that these two vicinal C-H bonds have essentially axial configurations. This was already established from the spectrum of the corresponding naphthopyran (67), as previously mentioned. The proton H-1 appeared as a doublet of quartets (J 1.5 and 7 Hz), the smaller coupling constant being due to long-range coupling between the pseudo-axial 4-H and 1-H; the latter therefore has to be in the pseudo-equatorial position.

In the spectrum of naphthopyranquinone (71) the negligible coupling between 1-H and 4-H suggests that both C-H bonds have the pseudo-equatorial configuration. This therefore fixes both the methyl group at C-1 and the C-4 hydroxyl group as pseudo-axial. The small vicinal coupling constant of 2.5 Hz between 3-H and 4-H of compound (71) therefore indicates that 3-H is again

axial, since 4-H is in the pseudo-equatorial position.



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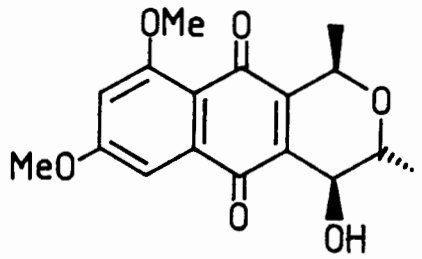

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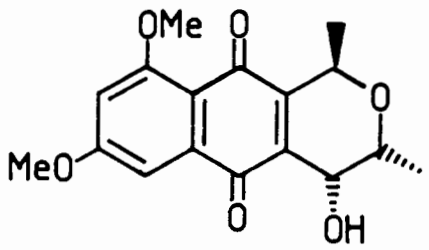
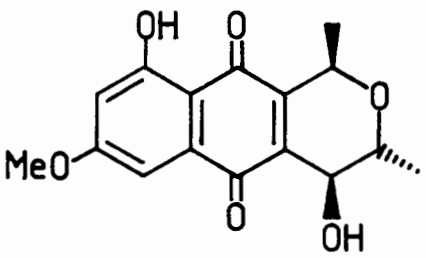


(71)

Demethylation of the dimethoxy quinones (69) and (70) with 5 equivalents of boron trichloride finally completed the synthesis of the title compounds (28) and (27) in yields of 57% and 62%, respectively. Treatment of the quinone (71) with two molar equivalents boron trichloride gave the corresponding, fairly unstable quinone A' derivative (77) in a yield of 38%.

While the former two compounds (27) and (28) could be purified by recrystalisation from acetone, compound (77) had to be isolated from a complex reaction mixture by preparative layer chromatography (eluant 50% ethyl acetate / light petroleum under nitrogen). A possible explanation for this observed difference in stability may be that the axial and pseudo-axial configurations of the adjacent hydrogen and hydroxyl substituents

at C-3 and C-4, respectively, of compound (77) may facilitate the elimination of water, followed by further decomposition.



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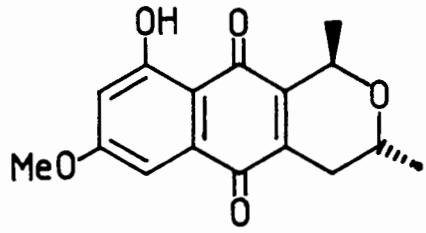

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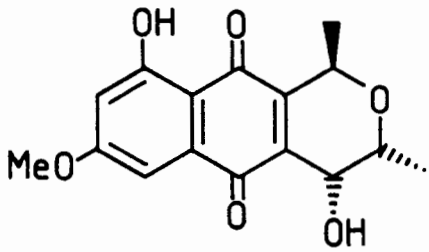
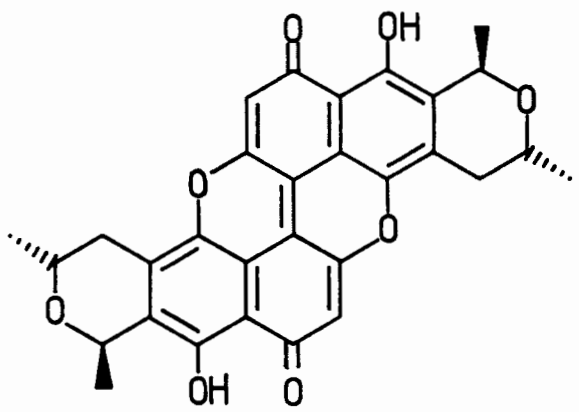


(77)

The ^{1}H n.m.r. spectra of all three compounds showed the presence of one methoxy group at about δ 3.90 as well as the formation of a sharp hydrogen-bonded hydroxy signal between δ 12.11 and 13.01.

Attempts to demethylate the trans-dimethylnaphthopyranquinone (69) to deoxy-quinone A (18) by using Lewis acids such as aluminium trichloride or boron tribromide under various reaction conditions resulted in extensive decomposition. Deoxyquinone A (18) was to be used to synthesise the extended quinonoid system (78), analogous to the blue extended quinone xylaphin (79) which had been prepared by Cameron et al[29] from quinone A (16) via an anaerobic coupling. The total deprotection was also attempted with 40% HBr in acetic acid as well as ethanethiol / sodium

hydride[30,31] in dimethyl formamide. However, this met with no success so that this scheme was abandoned. Presumably the more vigorous reaction conditions led to the decomposition of the moderately sensitive dihydropyran ring.



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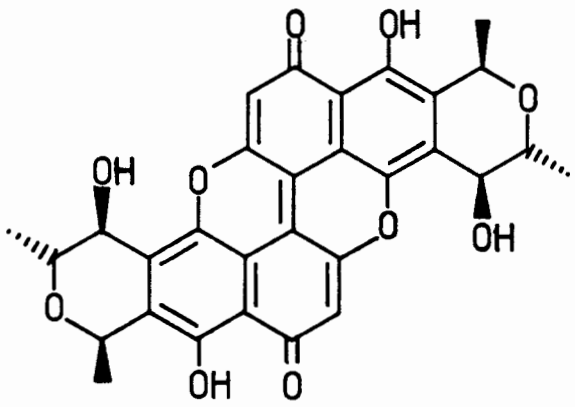

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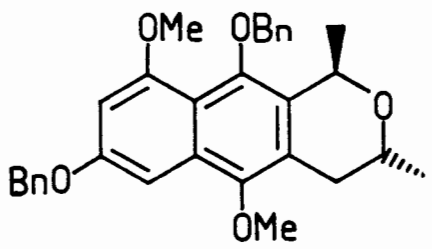
Chapter 3

THE CONVERSION OF A PRECURSOR TO QUINONE A INTO ITS C-4 EPIMER, FOLLOWED BY THE DEPROTECTION TO AFFORD QUINONE A'

During the course of the work described in this thesis, other members of Professor Giles' group were involved in the complete synthesis of quinones A (16), and deoxyquinone A (18) via the 7,10-dibenzyloxy-5,9-dimethoxy-naphthopyran (80).[32]



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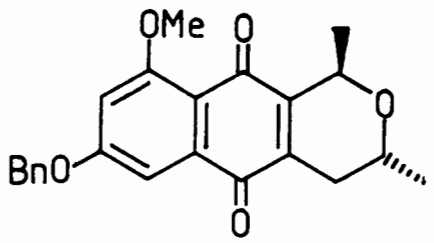

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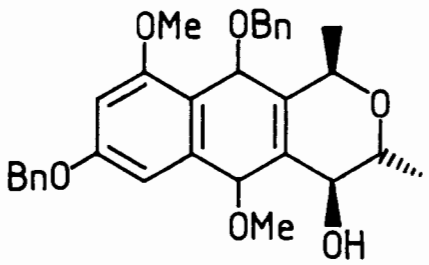

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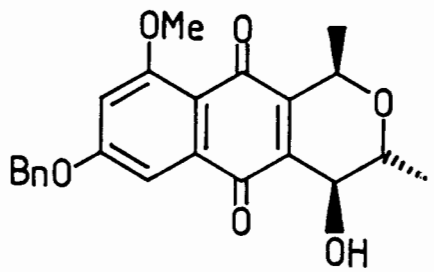

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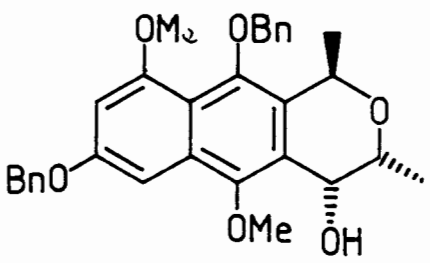

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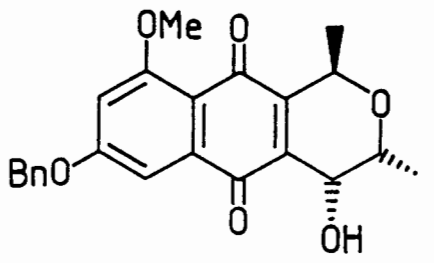


(85)

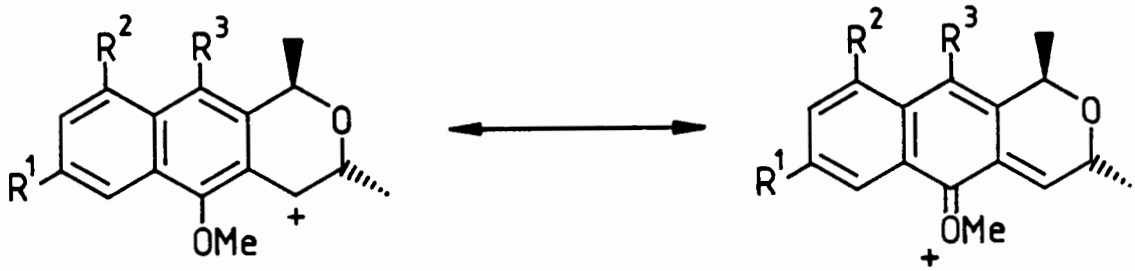
Quinone A' (17) however, had not been synthesised previously in quantities sufficient to characterise it fully (including microanalysis), since considerable difficulty had been encountered in the final deprotection of its immediate precursor, which had previously been available only in small quantities. This difficulty had not been observed for the corresponding compounds quinone A and deoxyquinone A.

The naphthopyran (80) was oxygenated to the two C-4 hydroxy epimers (81) and (82) with potassium t-butoxide in dimethyl sulphoxide under oxygen, as described in chapter 2 for compound (62). Oxidation of these naphthalenes with silver(11) oxide then provided the corresponding 5,10-quinones (83) to (85). Treatment of compounds (83) and (84) with an excess of boron trichloride effected the removal of both methyl and benzyl groups on oxygen, affording racemic mixtures of deoxyquinone A (18) and quinone A (16), respectively. Similar deprotection of the corresponding quinone (85) resulted in the complete decomposition of the product during the isolation and purification procedure. Quinone A' could, however, clearly be identified in the crude reaction mixture by thin layer chromatography by comparison with authentic, naturally derived quinone A'. This instability towards deprotection may again be due to, as for the quinone A' dimethyl ether (71), the axial and pseudo-axial configuration of the adjacent hydrogen and hydroxyl substituents at C-3 and C-4, respectively, which enable the facile elimination of water, followed by further decomposition.

A milder method, for the deprotection of compound (85) to quinone A' was therefore needed. None of the precursors (82) or (85) remained however, as the former was the minor product in the

hydroxylation of the naphthopyran (80). On the other hand, quantities of the major product (81) of this reaction were available and a method for its efficient conversion into the epimer (82) was sought.

It was mentioned in chapter 2 that the stabilized carbonium ion (73) was proposed as an intermediate of the cerium(IV) ammonium nitrate effected cyclisation of the conjugated naphthyl alcohol (19).



(73) $R^1 = R^2 = H$; $R^3 = OMe$

(86) $R^1 = R^2 = R^3 = OMe$

(87) $R^1 = R^3 = OCH_2Ph$; $R^2 = OMe$

This carbonium ion was then attacked by the nucleophile water to form the naphthopyrans (24) and (25), epimeric at C-4. In this reaction the compound (25), in which the hydroxyl group was pseudo-axial, predominated, probably because steric interactions with the peri-methoxy group were minimised in this position.

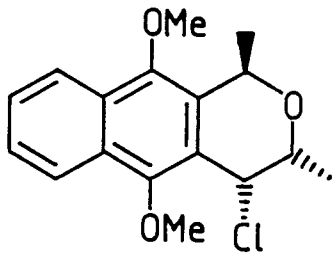
It was therefore argued, that if it were possible to generate the carbonium ion (87) from compound (81) in the presence of water, the major hydroxy epimer formed would be the desired quinone A' precursor (82).

In order to conserve compound (81), the analogues (24) and (67) were chosen as models. Initial attempts to epimerise these

alcohols to increase the proportion of the corresponding pseudo-axial alcohols rested on protonation of the hydroxyl group. It was anticipated that loss of water, assisted by the peri-methoxy substituent would give rise to the carbonium ions (73) or (87) [from (24) or (67) respectively] and that water would rejoin these ions to afford the products (25) or (68) as the major products, contaminated by a little of the starting material in each case.

The acids used for this purpose (TFA, HCl), however, either effected no change, or led to molecular decomposition. The trifluoroacetyl esters of the alcohols (24) and (67) were then made, but treatment of these gave similar results.

In view of the lack of success with this approach, an alternative route was investigated. Treatment of these two naphthopyrans with phosphorus pentachloride in dry ether afforded only the respective chloronaphthopyrans (88) and (89) in high yield with a little of the corresponding naphthopyran (91) and (92) in each case.



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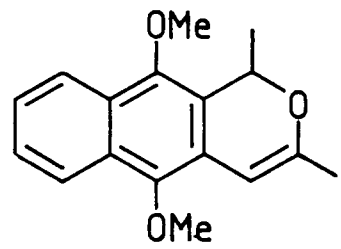

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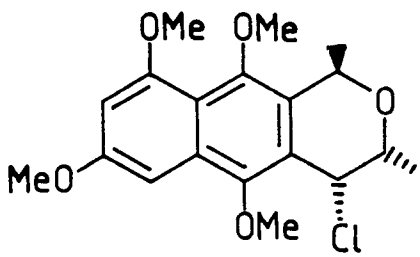

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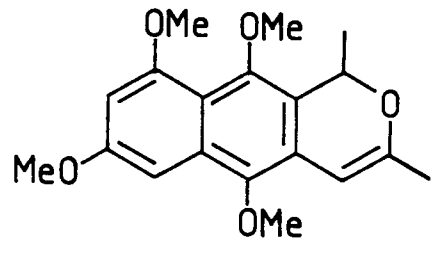


(92)

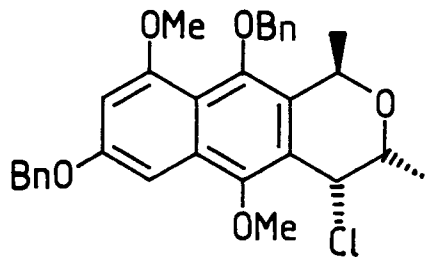
The ^{1}H n.m.r. spectrum of the two chlorocompounds (88) and (89) showed that the H-4 signal had shifted from δ 4.81 and δ 4.72 for the two starting compounds (24) and (67) to δ 5.34 and 5.29, respectively. This signified that a deshielding effect was being experienced by that particular proton. The mass spectrum of the product clearly indicated the presence of a chlorine atom since the isotope peaks of the molecular ions were in the ratio of 3 : 1, which is characteristic of chlorinated compounds. The stereochemistry of the chlorine substituent was established from the coupling constant of 1.5 Hz between H-3 and H-4 which showed these protons to be in a axial-pseudo-equatorial relationship, respectively. The spectrum of the pyran (92) showed a singlet at δ 1.98 for the C-3 methyl group and a singlet at δ 5.91 for the H-4 proton.

Identical treatment of the two pseudo-axial hydroxy epimers (25) and (68) gave the same corresponding products by t.l.c. in very similar yields. This supports the intermediacy of a stabilized carbonium ion which the chloride ion then attacks to yield the sterically less hindered product. The corresponding olefin could be formed by the loss of the 3-H proton from the carbonium ion or by elimination of HCl from the chloronaphthopyran. The latter is supported by the fact that both chloro-compounds (88) and (89) slowly decompose to form the corresponding more stable pyrans (91) or (92).

Treatment of the chloro-derivatives with a small excess of silver nitrate in acetonitrile and water afforded the corresponding 4-hydroxy naphthopyrans, with the pseudo-axial epimer predominating in a ratio of about 7 : 2. The yields as well as this ratio were improved when the intermediate chloro-compound was not

purified but immediately dissolved in acetonitrile and treated with silver nitrate and water. The carbonium ion, regenerated by the loss of chloride from the chloronapthopyrans (88) and (89) to form silver chloride, could be trapped competitively by the nucleophiles water and nitrate.[13] In order to favour the attack by water, the molar ratio of water to silver nitrate used in this reaction was of the order of 20 : 1.

Now that a highly successful method had been developed to epimerise the pseudo-equatorial alcohols to the isomeric pseudo-axial alcohols for the two model series, the related reaction was investigated for the alcohol (81) so that progress could be made with a proposed synthesis of quinone A'. The related conversion of the dibenzyloxy analogue (81) gave parallel results, affording compound (93 ; 7%), the chloro-compound (90 ; 13%), starting material (81 ; 22%) and finally compound (82) in a 55% yield.



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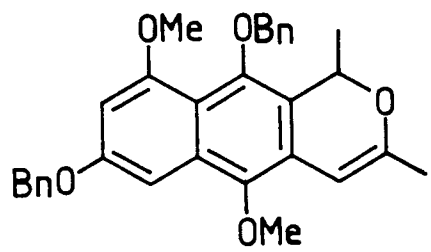
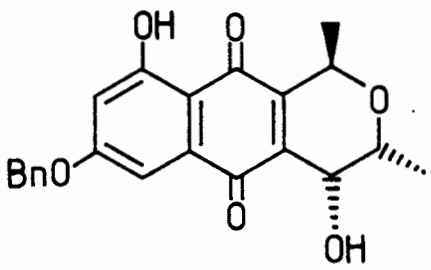


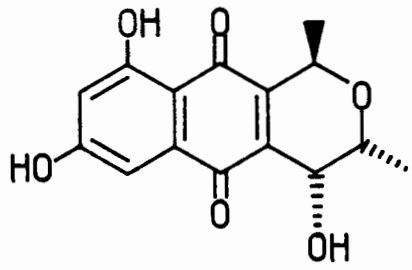
(93)

The naphthalene (82) was then converted to the yellow quinone (85) in a yield of 62% as described above. The successful deprotection of the quinones (83) and (84) to afford racemic deoxyquinone A and quinone A has already been described, as has the fact that similar treatment of the quinone (85), epimeric

with (84), led to decomposition, without isolation of the desired quinone A'. A possible reason for this anomaly in the latter case has been put forward. In view of the fact that the successful reactions had been performed with a considerable excess of boron trichloride, it was decided to reduce the amount of this reagent used. It appeared likely that a minimum of two molar equivalents would be required; one to bind between the hydroxyl group at C-4 and the carbonyl at C-5, while the second would be required to remove the methyl on oxygen at C-9. The quinone (85) was therefore treated with this proportion of the Lewis acid, whereupon 7-O-benzylquinone A' (94) was obtained in a yield of 34%, after purification by preparative layer chromatography under nitrogen, followed by recrystallisation from dichloromethane - cyclohexane. Column chromatography on deactivated silica gel or aluminium oxide resulted in total decomposition of the product.



(94)



(17)

Hydrogenation of compound (94) with Adam's catalyst (PtO_2) in methanol provided a hydroquinone which, upon aerial oxidation, gave the quinone A' (17) in a yield of 94%. It was purified by preparative layer chromatography (silica impregnated with 2% oxalic acid) and recrystallisation.

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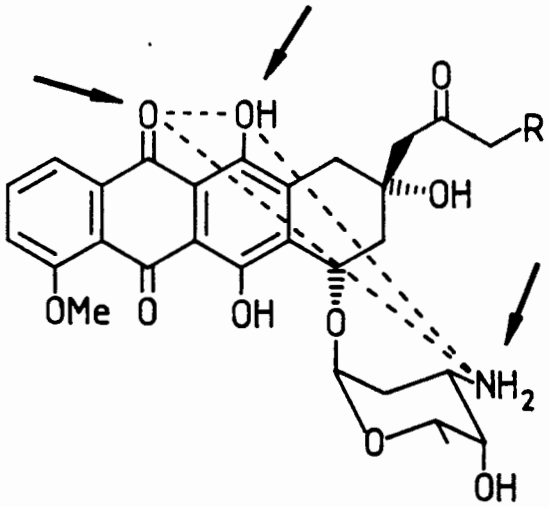
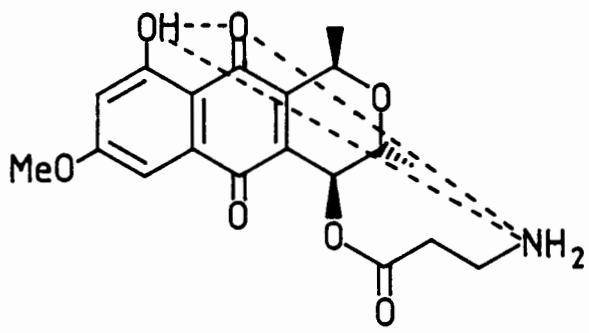
Many of the naturally occurring quinonoid compounds that have been shown to have antineoplastic or so-called anti-cancer activity possess nitrogen containing substituents. One group of these compounds is referred to as the anthracycline group, which includes adriamycin (95) and daunomycin (96).



(95) R = OH

(96) R = H

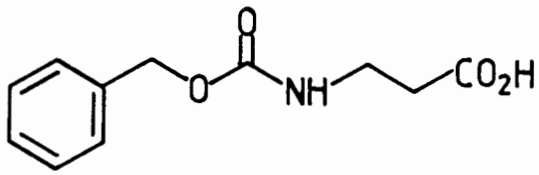


(97)

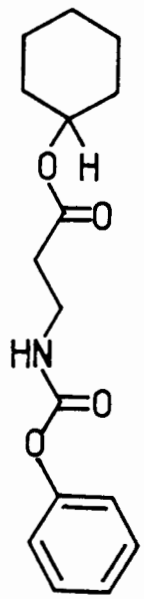
A hypothesis has been developed for compound (95) linking the relative spatial position of the three atoms, marked by arrows, to its anti-cancer activity, the so-called N-O-O triangulation hypothesis[33]. This led to the speculation that if it were possible to couple various nitrogen containing groups such as β-alanine, or 2-deoxy-2-amino-glucose to the C-4 hydroxyl group of either compound (67) or (70) it might enhance the activity of the modified quinone (27), as well as increase its solubility in biological systems.

By treating a mixture of cyclohexanol as model compound and the N-protected β-alanine (98) with dicyclohexylcarbodiimide (DCC), a

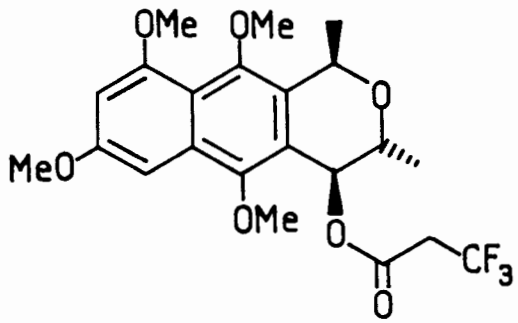
method used for coupling reactions to form peptides, the cyclohexyl-β-alanate derivative (99) was obtained. Similar treatment of the naphthopyran (67) did not meet with any success. Reaction of (67) with a mixture of trifluoroacetic anhydride and compound (98) afforded only the pseudo-equatorial trifluoroacetate (100), as indicated by its ^{1}H n.m.r. spectrum.



(98)



(99)



(100)

Work is continuing with the objective of preparing compounds of type (97) for evaluation as potential antineoplastic agents.

EXPERIMENTAL

General

1. Unless otherwise stated, all n.m.r. spectra were measured for solutions at ambient temperature in [^{2}H]chloroform using TMS as internal reference. ^{1}H n.m.r. spectra were recorded on the following instruments: 60 MHz, Varian EM-360 ; 90 MHz, Bruker WH-90 and 200 MHz, Varian VXR-200. ^{13}C spectra were recorded at 50.093 MHz on the Varian VXR-200 spectrometer.

2. Infrared spectra were recorded on a Perkin Elmer 237 spectrophotometer for films (in the case of oils) or nujol mulls (for solids).

3. Mass spectra were recorded on a VG Micromass 16 F mass spectrometer operating at 70 eV and ion source temperature between 180 and 220°C. High resolution mass spectra were measured on a Varian MAT 311 A spectrometer.

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

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

6. Column chromatography was carried out on dry-packed columns using Merck Kieselgel 60 (70 - 230 mesh) as adsorbent. Preparative layer chromatography (p.l.c.) was performed on glass-backed plates coated with Merck Kieselgel 60 F_{254}.

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

8. The phrase "residue obtained upon work-up" refers to the residue when the organic layer was separated, dried with anhydrous magnesium sulphate and the solvent removed under reduced pressure.

1,1-Dimethoxy-3-trimethylsilyloxybuta-1,3-diene (31)

a) 4,4-Dichlorobut-3-en-2-one

Acetyl chloride (100g ; 1.27mol) was mechanically stirred with ice/cooling and under nitrogen in a three-necked round bottom flask. Powdered aluminium chloride (100g ; 1.7 equivalents) was added in portions with vigorous stirring. After the addition was complete, the ice was replaced by a water-bath at room temperature and 1,1-dichloroethylene (71g ; 1.7 equivalents) was added dropwise over two hours with continous vigorous stirring, which was continued for another hour after the addition was complete. The reaction was quenched by pouring the mixture onto an ice/water mixture with stirring after which the product was extracted into dichloromethane (3 x 100ml). After separating the organic phase, it was washed with water (2 x 100ml), then dried with magnesium sulphate and the solvent removed under reduced pressure at a water-bath temperature below 30°C. The dark oil which was obtained was distilled under vacuum through a Dufton column to yield the product (66g ; 65%), b.p. 52-55°C at 10mmHg (lit.[16] 58°C / 15mmHg); δ 2.30 (3H, s, 1-CH_3), and 6.74 (1H, s, 3-H).

b) 4,4,4-Trimethoxybutan-2-one

The freshly distilled product from the previous reaction (22.86g; 0.165mol) was added dropwise to a solution of sodium methoxide [from sodium (7.32g ; 0.318mol)] in absolute methanol (170ml) over two hours. The reaction mixture, kept at room temperature in a water-bath, was stirred for another two hours at the same temperature before the yellow solution was filtered, concentrated and distilled under vacuum through a Dufton column to afford the product (17.61g ; 66%), b.p. 62-65°C at 6mm Hg (lit.[17] 82-84°C at

12mmHg) ; δ 2.25 (3H, s, 1-CH_3), 2.87 (2H, s, 3-CH_2), and 3.33 (9H, s, 3 x OCH_3).

c) 4,4-Dimethoxybut-3-en-2-one

The above product (21.42g ; 0.132mol) was heated with stirring in an open round bottom flask at 145°C for 5 hours to yield the enone (7.05g ; 41%), b.p. 82-84°C at 12mmHg (lit.[17] 104-105°C at 10mmHg); δ 2.23 (3H, s, 1-CH_3), 3.77 and 3.87 (each 3H, s, 2 x OCH_3), and 4.57 (1H, s, 3-H).

d) 1,1-Dimethoxy-3-trimethylsilyloxybuta-1,3-diene (31)

To a solution of the above dimethoxy-enone (33.52g, 0.258mol) and triethylamine (57.94g ; 2.2 equivalents) in dry benzene (70ml) chlorotrimethylsilane (52.45g ; 0.516mol) was added slowly. The reaction mixture was stirred at 40°C for 3 hours and then at room temperature for 16 hours, filtered and distilled to give the diene (31)(33.93g ; 63%), 85-90°C at 11mm Hg (lit.[17] 84-87°C at 10mmHg) ; δ 0.19 (9H, s, $Si[CH_3]_3$), 3.58 and 3.68 (each 3H, s, 2 x OCH_3), 3.99 and 4.12 (each 1H, d, J 1 Hz, 4,4-CH_2), and 4.41 (1H, s, 2-H).

1,7-(2-Propyloxy)-5-methoxy-4-naphthol (33)

A solution of 1,4-benzoquinone (1.85g ; 0.017mol) and freshly distilled diene (31)(5g ; 0.023mol) in dry benzene (30ml) was boiled under nitrogen for 1 hour to yield the intermediate adduct (32) which was not purified beyond evaporation of the solvent. It was immediately redissolved in dry dimethylformamide (50ml) followed by the addition of 2-bromopropane (14g; 0.11mol) and anhydrous potassium carbonate (15g ; 0.108mol). The mixture was

vigorously stirred at 60°C under nitrogen for 9 hours before the reaction was quenched with water (100ml) and extracted into diethyl ether (8 x 50ml). The combined organic phases were washed with water (3 x 100ml), dried with magnesium sulphate and concentrated under reduced pressure. The resulting brown oil was chromatographed (eluant 3% ethyl acetate in light petroleum) affording the product (33) (3.38g ; 68%), m.p. 52°C (from water/methanol); δ 1.34 and 1.44 (each 6H, d, J 6 Hz, 2 x $CH[C\underline{H}_3]_2$), 3.97 (3H, s, OCH_3), 4.55 (2H, septet, J 6Hz, 2 x $C\underline{H}[CH_3]_2$), 6.49 (1H, d, J 2 Hz, 6-H), 6.61 and 6.85 (each 1H, d, J 8 Hz, 2- and 3-H), 7.20 (1H, d, J 2 Hz, 8-H), and 8.83 (1H, s, OH, D_2O exchangeable).

1,5,7-Trimethoxy-4-naphthol (43)

1,4-Benzoquinone (13.18g, 0.122mol) and Brassard's diene (31) (33.03g ; 0.163mol) in dry benzene (140ml) were treated the same way as for compound (33) above to give the crude adduct (32). This was immediately redissolved in dry acetone (300ml) and boiled under nitrogen in presence of dimethyl sulphate (61.53g ; 4 equivalents based on the amount benxoquinone used) and anhydrous potassium carbonate (67,45g ; 4 equivalents) for 2.5 hours. The reaction mixture was filtered, the acetone removed under reduced pressure and the resulting brown oil redissolved in ether. This was washed with concentrated aqueous ammonia (3 x 100ml), water (1 x 50ml), diluted HCl (1 x 50ml) and finally again with water (2 x 50ml). The residue obtained after drying the organic phase with magnesium sulphate and removing the ether under reduced pressure was chromatographed (eluant 15% ethyl acetate in light petroleum) to afford the product (43)

(22.86g ; 80% based on benzoquinone used), m.p. 131-132°C (from light petroleum, lit.[20b] 131-132°C) (Found: C, 66.7; H, 5.9. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%); δ 3.84 (6H, s, 2 x OCH_3), 3.89 (3H, s, OCH_3), 6.42 (1H, d, J 2 Hz, 6-H), 6.55 and 6.62 (1H, d, J 8 Hz, 2- and 3-H), 7.09 (1H, d, J 2 Hz, 8-H), and 8.69 (1H, s, OH, D_2O exchangeable).

1,7-Di(2-propyloxy)-5-methoxy-3-trifluoroacetyl-4-naphthol (47)
The naphthol (33) (1.82g ; 6.27mmol) was dissolved in dry dichloromethane (12ml). Trifluoroacetic anhydride (8ml) was added and the mixture stirred for 2 hours before the reaction was quenched by the slow addition of water. Extraction with dichloromethane gave a dark solid after drying with magnesium sulphate and evaporation of solvent, which was chromatographed (20% ethyl acetate in light petroleum) to afford the product (47) (1.65g ; 80%), m.p. 76-77°C (2-propanol, lit[19] 76-77°C), δ 1.42 (12H, d, J 6.5 Hz, 2 x $CH[CH_3]_2$), 4.01 (3H, s, OCH_3), 4.70 (2H, septet, J 6.5 Hz, 2 x $CH[CH_3]_2$), 6.58 (1H, d, J 2.5 Hz, 6-H), 6.93 (1H, q, J 2.5 Hz, 2-H), 7.21 (1H, d, J 2.5 Hz, 8-H) and 12.89 (1H, s, OH, D_2O exchangeable).

3-(1,1-Dihydroxy-2,2,2-trifluoroethyl)-5-methoxy-7-(2-propyloxy)-1,4-naphthoquinone (29)
An aqueous solution of cerium(IV) ammonium nitrate (5.0g ; 9.1mmol) in 70ml water was added slowly to a solution of starting material (47) (1.50g ; 4.55mmol) in acetonitrile (300ml) at room temperature. The solution was stirred for a further 5 minutes, then poured into water (800ml) and extracted into dichloromethane. The combined organic phases were washed with water, dried

with magnesium sulphate and concentrated, giving a residue which was chromatographed (30% ethyl acetate in light petroleum) to afford the quinone (29) (1.26g ; 91%), m.p. 103.5-105°C (from dichloromethane - light petroleum, lit.[19] 104-106°C) ; δ 1.38 (6H, d, J 6.5 Hz, $CH[C\underline{H}_3]_2$), 3.95 (3H, s, OCH_3), 4.73 (1H, septet, $C\underline{H}(CH_3)_2$), 6.88 (1H, d, J 3 Hz, 8-H) 7.08 (1H, d, J 3 Hz, 6-H), 7.15 (1H, s, 2-H), and 7.41 (2H, s, 2 x OH, D_2O exchangeable).

4-Acetoxy-1,5,7-trimethoxynaphthalene (48)

The naphthol (43) (1.9g ; 8.11mmol) was dissolved in pyridine (30ml) and acetic anhydride and the reaction mixture stirred at 110°C for two hours, then thrown onto ice. The white crystalline solid was filtered off, washed with water and dried to afford the product (1.99g ; 90%), m.p. 145-145.5°C (from dichloromethane - light petroleum, lit.[20b] 145-146°C) (Found: C,65.4, H, 5.65. $C_{15}H_{16}O_5$ requires C,65.2, H, 5.84%) ; m/z 276 (M^+, 35%), 234 (78), 219 (100) and 43 (11) ; δ 2.32 (3H, s, $COCH_3$), 3.84, 3.90 and 3.93 (each 3H, s, 3 x OCH_3), 6.57 (1H, d, J 2 Hz, 6-H), 6.70 and 6.87 (each 1H, d, J 8 Hz, 2 and 3-H), and 7.22 (1H, d, J 2 Hz, 8-H).

3-Acetyl-1,5,7-trimethoxy-4-naphthol (49)

The acetate (48) (0.341g ; 1.2mmol) and freshly distilled boron trifluoride-diethyl ether (3.1ml) were stirred together for 30 minutes at 60°C (oil-bath temperature) after which the reaction mixture was thrown onto ice and extracted with dichloromethane. The residue obtained upon drying the organic phase with magnesium sulphate and evaporation of the solvent was chromatographed

(eluant 30% ethyl acetate in light petroleum) to give first the naphthol (43) (0.046g ; 16%) followed by the product (49) (0.242g ; 71%) as yelllow-green crystals, m.p. 173,5-174,5°C (from dichloromethane - light petroleum, lit[20b] 174-175°C) (Found: C, 65.4, H, 5.8. $C_{15}H_{16}O_5$ requires C, 65.20, H, 5.85%); m/z 276 (M^+, 100%), 261 (97), and 43 (24) ; δ 2.62 (3H, s, $COCH_3$), 3.94 (6H, s, 2 x CH_3), 3.98 (3H, s, OCH_3), 6.49 (1H, d, J 2 Hz, 6-H) 7.49 (1H, s, 2-H), 7.07 (1H, d, J 2 Hz, 8-H), and 14.01 (1H, s, OH, D_2O exchangeable)

Allyltributylstannane (58)

The Grignard reagent was prepared by the addition of allyl bromide (19.9g ; 0.165mol) in dry ether (165ml) to stirred magnesium filings (3.84g ; 0.158mol) in dry ether (60ml) under nitrogen at such a rate as to maintain gentle boiling. After the addition was complete, the reaction mixture was boiled for 15 minutes before cooling slightly. Tributyltin chloride (42g ; 0.129mol) in dry ether (50ml) was added dropwise to the vigorously stirred solution before boiling the mixture for 1.75 hours under reflux. The reaction was quenched by cooling the mixture to -15°C in a salt/ice mixture followed by the addition of a saturated aqueous ammonium chloride solution (33ml) and stirring for another hour. The solid precipitate was filtered off and washed with ether. The filtrate was allowed to separate into two phases, the organic layer isolated, and the aqueous phase extracted with ether (3 x 50ml). The combined ether extracts were dried with magnesium sulphate and the bulk of the ether removed under reduced pressure before the concentrate was distilled in vacuo to give the product (19.8g ; 46.5%), b.p. 129-133°C at 5mmHg ; δ 0.5 - 1.93 (46H, m,

all 29 aliphatic protons), 4.52 - 4.99 (2H, m, vinyl CH_2), and 5.57 - 6.35 (1H, m, vinyl CH) ; from the relative integration curves of the signals for the aliphatic protons and the vinyl proton, the purity of this sample was calculated as follows: % purity = 29/46 x 100 = 63.

3-Acetyl-1,4,5,7-tetramethoxy-2-prop-2-enylnaphthalene (54)

The acetyl naphthol (49) (1.00g ; 3.62mmol) was dissolved in acetonitrile (100ml). To this a solution of cerium(IV) ammonium nitrate was added over 10 minutes after which it was stirred for another 15 minutes. The deep orange solution was then thrown into water (1ℓ) and extracted with dichloromethane (4 x 75ml). After washing the organic phase with water (2 x 50ml) and drying with magnesium sulphate, the volume of the crude acetyl quinone (55) solution was reduced to about 60ml and immediately cooled in a dry-ice/acetone bath. The flask was flushed with nitrogen before boron trifluoride-diethyl ether (0.38ml ; 2.9mmol) was added, whereupon the solution turned dark brown. Allyltributylstannane (58) (1.8g ; 1.5 equivalents) was added and the reaction mixture stirred for 1 hour at -78°C after which it was allowed to warm up to room temperature. Water (200ml) was then added rapidly and the mixture, containing the crude adduct (59), extracted with dichloromethane (4 x 150ml) . The residue obtained after drying the combined organic phases with magnesium sulphate and removing the solvent under reduced pressure was immediately redissolved in dry acetone. Dimethyl sulphate (3.5ml ; 3.6mmol) and anhydrous potassium carbonate (5g; 3.6mmol) were added and the mixture heated overnight under nitrogen with reflux and vigorous stirring. It was then

allowed to cool to room temperature, the solid carbonate was filtered off, and the acetone removed under reduced pressure. The resulting brown oil was redissolved in diethyl ether, washed with concentrated aqueous ammonia (3 x 100ml), water (1 x 100ml) dilute hydrochloric acid (1 x 50ml) and finally water again. Drying the organic phase with magnesium sulphate and evaporation of the solvent under reduced pressure gave an oil which was chromatographed (eluant 15% ethyl acetate in light petroleum) to afford the product (0.70g ; 59% based on starting material [49]) as an oil ; δ 2.61 (3H, s, $COCH_3$), 3.56 (2H, dd, J 6 Hz and 2 Hz, aliphatic CH_2), 3.79, 3.89, 3.96 and 4.01 (3H each, s, OCH_3), 4.77 - 5.06 (2H, m, vinyl CH_2, 5.67 - 6.36 (1H, m, vinyl CH), 6.63 (1H, d, J 2 Hz, 6-H), and 7.07 (1H, d, J 2 Hz, 8-H).

3-(1-Hydroxyethyl)-1,4,5,7-tetramethoxy-2-prop-2-enyl-naphthalene (60)

To a stirred suspension of lithium aluminium hydride (1g) in dry ether (80ml) at room temperature a solution of compound (54) (1.94g ; 5.87mmol) in dry ether (20ml) was added dropwise during 5 minutes. After stirring for another 5 minutes the reaction was worked up by the dropwise addition of saturated aqueous ammonium chloride solution, followed by anhydrous magnesium sulphate. After filtration, the ether phase was concentrated and the yellow oil chromatographed (eluant 30% ethyl acetate in light petroleum) to give the product (1.79g ; 92%) as an oil ; δ 1.63 (3H, d, J 7 Hz, $CHC\underline{H}_3$), 3.70 (2H, m, CH_2), 3.82, 3.84, 3.90, and 3.94 (3H each, s, OCH_3), 4.10 (1H, br s, OH, D_2O exchangeable), 3.8 - 4.2 (2H, m, vinyl CH_2), 5.26 (1H, m, $C\underline{H}CH_3$), 5.9 - 6.3 (1H, m, vinyl

CH), 6.52 (1H, d, J 2.5 Hz, 6-H), and 6.98 (1H, d, J 2.5 Hz, 8-H).

3-(1-Deutero-1-hydroxyethyl)-1,4,5,7-tetramethoxy-2-prop-2-enylnaphthalene (61)

The ketone (54) (170mg ; 0.515mmol) was reduced as above, with the exception that lithium aluminium deuteride was used instead of the hydride, to afford the alcohol (61) (152mg, 89%) ; δ 1.62 (3H, s, $CDCH_3$), 3.50 - 3.76 (2H, m, CH_2), 3.83, 3.88, 3.92 and 3.96 (each 3H, s, 4 x OCH_3), ca. 4.04 (1H, br s, OH), 4.78 - 5.18 (2H, m, vinyl CH_2), 5.82 - 6.32 (1H, m, vinyl CH), 6.55 1H, d, J 2.5 Hz, 6-H) and 6.99 (1H, d, J 2.5 Hz, 8-H).

trans-3,4-Dihydro-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (62)

Compound (60) (4.33g ; 13.03mmol) was dissolved in dry dimethylformamide (25ml) at 55°C (external oil bath temperature) and nitrogen, dried by passing it through a calcium chloride containing tube, was bubbled through the solution for 40 minutes. Potassium t-butoxide (9.46g ; 84.3mmol) was added and the mixture stirred under nitrogen at that temperature for 7 minutes when t.l.c indicated that all starting material had been consumed. The reaction was quenched by the addition of water (100ml) and the mixture was extracted exhaustively with diethyl ether (6 x 30ml). The combined organic phases were washed with water (2 x 20ml) before drying with magnesium sulphate and removing the solvent under reduced pressure. The resulting oil was chromatographed (20% ethyl acetate in light petroleum) to afford the naphthopyran (62) (3.79g ; 88%) as the sole product; δ 1.39 (3H, d, J 6 Hz, 3-CH_3), 1.63 (3H, d, J 7 Hz, 1-CH_3), 2.56 (1H, dd, J 10 and 16.7 Hz, pseudo-axial 4-H), 3.06 (1H, dd, J 3.5 and

16.7 Hz, pseudo-equatorial 4-H), 3.79, 3.85, 3.94, and 3.98 (3H each, s, 4 x OCH_3), 3.9 - 4.3 (1H, m, axial 3-H), 5.31 (1H, q, J 7 Hz, pseudo-equatorial 1-H), 6.51 (1H, d, J 2.5 Hz, 8-H), and 6.96 (1H, d, J 2.5 Hz, 6-H).

trans-3,4-Dihydro-1-deutero-5,7,9,10-tetramethoxy-1,3-dimethyl-1D-naphtho[2,3-c]pyran (66)

The alcohol (61) (170mg ; 0.51mmol) was treated with potassium t-butoxide as described above for compound (62) to afford the deuterated naphthopyran (66) (151mg ; 89%) after chromatography; δ 1.40 (3H, d, J 7Hz, 3-CH_3), 1.63 (3H, s, 1-CH_3), 2.56 (1H, dd, J 10 and 16.6 Hz, pseudo-axial 4-H), 3.05 (1H, dd, J 3.3 and 16.6 Hz, pseudo-equatorial 4-H), 3.8 - 4.2 (1H, m, axial 3-H), 3.78, 3.83, 3.93 and 3.98 (3H each, s, 4 x OCH_3), 6.50 (1H, d, J 2.6 Hz, 8-H) and 6.95 (1H, d, J 2.6 Hz, 6-H).

(1R,3R,4S)-3,4-Dihydro-4-hydroxy-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (67) and (1R,3R,4R)-3,4-Dihydro-4-hydroxy-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (68) and their Enantiomers

a) The naphthopyran (62) (100mg; 0,301mmol) was dissolved in dry dimethylformamide (10ml) and the solution warmed in an oil bath at 55°C while air, dried by a calcium chloride tube, was passed through for 10 minutes. Potassium t-butoxide (230mg ; 2.03mmol) was added and the mixture stirred at 55°C for 3 hours under a stream of dry air. The reaction was quenched by adding water (50ml) and the products were extracted exhaustively with ether (5 x 30ml). The combined ether phases were washed with water (2 x 20ml), dried with magnesium sulphate and concentrated under

reduced pressure. The resulting residual oil was chromatographed (20% ethyl acetate in light petroleum) to yield firstly compound (67) (29mg ; 28%), m.p. 119 - 120°C (from dichloromethane / light petroleum, lit.[22] 119.5 - 120.5°C) ; δ 1.41 (3H, d, J 6.5 Hz, 3-CH_3), 1.67 (3H, d, J 6.5 Hz, 1-CH_3), 3.74, 3.90, 3.92, and 3.94 (3H each, s, 4 x OCH_3), ca. 3.91 (1H, dq, J 6.5 and 8 Hz, 3-H, partially obscured by OCH_3), 4.21 (1H, d, J 2 Hz, OH, D_2O exchangeable), 4.71 (1H, dd, J 8 and 2 Hz, 4-H), 5.18 (1H, q, J 6.5 Hz, 1-H), 6.51 (1H, d, J 2.2 Hz, 8-H), and 6.89 (1H, d, J 2.2 Hz, 6-H), followed by the epimeric product (68) (10.4mg; 10%), m.p. 133 - 134°C (from dichloromethane / light petroleum, lit[22] 133 - 134°C); δ 1.39 (3H, d, J 6.5 Hz, 3-CH_3), 1.56 (3H, d, J 7 Hz, 1-CH_3), 2.22 (1H, br s, OH, D_2O exchangeable), 3.74, 3.88, 3.93, and 3.99 (3H each, s, 4 x OCH_3), ca. 4.09 (1H, dq, J 2 and 6.5 Hz, 3-H), 4.68 (1H, d, J 2 Hz, 4-H), 5.26 (1H, q, J 7 Hz, 1-H), 6.50 (1H, d, J 2.5 Hz, 8-H), and 6.93 (1H, d, J 2.5 Hz, 6-H).

b) Compound (62) (223mg ; 0.671mmol) was treated as above, with the exception that dimethyl sulphoxide was used as solvent. After stirring for 2 hours, t.l.c still revealed the presence of starting material and more t-butoxide (0.3g ; 2.68mmol) was added. The mixture was stirred for another hour after which the reaction was quenched and worked up as before. Chromatography yielded starting material (62) (165mg ; 74%), which was followed by compound (67) (27mg, 12% or 47% of unrecovered starting material) and epimeric (68) (16mg, 7% or 27% of unrecovered starting material). Both were identical to the materials described above.

c) Compound (62) (109mg, 0.327mmol) was dissolved in dry dimethylformamide (9ml) before dried oxygen gas (calcium chloride and silica gel) was passed through the solution for 10 minutes at room temperature. Potassium t-butoxide (250g ; 7 equivalents) was then added. The mixture, which had turned dark brown, was stirred for 30 minutes while passing oxygen through after which it had lightened again. The reaction was quenched with water, worked up, and chromatographed as before. The two products eluted from the column were firstly compound (67) (52mg ; 48%), followed by epimeric (68) (16mg ; 14%). Both were indistinguishable from the materials described above.

d) The starting material (62) (92mg ; 0.292mmol) was treated as under c) above, but using dry dimethyl sulphoxide as solvent. Again the solution turned dark after adding the base and lightened again later. The usual work-up and chromatography gave the two products (67) and (68) in yields of 63% and 23%, respectively.

e) The starting material (62) (259mg ; 0.779mmol) was dissolved in dry dimethyl sulphoxide (20ml) and dry oxygen was passed through the solution for 15 minutes at room temperature, when 2.5ml of a solution of potassium metal in dimethyl sulphoxide (2M ; 5mmoles) were added in one batch. After stirring for 60 minutes, thin layer chromatography indicated the formation of a number of by-products apart from the desired compounds, so that the reaction was quenched although there was still starting material left. Usual work-up and chromatography gave starting material (100mg ; 39%) followed by compound (67) (51mg ; 19% or

31% of unrecovered starting material), and finally compound (68) (60mg ; 22% or 36% of unrecovered starting material) All compounds were identical to the compounds described above.

f) Compound (89) (44mg ; 0.120mmol), described later, was dissolved in acetonitrile (5ml) before water (1ml) and silver nitrate (102mg ; 0.6 mmol) were added and the mixture stirred at room temperature for 4.5 hours. Water (20ml) was then added and the mixture extracted into ether (4 x 10ml). Work-up of the combined ether extracts gave an oil which was subjected to p.l.c. (30% ethyl acetate - light petroleum) yielding starting material (89) (3mg ; 7%) as the compound with the highest R_f value, followed by the pseudo-equatorial 4-hydroxynaphthopyran (67) (4mg ; 10%) and finally the pseudo-axial 4-hydroxynaphthopyran (68) (15mg ; 36%), both being identical to the materials described above.

g) The starting material (67) (50mg ; 0.144mmol) was dissolved in dry ether (10ml) at room temperature. Phosphorus pentachloride (60mg ; 0.288mmol) was added and the mixture stirred for 10 minutes before the reaction was quenched with water (20ml). More ether (80ml) was added and the organic phase washed with deionized water (5 x 10ml). The solution was dried with magnesium sulphate and the solvent evaporated to give an oil which was immediately redissolved in acetonitrile (10ml). Silver nitrate (122mg ; 0.72mmol) and water (1.1ml) were added and the reaction mixture stirred for 5 hours before water was added and the mixture extracted with ether (5 x 20ml). The combined organic phases were dried magnesium sulphate, the solvent

evaporated under reduced pressure and the resulting oil subjected to p.l.c. (30% ethyl acetate - light petroleum) to give firstly compound (89) (3mg; 6%), as the material with the highest R_f value and identical to the material described later. This was followed by compound (67) 9mg ; 18%) and finally the isomeric product (68) (35mg ; 70%), both being indistiguishable from the compounds described above.

(±)-trans-3,4-Dihydro-7,9-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (69) and its Enantiomer [(±) Deoxyquinone A Dimethyl Ether]

The naphthopyran (62) (0.61g ; 1.84mmol) was dissolved in dioxane (75ml) at room temperature. Silver(11) oxide (1.36g ; 11.01mmol) was added to the vigorously stirred solution, followed slowly by nitric acid (6M ; 1.84ml ; 11.01mmol), after which the mixture was stirred for a further 5 minutes. The reaction was quenched by the addition of dichloromethane (300ml) and water (100ml) and was then extracted into dichloromethane. The combined organic phases were washed with water (1 x 50ml), dried with magnesium sulphate and the solvent removed under reduced pressure. The yellow powder obtained was recrystallised from dichloromethane / light petroleum to give the pure product (0.44g ; 79%), m.p. 241-242°C (lit.[15,22] 239.5 - 240.5°C); δ 1.34 (3H, d, J 6.3 Hz, 3-CH_3), 1.53 (3H, d, J 7 Hz, 1-CH_3), 2.16 (1H, dd, J 10 and 19 Hz, pseudo-axial 4-H), 2.66 (1H, dd, J 4 and 19 Hz , pseudo-equatorial 4-H), 3.94 and 3.96 (3H each, s, 2 x OCH_3), 4.0 (1H, m, 3-H), 4.96 (1H, q, J 7 Hz, 1-H), 6.71 (1H, d, J 2.5 Hz, 8-H), and 7.25 (1H, d, J 2.5 Hz, 6-H).

(1R,3R,4S)-3,4-Dihydro-7,9-dimethoxy-4-hydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (70) and its Enantiomer [(±)-Quinone A Dimethyl Ether]

Compound (67) (1.05g ; 3mmol) was oxidised with silver(II) oxide (2.23g ; 0.018mol) and nitric acid (6M ; 3ml ; 0.018mol) in dioxane (150ml) as above to afford the product (70) (0.82g ; 86%), m.p. 172 - 173°C (ethanol, lit.[22] 172.5 - 174°C) ; δ 1.40 (3H, d, J 6 Hz, 3-CH_3), 1.60 (3H, d, J 7 Hz, 1-CH_3), 3.80 (1H, br s, D_2O exchangeable, OH), ca 3.90 (1H, dq, J 6 and 8 Hz, 3-H, partially obscured by OMe and OH), 3.94 and 3.96 (3H each, s, OCH_3), 4.45 (1H, dd, J 1.5 and 8 Hz, 4-H), 4.94 (1H, dq, J 1.5 Hz and 7 Hz, 1-H), 6.74 (1H, d, J 2.5 Hz, 8-H), and 7.29 (1H, d, J 2.5 Hz, 6-H).

(1R,3R,4R)-3,4-Dihydro-7,9-dimethoxy-4-hydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (71) and its Enantiomer [(±)-Quinone A' Dimethyl Ether]

Compound (68) (160mg ; 0.46mmol) was oxidised as described for compound (67) above to give the product (71) (111mg ; 76%) as a yellow powder. For purification this was subjected to p.l.c (40% ethyl acetate in light petroleum ; Nitrogen atmosphere), m.p. 195 - 210°C (decomp. lit.[22] 200°C with decomposition; δ 1.38 (3H, d, 3-CH_3), 1.51 (3H, d, J 7 Hz, 1-CH_3), 2.30 (1H, br s, D_2O exchangeable, OH), 3.93 and 3.94 (3H each, s, OCH_3), ca 3.95 (1H, dq, J 2.5 Hz and 6 Hz, 3-H, obscured by OMe), 4.44 (1H, br s, 4-H), 4.99 (1H, q, J 7 Hz, 1-H), 6.69 (1H, d, 2.5 Hz, 8-H), and 7.24 (1H, d, J 2.5 Hz, 6-H).

(1R,3R,4R)-3,4-Dihydro-7-benzyloxy-4-hydroxy-9-methoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (85) and its Enantiomer

The starting material (82) (204mg ; 0.407mmol), described later, was dissolved in dioxane (25ml) at room temperature and oxidised to compound (85) (99mg ; 62%) as for compound (68) above ; δ 1.31 (3H, d, J 6 Hz, 3-CH_3), 1.44 (3H, d, J 6 Hz, 1-CH_3), 2.26 (1H, br s, OH), 3.85 (3H, s, OCH_3), ca. 3.9 (1H, dq, J 2.5 Hz and 6 Hz, partially obscured by OCH_3, 3-H), 4.38 (1H, d, J 2.5 Hz, 4-H), 4.91 (1H, q, J 6 Hz, 1-H), 5.11 (2H, s, OCH_2Ph), 6.78 (1H, d, J 2.5 Hz, 8-H) and 7.25 - 7.5 (6H, m, C_6H_5 and obscured 6-H).

(1R,3R,4S)-3,4-Dihydro -7-methoxy-4,9-dihydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (27) and its Enantiomer [(±)-7-O-Methyl Quinone A]

Compound (70) (0.82g ; 2.6mmol) was dissolved in dry dichloromethane (9ml) and cooled in an acetone / dry-ice bath to -78°C. Borontrichloride (0.15g ; 13mmol ; as a solution in dry dichloromethane) was added and the reaction mixture stirred at -78°C for 15 minutes. The reaction was quenched by the addition of water (20ml) and the mixture extracted with dichloromethane. The organic phase was dried with magnesium sulphate and concentrated to afford the crude product (0.49g ; 62%) as dark orange crystals (after recrystallisation from acetone); δ 1.25 (3H, d, J 5.5 Hz, 3-CH_3), 1.45 (3H, d, J 6.5 Hz, 1-CH_3), 3.78 (1H, br s, D_2O exchangeable, OH), ca. 3.90 (1H, dq, J 5.5 and 8 Hz, 3-H), 3.95 (3H, s, OCH_3), 4.39 (1H, br d, J 8 Hz, 4-H), 4.94 (1H, dq, J 1.5 and 6.5 Hz, 1-H, long range coupled to 4-H), 6.73 (1H, d, J 2.5 Hz, 8-H), 7.24 (1H. d, J 2.5 Hz, 6-H) and 12.11 (1H, br s,

D_2O exchangeable, 9-OH).

(±)-trans-3,4-Dihydro-9-hydroxy-7-methoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (28) and its Enantiomer [(±)-7-O-Methyl Deoxyquinone A]

The starting material (69) (100mg ; 0.331mmol) was dissolved in dry dichloromethane (10ml) and treated like compound (70) above with boron trichloride (0.194g ; 1.66mmol as a solution in dry dichloromethane) to afford the product (0.06g ; 57%), m.p. 176 - 178°C (from acetone, lit.[15] 176 - 177.5°C); δ 1.34 (3H, d, J 6 Hz, 3-CH_3), 1.55 (3H, d, 7 Hz, 1-CH_3), 2.13 (1H, dd, J 10 and 19 Hz, pseudo-axial 4-H), 2.74 (1H, dd, J 3.5 and 19 Hz, pseudo-equatorial 4-H), 3.87 (3H, s, OCH_3), 3.9 - 4.1 (1H, m, 3-H), 4.97 (1H, q, J 7 Hz, 1-H), 6.60 (1H, d, J 2.5 Hz, 8-H), 7.15 (1H, d, J 2.5 Hz, 6-H), and 12.53 (1H, br s, D_2O exchangeable, OH).

(1R,3R,4R)-3,4-Dihydro-4,9-dihydroxy-7-methoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (77) and its Enantiomer [(±)-7-O-Methyl Quinone A']

Starting material (71) (124mg ; 0.389mmol) was demethylated with boron trichloride (0.78mmol) as above and the solution stirred for 4 minutes when t.l.c. revealed that all starting material had been consumed. The reaction was quenched with water and worked up as above to give a dark brown oil which was subjected to p.l.c. (50% ether acetate in light petroleum under nitrogen), to give the product (45mg ; 38%) as an orange crystalline solid; δ 1.36 (3H, d, J 6.3 Hz, 3-CH_3), 1.50 (3H, d, J 6.8 Hz, 1-CH_3), 3.34 (1H, br s, D_2O exchangeable, 4-OH), 3.94 (3H, s, OCH_3), 3.97

(1H, dq, J 2.2 and 6.3 Hz, 3-H), 4.47 (1H, d, J 2.2 Hz, 4-H), 4.97 (1H, q, J 6.8 Hz, 1-H), 6.69 (1H, d, J 2.5 Hz, 8-H), 7.23 (1H, d, J 2.5 Hz, 6-H) and 13.01 (1H, s, D_2O exchangeable, 9-OH).

(1R,3R,4R)-7-Benzyloxy-3,4-dihydro-4,9-dihydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (94) and its Enantiomer [(±)-7-O-Benzyl Quinone A']

Compound (__) (82mg ; 0.207mmol) was dissolved in dry dichloromethane (30ml) and cooled to 0°C in a freezing mixture before boron trichloride (0.414mmol ; as a solution in dichloromethane) was added in one portion, whereupon the mixture turned dark. It was stirred for 6 minutes before the reaction was quenched by the addition of water (40ml), extracted into dichloromethane (4 x 30ml), dried with magnesium sulphate and concentrated under reduced pressure. The resulting dark brown oil was subjected to p.l.c. (solvent 50% ethyl acetate in light petroleum under nitrogen) to yield the product (27mg ; 34%) (R_f 0.65) as a dark orange crystalline solid, m.p. 152 - 153°C (from dichloromethane-cyclohexane) (Found: C, 69.2, H, 5.3; M^+ 380.12459. $C_{22}H_{20}O_6$ requires: C, 69.45, H, 5.3%; M 380.125964); ν_{max} 3481 (OH), 1661 and 1638 (C=O), and 1609 cm^{-1} (C=C); δ 1.36 (3H, d, J 6.3 Hz, 3-CH_3), 1.50 (3H, d, J 6.8 Hz, 1-CH_3), 3.97 (1H, dq, J 2.2 and 6.3 Hz, 3-H), 4.47 (1H, d, J 2.2 Hz, 4-H), 4.67 (1H, s, 4-OH, D_2O exchangeable), 4.97 (1H, q, J 6.8 Hz, 1-H), 5.12 (2H, s, OCH_2Ph), 6.68 (1H, d, J 2.4 Hz, 8-H), 7.24 (1H, d, J 2.4 Hz, 6-H), 7.38 (5H, s, C_6H_5), and 12.14 (1H, s, 9-OH, D_2O exchangeable).

(1R,3R,4R)-3,4-Dihydro-4,7,9-trihydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-quinone (17)and its Enantiomer [(±) Quinone A']

Adam's catalyst (PtO_2 ; 5mg) was suspended in dry methanol (5ml) and stirred under an atmosphere of hydrogen until the brown suspension turned black. A solution of starting material (9) (11mg ; 0.029mmol) in dry methanol (10ml) was added and the mixture, which quickly turned colourless, was stirred at room temperature under hydrogen for 30 minutes, when t.l.c. revealed after aerial reoxidation that all starting material had been consumed. The catalyst was filtered off and the solvent removed under reduced pressure to afford a dark orange solid which was chromatographed (p.l.c. ; silica gel impregnated with 2% oxalic acid ; solvent toluene - ethyl acetate 4:1) yielding the racemic quinone A' (17) (7.7mg ; 94%) as red-orange crystals, m.p. 230 - 270°C (decomp., from benzene - methanol, lit.[10] m.p. for the natural product 236°C) (Found: C, 61.75, H, 4.95; M^+ 290.079. $C_{15}H_{14}O_6$ requires: C, 62.05, H, 4.85%; M 290.079); ν_{max} 3445 (OH), 1659 and 1641 (C=O), and 1613 cm^{-1} (C=C); δ (acetone-d_6), 1.29 (3H, d, J 6.4 Hz, 3-CH_3), 1.48 (3H, d, J 6.8 Hz), 1-CH_3), 3.98 (1H, dq, J 2.1 and 6.4 Hz, 3-H), 4.38 (1H, d, J 2.1 Hz, 4-H), 4.84 (1H, q, J 6.8 Hz, 1-H), (1H, d, J 2.5 Hz, 8-H), 7.09 (1H, d, J 2.5 Hz, 6-H), 7.34 (1H, s, D_2O exchangeable, 7-OH), and 12.18 (1H, s, D_2O exchangeable, 9-OH); m/z 290 (M^+, 9%), 244 (100), 216 56 (63), and 43 (51).

(1R,3R,4R)-4-Chloro-3,4-Dihydro-5,10-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (88) and its Enantiomer and 5,10-Dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (91)

Compound (24)[13] (70mg ; 0.234mmol) was dissolved in dry ether (5ml) and cooled to 0°C in an ice / water bath before phosphorus pentachloride (100mg ; 2 equivalents) was added in one batch. The mixture was stirred for 5 minutes when t.l.c. indicated that all starting material had been consumed. The reaction was quenched with water (10ml) and the mixture extracted with ether (3 x 10ml) which was washed with water (1 x 10ml) and dried with magnesium sulphate. The oil obtained after removing the solvent under reduced pressure was chromatographed (p.l.c. ; 5% ethyl acetate in light petroleum) to yield compound (91) (5mg ; 8%) as the product with the higher R_f value, as an oil; δ 1.46 (3H, d, J 6.84 Hz, 1-CH_3), 1.98 (3H, s, 3-CH_3), 3.86 and 3.92 (each 3H, s, OCH_3), 5.72 (1H, q, J 6.8 Hz, 1-H), 5.94 (1H, s, 4-H), 7.32 - 7.46 (2H, m, 6- and 9-H) and 7.86 - 8.06 (2-H, m, 7- and 8-H). This was followed by the chloronaphthopyran (88) (57mg ; 77%) also as an oil; δ 1.45 (3H, d, J 6.3 Hz, 3-CH_3), 1.59 3H, d, J 6.8 Hz, 1-CH_3), 3.92 and 4.11 (each 3H, s, OCH_3), 4.26 (1H, dq, J 1.5 and 6.3 Hz, 3-H), 5.34 (1H, d, J 1.5 Hz, 4-H), 5.38 (1H, q, J 6.8 Hz, 1-H), 7.42 - 7.54 (2H, m, 6- and 9-H), and 7.94 - 8.10 (2H, m, 7- and 8-H).

(1R,3R,4S)-3,4-Dihydro-5,10-dimethoxy-4-hydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (24) and (1R,3R,4R)-3,4-Dihydro-5,10-dimethoxy-4-hydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (25) and their Enantiomers

a) Compound (88) (30mg ; 0.098mmol) was dissolved in

acetonitrile (5ml) at room temperature. Water (0.25ml) was added, followed by silver nitrate (33mg ; 0.196mmol) after which the solution was stirred for 1 hour, during which time it turned cloudy. Water (35ml) was added and the mixture extracted with ether. The oily residue obtained after the usual work-up was subjected to p.l.c. (30% ethyl acetate - light petroleum) to give product (24) (5mg ; 18%) as the compound with the higher R_f value; δ 1.41 (3H, d, J 6 Hz, 3-CH_3), 1.67 (3H, d, J 6 Hz, 1-CH_3), 3.89 and 4.00 (each 3H, s, OCH_3), ca 4.1 (1H, partially concealed by OCH_3, dq, J 6 and 7.6 Hz, 3-H), 4.21 (1H, br s, D_2O exchangeable, OH), 4.79 (1H, d, J 7.6 Hz, pseudo-axial 4-H), 5.23 (1H, q, J 6 Hz, 1-H), 7.49 - 7.58 (2H, m, 7- and 8-H) and 7.99 - 8.08 (2H, m, 6- and 9-H). This was followed by compound (25) (16mg ; 57%), of lower R_f; δ 1.43 (3H, d, J 6.6 Hz, 3-H_3), 1.60 (3H, d, J 6.6 Hz, 1-CH_3), 2.21 (1H, broad d, J 6 Hz, D_2O exchangeable, OH), 3.89 and 4.08 (3H each, s, OCH_3), ca 4.13 (1H, dq, J 1.5 and 6.6 Hz, 3-H), 4.78 (1H, broad d, J 6 Hz, pseudo-equatorial 4-H), 5.32 (1H, q, J 6.6 Hz, 1-H), 7.47 - 7.54 (2H, m, 7- and 8-H) and 7.98 - 8.14 (2H, m, 6- and 9-H). Both compounds were identical to the materials described in the literature.[13]

b) Compound (24) (160mg ; 0.555mmol) was dissolved in dry ether (10ml) and cooled to 0°C (ice / water bath). Phosphorus pentachloride (230mg ; 1.11mmol) was added in one batch and the solution stirred for 10 minutes until, by t.l.c., all starting material had been consumed. The reaction was quenched with water, the mixture extracted with ether and the combined organic phases washed with deionised water (4 x 10ml) to remove all chloride. After drying with magnesium sulphate, the solvent was

removed under reduced pressure and the resulting oil immediately redissolved in acetonitrile (12ml). Water (1ml) and silver nitrate (188mg ; 1.11mmol) were added and the mixture stirred for 2 hours at room temperature. Water was added and the products extracted into dichloromethane. The organic phase was dried with magnesium sulphate, the solvent removed and the resulting oil chromatographed (30% ethyl acetate in light petroleum) to yield firstly compound (91) (11mg ; 7%) followed by the chloronaphthopyran (88) (10mg ; 6%), compound (24) (starting material ; 16mg ; 10%) and finally compound (25) (74mg ; 46%), each identical with authentic material.[13]

(1R,3R,4R)-4-Chloro-3,4-Dihydro-5,7,9,10-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (89) and its Enantiomer and 5,7,9,10-Tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (92)

a) The starting material (67) (48mg ; 0.138mmol) was dissolved in dry ether (5ml) and chlorinated with phosphorus pentachloride (57mg ; 0.276mmol) as described above. The reaction mixture was stirred for 10 minutes at room temperature before water (30ml) was added to decompose the excess phosphorous pentachloride. After extraction with ether, the organic phase was washed with water (2 x 10ml), dried with magnesium sulphate and concentrated under reduced pressure. The resulting oil was subjected to p.l.c. (solvent 20% ethyl acetate - light petroleum) to give the naphthopyran (92) (4mg ; 9%) as the product with the higher R_f value, as an oil (Found: C, 69.15 ; H, 6.7. $C_{19}H_{22}O_5$ requires C, 69.05 ; H, 6.70%); ν_{max} (film) 1647, 1616, 1600 and 1581 (C=C) cm^{-1} ; δ 1.44 (3H, d, J 7 Hz, 1-CH_3), 1.98 (3H, s, 3-CH_3),

3.83, 3.86, 3.93, and 3.98 (each 3H, s, OCH_3), 5.72 (1H, q, J 7 Hz, 1-H), 5.91 (1H, s, 4-H), 6.44 (1H, d, J 2.3 Hz, 8-H) and 6.95 (1H, d, J 2.3 Hz, 6-H); m/z 330 (M^+, 100%), 315 (74), 300 (13), and 285 (18). This was followed by the oily chloronaphthopyran (89) (44mg ; 87%) (Found: C, 62.35; H, 6.0. $C_{19}H_{23}ClO_5$ requires C, 62.20 ; H, 6.30%); ν_{max} 1620, 1595 and 1581 (C=C) and 679 and 650 (C-Cl) cm^{-1} ; δ 1.46 (3H, d, J 6 Hz, 3-CH_3), 1.58 (3H, d, J 6 Hz, 1-CH_3), 3.83, 3.94, 3.98 and, 4.07 (each 3H, s, OCH_3), 4.21 (1H, dq, J 1.5 and 6 Hz, 3-H), 5.29 (1H, d, J 1.5 Hz, pseudo-equatorial 4-H), 5.37 (1H, q, J 6 Hz, 1-H), 6.54 (1H, d, J 2.3Hz, 8-H) and 6.94 (1H, d, J 2.3 Hz, 6-H); m/z 368 (M^+ ; 8%), 366 (M+2; 24%), 351 (43), 330 (100), and 315 (89).

b) Compound (68) (48mg ; 0.138mmol) was chlorinated as for compound (67) above. Identical work-up and chromatography yielded the naphthopyran (92) (4mg ; 9%) as the product with the higher R_f value followed by compound (89) (32mg ; 64%), both as oils and identical to the materials discribed above.

(1R,3R,4R)-4-Chloro-7,10-dibenzyloxy-3,4-Dihydro-5,9-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (89)and its Enantiomer and 7,10-dibenzyloxy-5,9-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (93)

Compound (81) 52mg ; 0.104mmol) was dissolved in dry ether (20ml) and cooled to 0°C (ice / water bath). Phosphorus pentachloride (43mg ; 0.208mmol) was added and the mixture stirred until all starting material had been consumed, as revealed by t.l.c. After 10 minutes the reaction was quenched with water and the products

extracted into ether. The combined organic phases were dried with magnesium sulphate concentrated and the resulting oil subjected to p.l.c. (20% ethyl acetate in light petroleum), yielding the naphthopyran (93) (4mg ; 8%) as the compound with the higher R_f value (Found: M^+ 482,207. $C_{31}H_{30}O_5$ requires M 482.209); 1.44 (3H, d, J 6.6 Hz, 1-CH_3), 1.98 (3H, d, J 0.8 Hz, 3-CH_3), 3.79 and 3.84 (each 3H, s, OCH_3), 4.79 and 5.09 (each 1H, d, J 10.7 Hz, 10-OCH_2Ph), 5.19 (2H, s, 7-OCH_2Ph), 5.73 (1H, q, J 6.6 Hz, 1-H), 5.92 (1H, q, J 0.8 Hz, 4-H), 6.53 (1H, d, J 2.3 Hz, 8-H), 7.03 (1H, d, J 2.3 Hz, 6-H) and 7.3 - 7.56 (10H, m, 2 x C_6H_5). This was followed by the chloronaphthopyran (90) (48mg ; 89%) as colourless crystals, m.p. 62°C (from dichloromethane - light petroleum) (Found: C, 71.65 ; H, 6.05. $C_{31}H_{31}ClO_5$ requires C, 71.75 ; H, 6.00%); ν_{max} 1618, 1595 and 1581 (C=C), 830 and 696 (C-Cl) cm^{-1} ; δ 1.47 (3H, d, J 6.1 Hz, 3-CH_3), 1.59 (3H, d, J 6.6 Hz, 1-CH_3), 3.85 and 3.97 (each 3H, s, OCH_3) 4.26 (1H, dq, J 1.3 Hz and 6.1 Hz, 3-H), 4.78 and 5.09 (each 1H, d, J 9.2 Hz, 10-OCH_2Ph), 5.21 (2H, s, 7-OCH_2Ph), 5.29 (1H, d, J 1.3 Hz, 4-H), 5.41 (1H, q, J 6.6 Hz, 1-H), 6.63 (1H, d, J 2.3 Hz, 8-H), 7.01 (1H, d, J 2.3 Hz, 6-H), and 7.30 - 7.56 (10H, m, 2 x C_6H_5).

(1R,3R,4S)-3,4-Dihydro-5,9-dimethoxy-4-hydroxy-7,10-dibenzyloxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (81) and (1R,3R,4R)-3,4-Dihydro-5,9-dimethoxy-4-hydroxy-7,10-dibenzyloxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (82) and their Enantiomers

Compound (81)[32] (46mg ; 0.092mmol) was dissolved in dry ether (5ml) at room temperature. Phosphorus pentachloride (40mg ; 0.184mmol) was added in one batch and the mixture stirred for 6 minutes when t.l.c. indicated that all starting material had been

consumed. The reaction was stopped with water (20ml) before more ether (50ml) was added, the organic phase separated and washed with deionized water (5 x 15ml) to remove all chloride before it was dried with magnesium sulphate and the ether removed under reduced pressure. The resulting oil was immediately redissolved in acetonitrile (5ml) at room temperature before deionized water (1ml) was added, followed by silver nitrate (83mg ; 0.46mmol) and the mixture stirred for 3.5 hours at room temperature in the dark, after which water (30ml) was added. Extraction into ether (5 x 15ml), drying with magnesium sulphate and evaporation of the solvent under reduced pressure gave an oil which was chromatographed (10% ethyl acetate in light petroleum) yielding firstly the naphthopyran (93) (3mg ; 7%) followed by the chloro-compound (90) (6mg ; 15%), both identical to the materials described above. This was followed by starting material (81)[32] (10mg ; 22%); δ 1.40 (3H, d, J 6 Hz, 3-CH_3), 1.68 (3H, d, J 7 Hz, 1-CH_3), 3.86 and 3.89 (each 3-H, s, OCH_3), 4.03 (1H, dq, J 6 and 8 Hz, 3-H), 4.30 (1H, d, J 3 Hz, OH, D_2O exchangeable), 4.69 (1H, d, J 10 Hz, 10-OCH), 4.74 (1H, dd, J 3 and 8 Hz, 4-H), 5.06 (1H, d, J 10 Hz, 10-OCH), 5.14 (1H, q, J 7 Hz, 1-H), 5.20 (2H, s, 7-OCH_2Ph), 6.64 (1H, d, J 2 Hz, 8-H), 7.02 (1H, d, J 2 Hz, 6-H), and 7.35 - 7.65 (10H, m, 2 x C_6H_5); m/z 500 (M^+, 5%), 482 (10), 409 (5), 391 (20), 377 (15), and 91 (100); and finally its epimer (82) (25mg ; 55%); δ 1.41 (3H, d, J 6 Hz, 3-CH_3), 1.60 (3H, d, J 7 Hz, 1-CH_3), 2.20 (1H, d, J 9 Hz, OH, D_2O exchangeable), 3.85 and 3.96 (each 3-H, s, OCH_3), 4.16 (1H, dq, J 2 and 6 Hz, 3-H), 4.72 (1H, dd, J 2 and 9 Hz, 4-H), 4.74 and 5.08 (each 1H, d, J 10 Hz, 10-OCH_2Ph), 5.21 (2H, s, 7-OCH_2Ph), 5.29 (1H, q, J 7 Hz, 1-H), 6.68 (1H, J 2Hz, 8-H), 7.08 (1H, d, J 2Hz, 6-H), and 7.31 -

7.60 (10H, m, 2 x C_6H_5); m/z 500 (M^+, 8%), 482 (17), 408 (8), 391 (30), 377 (18), and 91 (100).

N-carbobenzyloxy-β-alanine (98)

β-Alanine (0.891g ; 10mmol) was vigorously stirred with water (25ml), acetone (25ml) and sodium hydrogen carbonate (8.2g ; 10 equivalents) to maintain pH 8. Benzylchloroformate (11mmol) was added in one portion and the mixture stirred at room temperature for 30 minutes after which the acetone was removed under reduced pressure and the resulting mixture extracted with diethyl ether to remove the excess benzylchloroformate. The aqueous phase was then chilled with ice, acidified with hydrochloric acid (1M) to pH 2 and extracted with ethyl acetate (3 x 50ml). The organic extract was dried with magnesium sulphate and the solvent removed to give the white crystalline product (1.38g ; 62%), m.p. 97- 98.5°C (from ethyl acetate - light petroleum) (Found: C, 59.3, N, 6.30, H, 6.0. $C_{11}H_{13}NO_4$ requires: C, 59.20, N, 6.25, H, 5.85%); δ 2.58 (2H, br t, J 5.7 Hz, CH_2CO_2H), 3.45 (2H, br q, J 5.7 Hz, collapsing into br s after D_2O wash, $NHCH_2$), 5.09 (2H, s, CH_2Ph), 5.37 (1H, br s, NH, D_2O exchangeable), 7.33 (5H, s, C_6H_5) and 9.05 (1H, br s, D_2O exchangeable, CO_2H) ; m/z 223 (M^+ ; 45%).

Cyclohexyl-N-carbobenzyloxy-β-alanate (99)

Trifluoroacetic anhydride (0.89g ; 4.24mmol) was added to the N-protected amino acid (98) (0.86g ; 3.85mmol), dissolved in dry dichloromethane (15ml), and the mixture stirred at room temperature for 5 minutes. Cyclohexanol (0.3g ; 3mmol) was added, the solution stirred for 20 minutes at room temperature

and then boiled under reflux for another 10 minutes. After the addition of water (30ml), the products were extracted into dichloromethane, dried with magnesium sulphate and concentrated under reduced pressure. The oily residue was chromatographed (30% ethyl acetate in light petroleum) to afford the product (0.27g ; 30%) as an oil (Found: C, 66.9, H, 7.6, N, 4.7. $C_{17}H_{23}NO_4$ requires: C, 66.85, H, 7.60, N, 4.60%); δ 1.10 - 2.05 (11H, m, C_6H_{11}), 2.50 (2H, t, J 7.2 Hz, $NHCH_2$), 3.46 (2H, q, J 7.2 Hz, CH_2CO_2R), 4.77 (1H, br s, NH), 5.08 (2H, s, CH_2Ph), 7.33 (5H, s, C_6H_5).

(1R,3R,4S)-3,4-Dihydro-5,7,9,10-tetramethoxy-4-trifluoroacetyl-1,3-dimethyl-1H-naphtho[2,3-c]pyran (100) and its Enantiomer

To a solution of the N-protected amino acid (0.141g ; 0.62mmol) and trifluoroacetic anhydride (0.13g ; 0.62mmol) in dry dichloromethane (8ml) compound (67) (72mg ; 0.21mmol) in dry dichloromethane (4ml) was added and the solution stirred at room temperature for 20 minutes. Water (20ml) was added and the mixture extracted with dichloromethane. The oily residue obtained upon work-up was chromatographed (20% ethyl acetate - light petroleum) to give compound (100) (23mg ; 26%) as an oil; δ 1.30 (3H,d, J 6.3 Hz, 3-CH_3), 1.68 (3H, d, J 6.3 Hz, 1-CH_3), 3.76, 3.83, 3.93, and 3.97 (3H each, s, OCH_3), 4.1 - 4.4 (1H, m, 3-H), 5.23 (1H, q, J 6.3 Hz, 1-H), 6.19 (1H, d, 6.3 Hz, 4-H), 6.58 (1H, d, J 2.3 Hz, 8-H) and 6.92 (1H, d, J 2.5 Hz, 6-H), followed by starting compound (67) (30mg ; 49%) identical to authentic material, described earlier.

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