THE SYNTHESIS OF DERIVATIVES OF NATURALLY OCCURRING NAPHTHALENES

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DOCTOR OF PHILOSOPHY

by

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to my parents

with love and gratitude

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SUMMARY

The ansamycins are a large group of natural products which have attracted considerable attention, largely as a result of their range of biological activity. The laboratory synthesis of an ansamycin has been simplified into the independent construction of the aromatic nucleus and the ansa chain, followed by their combination to form the macrocyle.

The project described in Chapter 1 was designed to devise a novel, convenient, and efficient synthesis of a substituted 1,4-naphthoquinone which would function as a model for the naphthoquinonoid nucleus of the rifamycin subclass of these antibiotics.

In this synthesis, 1,4-benzoquinone was converted into 8-acetyl-5,7-dihydroxy-6-methyl-3-propionylamino-1,4-naphthoquinone in six steps in an overall yield of 20%. The key step in this reaction sequence was the introduction of the C-6 methyl group *via* a regioselective lithiation/methylation reaction.

Compounds which can be structurally defined as bioreductive alkylating agents have considerable potential as antineoplastic agents, according to H.W. Moore [Science, 1977]. The protoaphins possess certain structural features which suggest their capability to function as such alkylating agents.

Reductive cleavage of the aphid pigment, protoaphin-*fb* has been shown to give quinone A together with glucoside B, while

protoaphin-*sl* on similar treatment affords quinone A', epimeric with quinone A at C-4, together with the same glucoside B. Professor Giles and co-workers have synthesised the 7,9-dideoxyquinone derivatives of both quinone A and A', as well as quinone A and A' themselves.

The second chapter in this thesis describes three different approaches to the synthesis of a 4,10-dihydroxy-7,9-dimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran analogous to glucoside B. The first two routes describe the construction of a naphtho-[2,3-*c*]pyran of the correct relative stereochemistry using the novel reactions pioneered in this Department during the synthesis of 7,9-dideoxyquinone A. In the first method, the pyran ring was constructed with a C-5 oxygen substituent which was subsequently removed. The second method however, differs substantially from this route in that the C-5 substituent was not present during ring closure, hence eliminating the need to remove it at a later stage.

The key step in the third approach involved the isomerisation of a dioxolane substituted naphthalene by an intramolecular version of the Mukaiyama reaction. Treatment of a C-8 brominated dioxolanyl naphthalene with titanium tetrachloride resulted in the formation of two angular naphtho[1,2-*c*]pyrans with the same relative stereochemistry of the pyran ring. An interesting bromine migration occurred after isomerisation had taken place. However, it is suggested that decreasing the size of the C-4 protecting group on the naphthalene nucleus prior to isomerisation, may allow the formation of the linear naphthopyran.

CONTENTS

1

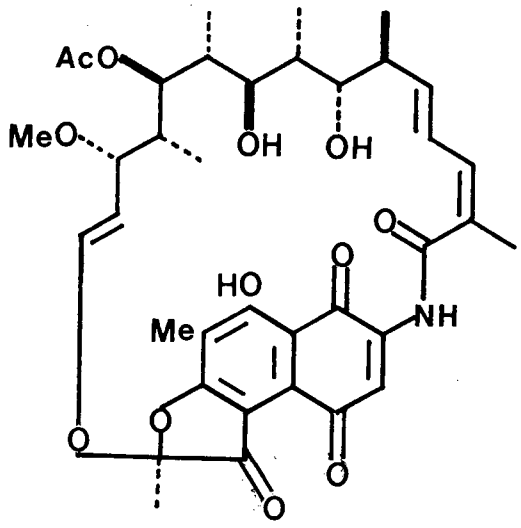
A NOVEL APPROACH TO THE SYNTHESIS OF THE NAPHTHOQUINONOID NUCLEUS OF THE ANSAMYCIN ANTIBIOTICS

1.1 Introduction

The ansamycin antibiotics are a large class of metabolites which have attracted considerable interest recently from both chemical and clinical viewpoints.[1] Their structures are highly substituted macrocyclic lactams, characterised by a polyketide derived aliphatic (ansa) chain linking two non-adjacent positions of a highly substituted nucleus. They represent some of the more complex antibiotics thus far isolated. The name ansamycin is derived from the latin word ansa meaning handle-like,[2,3] which describes the shape of the amide and carbon-carbon linked bridge.

Chemically, the large number of antibiotics belonging to this group can be divided into two sub-classes, based upon the structure of the nucleus. First, those where the ansa bridge is attached to a naphthalene or naphthoquinonoid nucleus, e.g. the rifamycins, and secondly, those where the ansa bridge is attached to a benzene or benzoquinonoid nucleus, e.g. the maytansinoids. A representative structure from each group is illustrated by rifamycin S (1) and maytansinol(2).

The rifamycins were the first ansamycins to be characterised. They were isolated from the fermentation medium *Nocardia mediterranei* by Sensi, Greco, and Ballotta in 1959.[4] Their structure was elucidated chemically by Prelog and Oppolzer,[5] and X-ray crystallographically by Brufani, Giacomello, and Vaciago.[6]



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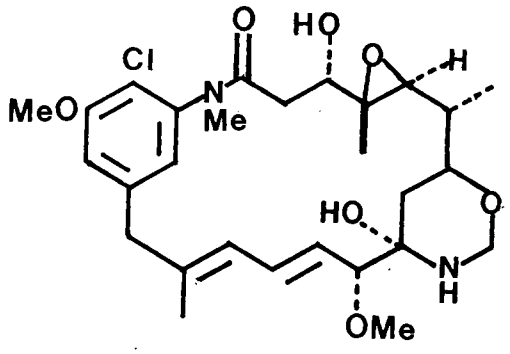

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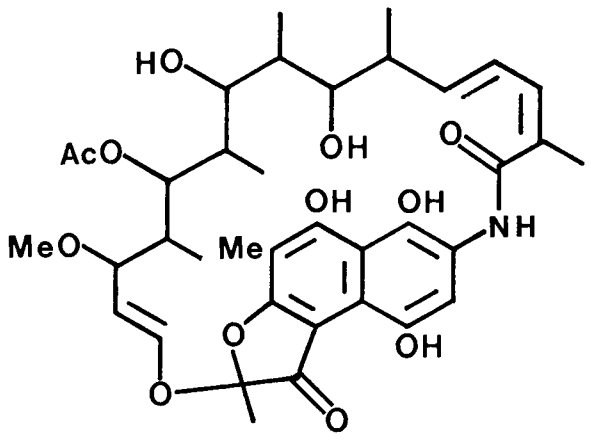
As a group, the ansamycins have a broad spectrum of biological activity, and are particularly effective as antibacterial agents. Rifamycin SV (3) and a semi-synthetic derivative of



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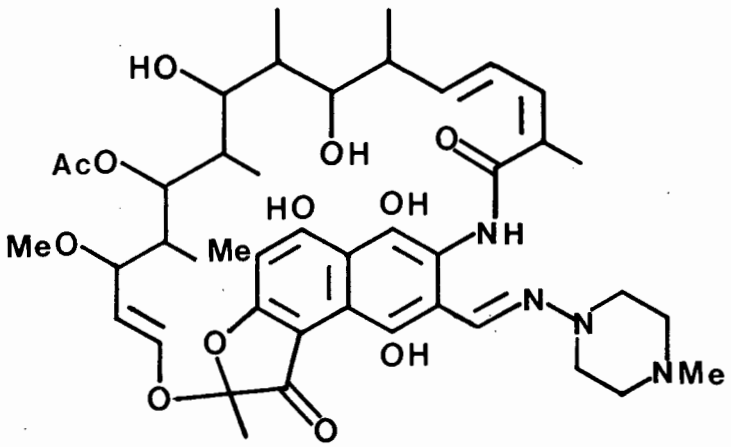
rifamycin B, rifampicin (4), are widely used in clinical medicine today. Rifampicin is a broad-spectrum antibiotic of primary importance in the treatment of tuberculosis and other gram-positive organisms.[7] Other derivatives of the rifamycin

and streptovaricin sub-groups are biological probes.[1d] The ansamycins are also potential anti-tumour agents.[1b] The streptovaricin complex for example, is reported to be highly active in inhibiting the murine leukemia virus. Maytansine and analogues have also been shown to be effective as anti-tumour agents.[8] The rubradirins have been shown to be potent inhibitors of polypeptide biosynthesis in cell-free systems directed with messenger ribonucleic acid.[9] Geldanamycin however, differs from other ansamycins in that its principal activity is directed against protozoa rather than against bacteria.[10]



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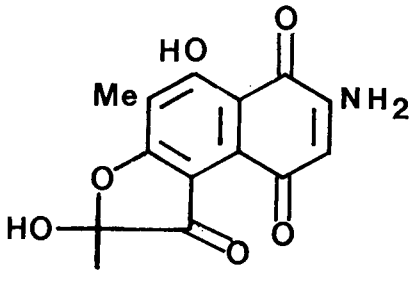
Both the clinical value and structural complexity of the ansamycins have made them a considerable synthetic challenge. It has been noted[1d] that the antibacterial activity of the ansamycin antibiotics can withstand considerable variation in structure. For example, a number of derivatives of rifamycin B are more active than the antibiotic itself. There is thus

a strong interest in finding potentially useful analogues of the ansamycins.

The maytansinoids and rifamycin S for which total syntheses have been achieved, have received the greatest attention. The laboratory synthesis has in general been simplified into the independent construction of the aromatic nucleus and the stereochemically complex ansa chain,[11] followed by their combination to form the macrocycle.[12] However, since this thesis is primarily concerned with the nuclei of naphthoquinonoid ansamycins, only those syntheses related to these antibiotics will be mentioned.

Kishi[13,14] and co-workers reported the first complete synthesis of rifamycin S (1) in 1980. This is the only total synthesis of a naphthoquinonoid ansamycin that has been reported to date. Kishi applied the above approach, namely disconnection at the two carbon-heteroatom bonds to give the aromatic moiety (5) and the ansa bridge (6), containing all eight asymmetric centres. Having synthesised these two fragments, they were joined to afford the natural compound.



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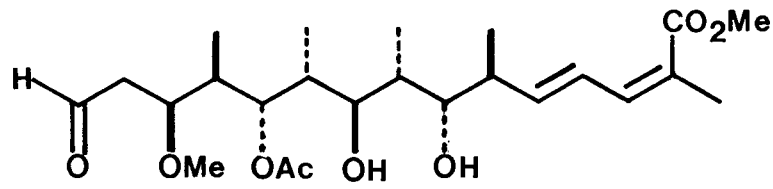

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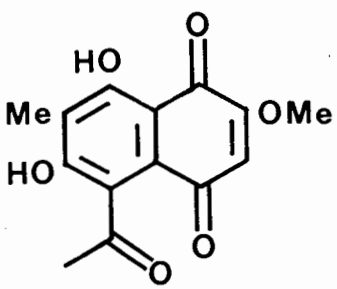
Since this original synthesis, a number of papers have been published on the synthesis of both the multichiral ansa sequence of rifamycin S[15] and the naphthoquinone moiety of various ansamycins,[16] namely the rifamycins, streptovaricins, actamycins, and rubradirins.

One of these syntheses is that of Parker and Petraitis,[16a] who developed a route toward the naphthoquinone (7), a model for the nuclei of the rifamycins and streptovaricins, in a 9% yield over eight steps. Introduction of the amine required at C-3 was not attempted for this quinone, but should be a trivial process.[17] Spectroscopically, quinone (7) is very similar to the naphthoquinone (8), a degradation product of rifamycin S.[18]



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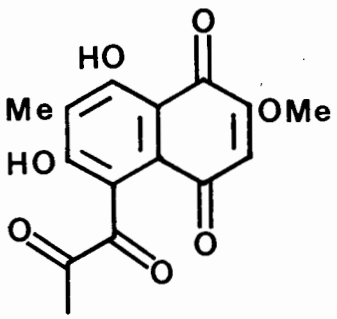

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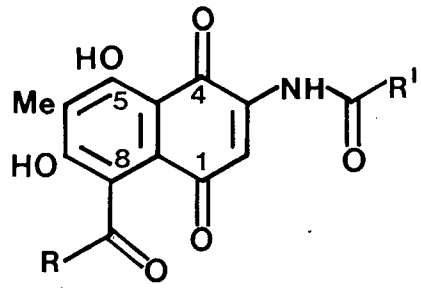
The development of efficient methods toward the synthesis of the ansamycins is important, as these approaches have the flexibility to allow the identification of particular functional groups and structural features necessary for biological activity. Clinically useful analogues may thus be achieved.

Several of the many problems associated with the total synthesis of the ansamycin macrolides have been successfully resolved. However, many of the methods mentioned earlier for synthesis of the naphthoquinonoid nuclei, are low yielding over a large number of steps, or involve long synthetic manipulations. The project to be described was therefore designed to investigate a novel and convenient synthesis of a 1,4-naphthoquinonoid nucleus with a substitution pattern typical of a number of the naphthoquinonoid ansamysins. The synthesis of this quinone would hopefully be more efficient, higher yielding, and possibly more flexible than the other methods developed so far.

Examination of the nuclei of the various naphthoquinonoid ansamycins, resulted in the emergence of the aminonaphthoquinone (9) as the basic target molecule. This compound bears a C-5* oxygen functionality and would thus be a good model



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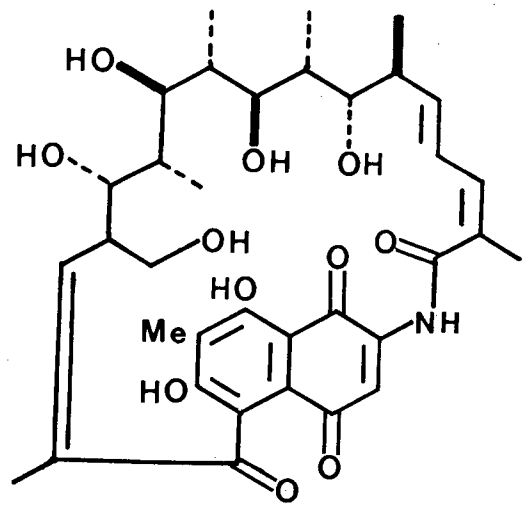

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* For purposes of consistency, this numbering system will be used throughout this chapter.

for the more complex nuclei of the rifamycins and streptovaricins. In particular, it would be a promising aromatic segment for the complete synthesis of rifamycin W (10), which has been suggested to be the biosynthetic progenitor of all the rifamycins.[19]

In planning the synthesis of the target molecule, it should be borne in mind that the ansamycin nuclei are highly substituted and thus demand the consideration of a regiocontrolled synthesis. This synthesis should also be flexible enough to allow the subsequent introduction of a substituent at C-2 for various ansamycins, e.g. methyl for the streptovaricins.

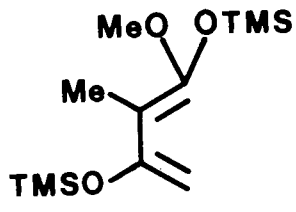
The synthesis of the target molecule (9) was indeed successful. One of the key steps in the reaction sequence was the introduction of the C-6 methyl group *via* a regioselective lithiation/methylation reaction. The final naphthoquinone was obtained in a yield of 20% from 1,4-benzoquinone in six steps.

1.2 Synthesis of 8-acetyl-5,7-dihydroxy-6-methyl-3-propionylamino-1,4-naphthoquinone.

At the onset of the investigation to be described, it was decided that the best way to construct a quinonoid nucleus such as compound (9) was through use of the Diels Alder reaction. This method allows for the required substitution to be defined in the diene and dienophile, but can suffer from limited regiocontrol.

The use of highly oxygenated dienes in Diels Alder reactions for the synthesis of natural products has attracted much interest recently.[20] Several trimethylsilyloxy-substituted butadienes have been used for such transformations.[20] These dienes are readily available from the appropriate carbonyl compound by a silyl enol ether preparation.[21]

Trost and Pearson[16g] used the known diene (11)[22] in a cycloaddition reaction with dibromotoluquinone (12) in their synthesis directed toward the streptovaricin D nucleus (13). Reaction of diene (11) with the dienophile (12) followed by aqueous acid work-up gave only one product, the dihydroxynaphthoquinone (14) in 18% yield. This regiospecificity was consistent with the bromine group directing the addition of the more nucleophilic terminus of the diene to the unsubstituted carbon of the quinonoid ring. This directing effect by bromine had previously been noted by Cameron[23] and Brassard.[24]



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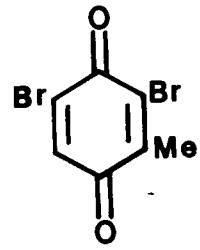

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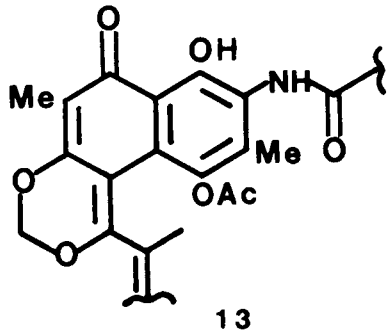

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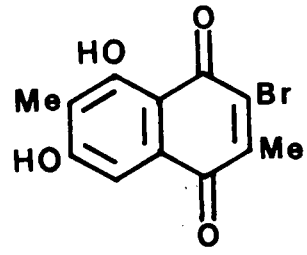

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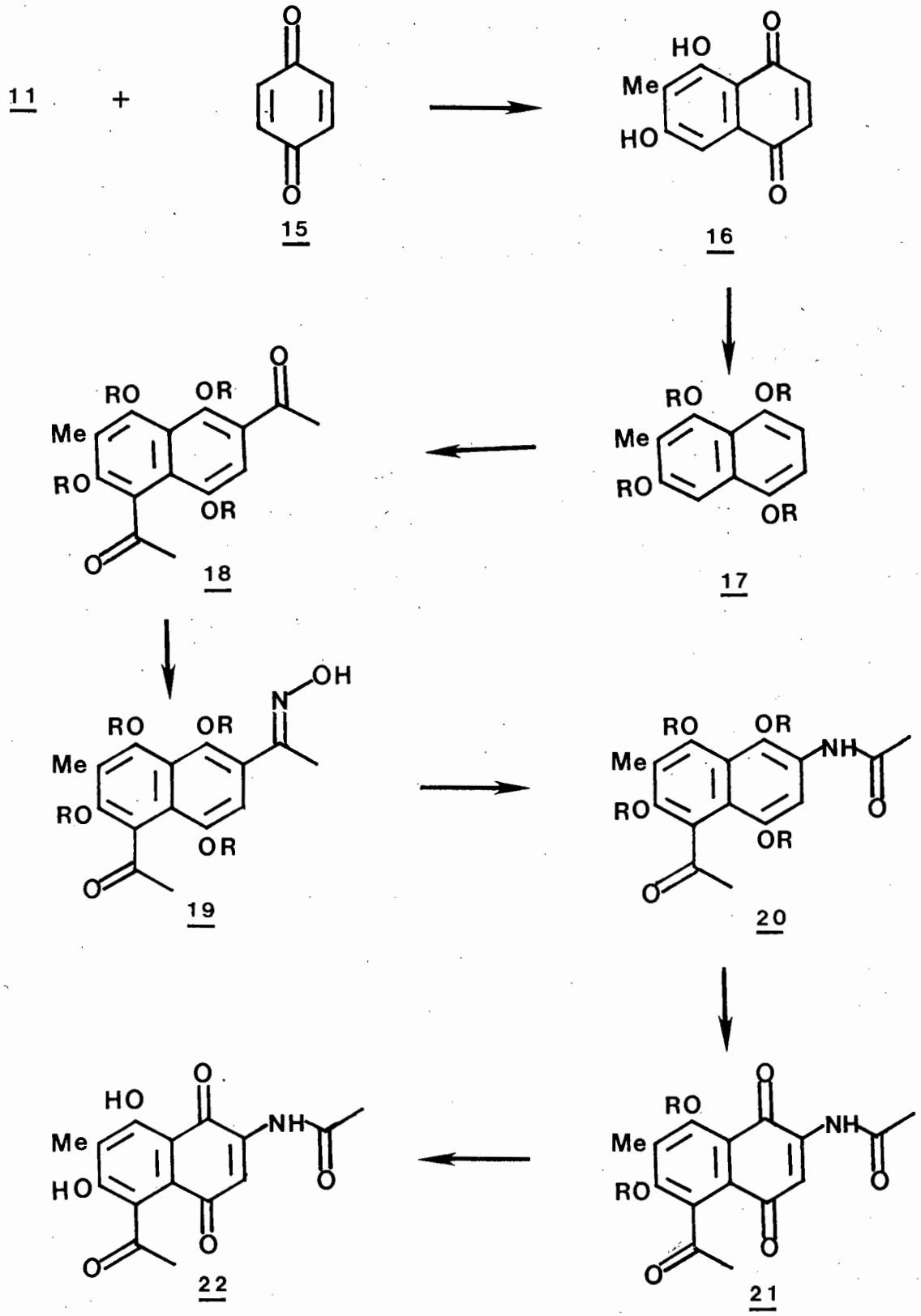
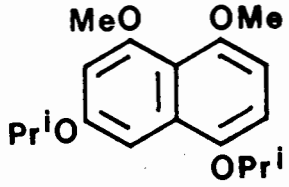
The Diels Alder reaction of the same known diene (11) with 1,4-benzoquinone (15) would be expected to result in naphthoquinone (16). This product possesses a number of the basic structural features required by the target molecule (9), namely oxygenation at carbons 1, 4, 5, and 7, as well as a C-6 methyl substituent. Following this, the proposed reaction sequence for the synthesis of naphthoquinone (22), an analogue of the target molecule (9), is shown in Scheme 1.

The ansa bridge is joined to the nucleus at positions C-3 and C-8. It was proposed in the reaction scheme that substitution at these positions be achieved by a reaction established in this Department.[25] The acetylation of 4,5-dimethoxy-1,7-di-(2-propyloxy)naphthalene (23) with a premixed solution of acetic acid and trifluoroacetic anhydride was reported to



SCHEME 1

afford a mixture of two mono-acetyl derivatives, namely the C-3 acetyl compound (24) and the C-8 acetyl isomer (25), the latter predominating. A small amount of the 3,8-diacetyl derivative (26) was also formed. Furthermore, it was found that the utilisation of a large excess of reagent, and a longer reaction time, cleanly afforded the diacetyl compound (26) as the sole product in high yield. This compound appeared to be a plausible precursor to the construction of ansamycin analogues.



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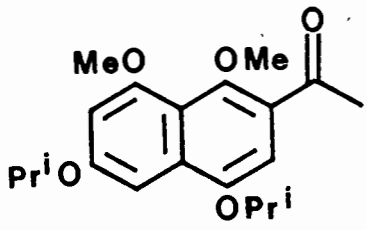

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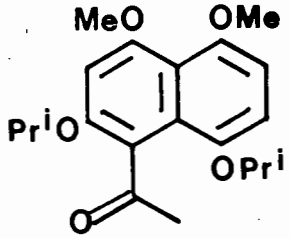

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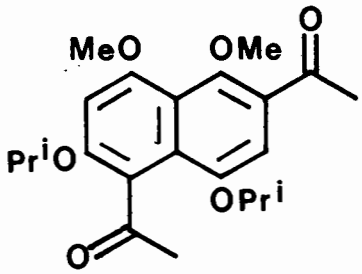

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A further important consideration in the planning of this synthesis, was the presence of the acetylamino substituent at C-3 of the target compound. This substituent imitates the amide function of the ansa bridge of the ansamycins. It was envisaged that a nitrogen could be inserted between the naphthalene ring and the C-3 acetyl group of compound (18) by means of a Beckmann rearrangement. Two conditions for this reaction would have to be met: first, that on treatment of

compound (18) with hydroxylamine, a monoxime should be formed only at the C-3 acetyl group to give compound (19), and secondly, that the hydroxy group of this oxime be *anti* to the naphthyl group, so that the naphthyl group rather than the methyl would migrate. If these requirements could be met, a Beckmann rearrangement of the oxime would yield the required amide (20).

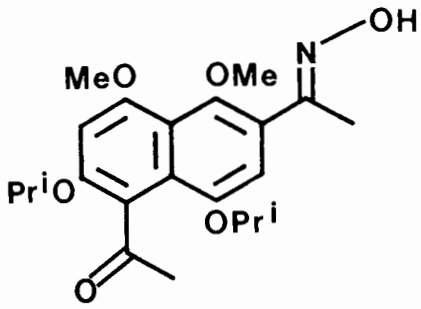
The investigation into the feasibility of the formation of the monoxime and the subsequent Beckmann rearrangement was carried out by a co-worker in this Department on the diacetyl naphthalene (26).[26] The amide derived from this reaction would also serve as a model for the rifamycins but would be lacking the C-6 methyl substituent.

In considering the reaction of compound (26), both of the above provisos seemed reasonable on steric grounds. The C-8 acetyl group is flanked by both an *ortho*- and a *peri*-iso-propoxy substituent and is thus considerably more crowded than the alternate C-3 acetyl group with only a methoxy *ortho* to it. The oxime would thus be formed preferentially at the less crowded C-3 site. The derived hydroxy group of the oxime formed would be expected to be *anti* to the naphthyl group in order to minimise crowding between the methoxy and oxime functions, especially as there is little reason to expect hydrogen bonding between the two groups.

Experimental evidence for the first suggestion that the C-8 acetyl substituent was indeed more crowded than the C-3 group in compound (26), was provided by both infrared and ^{1}H n.m.r

spectroscopy. In the former, two carbonyl stretching frequencies appeared at 1660 and 1707 cm^{-1}, assigned to the C-3 and C-8 acetyl carbonyls respectively, while for the latter, the 3- and 8-acetyl protons gave rise to chemical shifts of δ 2.72 and 2.55 in that order.[25] These figures suggest that the C-8 acetyl group is twisted out of the plane of the naphthalene ring.

Research done in this Department showed that compound (26) could be converted into amide (28) *via* the monoxime (27). The ^1H n.m.r. spectrum of the amide showed *inter alia* two one-proton singlets at δ 6.58 (6-H) and 8.00 (2-H), as well as two three-proton singlets at δ 2.52 and 2.21, due to the ketonic and amidic methyls respectively. The C-8 carbonyl and amidic carbonyl bands appeared at 1703 and 1658 cm^{-1} respectively in the infrared spectrum. The structure of the amide (28) was confirmed by X-ray crystallography.[26]



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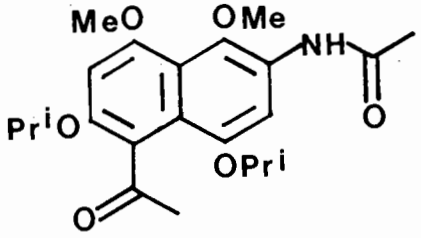

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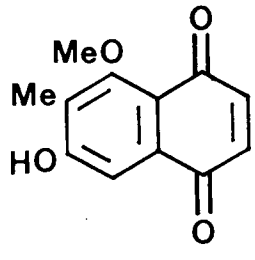
Verification of this assignment was valuable in a number of ways. First of all, it showed that the sites of acetylation of naphthalene (23) were indeed C-3 and C-8, to afford the diacetyl derivative (26). Secondly, it left no doubt as to which of the two acetyl groups had been involved in the

formation of the monoxime, and the subsequent Beckmann rearrangement. Thirdly, it confirmed migration of the naphthyl group in the Beckmann rearrangement, although this had already been substantiated by ^{1}H n.m.r. spectroscopy. Finally, it showed, in the crystalline state and no doubt also in solution, that the planes of the 8-acetyl carbonyl and the naphthalene ring are virtually at right angles. This last factor gave rise to a situation that approach by the nucleophilic hydroxylamine was strongly discouraged by the flanking isopropoxy substituents at C-1 and C-7.

The planned reaction sequence depicted in Scheme 1 should therefore be successful. Careful consideration would have to be given to the choice of the protecting group R (which may be all the same, or different) on the naphthalene (17) to enable the formation of the monoxime (19) and hence the amide (20).

1,4-Benzoquinone was therefore reacted with the diene (11)[22] at -78°C in the presence of pyridine. After aqueous acid work-up, a mixture of the dihydroxynaphthoquinone (16) and its monomethyl ether (29) were obtained. The individual quinones were identified by their ^{1}H n.m.r. spectra and by high resolution mass spectrometry.



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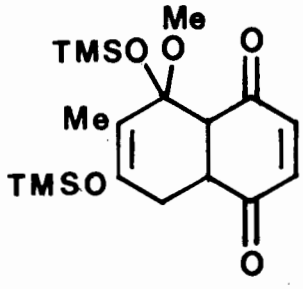
The formation of both the dihydroxy and hydroxymethoxy products from the cycloaddition reaction was unexceptional,[24] reflecting competitive loss of the trimethylsilyloxy and methoxy groups during aromatisation of the initially formed cycloadduct (30). However, the yields of these two naphthoquinones were very low. They also proved difficult to separate as they tended to decompose upon chromatography. The mixture of these quinones was therefore methylated with silver(I) oxide and methyl iodide to give the dimethyl ether (31) in a 30% overall yield from 1,4-benzoquinone.



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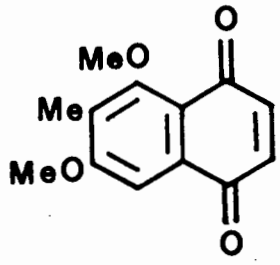

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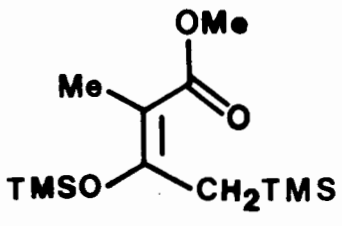
Diene (11) undergoes an intramolecular 1,5-silyl migration from oxygen to carbon giving a new α,β-unsaturated ester (32), at temperatures higher than 60°C.[22] Thus it was difficult to obtain this diene in 100% purity. This could be a contributing factor to the low yield in the Diels Alder reaction.



32

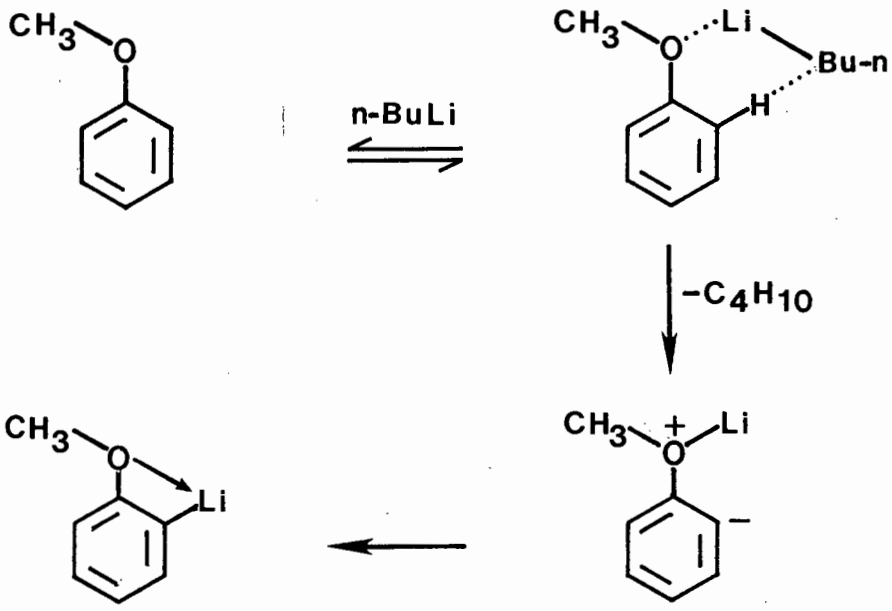
Due to the impracticality of this procedure as well as the uninspiring yields obtained, this route to the naphthalene nucleus was abandoned.

An alternative approach was sought which could overcome these difficulties. 4,5-Dimethoxy-1,7-di-(2-propyloxy)naphthalene (23) offered potential as a new starting material, as it has the correct oxygenation pattern although lacking the C-6 methyl substituent. This naphthalene also satisfied the steric requirements for formation of a monoxime at C-3 since the investigation of this reaction was done on naphthalene (26) with the same protecting groups. Provided therefore that a methyl group could be substituted into the C-6 position of compound (23), the reaction sequence should proceed as planned in Scheme 1.

Naphthalene (23) has two *ortho*-directing lithiating groups *meta* to each other at C-5 and C-7, and thus offers the possibility of further elaboration to a compound possessing the C-6 methyl function. It was envisaged that the naphthalene (23) could be lithiated and subsequently methylated between the two *meta*-alkoxy substituents since there existed ample evidence in the literature for the *ortho*-lithiation of anisoles.[27]

The ortho-metalation/electrophilic substitution sequence has become recognised today as an efficient route for the regiospecific synthesis of a variety of polysubstituted aromatic and heteroaromatic compounds. The widely accepted mechanism for aromatic lithiation is due to Roberts and Curtin.[27a]

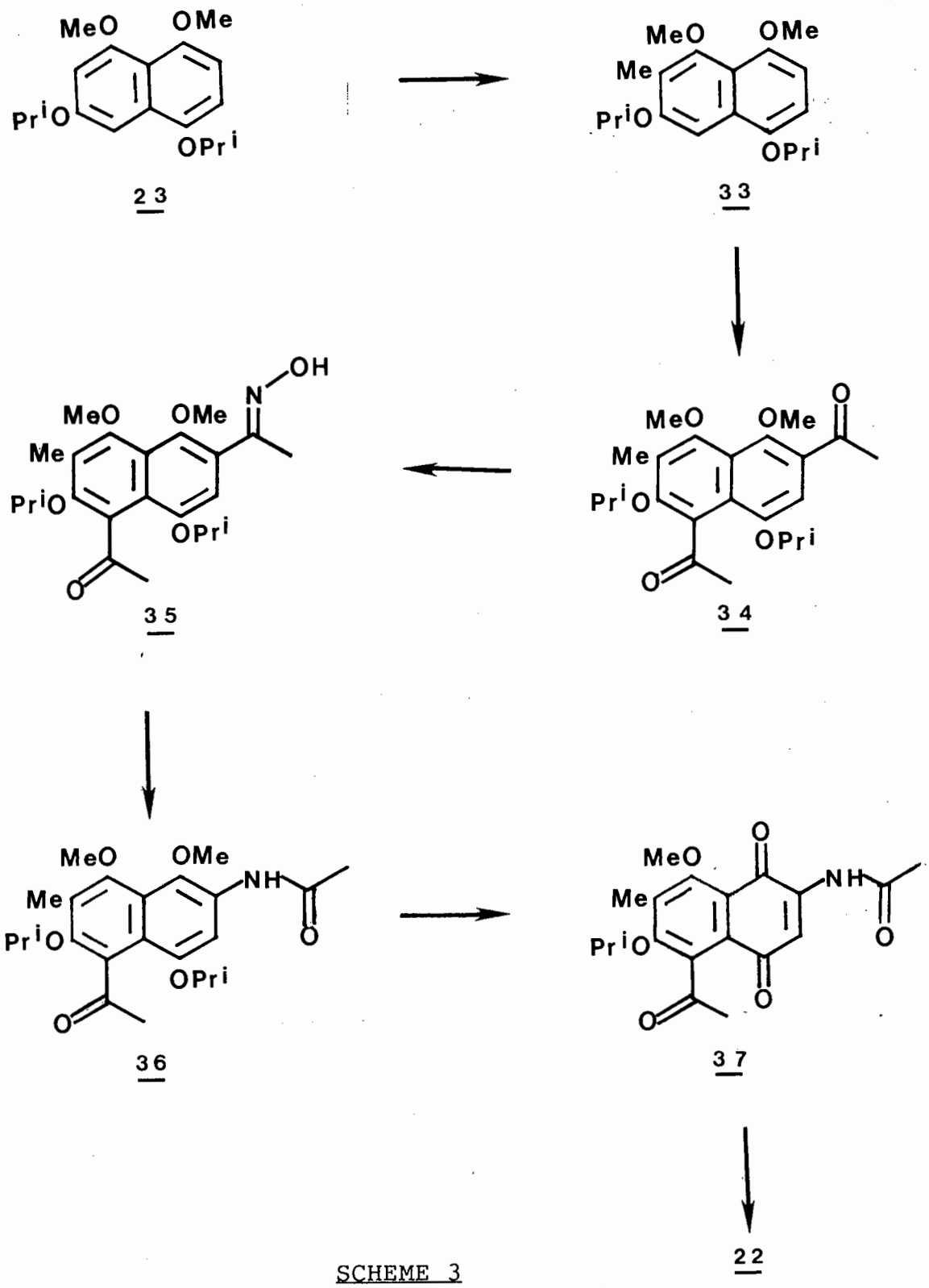
This is illustrated in Scheme 2 for the lithiation of anisole.



SCHEME 2

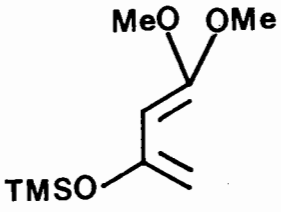
Complexation is an essential feature of this mechanism. When a substrate carries more than one lithiation directing group, the reaction will occur *ortho* (or sterically close) to that group which will complex better with the lithiating agent. If the substrate has more than one site available for lithiation, the reaction will occur predominantly at that position which carries the most acidic hydrogen. The acidity to be considered is that of those protons which are *ortho* or sterically close with respect to the better complexing group. Steric factors are also important in a lithiation reaction and will play a role in deciding reactivity and positional selectivity. The steric factors involved would be related to ring size and steric crowding present in the transition state corresponding to the proton abstraction process.

Scheme 3 depicts the new reaction sequence starting from naphthalene (23) and includes the planned C-6 methylation.

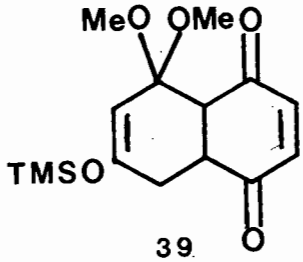


SCHEME 3

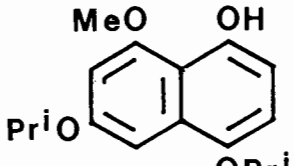
Naphthalene (23) was prepared in the following manner. Diels Alder reaction of Brassard's diene (38)[28] with 1,4-benzoquinone and subsequent alkylation of the crude adduct (39) with potassium carbonate and isopropyl bromide in dry dimethylformamide, afforded the naphthol (40). This naphthol was then methylated with dimethyl sulphate and potassium carbonate in boiling acetone to afford the naphthalene (23).



38



39



40

Naphthalene (23) was then treated with 1.2 molar equivalents of *n*-butyl lithium and the anion generated quenched with methyl iodide. Only one product was obtained, to which was assigned the structure (33) having expected that lithiation/methylation has occurred regioselectively between the *meta*-orientated methoxy and isopropoxy groups. The molecular ion obtained by mass spectrometry was consistent with the molecular mass of 318 expected for compound (33). This product was obtained in a yield of 81%.

Further support for this assignment was provided by a comparison of the ^1H n.m.r. spectra of the starting material

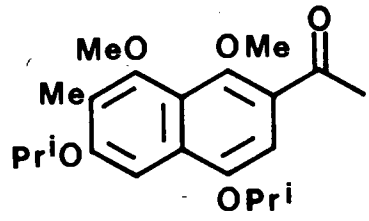
(23) and product (33) of this reaction. For naphthalene (23) the spectrum showed two *ortho*-coupled protons (2-H and 3-H) at δ 6.56 and 6.79 (J 8 Hz) and two *meta*-coupled protons at δ6.52 and 7.19 (J 2 Hz), the latter pair of signals being assigned to 6-H, as the more shielded proton, and 8-H as the more deshielded proton respectively.[25] In the product (33), the observed aromatic signals were two doublets at δ 6.52 and 6.68 (J 9 Hz), and a singlet at δ 7.38. Thus, the more shielded of the *meta*-coupled protons (6-H) in the starting material had been replaced by a methyl group in the product. This new substituent appeared as a three-proton singlet at δ 2.28.

The next step towards obtaining the fully substituted naphthalene nucleus was the diacetylation of compound (33). Using the method outlined in the literature,[25] naphthalene (33) was treated with an excess of premixed acetic acid and trifluoroacetic anhydride. The ^{1}H n.m.r. spectrum of the sole product obtained showed two singlets in the methyl region, at δ 2.28 and 2.76, due to the aromatic methyl and an acetyl methyl respectively. The aromatic region showed two singlets at δ 7.08 and 7.40. The infrared spectrum showed only one band in the carbonyl region at 1662 cm^{-1}. The product was therefore not the diacetylated product (34) anticipated, the ^{1}H n.m.r and infrared signals suggesting the product to be a monoacetyl derivative.

Apart from the multiplicity and position of the aromatic protons of the product, these spectroscopic observations are entirely consistent with acetylation having occurred at C-3

rather than C-8, since two series of 1,4,5,7-tetraalkoxy-naphthalenes acetylated at C-3 or C-8 have been prepared.[25] The infrared spectra of these naphthalenes show that the C-3 carbonyl stretches are at *ca.* 1660 - 1670 cm^{-1}, whereas those for C-8 are at about 1700 - 1720 cm^{-1}, reflecting the fact that the acetyl carbonyl at C-8 is not coplanar with the naphthalene ring. Similarly, in the ^1H n.m.r.spectrum, the C-3 acetyl resonance appears in the range δ 2.70 - 2.80, deshielded from the values (δ 2.50 - 2.60) commonly observed for the isomeric C-8 acetyl derivatives.

The product obtained was thus the C-3 monoacetyl derivative (41). No further acetylation at C-8 could be induced, either by altering the quantity of mixed anhydride added or by raising the temperature of the reaction. This is presumably on account of the buttressing effect of the C-6 methyl causing steric crowding at the single unsubstituted aromatic position on the ring bearing this methyl.



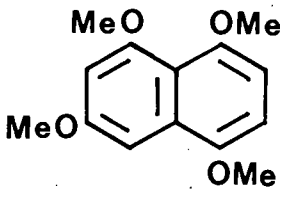
41

A Friedel Crafts acetylation was not attempted, due to the number of alkoxy groups that could be affected by such an acidic medium.

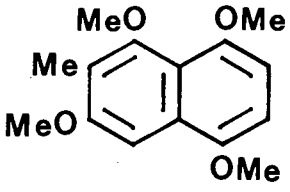
In view of the considerable steric crowding introduced by the additional substituent on the naphthalene ring, it was decided that further efforts should be undertaken on 1,4,5,7-tetramethoxynaphthalene (42)[28] rather than the di-isopropoxy derivative (23). It was hoped that by reducing the size of the protecting groups on O-1 and O-7, these methoxy substituents would still be sufficiently large to discourage oxime formation at the C-8 acetyl, while more readily accommodating an additional methyl group at C-6.

The naphthalene (42) has been previously described.[29] For this work it was conveniently prepared (as for the related assembly of naphthalene (23)) from the Diels Alder adduct (39) derived from Brassard's diene and 1,4-benzoquinone,[25] which was then exhaustively methylated with dimethyl sulphate and potassium carbonate in boiling acetone.

Naphthalene (42) was then treated with *n*-butyl lithium followed by methyl iodide as for the isopropyl analogue (23) above, to give the C-6 methylated product (43) in 82% yield.



42

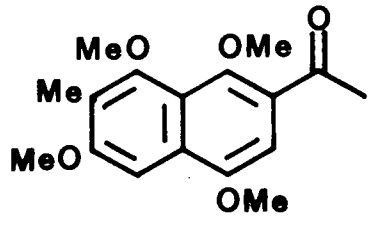


43

Once again, evidence for this methylation was provided by comparison of the ^1H n.m.r. spectra of the starting material (42) and product (43) of this reaction. Further proof was

provided by oxidising naphthalene (43) to the naphthoquinone using silver(II) oxide and nitric acid. The quinonoid product was compared by infrared and ^{1}H n.m.r. spectroscopy, melting point and mixed melting point, with the quinone (31) obtained *via* diene (11). In this quinone the methyl group is established at C-6 from the structure of the diene. The two quinones were identical by all the comparative criteria used, thus proving conclusively that lithiation had occurred at C-6 as expected.

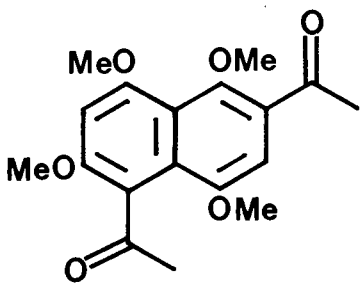
Naphthalene (43) was then treated with an excess of premixed acetic acid and trifluoroacetic anhydride. It was hoped that as the steric crowding introduced by methoxy groups at C-1 and C-7 would be less than isopropoxy groups in the same positions, the desired diacetylated compound might be more readily obtained. However, the C-3 monoacetyl derivative (44) was obtained as the sole product, as shown by ^{1}H n.m.r. and infrared spectroscopy. This result directly paralleled the conversion of naphthalene (33) to the acetyl derivative (41).



44

Obviously, decreasing the size of the O-1 and O-7 protecting groups does not reduce the steric constraint at the C-8 position sufficiently to enable acetylation to occur. It was

thus wondered whether these methoxy groups would also be sufficiently large to discourage oxime formation at the C-8 acetyl of compound (45). This was shown to be the case as compound (45) was successfully converted into amide (46).[26]



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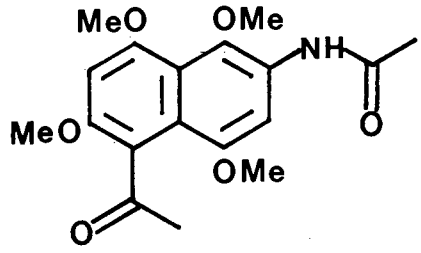
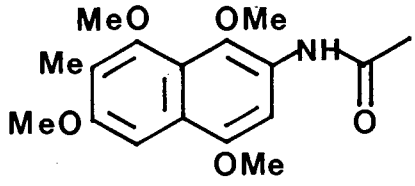


46

The ketone (44) was converted into the analogous acetylamino-naphthalene (47) *via* reaction with hydroxylamine followed by a Beckmann rearrangement. The infrared spectrum of this product showed an absorption band at 1653 cm^{-1} due to the amide carbonyl. The ^1H n.m.r spectrum showed a new three-proton singlet at δ 2.24 due to the amidic methyl group.

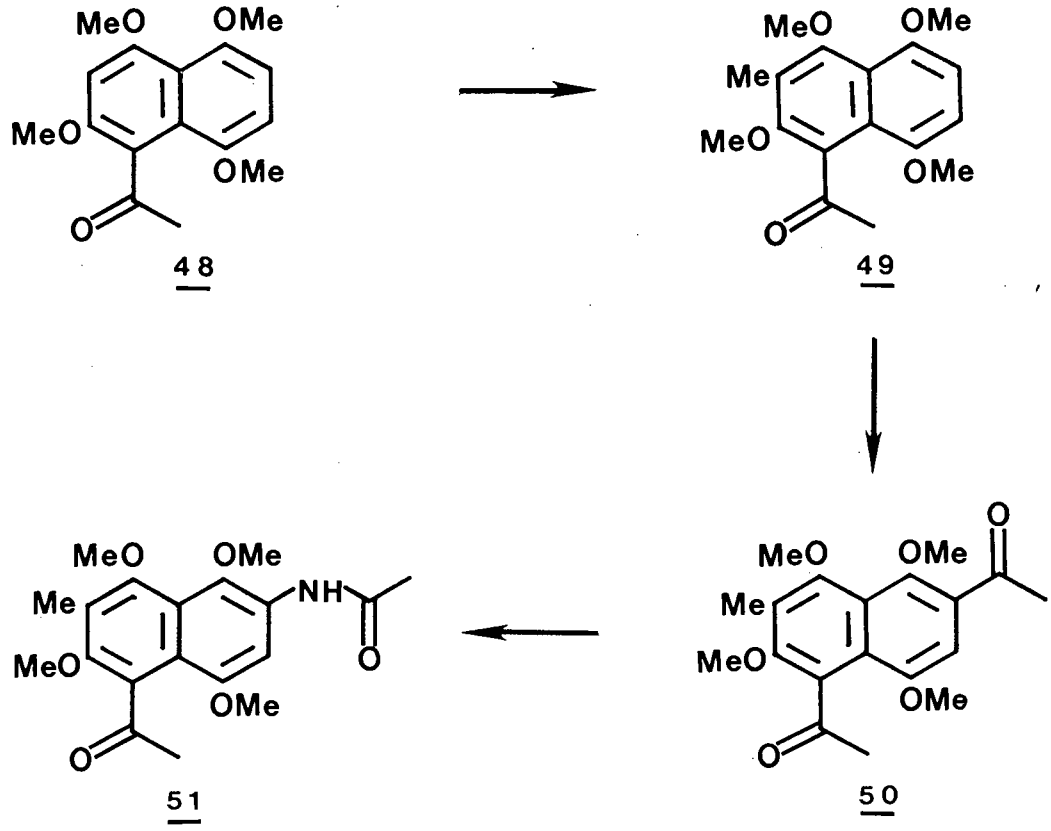


47

Furthermore, the spectrum shows that the amide group has a considerable deshielding affect on the neighbouring aromatic proton. In the starting material (44) the signal for 2-H is at δ 7.25, whereas in the product (47) it appears at δ 8.20. The singlet for 8-H remains unchanged.

Attempts to acetylate this amide (47) with an excess of mixed anhydride were unsuccessful.

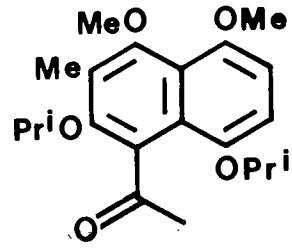
The 8-acetyl naphthalene (48), the major product of mono-acetylation of 1,4,5,7-tetramethoxynaphthalene[27a] was also considered as a starting point in the synthesis of the target molecule. The proposal, as outlined in Scheme 4, was to first methylate compound (48) at C-6, followed by acetylation at C-3.



SCHEME 4

The conversion of the naphthalene (48) into the C-6 methyl derivative (49) was envisaged using an excess of *n*-butyl lithium. This would presumably abstract one of the more acidic acetyl protons first, followed by the C-6 aromatic proton. The dianion so derived could subsequently be quenched by the addition of just sufficient methyl iodide to alkylate the more reactive aromatic anion, yielding the desired product.

The investigation of the lithiation/alkylation postulate was carried out initially on the naphthalene derivative (25), as a large stock of this material was on hand. The addition of five molar equivalents of *n*-butyl lithium gave a dark red dianionic solution. Just sufficient methyl iodide was added dropwise to this solution to discharge the colour, thereby permitting the isolation of the required product (52) in a yield of 95%. No product (53) of dimethylation was observed under these optimised conditions.



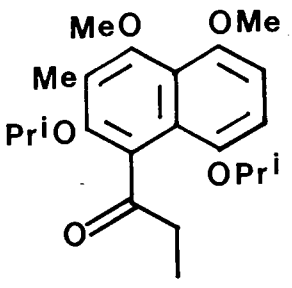
52

The ^{1}H n.m.r spectrum of product (52) showed *inter alia* the presence of a new three-proton singlet in the methyl region at δ 2.32, as well as the disappearance of the singlet at

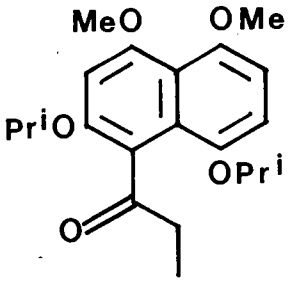
δ 6.68 for 6-H in the starting material (25). The 8-acetyl singlet appeared at δ 2.54.

If the dianionic solution was quenched by the addition of an excess of methyl iodide, the dimethylated naphthalene (53) was obtained in a yield of (73%). The ^{1}H n.m.r. spectrum of this compound exhibited a doublet of quartets at δ 2.84 (J 2 and 8 Hz) for the methylene protons, the C-8 acetyl singlet of the starting material having disappeared. This effect is probably due to restricted rotation, resulting from steric interaction with the adjacent isopropyl groups. The signal for the C-8 acetyl methyl protons was obscured by those of the isopropyl methyls.

The mono-anion of naphthalene (25), with one of the more acidic acetyl protons abstracted, could be formed by the addition of a 2.5 molar excess of *n*-butyl lithium and slightly different reaction conditions. This solution was pale yellow in colour. Upon quenching with methyl iodide, the product (54) of acetyl alkylation was obtained. The ^{1}H n.m.r. of this product showed the same splitting pattern for the methylene protons as observed for the naphthalene (53).



53



54

The dimethylated naphthalene (53) could be made *via* an alternative method. Compound (23) was treated with a premixed solution of trifluoroacetic anhydride and propionic acid to give the 8-acylated product (54). Naphthalene (54) was then lithiated and subsequently methylated at C-6, using the same procedure whereby the C-6 methyl compound (52) was obtained from the 8-acetyl derivative (25). The yield of naphthalene (53) obtained by this method was 78% from compound (54).

The desired C-6 methyl tetramethoxynaphthalene (49) was then prepared from compound (48) in the same manner as the 1,7-di-isopropoxy derivative (52) described above. The yield of this reaction was also 95%.

Further acetylation of the naphthalene (49) was attempted using a nine molar excess of premixed acetic acid and trifluoroacetic anhydride. One product was quantitatively obtained. This compound possessed an R_f value higher than that of starting material and not lower as would be expected for the desired product (50). This unexpected product proved to be the isomeric naphthyl ketone (44) described earlier, as judged by comparison of the ^1H n.m.r. spectrum of the product with that of the original material. Their mass spectra and fingerprint regions of their infrared spectra were compared and the two compounds found to be identical.

Clearly a deacetylation/reacetylation reaction had taken place. This reaction is presumably initiated by protonation of naphthalene (49) at C-8, the carbon bearing the acetyl substituent, by the trifluoroacetic acid generated on

formation of the mixed anhydride. The derived σ-complex would lose the C-8 acylium ion, reforming the mixed anhydride which would then reacetylate the intermediate (43) at the less crowded C-3 position to give product (44).

This reaction was shown to be intermolecular by treating the 8-propionyl naphthalene (53) with an excess of acetic acid and trifluoroacetic anhydride at room temperature. The product was shown to be the C-3 acetyl naphthalene (41) by inspection of the ^{1}H n.m.r., infrared, and mass spectra.

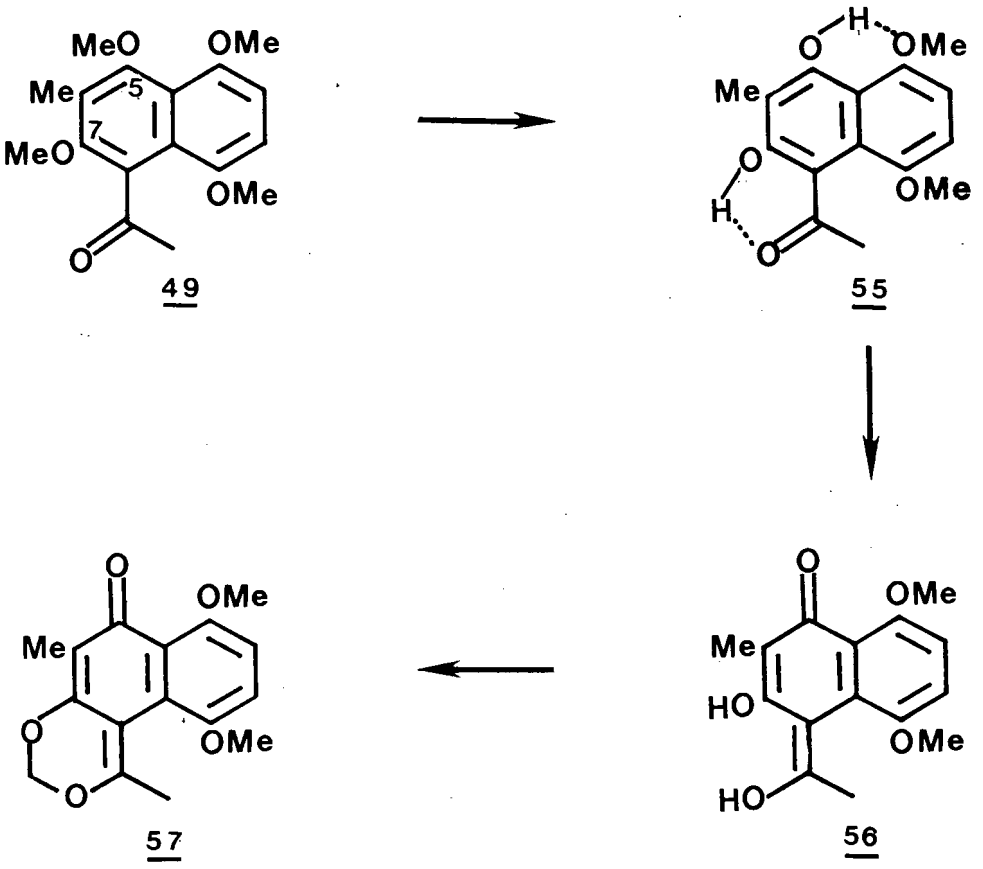
These rearrangements took a number of days to complete. However, if they were carried out in boiling chloroform or with triflic anhydride in place of trifluoroacetic anhydride, they were completed in a far shorter time.

Since this attempt to further acetylate the 8-acetyl naphthalene (49) had not succeeded, it was decided to attempt a C-6 methylation of naphthalene (45), which already possessed the two required acetyl substituents. Such a reaction would be an extension of the methylations of the 8-monoacetyl derivatives (25) and (48) to yield their C-6 methyl analogues (52) and (49) respectively: the fact that these methylations had both proceeded in 95% yield led to speculation that the corresponding methylation of diacetyl naphthalene (45) might also proceed favourably to yield compound (50).

Compound (45) was obtained in very good yield by acetylation of 1,4,5,7-tetramethoxynaphthalene (42).[29a] Treatment of this compound with six molar equivalents of *n*-butyl lithium in dry

tetrahydrofuran gave a disappointing result. The C-6 methyl naphthalene (50) was not formed, a mixture of some complexity being obtained. This mixture was not further investigated.

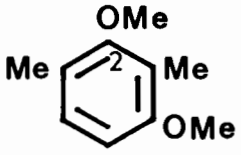
The 8-acetyl naphthalene (49) can be seen as a potential precursor to a model (57) for the streptovaricin nuclei such as compound (13), according to the reaction sequence depicted in Scheme 5.



SCHEME 5

Treatment of naphthalene (49) with the Lewis acid boron trichloride would remove the O-7 methyl group as it is *peri* to a carbonyl function. Sargent[30] has reported that the

buttressing effect of a methoxy and methyl group will provide sufficient steric effect for demethylation to occur at O-2 in compounds such as (58) and (59). Thus it would appear that the methyl group at O-5 of naphthalene (49) would also be removed upon reaction with boron trichloride. The product formed would therefore be the naphthalene (55), deprotected at both O-5 and O-7.



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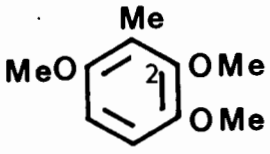
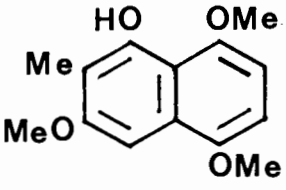


59

The moderately electron rich naphthalene (55) may have some tendency to exist in tautomeric equilibrium with the compound (56). If this product is formed, even if only in small quantities, reaction with diiodomethane and potassium carbonate could result in the formation of the model compound (57).

The 6-methyl naphthalene (43) was used as a model to determine whether the O-5 (rather than the O-4) methyl could be selectively deprotected. Compound (43) was thus treated with six molar equivalents of boron trichloride at -78°C to yield a single product, assigned the structure of naphthol (60).



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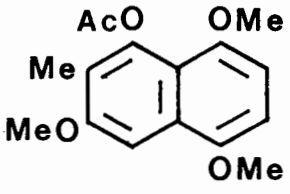
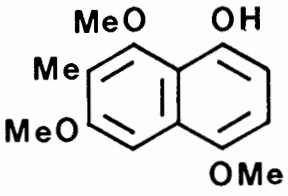


61

The ^{1}H n.m.r. spectrum of this compound showed a hydroxyl resonance as a sharp singlet at δ 9.71. The napththol (60) was immediately converted into the acetate (61) by treatment with acetic anhydride and pyridine.

Confirmation of the structure for (61) was obtained by making the isomeric acetate (63). Quinone (31) was reductively monomethylated to give the naphthol (62), the ^{1}H n.m.r. spectrum of which showed a singlet at δ 9.08 due to the hydroxy group. Acetylation of this naphthol gave the acetate (63). This acetate was compared by ^{1}H n.m.r. and infrared spectroscopy, as well as *via* melting point, with the acetate (61). These two acetates were unambiguously different, hence proving that the O-5 methyl group had been cleaved from compound (43) by boron trichloride.



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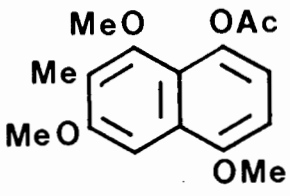


63

Although the reaction sequence as depicted in Scheme 5 appears to have potential in view of the result described above, this project was put aside due to the success of results still to be discussed.

The amide (46) obtained from the diacetyl naphthalene (45),[26] was the next compound considered for methylation at C-6. It

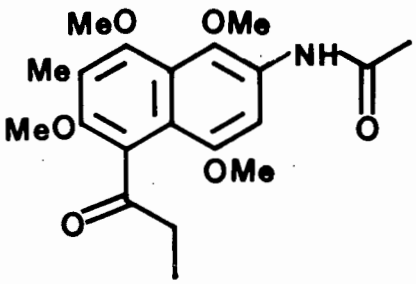
was hoped that the acetylaminonaphthalene (51) would be obtained.

The amide (46) was thus treated with five molar equivalents of *n*-butyl lithium followed by just enough methyl iodide to quench the orange colour of the solution. The reaction mixture afforded largely a single product as shown by thin layer chromatography. Complexation of *n*-butyl lithium with the external complexing agent tetramethylethylenediamine improved the yield of this product to 60% (based upon the molecular ion of highest mass). The mass spectrum of this product showed that the signal corresponding to the highest mass had an *m/z* value of 375, indicating that two methyl groups had been added during the course of the reaction.

The infrared spectrum of the product showed only one carbonyl absorption band at 1695 cm^{-1}. It was assumed that the amide carbonyl band, which should appear at *ca.* 1660 cm^{-1}, was masked by the absorption band of the C-8 acetyl carbonyl.

The ^1H n.m.r. spectrum showed the presence of only one aromatic singlet at low field (δ 8.10) corresponding to a proton *ortho* to an acylamino function (*c.f.* the value for 2-H at δ 8.20 for naphthalene (47)). In addition to four methoxy signals two *C*-methyl singlets occurred at δ 2.36 and 2.51. Furthermore, the presence of a quartet at δ 2.49 (*J* 8 Hz) and a triplet at δ 1.29 (*J* 8 Hz) suggested that a propionyl group had been formed at either the *C*- or *N*-acetyl of compound

(46). The product could thus be assigned either structure (64) or (65).



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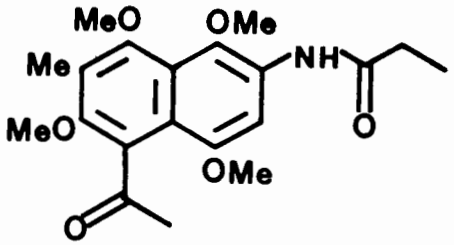
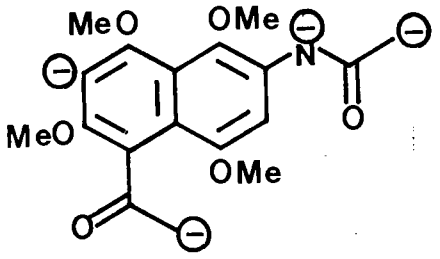
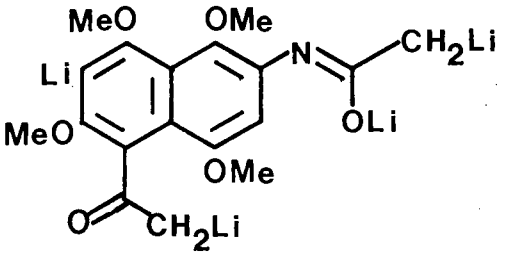


65

Treatment of the amide (46) with an excess of *n*-butyl lithium no doubt facilitates the removal of four protons. In qualitatively considering the ease of removal of these protons, the proton on nitrogen would be the most facile, followed by one from the C-8 acetyl group, then that from the C-6 position, and also a further proton from the acetylamino function, the order of removal of the last two protons being less immediately obvious. This process would give rise to the tetra-anion (66), which may also be drawn as the corresponding tetralithio derivative (67). Methylation of the tetra-anion would occur in the reverse sense, (in the order of decreasing nucleophilicity), i.e. on the acetylamino and aromatic carbons initially. The anticipated product of dimethylation would therefore be the naphthalene (65). This assignment is further supported by the chemical shift of the crowded C-8 acetyl methyl singlet at δ 2.51 in the ^{1}H n.m.r. spectrum, which was consistent with the value for this substituent as discussed earlier.

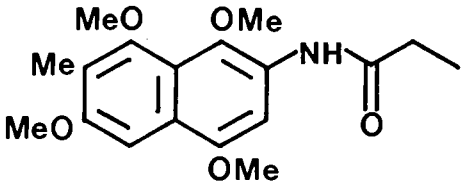


66



67

In order to confirm the structure of the product obtained, it was dissolved in methylene chloride and treated with trifluoroacetic acid. From a result obtained earlier, namely the intermolecular rearrangment of 8-acetyl naphthalene (49) to give the 3-acetyl isomer (44), the product expected would be that of deacetylation at C-8. If the assignment of the structure (65) was correct, the product expected would be naphthalene (68).



68

Indeed, a single product of higher R_f was quantitatively obtained. The ^1H n.m.r. spectrum showed the loss of the acetyl singlet at δ 2.51. The signals typical of a propionyl group, *viz.* the quartet and triplet at δ 2.50 and 1.30 respectively were still present. The mass spectrum supported the assignment of structure (68) with a molecular ion at *m/z* 333, while the infrared spectrum showed no carbonyl absorption

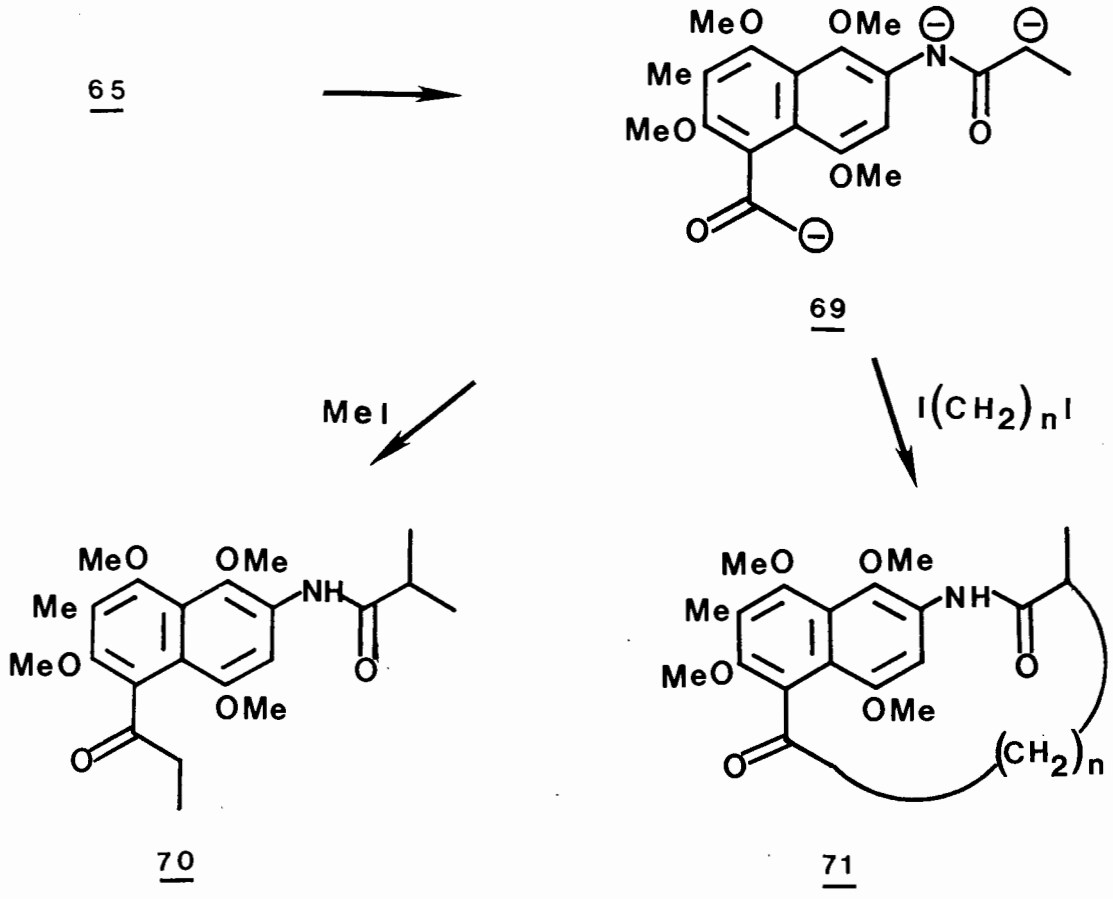
at a wave number higher than 1660 cm^{-1}. Thus in the previous methylation reaction, chain extension had occurred at the acetamido function to give product (65).

Had chain extension occurred at the C-8 acetyl group, the product of deacetylation of the derived naphthalene (64) would have been the amide (47) as obtained earlier. Apart from the obvious differences of the acylamino groups, the ^1H n.m.r. spectra of compounds (68) and (47) were identical.

Kinoshita[16e] has synthesised the acetamide (64). The ^1H n.m.r. spectrum of this compound showed two three-proton singlets at δ 2.25 and 2.36 for the acetamide acetyl and the aromatic methyl respectively. The aromatic and amide protons appear as a broad singlet at δ 8.08. In comparison, the ^1H n.m.r. spectrum of amide (65) showed the two *C*-methyl signals at δ 2.36 and 2.51, and the amide and aromatic protons at δ 8.10.

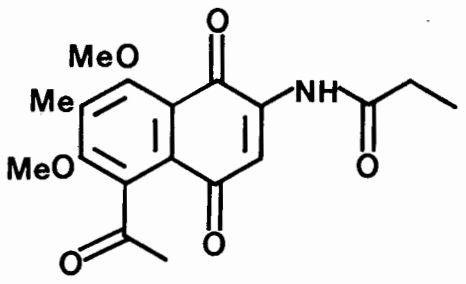
Many ansamycins carry a methyl substituent at the α-carbon of the acylamino group. Hence the methylation of naphthalene (46), not only at C-6 but also on the acetylamino substituent was useful. In an attempt to utilise this chain extension further, amide (65) was treated with four molar equivalents of *n*-butyl lithium followed by quenching with methyl iodide. It was hoped that the reaction would proceed *via* the tri-anionic intermediate (69) to give the desired product (70). If this reaction could be achieved, the proposal was to quench the reaction with a long chain dihalide such as

$I(CH_2)_nI$ in place of methyl iodide, to obtain the product (71), with a model ansa chain.



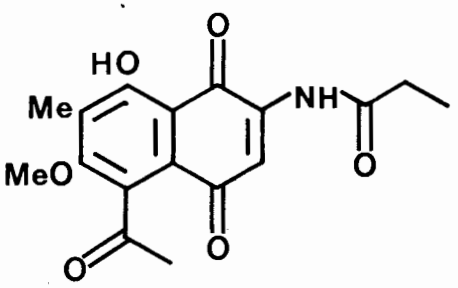
However, quenching of the anionic intermediate yielded one product, the ^1H n.m.r. spectrum of which suggested it to be a *N*-methylated acetamide. The signal at δ 8.10 for the amide proton had disappeared, two singlets at δ 3.31 and 3.33 appearing for a *N*-methyl group. This might conceivably represent a situation of restricted rotation about the amido grouping, well known to occur at the usual operating temperature of n.m.r spectrometers, even for simple amides such as dimethylformamide. The *C*-methyl signal had also disappeared. This reaction was not investigated further.

The naphthalene (65) was easily oxidised to quinone (72) using Rapoport's general method.[31] The ^{1}H n.m.r. spectrum showed the loss of two methoxy singlets and the infrared spectrum showed the appearance of two further bands in the carbonyl region at 1675 and 1636 cm^{-1}.



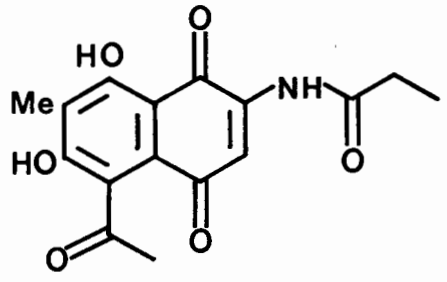
72

At this stage, the only remaining problem in the synthesis of the target molecule consisted of the deprotection of the methoxy groups at C-5 and C-7. Thus, naphthoquinone (72) was treated with a large excess of the Lewis acid aluminium trichloride, and stirred at room temperature for five hours. A product of higher R_f was obtained. The ^{1}H n.m.r. spectrum of the compound showed that one methoxy group had been cleaved and the presence of a hydroxy group was noted at δ 12.51. The product was thus quinone (73).



73

However, if the reaction mixture was stirred for 52 hours, a different product of lower R_f was obtained. No methoxy signals were observed in the ^1H n.m.r. spectrum and the mass spectrum confirmed the loss of a further methyl group by exhibiting the molecular ion at *m/z* 317. The product was therefore the naphthoquinone (74), an analogue of the target molecule (9). This naphthoquinone was obtained in a yield of 87%.



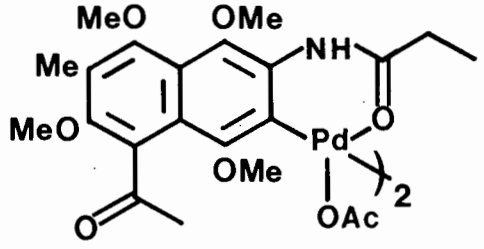
74

Some ansamycins are further substituted at the C-2 position. It was therefore decided to try to extend this synthesis to include this possibility.

A reaction has recently been reported whereby acetamides can be exclusively *ortho*-methylated.[32] This is achieved by treatment of the acetamide with stoichiometric amounts of palladium acetate and methyl iodide in acetonitrile. Various electrophiles such as allyl iodide or ethyl iodide can be used to obtain other *ortho*-alkylated products.

Amide (65) was treated with palladium acetate and methyl iodide according to the method outlined in the literature,

but starting material was recovered. The failure of this reaction could once again be attributed to steric factors, since the first step of the reaction process is *ortho*-metalation of the acetamide, giving the crowded intermediate (75).



75

In an attempt to introduce a chlorine substituent into the naphthalene ring at C-2, the amide (65) was treated with *N*-chlorosuccinimide in methylene chloride at room temperature. However, the only product obtained was the naphthoquinone (72). No further attempts at introducing a C-2 substituent were made.

It is anticipated that the synthesis described in this chapter may be varied by changing the nature of the acylating groups, *via* analogues of the naphthalene (45), in which both acyl groups are the same or different. Kinoshita[16e] has shown that a propionyl substituent at C-8 in a naphthalene such as (64), can be converted, *via* oxidation to pyruvyl, into the hydroxydihydrofuranone ring which is present in rifamycin B, rifamycin S, and rifampicin.

However, since the synthesis of the original target molecule was successful, and could be favourably compared with previously reported syntheses, this project was ended at this point. The final yield of the naphthoquinone (74) was 20% (based on 1,4-benzoquinone) and involved a total of six steps.

EXPERIMENTAL

General procedures:

^{1}H n.m.r spectra were recorded using a 200 MHz Varian VXR-n.m.r.spectrometer unless otherwise stated. At 90 MHz, spectra were recorded on a Bruker WH-90 n.m.r. spectrometer. ^{13}C n.m.r spectra were recorded on the former instrument at a frequency of 50.1 MHz. All n.m.r. spectra were recorded at room temperature in deuterochloroform using tetramethylsilane as an internal standard unless otherwise stated.

Mass spectra were recorded on a VG micromass 16F mass spectrometer at 70eV and an ion source temperature between 180 and 220°C. High resolution mass spectra were recorded on a Varian MAT 311A spectrometer at the University of Stellenbosch.

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

Melting points were determined on a Fischer-John apparatus and are uncorrected. Elemental analyses were performed on a Hireaus CHN-RAPID analyser.

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

tography (t.l.c.) was carried out on aluminium plates coated with the same material.

Light petroleum refers to the fraction of boiling point 60 - 90°C and ether to diethyl ether. Sodium hydride (Merck) was supplied as a dispersion in paraffin oil. Raney Nickel catalyst (Merck) was supplied in 50% water. The phrase "residue upon work-up" refers to the residue obtained when the organic layer was separated, dried over magnesium sulphate, filtered, and the solvent evaporated to dryness.

Where necessary, solvents and reagants were dried and purified according to the procedures described by Perrin *et al.*[33]

Synthesis of 8-acetyl-5,7-dihydroxy-6-methyl-3-propionyl-amino-1,4-naphthoquinone.

5,7-Dihydroxy-6-methyl-1,4-naphthoquinone (16) *and 7-Hydroxy-5-methoxy-6-methyl-1,4-naphthoquinone* (29).- 1,4-Benzoquinone (1.00 g, 9.25 mmol) was dissolved in dry toluene (120 ml) under nitrogen at -78°C. Diene (11)[22] (2.53 g, 9.25 mmol) and dry pyridine (1.48 ml, 18.5 mmol) were added. The solution was stirred for 5 min at -78°C and then warmed to room temperature over 1 h. The toluene was evaporated off and the organic residue extracted into methylene chloride and washed with dilute hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the quinone (16)

(340 mg, 18%) (Found: M^+, 204.0421. $C_{11}H_8O_4$ requires M, 204.0422); δ_H (90 MHz) 2.12 (3 H, s, $ArCH_3$), 3.11 (1 H, br. s, 7-OH), 6.90 (2 H, s, 2- and 3-H), 7.11 (1 H, s, 8-H), and 12.92 (1 H, s, 5-OH), followed by quinone (29) (302 mg, 15%) (Found: M^+, 218.0569. $C_{12}H_{10}O_4$ requires M, 218.0578); δ_H (90 MHz) 2.20 (3 H, s, $ArCH_3$), 2.95(1 H, br. s, 7-OH), 3.80 (3 H, s, OCH_3), 6.83 (2 H, s, 2- and 3-H), and 7.36 (1 H, s, 8-H).

5,7-*Dimethoxy*-6-*methyl*-1,4-*naphthoquinone* (31).- 1,4-Benzoquinone (1.00 g, 9.25 mmol) was dissolved in dry toluene (120 ml) under nitrogen at -78°C. Diene (11) (2.53 g, 9.25 mmol) and dry pyridine (1.48 ml, 18.5 mmol) were added. The solution was stirred for 5 min at -78°C and then warmed to room temperature over 1 h. The toluene was evaporated off and the organic residue extracted into methylene chloride and washed with dilute hydrochloric acid. The residue obtained upon work-up was dissolved in dry chloroform (200 ml). Methyl iodide (60 ml) and silver(I) oxide (4 g) were added and the solution stirred for 96 h at room temperature. The solution was filtered and the solvent evaporated. The residue was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the quinone (31) (644 mg, 30%) as yellow needles, m.p. 126 - 127°C (methylene chloride-light petroleum) (Found: M^+, 232.0736. $C_{13}H_{12}O_4$ requires M, 232.0735); $\nu_{max.}$ 1672 and 1654 (C=O), and 1582 (C=C) cm^{-1}; δ_H (90 MHz) 2.21 (3 H, s, $ArCH_3$), 3.80 and 3.97 (each 3 H, s, OCH_3), 6.78 (2 H, s, 2- and 3-H), and 7.36 (1 H, s, 8-H); m/z 232 (M^+, 100%), 217 (28), 202 (20), and 187 (24).

4,5-Dimethoxy-6-methyl-1,7-di-(2-propyloxy)naphthalene (33).- Naphthalene (23) (250 mg, 0.82 mmol) was dissolved in dry tetrahydrofuran (10 ml) at -78°C under nitrogen. *n*-Butyl lithium (0.98 mmol, 1.2 mol equiv.) was added over 2 min. The solution was stirred at -78°C for 30 min, warmed to 0°C and stirred for a further 30 min. Methyl iodide (0.51 ml, 8.20 mmol) was added and the reaction mixture left to stir at room temperature for 15 min. The mixture was added to water and extracted exhaustively with ether. The organic layer was dried with magnesium sulphate, filtered and evaporated to dryness. The residue was purified by chromatography (eluant 10% ethyl acetate-light petroleum) to give the product (33) (210 mg, 81%) as a yellow oil (Found: C, 71.9; H, 8.3. $C_{19}H_{26}O_4$ requires C, 71.7; H, 8.2%); $\nu_{max.}$(film) 1602 (C=C) cm^{-1}; δ_H (90 MHz) 1.37 and 1.40 (each 6 H, d, *J* 7 Hz, $CH(C\underline{H}_3)_2$), 2.28 (3 H, s, $ArCH_3$), 3.78 and 3.88 (each 3 H, s, OCH_3), 4.48 and 4.70 (each 1 H, septet, *J* 7 Hz, $C\underline{H}(CH_3)_2$), 6.52 and 6.68 (each 1 H, d, *J* 9 Hz, 2- and 3-H), and 7.38 (1 H, s, 8-H); *m/z* 318 (M^+, 88%), 275 (46), and 232 (100).

3-Acetyl-4,5-dimethoxy-6-methyl-1,7-di-(2-propyloxy)naphthalene (41).-

Naphthalene (33) (100 mg, 0.31 mmol) was dissolved in dry methylene chloride (5 ml). A premixed solution of trifluoroacetic anhydride (600 mg, 2.88 mmol) and acetic acid (173 mg, 2.88 mmol) was added. The mixture was stirred at room temperature for 48 h and then quenched by the successive additions of an excess of methanol and a saturated sodium hydrogen carbonate solution. The organic material was

extracted into methylene chloride and the residue obtained upon work-up chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the product (41) (65 mg, 58%) as a yellow oil (Found: C, 70.05; H, 7.95. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%); $\nu_{max.}$ (film) 1662 (C=O) and 1602 (C=C) cm^{-1}; δ_H (90 MHz) 1.40 and 1.41 (each 6 H, d, *J* 7 Hz, $CH(C\underline{H}_3)_2$), 2.28 (3 H, s, $ArCH_3$), 2.76 (3 H, s, $COCH_3$), 3.80 and 3.82 (each 3 H, s, OCH_3), 4.58 - 4.90 (2 H, m, 2 X $C\underline{H}(CH_3)_2$), 7.08 (1 H, s, 2-H), and 7.40 (1 H, s, 8-H); *m/z* 360 (M^+, 100%), 317 (29), 275 (55), and 260 (15).

1,4,5,7-*Tetramethoxy*-6-*methylnaphthalene* (43).- 1,4,5,7-Tetramethoxynaphthalene (42) (140 mg, 0.56 mmol) was dissolved in dry tetrahydrofuran (10 ml) at -78°C and the reaction vessel was flushed with nitrogen. *n*-Butyl lithium (0.78 mmol, 1.4 mol equiv.) was added over 2 min. The solution was stirred at -78°C for 30 min, warmed to 0°C and stirred for a further 30 min. Methyl iodide (0.35 ml, 5.60 mmol) was added and the solution left to stir at room temperature for 15 min. Water was then added to the mixture and the solution extracted with ether. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the product (43) (120 mg, 82%) as a colourless oil (Found: C, 68.45; H, 7.1. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); $\nu_{max.}$ (film) 1605 and 1589 (C=C) cm^{-1}; δ_H (90 MHz) 2.30 (3 H, s, $ArCH_3$), 3.77 (3 H, s, OCH_3), 3.90 (9 H, s, 3 X OCH_3), 6.61 (2 H, s, 2- and 3-H), and 7.34 (1 H, s, 8-H); *m/z* 262 (M^+, 100%), 247 (88), 232 (8), and 131 (15).

3-Acetyl-1,4,5,7-tetramethoxy-6-methylnaphthalene (44).-

(a) Compound (43) (107 mg, 0.41 mmol) was dissolved in dry methylene chloride (5 ml). A premixed solution of trifluoroacetic anhydride (777 mg, 3.70 mmol) and acetic acid (222 mg, 3.70 mmol) was added. This solution was stirred at room temperature for 20 h. The reaction was quenched by the addition of methanol and a saturated aqueous solution of sodium hydrogen carbonate. The organic material was extracted into methylene chloride and the residue obtained upon work-up chromatographed (eluant 10% ethyl acetate-light petroleum) to give the product (44) (98 mg, 79%) as a yellow oil (Found: C, 67.25; H, 6.65. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$ (film) 1662 (C=O) and 1603 (C=C) cm^{-1}; δ_H (90 MHz) 2.30 (3 H, s, $ArCH_3$), 2.74 (3 H, s, $COCH_3$), 3.79, 3.81, 3.94, and 3.96 (each 3 H, s, OCH_3), 7.25 (1 H, s, 2-H), and 7.34 (1 H, s, 8-H); *m/z* 304 (M^+, 100%), 289 (30), 246 (12), and 231 (12).

(b) Compound (49) when treated as described above in (a), gave rise to product (44) in quantitative yield, whose t.l.c. behaviour and i.r., ^1H n.m.r., and mass spectra were identical with material described in (a) above.

3-Acetylamino-1,4,5,7-tetramethoxy-6-methylnaphthalene (47).- The naphthalene (44) (300 mg, 0.99 mmol) was dissolved in absolute ethanol (20 ml) and treated with hydroxylamine hydrochloride (200 mg, 2.49 mmol) in a solution of potassium hydroxide (400 mg, 0.98 mmol) in water (10 ml). The solution

was boiled for 1 h and then diluted with water (50 ml) and acidified with dilute hydrochloric acid. The mixture was then extracted with ether, dried over magnesium sulphate and filtered. The crude oxime derived upon evaporation of the solvent was dissolved in dry ether (80 ml). After treatment of this solution with phosphorus pentachloride (250 mg, 1.20 mmol) at 0°C for 2.5 h, water was added to quench the reaction and the mixture extracted with ether. The residue obtained upon work-up was chromatographed (eluant 30 % ethyl acetate-light petroleum) to yield the amide (47) (205 mg, 65%) as white needles, m.p. 131 - 132°C (light petroleum-methylene chloride) (Found: C, 63.95; H, 6.75; N, 4.15. $C_{17}H_{21}NO_5$ requires C, 63.95; H, 6.6; N, 4.4%); $\nu_{max.}$ 3230 (NH), 1653 (C=O), and 1604 (C=C) cm^{-1}; δ_H (90 MHz) 2.24 (3 H, br. s, $NHCOCH_3$), 2.29 (3 H, s, $ArCH_3$), 3.75, 3.80, 3.92, and 3.98 (each 3 H, s, OCH_3), 7.32 (1 H, s, 8-H), and 8.20 (2 H, br. s, NH and 2-H); *m/z* 319 (M^+, 65%), 304 (25), 262 (100), and 245 (16).

8-*Acetyl*-1,4,5,7-*tetramethoxy*-6-*methylnaphthalene* (49).- Naphthalene (48) (171 mg, 0.59 mmol) was dissolved in dry tetrahydrofuran (15 ml) and the reaction vessel flushed with nitrogen. *n*-Butyl lithium (2.95 mmol, 5 mol equiv.) was added to this solution at -78°C. The red mixture was then warmed to 0°C and stirred for 15 min. Methyl iodide was added dropwise to just disperse the red colour, and this clear solution was left to stir for 1 min before quenching the reaction by the addition of water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to

afford the product (49) (170 mg, 95%) as white needles, m.p. 107 - 108°C (2-propanol) (Found: C, 67.15; H, 6.45. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$ 1704 (C=O), 1612 and 1578 (C=C) cm^{-1}; δ_H (90 MHz) 2.35 (3 H, s, $ArCH_3$), 2.56 (3 H, s, $COCH_3$), 3.75, 3.78, 3.80, and 3.93 (each 3 H, s, OCH_3), and 6.74 (2 H, s, 2- and 3-H); *m/z* 304 (M^+, 100%), 289 (77), 273 (35), and 259 (13).

8-Acetyl-4,5-dimethoxy-6-methyl-1,7-di-(2-propyloxy)naphthalene (52).-

Compound (25) (253 mg, 0.73 mmol) was dissolved in dry tetrahydrofuran (15 ml) and the reaction vessel was flushed with nitrogen. *n*-Butyl lithium (1.09 mmol, 1.5 mol eqiuv.) was added to the solution at -78°C and the resultant red solution immediately warmed to 0°C and stirred for 12 min. Methyl iodide was added dropwise to this solution to just disperse the red colour. After 1 min water was added to the clear solution. The mixture was extracted into methylene chloride and washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the product (52) (249 mg, 95%) as white cubes, m.p. 53 - 54°C (light petroleum) (Found: C, 69.95; H, 7.65. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%); $\nu_{max.}$ 1707 (C=O), 1604 and 1579 (C=C) cm^{-1}; δ_H (90 MHz) 1.18 - 1.42 (12 H, m, 2 X $CH(C\underline{H}_3)_2$), 2.32 (3 H, s, $ArCH_3$), 2.54 (3 H, s, $COCH_3$), 3.78 and 3.92 (each 3 H, s, OCH_3), 4.36 and 4.64 (each 1 H, septet, *J* 7 Hz, $C\underline{H}(CH_3)_2$), 6.64 and 6.74 (each 1 H, d, *J* 10 Hz, 2- and 3-H); *m/z* 360 (M^+, 75%), 318 (32), 276 (100), and 261 (68).

4,5-Dimethoxy-6-methyl-8-propionyl-1,7-di-(2-propyloxy)-naphthalene (53).-

(a) Naphthalene (25) (50 mg, 0.14 mmol) was dissolved in dry tetrahydrofuran (10 ml) and the reaction was vessel flushed with nitrogen. *n*-Butyl lithium (0.84 mmol, 6 mol equiv.) was added to this solution at -78°C and the dark red solution immediately warmed to 0°C and stirred for 15 min. An excess of methyl iodide (0.10 ml, 1.60 mmol) was added and after 5 min the reaction was quenched by the addition of water. The organic material was extracted into methylene chloride and washed with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the product (53) (38 mg, 73%) as a colourless oil (Found: C, 70.4; H, 7.9. $C_{22}H_{30}O_5$ requires C, 70.6; H, 8.0%); $\nu_{max.}$ (film) 1709 (C=O), 1610 and 1577 (C=C) cm^{-1}; δ_H (90 MHz) 1.10 - 1.38 (15 H, m, 2 X $CH(C\underline{H}_3)_2$ and $CH_2C\underline{H}_3$), 2.30 (3 H, s, $ArCH_3$), 2.84 (2 H, dq, *J* 2 and 8 Hz, $C\underline{H}_2CH_3$), 3.76 and 3.90 (each 3 H, s, OCH_3), 4.34 and 4.40 (each 1 H, septet, *J* 7 Hz, $C\underline{H}(CH_3)_2$), 6.62 and 6.70 (each 1 H, d, *J* 10 Hz, 2- and 3-H); *m/z* 374 (M^+, 30%), 332 (16), 290 (34), and 261 (100).

(b) Naphthalene (54) (40 mg, 0.11 mmol) was dissolved in dry tetrahydrofuran (5 ml) and the reaction vessel flushed with nitrogen. *n*-Butyl lithium (0.55 mmol, 5 mol equiv.) was added at -78°C and the solution warmed to 0°C and stirred for 15 min under nitrogen. Methyl iodide (0.03 ml, 0.50 mmol) was added and the reaction quenched after 1 min by the addition of water. The reaction was worked

up as for (a) above giving rise to a product (53) (32 mg, 78%), whose t.l.c. behaviour and i.r., ^{1}H n.m.r., and mass spectra were identical with material described in (a) above.

4,5-*Dimethoxy*-8-*propionyl*-1,7-*di*-(2-*propyloxy*)*naphthalene* (54).-

(a) Naphthalene (25) (52 mg, 0.15 mmol) was dissolved in dry tetrahydrofuran (5ml) and the reaction vessel was flushed with nitrogen. *n*-Butyl lithium (0.38 mmol, 2.5 mol equiv.) was added at -78°C and the pale yellow solution stirred for 0.5 h at this temperature under nitrogen. The solution was warmed to 0°C and stirred for a further 0.5 h. An excess of methyl iodide (0.2 ml, 3 mmol) was added and the mixture stirred for 5 min at room temperature. Water was added to quench the reaction and the organic material extracted into methylene chloride. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the product (54) (45 mg, 83%) as white needles, m.p. 90 - 91°C (light petroleum) (Found: C, 69.9; H, 7.65. $C_{21}H_{28}O_5$ requires C, 70.0; H, 7.8%); $\nu_{max.}$ 1708 (C=O), 1610 and 1592 (C=C) cm^{-1}; δ_H (90 MHz) 1.09 - 1.41 (15 H, m, $CH_2C\underline{H}_3$ and $CH(C\underline{H}_3)_2$), 2.82 (2 H, dq, *J* 3 and 8 Hz, $C\underline{H}_2CH_3$), 3.87 and 3.93 (each 3 H, s, OCH_3), 4.54 and 4.56 (each 1 H, septet, *J* 7 Hz, $C\underline{H}(CH_3)_2$), 6.60 (1 H, s, 6-H), and 6.67 (2 H, s, 2- and 3-H); *m/z* 360 (M^+, 59%), 318 (25), 304 (15), 289 (22), 275 (14), 247 (100), and 219 (22).

(b) Naphthalene (23) (418 mg, 1.37 mmol) was dissolved in dry methylene chloride (10 ml) and a premixed solution of propionic acid (102 mg, 1.37 mmol) and trifluoroacetic anhydride (289 mg, 1.37 mmol) added. The reaction mixture was stirred at room temperature for 15 h before adding a second aliquot of mixed anhydride (1.37 mmol). The solution was stirred for a further 10 h. Excess methanol and a solution of saturated sodium hydrogen carbonate were added to quench the reaction. The solution was extracted with methylene chloride and the residue upon work-up chromatographed (eluant 10% ethyl acetate-light petroleum) to yield a product (54) (370 mg, 75%), whose m.p., t.l.c. behaviour, ^{1}H n.m.r., i.r., and mass spectra were identical with material described in (a) above.

5-*Acetoxy*-1,4,7-*trimethoxy*-6-*methylnaphthalene* (61).- The naphthalene (43) (324 mg, 1.24 mmol) was dissolved in dry methylene chloride (20 ml) at -78°C. This solution was treated with a solution of boron trichloride (870 mg, 7.44 mmol) in methylene chloride. After 1.25 h the mixture was added to water and extracted with diethyl ether. After drying over magnesium sulphate, the organic solvent was filtered and evaporated to yield 1,4,7-trimethoxy-6-methyl-5-naphthol (60) as an oily residue. δ_H (90 MHz) 2.21 (3 H, s, $ArCH_3$), 3.91, 3.94, and 3.96 (each 3 H, s, OCH_3), 6.34 (2 H, s, 2- and 3-H), 7.14 (1 H, s, 8-H), and 9.71 (1 H, s, 5-OH, D_2O exchangeable). The residue was immediately dissolved in dry pyridine (5 ml) and acetic anhydride (5 ml), and the solution stirred at 90°C for 1.5 h. The reaction mixture was

thrown onto crushed ice, and the resulting white crystalline solid filtered off, washed with water, and dried to afford the acetate (61) (187 mg, 52%) as white needles, m.p. 110 - 111°C (2-propanol) (Found: C, 65.85; H, 6.1. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%); $\nu_{max.}$ 1759 (C=O) and 1606 (C=C) cm^{-1}; δ_H (90 MHz) 2.19 (3 H, s, $OCOCH_3$), 2.36 (3 H, s, $ArCH_3$), 3.84, 3.93, and 3.95 (each 3 H, s, OCH_3), 6.56 and 6.66 (each 1 H, d, *J* 10 Hz, 2- and 3-H), and 7.43 (1 H, s, 8-H); *m/z* 290 (M^+, 49%), 248 (100), and 233 (92).

4-Acetoxy-1,5,8-trimethoxy-6-methylnaphthalene (63).- Quinone (31) (274 mg, 1.18 mmol) was dissolved in ether (30 ml) and shaken with an aqueous solution of sodium dithionite. The residue obtained upon work-up of the colourless solution was immediately dissolved in dry acetone (50 ml). Potassium carbonate (500 mg, 3.54 mmol) and dimethyl sulphate (3.5 ml, 3.54 mmol) were added and the solution was boiled under nitrogen for 4.5 h. The cooled solution was filtered, evaporated to dryness, and the residue dissolved in ether. This solution was washed successively with concentrated ammonia (twice), water, dilute hydrochloric acid, and then again with water. The oily residue obtained upon work-up contained 1,5,7-trimethoxy-6-methyl-4-naphthol (62). δ_H (90 MHz) 2.28 (3 H, s, $ArCH_3$), 3.88, 3.92, and 3.97 (each 3 H, s, OCH_3), 6.66 (2 H, s, 2- and 3-H), 7.30 (1 H, s, 8-H), and 9.08 (1 H, s, 4-OH, D_2O exchangeable). This residue was dissolved in dry pyridine (5 ml) and acetic anhydride (5 ml) added. The solution was heated at 90°C for 2 h and then thrown onto crushed ice. The resultant white crystalline

solid was filtered off, washed with water, and dried to afford the acetate (63) (120 mg, 35%) as white needles, m.p. 116 - 117°C (2-propanol) (Found: C, 65.9; H, 6.05. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%); $\nu_{max.}$ 1751 (C=O) and 1603 (C=C) cm^{-1}; δ_H (90 MHz) 2.19 (3 H, s, $OCOCH_3$), 2.36 (3 H, s, $ArCH_3$), 3.84, 3.94, and 3.93 (each 3 H, s, OCH_3), 6.67 and 6.85 (each 1 H, d, *J* 9 Hz, 2- and 3-H), and 7.43 (1 H, s, 8-H); *m/z* 290 (M^+, 28%), 248 (95), and 233 (100).

8-Acetyl-1,4,5,7-tetramethoxy-6-methyl-3-propionylamino-naphthalene (65).-

Tetramethylethylenediamine (0.18 ml, 1.15 mmol) was dissolved in dry tetrahydrofuran (8 ml) and the reaction vessel flushed with nitrogen. *n*-Butyl lithium (1.15 mmol, 5 mol equiv.) was added to this solution at 0°C. Amide (46) (80 mg, 0.23 mmol) dissolved in dry tetrahydrofuran (10 ml), was added at -78°C over 5 min. The solution was then stirred at 0°C for 15 min. Sufficient methyl iodide was added in order to disperse the orange colour of the solution, and the reaction mixture stirred at room temperature for 15 min before quenching by the addition of water. The organic material was extracted into ether and washed exhaustively with water. The residue obtained upon work-up was flash-chromatographed (eluant 30% ethyl acetate-light petroleum) to give the amide (65) (52 mg, 60%) as white needles, m.p. 154 - 155°C (light petroleum-methylene chloride) (Found: C, 63.95; H, 6.5; N, 3.75. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); $\nu_{max.}$ 3337 (NH), 1695 (8 C=O), 1618 and 1581 (C=C) cm^{-1}; δ_H (90 MHz) 1.29 (3 H, t, *J* 8 Hz, CH_2CH_3), 2.36 (3 H, s, $ArCH_3$), 2.49 (2

H, q, *J* 8 Hz, $C\underline{H}_2CH_3$), 2.51 (3 H, s, $COCH_3$), 3.72 (6 H, s, 2 X OCH_3), 3.79 and 3.88 (each 3 H, s, OCH_3), and 8.10 (2 H, br. s, 2-H and NH); *m/z* 375 (M^+, 89%), 360 (18), and 304 (100).

1,4,5,7-Tetramethoxy-6-methyl-3-propionylaminonaphthalene (68).-

The amide (65) (30 mg, 0.08 mmol) was dissolved in dry methylene chloride (3 ml). A catalytic amount of trifluoroacetic acid was added and the reaction mixture boiled for 48 h. The reaction was quenched by the addition of water. The organic material was extracted with ether and washed with aqueous sodium hydrogen carbonate. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to afford the product (68) (27 mg, 100%) as off-white needles, m.p. 110 - 111°C (methylene chloride-light petroleum) (Found: C, 64.5; H, 6.8; N, 4.1. $C_{18}H_{23}NO_5$ requires C, 64.9; H, 6.9; N, 4.2%); $\nu_{max.}$ 3251 (NH), 1660 (C=O), and 1607 (C=C) cm^{-1}; δ_H (90 MHz) 1.30 (3 H, t, *J* 8 Hz, $CH_2C\underline{H}_3$), 2.30 (3 H, s, $ArCH_3$), 2.50 (2 H, q, *J* 8 Hz, $C\underline{H}_2CH_3$), 3.76, 3.80, 3.92, and 4.00 (each 3 H, s, OCH_3), 7.34 (1 H, s, 8-H), and 8.10 (2 H, br. s, 2-H and NH); *m/z* 333 (M^+, 75%), 318 (15), and 262 (100).

8-Acetyl-5,7-dimethoxy-6-methyl-3-propionylamino-1,4-naphthoquinone (72).-

Naphthalene (65) (36 mg, 0.096 mmol), silver(II) oxide (48 mg, 0.39 mmol) and dioxane (8 ml) were stirred together at room

temperature and the reaction initiated by the addition of nitric acid (6 M, 0.38 mmol). After 5 min the reaction was quenched by the addition of methylene chloride (10 ml) and water (5 ml). The organic layer was separated and washed with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the quinone (72) (32 mg, 97%) as yellow needles, m.p. 183 - 184°C (methanol) (Found: C, 62.55; H, 5.45; N, 4.05. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.1%); $\nu_{max.}$ 3180 (NH), 1696 (8 C=O), 1675 and 1636 (C=O), and 1620 (C=C) cm^{-1}; δ_H (90 MHz) 1.24 (3 H, t, *J* 8 Hz, $CH_2C\underline{H}_3$), 2.31 (3 H, s, $ArCH_3$), 2.50 (3 H, s, $COCH_3$), 2.51 (2 H, q, *J* 8 Hz, $C\underline{H}_2CH_3$), 3.78 and 3.87 (each 3 H, s, OCH_3), 7.74 (1 H, s, 2-H), and 8.46 (1 H, br. s, NH); *m/z* 345 (M^+, 15%), 330 (23), and 274 (100).

8-*Acetyl*-5-*hydroxy*-7-*methoxy*-6-*methyl*-3-*propionylamino*-1,4-*naphthoquinone* (73).-

Quinone (72) (20 mg, 0.058 mmol) was dissolved in dry methylene chloride (4 ml). Aluminium trichloride (154 mg, 1.15 mmol) was added and the solution stirred at room temperature for 5 h. Water was added and the organic layer was extracted into ethyl acetate. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate-light petroleum) to yield the quinone (73) (15 mg, 78%) as yellow needles, m.p. 182 - 183°C (methanol) (Found: C, 61.6; H, 5.05; N, 4.25. $C_{17}H_{17}NO_6$ requires C, 61.6; H, 5.1; N, 4.2%); $\nu_{max.}$ 3180 (NH), 1696 (8 C=O), 1654 (C=O), and 1582 (C=C) cm^{-1}; δ_H (90 MHz) 1.24 (3 H, t, *J* 7 Hz, $CH_2C\underline{H}_3$), 2.24 (3 H, s, $COCH_3$),

2.48 (3 H, s, $ArCH_3$), 2.53 (2 H, q, *J* 7 Hz, $C\underline{H}_2CH_3$), 3.76 (3 H, s, OCH_3), 7.77 (1 H, s, 2-H), 8.30 (1 H, br. s, NH), and 12.15 (1 H, s, 5-OH, D_2O exchangeable); *m/z* 331 (M^+, 25%), 316 (18), and 260 (100).

8-Acetyl-5,7-dihydroxy-6-methyl-3-propionylamino-1,4-naphthoquinone (74).-

Quinone (72) (70 mg, 0.20 mmol) was dissolved in dry methylene chloride (10 ml). Aluminium trichloride (529 mg, 4 mmol) was added and the solution stirred at room temperature for 52 h. The reaction was quenched by the addition of water, and the organic layer extracted into ethyl acetate. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate-light petroleum) to yield the quinone (74) (55 mg, 87%) as orange needles, m.p. 183 - 184°C (methanol) (Found: C, 60.15; H, 4.5; N, 4.3; M^+, 317.0878. $C_{16}H_{15}NO_6$ requires C, 60.55; H, 4.75; N, 4.4%; *M*, 317.0899); $\nu_{max.}$ 3528 and 3407 (OH), 3325 (NH), 1704 (8 C=O), 1639 (C=O), 1617 and 1581 (C=C) cm^{-1}; δ_H (90 MHz) 1.26 (3 H, t, *J* 8 Hz, $CH_2C\underline{H}_3$), 2.18 (3 H, s, $COCH_3$), 2.37 (3 H, s, $ArCH_3$), 2.54 (2 H, q, *J* 8 Hz, $C\underline{H}_2CH_3$), 7.76 (1 H, s, 2-H), 8.38 (1 H, br. s, NH), 9.20 (1 H, br. s, 7-OH, D_2O exchangeable), and 12.12 (1 H, s, 5-OH, D_2O exchangeable); *m/z* 317 (M^+, 57%), 261 (20), 246 (100), and 233 (20).

REFERENCES

1. For reviews on ansamycin antibiotics see:
   (a) V. Prelog, *Pure Appl. Chem.*, 1963, 7, 551.
   (b) K.L. Rhinehart, Jr., *Acc. Chem. Res.*, 1972, 5, 57.
   (c) P. Sensi, *Pure Appl. Chem.*, 1975, 41, 15.
   (d) K.L. Rhinehart, Jr. and L.S. Shield, *Prog. Chem. Nat. Prod.*, 1976, 33, 231.
   (e) W. Wherli, *Top. Curr. Chem. Org. Nat. Prod.*, 1977, 72, 22.

2. V. Prelog and W. Oppolzer, *Helv. Chim. Acta.*, 1973, 56, 2279.

3. A. Lüttringhaus and H. Gralheer, *Justus Liebigs Ann. Chem.*, 1942, 67, 550.

4. P. Sensi, A.M. Greco, and R. Ballotta, *Antibiot. Ann.*, 1960, 262.

5. (a) W. Oppolzer, V. Prelog, and P.Sensi, *Experientia*, 1960, 16, 412.
   (b) W. Oppolzer and V. Prelog, *Helv. Chim. Acta*, 1973, 56, 2287.

6. M. Brufani, W. Fedeli, G. Giacomello, and A. Vaciago, *Experientia*, 1964, 20, 339.

7. W. Lester, *Ann. Rev. Microbiol.*, 1972, 26, 85.

8. S.M. Kupchan, Y. Komoda, A.R. Branfman, R.G. Dailey, Jr., and V.A. Zimmerly, *J. Am. Chem. Soc.*, 1974, 96, 3706.

9. F. Reusser, *Biochem.*, 1973, 12, 1136.

10. C. de Boer, P.A. Meulman, R.J. Wnuk, and D.H. Peterson, *J. Antibiot.*, 1970, 23, 442.

11. (a) E.J. Corey and T. Hase, *Tetrahedron Lett.*, 1979, 20, 335.
(b) E.J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 20, 2317.
(c) P.A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, 1978, 100, 3950.

12. E.J. Corey and D.A. Clark, *Tetrahedron Lett.*, 1980, 21, 2045.

13. (a) H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M.R. Johnson, and Y. Kishi, *J. Am. Chem. Soc.*, 1980, 102, 7962.
(b) H.Iio, H. Nagaoka, and Y. Kishi, J. Am. Chem. Soc., 1980, 102, 7965.

14. (a) Y. Kishi, *Pure Appl. Chem.*, 1981, 53, 1163.
(b) H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, 37, 3873.

15. For some recent examples directed toward the synthesis of the multichiral chain of rifamycin S see:

(a) S. Masamune, B. Imperiali, and D.S. Garvey, *J. Am. Chem. Soc.*, 1982, 104, 5528.

(b) M. Nakata, H. Enari, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, 1982, 55, 3283.

(c) S. Hannesian, J.R. Pougny, and I.K. Boessenkool, *J. Am. Chem. Soc.*, 1982, 104, 6164.

(d) B. Fraser-Reid, L. Magdzinski, and B. Molino, *J. Am. Chem. Soc.*, 1984, 106, 731.

(e) W.C. Still and J.C. Barrish. *J. Am. Chem. Soc.*, 1983, 105, 2487.

(f) A.V. Rama Roa, J.S. Yadov, and V. Vidyasagar, *J. Am. Chem. Soc., Chem. Commun.*, 1985, 55.

16. For some recent synthetic efforts directed towards naphthoquinonoid nuclei see:

(a) K.A. Parker and J.J. Petraitis, *Tetrahedron Lett.*, 1981, 22, 397.

(b) A.P. Kozikowski, K. Sugiyama, and J.P. Springer, *Tetrahedron Lett.*, 1980, 21, 3257.

(c) H. Nagaoka, G. Schmid, H. Iio, and Y. Kishi, *Tetrahedron Lett.*, 1981, 22, 899.

(d) T.R. Kelly, M. Behforouz, and J. Vaya, *Tetrahedron Lett.*, 1983, 24, 2331.

(e) M.Nakata, S. Wada, K. Tatsuta, and M. Kinoshita, A. Echavarren, *Bull. Chem. Soc. Jpn.*, 1985, 58, 1801.

(f) M. Nakata, M. Kinoshita, S. Ohba, and Y. Saito, *Tetrahedron Lett.*, 1984, 25, 1373.

(g) B.M. Trost and W.H. Pearson, *Tetrahedron Lett.*, 1983, 24, 269.

(h) R.W. Rickards, Proceedings of 5th Asian Symposium on Medicinal Plants and Spices, Seoul, South Korea, August 1984, pp 615 - 624.

17. H.W. Moore and K. Folkers, *J. Am. Chem. Soc.*, 1966, 88, 56.

18. W. Kump and H. Bickel, *Helv. Chim. Acta*, 1973, 56, 2323.

19. E. Martinelli, G.G. Gallo, P. Antonini, and R.J. White, *Tetrahedron*, 1974, 30, 3087.

20. (a) D.W. Cameron, C. Conn, and G.I. Feutrill, *Aust. J. Chem.*, 1981, 34, 1945.

(b) D.W. Cameron, G.I. Feutrill, and P. Perlmutter, *Tetrahedron Lett.*, 1981, 22, 3273.

21. (a) T.H. Chan and P. Brownbridge, *J. Am. Chem. Soc.*, 1980, 102, 3534.

(b) T. Ibuka, Y. Mori, and Y. Inubishi, *Tetrahedron Lett.*, 1976, 17, 3169.

(c) S. Torkelson and C. Ainsworth, *Synthesis*, 1976, 722.

22. G. Anderson, D.W. Cameron, G.I. Feutrill, and R.W. Read, *Tetrahedron Lett.*, 1981, 22, 4347.

23. D.W. Cameron, G.I. Feutrill, P.G. Griffiths, and D.J. Hodder, *J. Chem. Soc., Chem. Commun.*, 1978, 688.

24. J. Savard and P. Brassard, *Tetrahedron Lett.*, 1979, 20, 4911.

25. (a) R.G.F. Giles, S.C. Yorke, I.R. Green, and V.I. Hugo, *J. Chem. Soc., Chem. Commun.*, 1984, 554.
(b) R.G.F. Giles, I.R. Green, M.L. Niven, and S.C. Yorke, *J. Chem. Soc., Perkin Trans. I*, in press.

26. C.B. de Koning, Department of Organic Chemistry, University of Cape Town, Personal Communication.

27. (a) J.D. Roberts and D.Y. Curtin, *J. Am. Chem. Soc.*, 1946, 68, 1658.
(b) K.S. Bhide, R.B. Mujumdar, and A.V. Rama Rao, *Indian J. Chem. (B)*, 1976, 14, 168.
(c) H.D. Locksley and I.G. Murray, *J. Chem. Soc. (C)*, 1970, 392.

28. P. Brassard and J. Banville, *J. Chem. Soc., Perkin Trans. I*, 1976, 1852.

29. (a) T.A. Chorn, R.G.F. Giles, I.R. Green, V.I. Hugo, P.R.K. Mitchell, and S.C. Yorke, *J. Chem. Soc., Perkin Trans. I*, 1984, 1339.
(b) A.J. Birch, D.N. Butler, and J.B. Sidall, *J. Chem. Soc.*, 1964, 2941.

30. C.F. Carvalho and M.V. Sargent, *J. Chem. Soc., Chem. Commun.*, 1984, 227.

31. C.D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 1972, 94, 227.

32. S.J. Tremont and H.U. Rahman, *J. Am. Chem. Soc.*, 1984, 106, 5759.

33. D.D. Perrin, W.F.F. Armarego, and D.R. Perrin, "Purification of Laboratory Chemicals", Second ed., 1980, Pergamon Press, Oxford.

2

AN INVESTIGATION INTO

THE SYNTHESIS OF NAPHTHOPYRANS

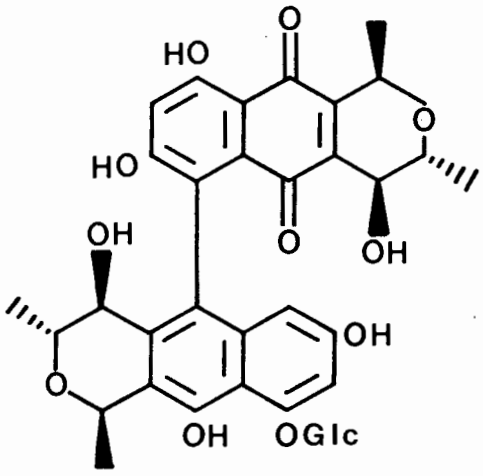
RELATED TO GLUCOSIDE B

2.1 Introduction

A large number of quinones exist in nature.[1] Naphthoquinones form a major part of this family of compounds and have been isolated from such diverse sources as higher plants, fungi, bacteria, lichens, aphids, and echinoderms. A number of these compounds have been shown to possess medicinally important physiological activity.

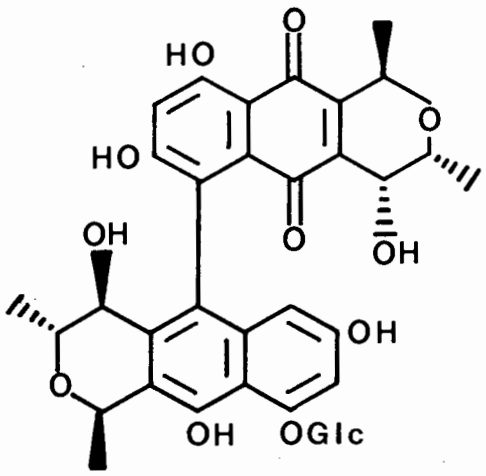
In 1948 Todd[2] reported the existence of a remarkable group of colouring matters called "aphins". These substances occur in the haemolymph of many dark species of *Aphididae*, or are derived from compounds present in the haemolymph.

These aphins, such as (1) to (3),[1,3] have been shown to be binaphthyl derivatives containing two naphtho[2,3-*c*]pyran ring systems, the one as a 5,10-quinone, and the other as a naphthyl glucoside.



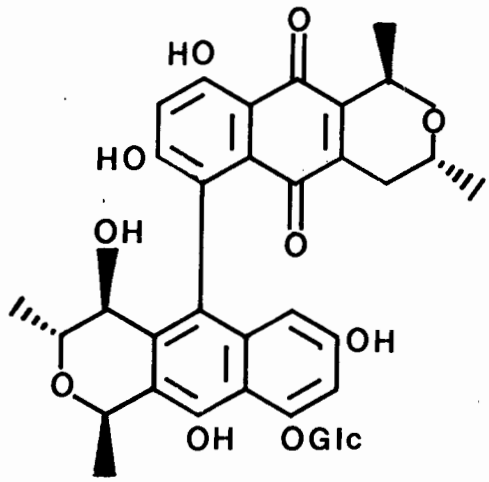
Protoaphin-*fb*

1



Protoaphin-*sl*

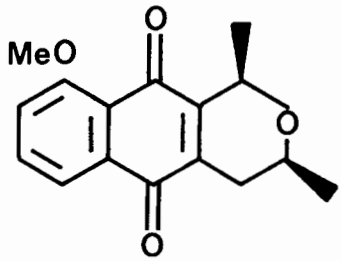
2



Deoxyprotoaphin

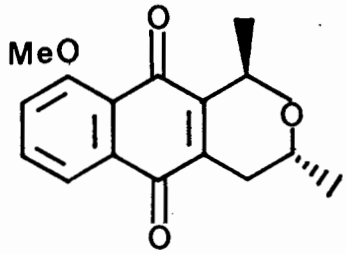
3

Other such quinones containing this naphtho[2,3-*c*]pyran ring system are the eleutherins (4) and (5),[4,5,6] kalafungin (6),[7] and the nanaomycins (7) to (10).[8,9]



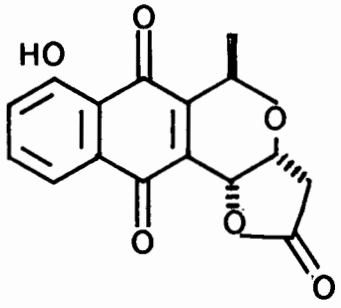
(+)-Eleutherin

4



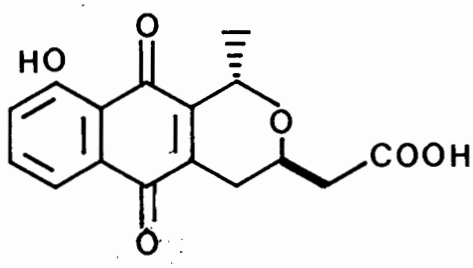
(-)-Eleutherin

5



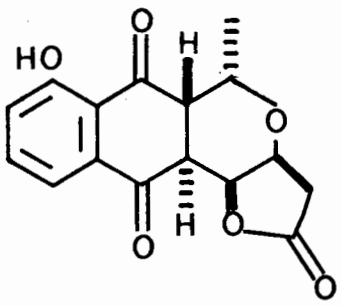
Kalafungin

6



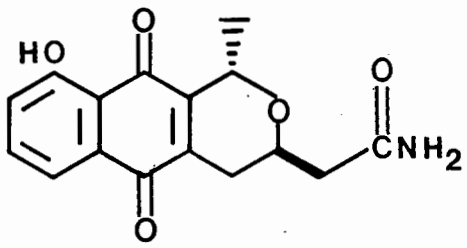
Nanaomycin A

7



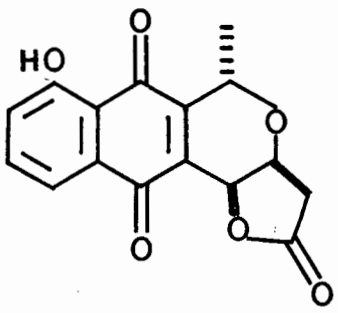
Nanaomycin **B**

8



Nanaomycin C

9

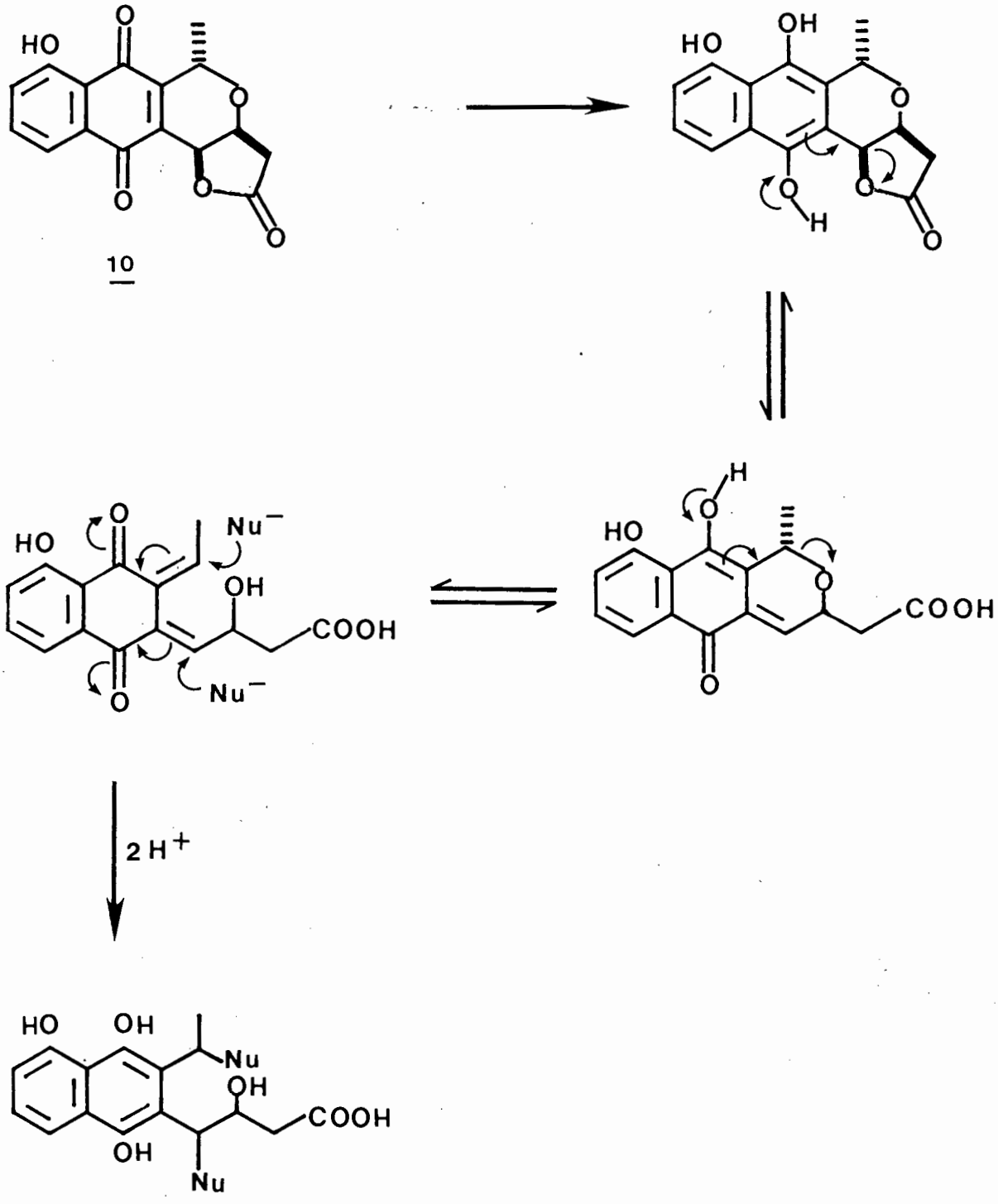


Nanaomycin D

10

As a result of their structural features, these compounds were listed in a review by Moore,[10] as having the potential to behave as bioreductive agents. This process involves the reduction of the molecular species *in vivo* and ring-opening of the derived hydroquinone by the expulsion of a good leaving group which is benzylic to the phenolic system. This generates a quinone methide which, being an α,β-unsaturated carbonyl compound, readily alkylates nucleophiles. Such bioreductive alkylating agents could be expected to possess significant antineoplastic activity.

For example, the antibiotic nanoamycin D contains a fused pyrano-γ-lactone moiety, and thus functions as a dialkylating agent by the mechanism of alkylation outlined in Scheme 1.



SCHEME 1

By the same mechanism of quinone methide formation, the protoaphins (1) to (3), might also be able to act as bio-reductive alkylating agents.

Our extensive knowledge of the protoaphins is due to the investigations of Lord Todd and co-workers in 1948.[2,11] The initial isolation of the protoaphins was difficult due to their lability in biological systems. The water soluble protoaphins which occur in the haemolymph of living aphids, are attacked after the death of the insect, by a specific enzyme system present in them.[2] This converts them sequentially *via* a series of transformations, starting with the hydrolysis of the glucosidic linkage, into a series of related pigments, *viz*. the xanthoaphins, chrysoaphins, and finally the erythroaphins.

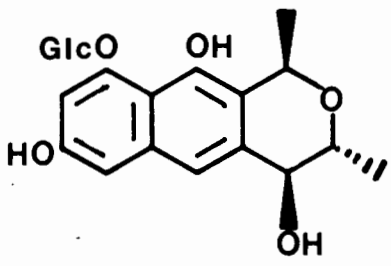
The same changes can be initiated by pigment-free enzyme extract prepared from fresh insects. Whether this enzyme reaction is carried out *in vitro* or *in vivo*, the xantho-aphins, which are unstable, yellow fluorescent, fat-soluble substances, are obtained as the first isolable products. The chrysoaphins are orange, somewhat more stable compounds and can also be obtained from the xanthoaphins by mild acid or alkali treatment. The erythroaphins are the stable, red fluorescent end products of the aphin series. Thus in order to isolate the protoaphins, this enzyme system must be carefully deactivated without damaging the protoaphin. This can be achieved either by use of organic solvents[2] or by heating.[12]

A yellow, acidic, hygroscopic substance, protoaphin-*fb* (1) was isolated from the haemolymph of the broad bean aphid, *Aphis fabae* Scop., whilst a similar stereoisomeric material protoaphin-*sl* (2) was isolated from the brown willow aphid

Tuberolachnus salignus Gmelin. In 1972, Cameron and Banks[13] isolated deoxyprotoaphin (3) from the aphid *Dactynotus cirsii* L., a compound differing from the above two in that it lacked the hydroxy group at the epimeric centre at C-4 of the pyran ring.

On mild reduction, either with neutral sodium dithionite,[14] or by catalytic hydrogenation[15] and aerial re-oxidation, these protoaphins were cleaved to afford in each case an acidic quinone and a naphthalenic glucoside. This systematic simplification brought about by the cleavage of the binaphthyl linkage greatly assisted structural elucidation.

Protoaphin-*fb* (1) and protoaphin-*sl* (2) were found to give the same glucosidic component, glucoside B (11), but two different quinones, namely quinone A (12) and quinone A'(13) respectively. These two quinones are epimeric at C-4. Deoxyprotoaphin (3) similarly gave glucoside B and a quinone, deoxyquinone A (14). Glucoside B has also been found in the bright orange *Aphis nerii*, along with related compounds, principally the yellow pigment neriaphin (15).[16]



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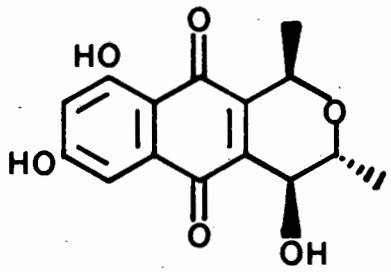

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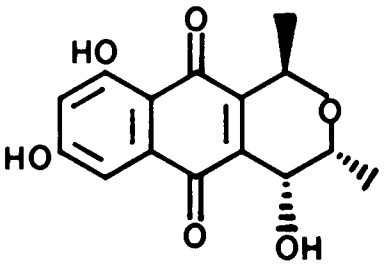

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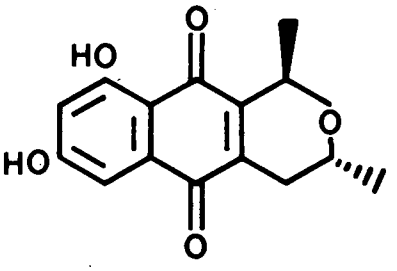

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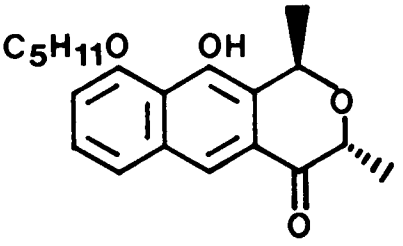

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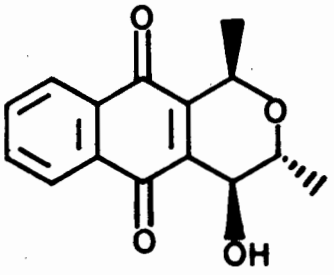
The structures and absolute stereochemistry of these naphthopyrans were formulated by a comparison of the fragments obtained upon various degradations, with known compounds of established stereochemistry, e.g. D,D-(+)-dilactic acid, as well as through detailed analyses of their n.m.r.spectra.[17]

Glucoside B is very susceptible to aerial oxidation even in the solid state and darkens within a few days, while its solution in alkali turns black immediately. Its aglycone is even less stable and has not been obtained other than under nitrogen. The structure of glucoside B was however, confirmed by oxidation with Fremy's salt to quinone A after

loss of the sugar residue.[14] The β-configuration of the glucosyl moiety was confirmed by its facile hydrolysis upon treatment with almond emulsion, known to cleave β-glucosides, whereas α-glucosidases do not effect this cleavage.[18] Reductive removal of the benzylic hydroxy group of quinone A with alkaline sodium stannite gave deoxyquinone A (14).[19]

The *in vitro* linkage of the two halves of the protoaphins has been achieved by Cameron and Chan.[15] When quinone A and glucoside B were left at 80°C in aqueous solution at pH 6.6, an 18% yield of protoaphin-*fb* was obtained. A partial synthesis of protoaphin-*sl* (2) has also been achieved by a similar coupling of quinone A′ and glucoside B.

A synthesis of quinone A, quinone A′, and glucoside B would thus constitute a synthesis of protoaphin-*fb* and protoaphin-*sl*. The synthesis of the racemates of 7,9-dideoxyquinone A (16) and A′ (17), derivatives of the naturally derived quinones (12) and (13), has been successfully undertaken in this Department.[20] The correct stereochemistry about the pyran ring was obtained by use of cerium(IV) ammonium nitrate to effect oxidative cyclisation of the dimethoxynaphthalene (18) into the required products.



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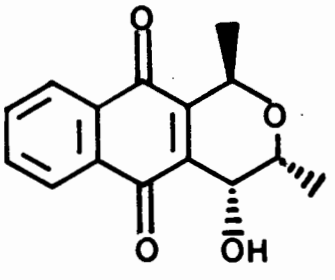

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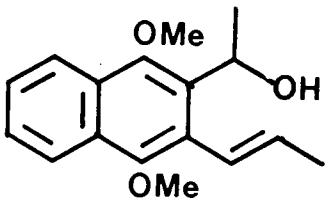

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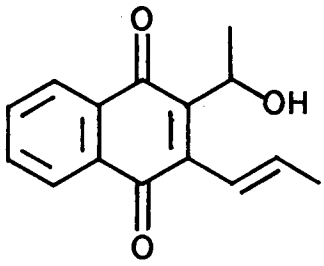

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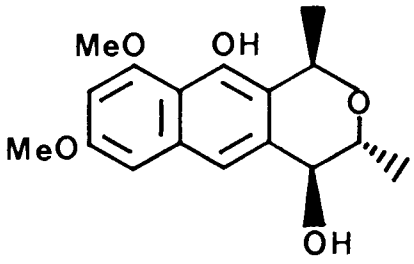
Oxidative demethylation of the alcohol (18) with silver(II) oxide gave the quinonoid alcohol (19) which did not undergo spontaneous cyclisation to afford the naphthopyranquinones. This confirmed that cyclisation to the pyran moiety occurred prior to oxidation to the quinone level.[20]

A synthesis of glucoside B has to date not been reported. This project was thus designed to investigate possible syntheses of a compound possessing a naphtho[2,3-*c*]pyran system, such as the naphthopyran (20), which would function as a model for glucoside B (11).



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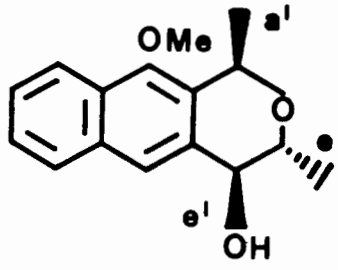
Three different approaches are described in this chapter. Potential routes considered involved fusing the appropriately substituted pyran ring to suitable naphthalenic precursors by synthetic manipulation. In view of the fact that quinone A and glucoside B have the same relative stereochemistry of substituents in the pyran ring, the possibility arose of using the novel reactions pioneered in this Department during the synthesis of 7,9-dideoxyquinone A[21] and the dimethyl ether of quinone A.[22]

The first method to be described, used these reactions to construct a naphtho[2,3-*c*]pyran of the correct relative stereochemistry, with a C-5 oxygen substituent which was subsequently removed. In other words, a synthetic precursor of quinone A derivatives was modified by removal of the C-5 oxygen substituent. The second method involved a similar construction of the pyran ring system but without a C-5 oxygen substituent, and so differs substantially from the first method.

The third approach involved the use of an entirely novel procedure. The key step in this reaction sequence was the isomerisation of a naphthyl substituted dioxolane ring by an intramolecular version of the Mukaiyama reaction.[23] This procedure resulted in the formation of a naphtho[1,2-*c*]pyran with the correct relative stereochemistry as required by glucoside B. However, it is hoped that further research into the application of this method will provide the desired naphtho[2,3-*c*]pyran (20).

2.2 The Synthesis of 4-hydroxy-1,3-dimethyl-10-methoxy-1*H*-naphtho[2,3-*c*]pyran, a Partially Oxygenated Analogue of Glucoside B.

In this present work, a strategy towards the synthesis of a model for glucoside B, the 10-methoxynaphtho[2,3-*c*]pyran (21) was investigated.



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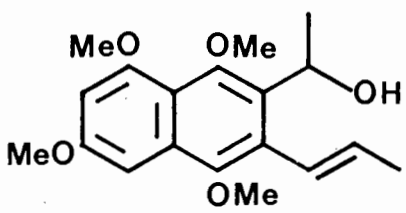
Glucoside B and quinone A have the same stereochemistry of substituents about the pyran ring, where the C-1 and C-3 methyls are *pseudo*-axial and equatorial respectively, and the C-4 hydroxy group is *pseudo*-equatorial in each case. This fact leadsto the possibility of adapting the methods developed in this Department for the synthesis of 7,9-dideoxyquinone A and the dimethyl ether of quinone A, to the synthesis of the glucoside B model. One approach would be to take a synthetic precursor to 7,9-dideoxyquinone A, or a derivative thereof, and remove the C-5 oxygen substituent at some stage to yield the naphthopyran (21).

The synthesis of 7,9-dideoxyquinone A (16) was successfully achieved in this Department by two different methods, both of

which were reported in 1983. The first route[20] to be established involved the oxidative cyclisation of the naphthalene (18) with cerium(IV) ammonium nitrate to afford the quinone A (16) and quinone A'(17) analogues directly. However, an attempted application of this method to the corresponding tetramethoxy derivative (22), in anticipation of it giving rise to the dimethyl ethers of quinone A (23) and quinone A' (24), resulted only in decomposition of starting material.[22] Therefore an alternative method had to be elaborated. This was achieved[21] using two novel reactions consecutively.



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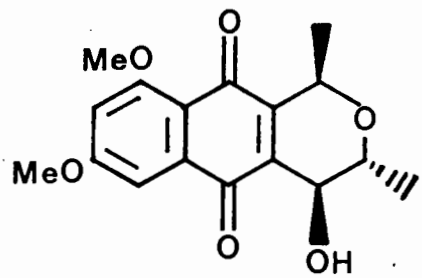

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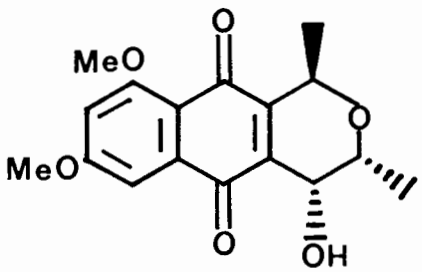

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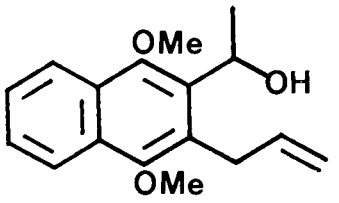
The first reaction involved the cyclisation of alcohol (25) with potassium *t*-butoxide in dimethylformamide under nitrogen to give only the *trans*-dimethylpyran in quantitative yield after five minutes. The structure of this product was assigned by ^{1}H n.m.r. spectroscopy. Longer reaction times resulted in the concurrent formation of the *cis*-dimethylpyran

(27) due to epimerisation of the *trans*-isomer (26) at C-1. It was also noted that the conjugated alkenyl alcohol (18) cyclised to yield compound (26) under the same conditions, the formation of the *cis*-isomer (27) again being observed for longer reaction times.



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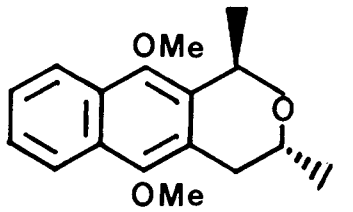

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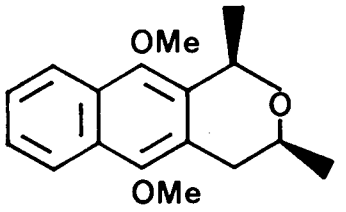
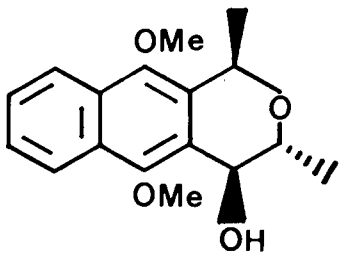


27

Similar treatment of alcohol (25) without the exclusion of air and for longer reaction times, resulted in the formation of the two isomeric alcohols (28) and (29) in the ratio 4:1. These products were identified by ^{1}H n.m.r. spectroscopy. The yields were moderate.



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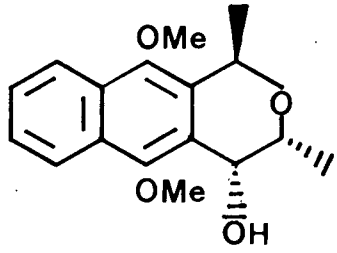

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However, the hydroxynaphthopyrans (28) and (29) were best prepared *via* the *trans*-dimethylpyran (26) by treating this compound with potassium *t*-butoxide in dimethylformamide in the presence of air for two hours. The *cis*-dimethylpyran (27) was also formed, as a result of isomerisation, in a yield of 18%. The yields of the isomeric 4-hydroxy pyrans (28) and (29) under these conditions were 36% and 9% respectively. These yields have been more than doubled by substitution of dimethyl sulphoxide as the reaction solvent.

The naphthopyrans (28) and (29) were oxidised to the quinones (16) and (17) respectively with silver(II) oxide and nitric acid.

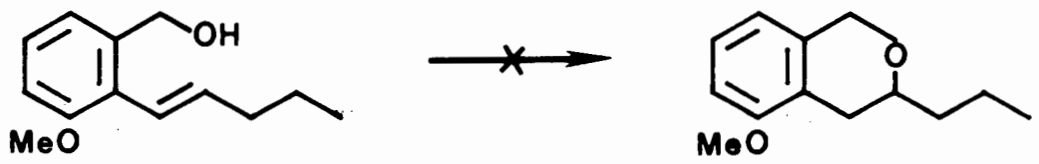
These base-induced cyclisation and oxygenation reactions also worked extremely well on the tetraoxygenated series of naphthalenes, starting with the alcohol (22).[22] This reaction sequence has now lead to the syntheses of the racemates of quinones A and A', as well as deoxyquinone A, in this Department.[24]

No conclusive general mechanisms for these base-promoted reactions have been formulated although tentative explanations have been offered.[21] Other possibilities may be operative and these mechanisms are the subject of current study at the University of Cape Town.

This series of reactions involving base-catalysed cyclisation and oxygenation, was the method of choice in investigating a route to the model for glucoside B, in which a precursor to

quinone A derivatives was to be modified by removal of the C-5 oxygen substituent.

Motivation for removal of the C-5 substituent, after effecting cyclisation of a suitable naphthyl alcohol, was provided by previous investigations into the mechanism of this reaction which have shown that steric effects are of major importance.[25] It has been shown that those alcohols where both the hydroxy alkyl and alkenyl side chains are flanked by methoxy groups cyclise readily and in high yields. For example, alcohol (30) does not undergo cyclisation to give the product (31), whereas the related dimethoxyalcohol (32) cyclises in a yield of 85% to afford the benzopyran (33). On the other hand, alcohol (34) with a methoxy group *ortho* to the hydroxyalcohol function, cyclises in a yield of 25% to give the product (35).



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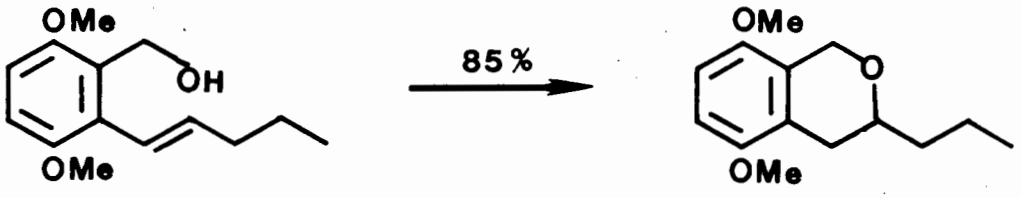

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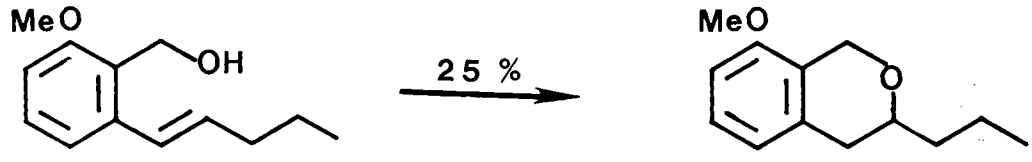


34 35

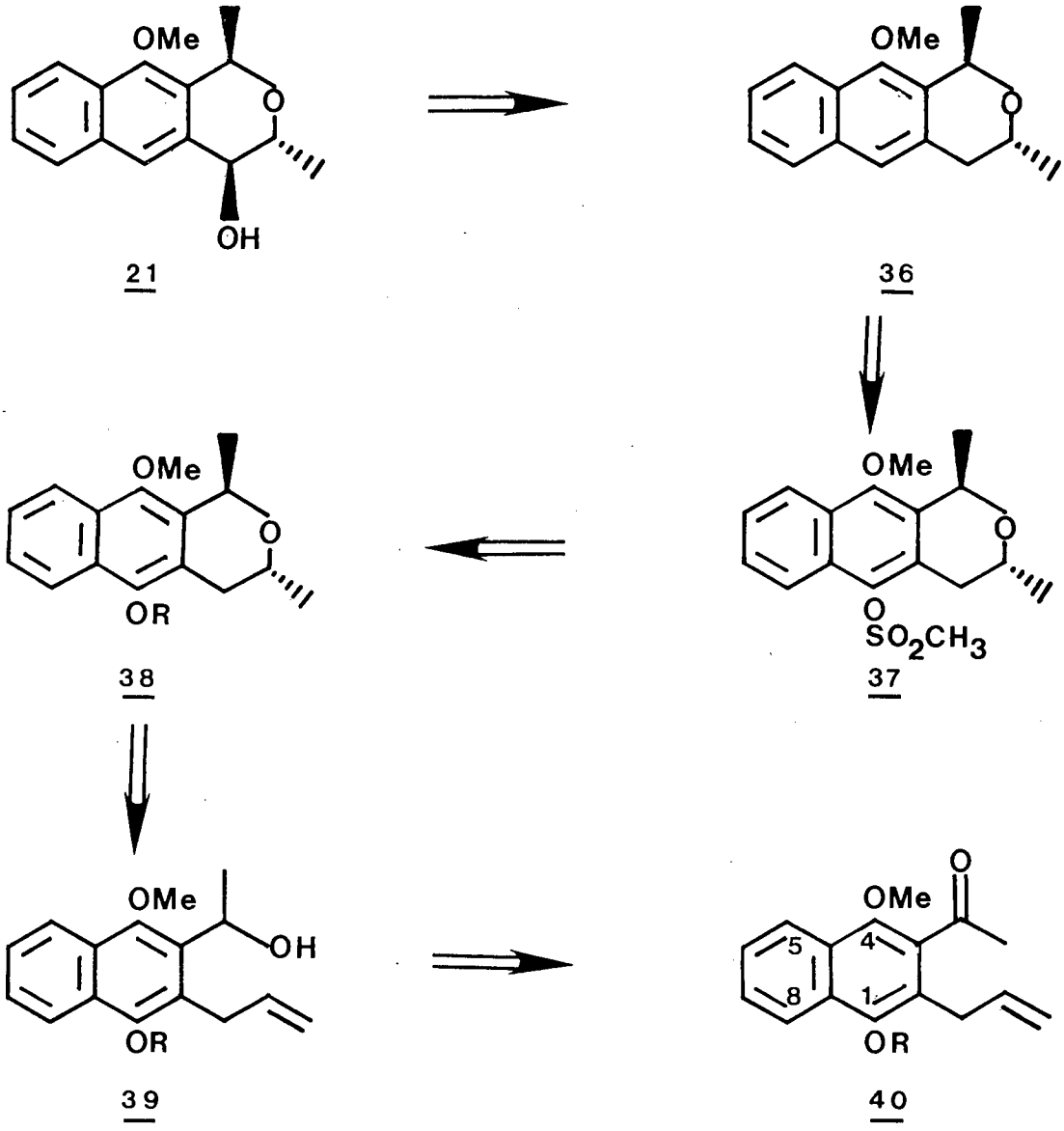
From the above three reactions it can be seen that steric factors obviously play an important role in the cyclisation reaction. Thus, in choosing a suitable naphthalenic alcohol precursor for this project, it was decided that a substituent *ortho* to the alkenyl group was necessary in order for cyclisation to occur in high yield. Furthermore, the nature of this substituent was important, since it would have to be removed after cyclisation had occurred.

The methods available in the literature for replacement of oxygen by hydrogen are limited.[26,27] One of these methods states that phenolic hydroxy groups in general can be removed in the form of their sulphonic esters by catalytic hydrogenation. However, the use of this procedure in this project might introduce difficulties due to the alternative more facile hydrogenolysis of the other two benzyl-oxygen bonds, *viz.* the C-1 to oxygen bond of the pyran ring, and the carbon-oxygen bond of the C-4 hydroxy group, particularly in view of the considerable strength of an aromatic oxygen bond.

For this reason, it was decided to C-4 hydroxylate the naphthopyran after removal of the C-5 phenolic group. However, since the precise structural requirements for this

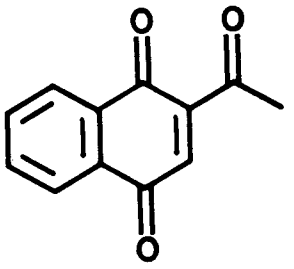
reaction have not yet been explored, it was by no means certain that such a reaction would take place without the presence of the C-5 alkoxy substituent.

Taking cognisance of the above considerations, a retro-synthetic analysis of the model (21) would be as shown in Scheme 2.



SCHEME 2

The first step was to choose a suitable protecting group R. The ketonic naphthalene (40 : R=Me) is known and is made in good yield *via* allylation of quinone (41) using allyltrimethylstannane and borontrifluoride-diethyl ether.[21,28] However, a methoxy group at C-4* would not be suitable, as it is not easily preferentially removed in order to substitute it with the required sulphonic ester group.

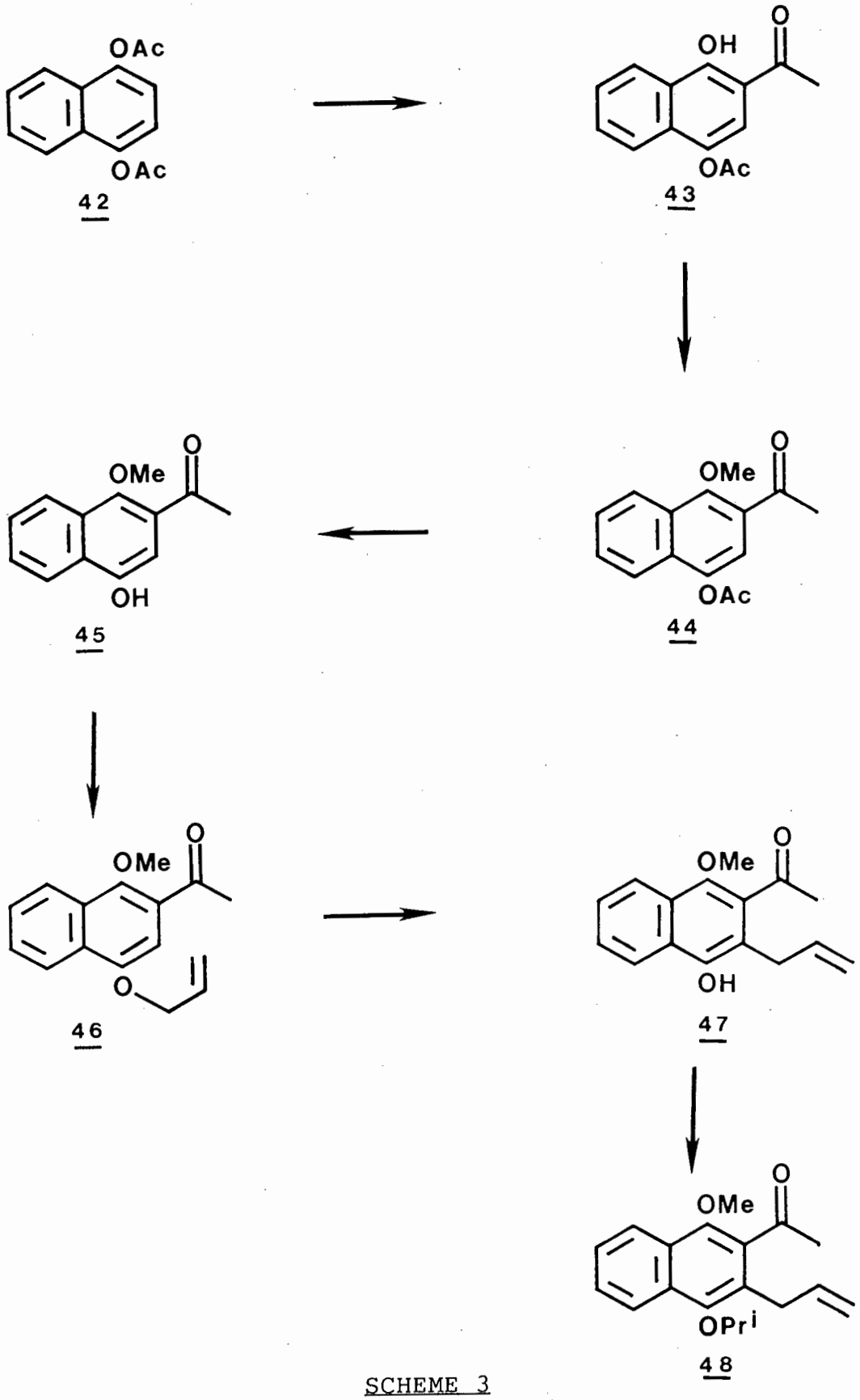


41

It was decided to use an isopropyl protecting group as this is cleaved before a methyl group by boron trichloride.[29] Naphthalene (48) with the required substituents, could be derived from 1,4-diacetoxynaphthalene (42)[30] (Scheme 3).

1,4-Diacetoxynaphthalene (42) underwent a Fries rearrangement upon heating with zinc chloride in acetic anhydride to give the naphthol (43).[31] Naphthol (43) was smoothly methylated in dry acetone with dimethyl sulphate and potassium carbonate to give the methyl ether (44) in a yield of 84%. The ^{1}H n.m.r. spectrum of this compound showed a singlet at δ 3.99 for the methoxy protons.

* For purposes of consistency, this numbering system will be used for all naphthalenes discussed in this chapter.


OAc
OAc
42
OH
O
OAc
43
OMe
O
OAc
44
OMe
O
OH
45
OMe
O
O
46
OMe
O
OH
47
OMe
O
OPr^{i}
48

SCHEME 3

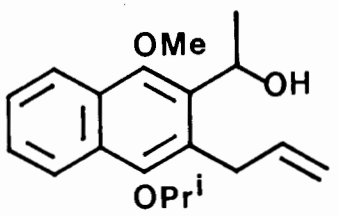
Treatment of naphthalene (44) with a 1% methanolic potassium hydroxide solution cleaved the acetoxy group to afford the naphthol (45) as indicated by the disappearance of the acetyl singlet at δ 2.45 of the ^{1}H n.m.r. spectrum. The signal at δ 2.82 is due to the C-3 acetyl remaining in the product. The infrared spectrum showed only one carbonyl absorption band at 1652 cm^{-1}, the band at 1756 cm^{-1} having disappeared.

Naphthol (45) was allylated by boiling in dry acetone in the presence of allyl bromide and potassium carbonate. The *O*-allyl ether (46) was obtained as confirmed by the ^{1}H n.m.r. spectrum which no longer showed the hydroxy signal at δ 7.41. The methylene protons resonated as a broad doublet (J 5 Hz) at δ 4.72, and the aromatic proton 2-H appeared as a singlet at δ 7.04. The mass spectrum showed the molecular ion at m/z 256.

This naphthyl ether (46) readily underwent a Claisen rearrangement when heated under nitrogen at 160°C to afford the tetrasubstituted naphthol (47) in excellent yield (87%). The ^{1}H n.m.r. spectrum showed that the methylene protons of the allyl group had shifted to δ 3.42, consistent with the transfer of allyl from oxygen to carbon. The hydroxy group appeared as a broad singlet at δ 5.60.

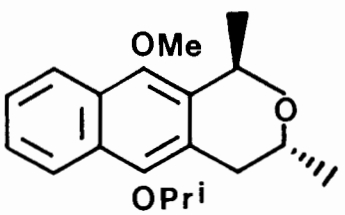
Naphthol(47) was found to be extremely unstable, darkening considerably upon standing, both as a neat oil and in a solvent. It was thus treated immediately upon formation with isopropyl bromide and potassium carbonate in dry dimethyl-

formamide to give the naphthalenic ketone (48). This ketone was easily reduced with lithium aluminium hydride to give the alcohol (49). The infrared spectrum of this alcohol showed an absorption band at 3429 cm^{-1} for the hydroxy group, while in the ^1H n.m.r. spectrum, the acetyl signal of the ketone (48) was replaced in alcohol (49) by the appropriate signals for the new 1-hydroxyethyl group.



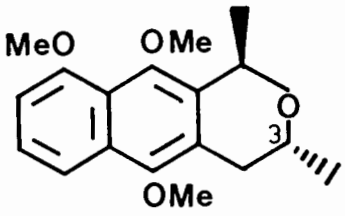
49

The next step in the reaction sequence was the base-promoted cyclisation of alcohol (49) to yield the required *trans*-dimethylpyran (50). Thus, alcohol (49) was treated with a six molar excess of potassium *t*-butoxide in dry dimethylformamide at room temperature. Nitrogen was continuously passed over the surface of the solution in order to exclude air from the reaction. The reaction was monitored by t.l.c., which showed that after twenty minutes all starting material had been consumed and a single product formed.



50

^{1}H n.m.r. spectroscopy showed the product to be the *trans*-dimethylpyran (50) as expected. Identification of the stereochemistry of this compound was based upon reported data for the pyrans (51) to (54).[21] The 3-H multiplets for the *trans*-isomers (51) and (52) appear at δ 3.9 - 4.3, while those of the *cis*-isomers (53) and (54) appear in the range δ 3.5 - 3.8. The chemical shifts of the 1-H quartets also differ, those for the *trans*-compounds appearing at *ca.* δ 5.3 while those for the *cis*-compounds occur at *ca.* δ 5.2.



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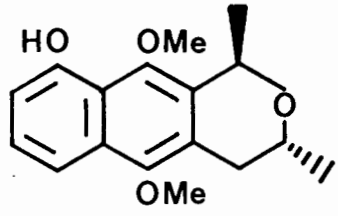

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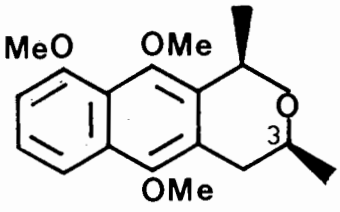

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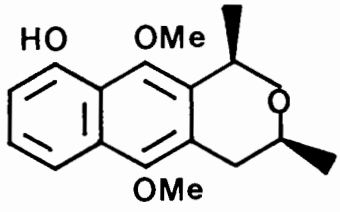


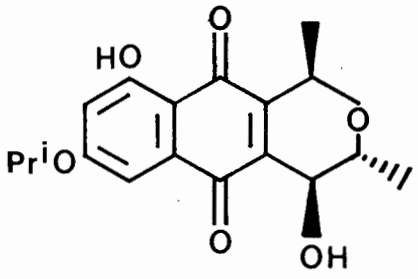
54

The ^{1}H n.m.r. spectrum of naphthopyran (50) showed the 3-H multiplet at δ 3.8 - 4.3 and the 1-H quartet (J 8 Hz) appeared at δ 5.32, confirming the structural assignment. Thus, having obtained the naphthopyran ring system with the correct relative stereochemistry of the methyl substituents

at C-1 and C-3, the isopropyl group at C-5 had to be replaced with a methanesulphonyl group in order to facilitate removal of the oxygen substituent at this position.

The naphthopyran (50) was treated with the Lewis acid boron trichloride at -78°C. However, the isopropyl group could not be removed, even with a large excess of boron trichloride, or by performing the reaction at higher temperatures.

While this project was progressing, a similar problem was experienced in this Department in that the naphthoquinone (55) was found to be resistant to deisopropylation, thereby not yielding racemic quinone A (12).[24] This problem was readily solved by removal of isopropyl from compound (56), a precursor of quinone (55), together with the methyl on oxygen *ortho* to the acetyl group. The derived phenolic groups were subsequently benzylated, leading ultimately to the conversion of naphthalene (56) to the desired quinones (12), (13), and (14).



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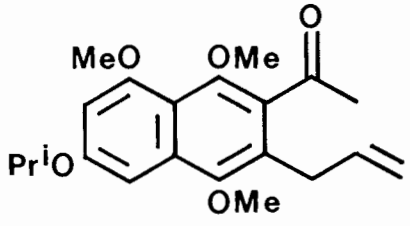
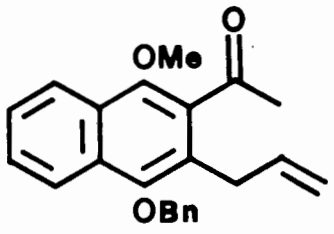


56

The result presently being described, together with those found for compounds (55) and (56), shows that the use of

isopropyl as a protecting group on aromatic oxygens can lead to varying degrees of success in synthesis.

It was therefore decided to benzylate the naphthol (47), as this protecting group was considered easier to remove. The benzyl ether (57) was readily obtained by treatment of naphthol (47) with benzyl bromide and potassium carbonate in dry acetone. The mass spectrum showed the molecular ion at *m/z* 346, corresponding to the expected mass of the product.

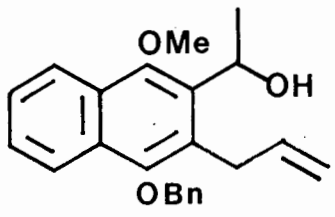


57

It is worthy of note, that in making compounds (48) and (57), both of which have fully substituted aromatic rings, the acetyl carbonyl absorption is increased to about 1700 cm^{-1}, from a value of approximately 1670 cm^{-1} in the trisubstituted naphthalenes such as (44) and (46). This increase is no doubt due to steric compression in the fully substituted ring which causes the acetyl to twist somewhat out of coplanarity with the aromatic system. The corresponding value reported for the dimethyl ether (methyl in place of isopropyl or benzyl) is reported at 1709 cm^{-1}, reflecting a similar situation, in spite of the fact that a smaller protecting group was used. A related observation in the synthesis of an ansamycin nucleus was reported earlier in this thesis (p 14), where the crowded acetyl at C-8 in structure (28) showed an infrared

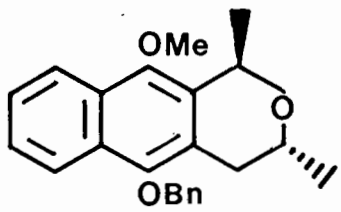
absorption at 1703 cm^{-1}. X-ray crystallographic analysis showed the acetyl in that case to be virtually orthogonal to the naphthalene ring.

The benzyl ether (57) was then reduced with lithium aluminium hydride to afford the corresponding alcohol (58). Evidence for the formation of this product was the appearance of an absorption band at 3375 cm^{-1} for the hydroxy group, coinciding with the disappearance of the carbonyl absorption band at 1700 cm^{-1}.



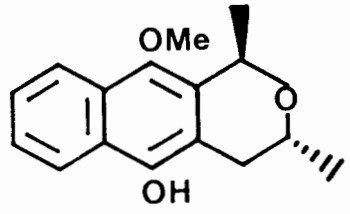
58

As with the isopropyl alcohol (49), compound (58) was treated with potassium *t*-butoxide in dry dimethylformamide under nitrogen. One product (72%) was obtained, which was shown by the ^1H n.m.r. spectrum to be the *trans*-isomer (59). The characteristic signals were the 3-H multiplet which appeared at δ 4.0 - 4.2, and the 1-H quartet at δ 5.34.



59

Removal of the benzyl group was achieved by treatment of compound (59) with two molar equivalents of boron trichloride at -78°C. This resulted in the formation of naphthol (60) which was found to be very unstable in air. Naphthol (60) was thus converted directly into the methanesulphonate ester (37) through reaction with methanesulphonyl chloride and pyridine. The ^1H n.m.r. spectrum of this product showed a new methyl singlet at δ 3.38 for the methanesulphonyl group, and the infrared spectrum displayed two absorption bands at 1559 and 1167 cm^{-1}, characteristic for this substituent.



60

In spite of difficulties anticipated with the preferential hydrogenolysis of the C-1 to oxygen bond of this 5-methanesulphonate (37), it was treated with 5% palladium-on-carbon in methanol containing triethylamine under hydrogen. However, no cleavage product was obtained, starting material being recovered quantitatively.

It has been noted that the fission of aryl sulphonates can also be achieved by the use of an excess of Raney nickel catalyst.[32] Thus, compound (37) was boiled with an excess of Raney nickel catalyst in aqueous ethanol, and after two hours a single product was obtained in the very reasonable yield of

65%. The ^{1}H n.m.r. spectrum of this compound showed clearly that it was still a naphthopyran and that the pyran ring had not been cleaved. The methyl singlet of the methanesulphonyl substituent had disappeared and a singlet for 5-H appeared at δ 7.38. The 3-H multiplet appeared at δ 3.98 - 4.36 and the 1-H quartet was at δ 5.34, the regions expected for *trans*-dimethylnaphtho[2,3-*c*]pyrans. The product thus had the expected structure (36).[21] This was further confirmed by the mass spectrum, which showed a molecular ion at *m/z* 242.

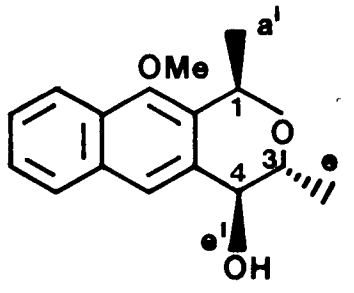
The remaining step in the synthesis of target molecule (21) was the C-4 hydroxylation of the *trans*-dimethylpyran (36). This compound was therefore treated with potassium *t*-butoxide in oxygenated dry dimethyl sulphoxide at room temperature. Dry air was continuously passed through the solution. After fifteen minutes a single product was obtained.

The product was clearly a hydroxylated naphthopyran, as suggested by the infrared spectrum which showed an absorption band at 3410 cm^{-1}. The molecular ion apppeared at *m/z* 258 in the mass spectrum.

The stereochemistry of the hydroxylated product was easily confirmed by ^{1}H n.m.r. spectroscopy. The spectrum showed *inter alia* three one-proton signals, namely a doublet of quartets at δ 3.98 (*J* 8 and 7 Hz), a doublet at δ 4.49 (*J* 5 Hz), and a quartet at δ 5.28 (*J* 7 Hz), due to 3-H, 4-H, and 1-H respectively. Upon washing with deuterium oxide the coupling constant of the doublet at δ 4.49 increased to 8 Hz. The aromatic proton appeared at δ 7.84. The large coupling

constant between 3-H and 4-H indicates a large dihedral angle between them, hence implying an arrangement close to *trans*-diaxial between these two protons. The C-3 methyl and C-4 hydroxy groups will thus be equatorial and *pseudo*-equatorial respectively, based on the reasonable assumption that the preferred configuration of the bulkier group at C-3 will be equatorial. The C-1 methyl would remain *pseudo*-axial in order to minimise *peri*-interactions with the neighbouring methoxy group.

The product was thus assigned the structure of the target molecule (21), with the correct stereochemistry of the pyran ring as required by glucoside B. This series of experiments therefore strongly suggests that the naphthopyran ring system of glucoside B can be synthesised by a route of this type, provided that the addition of oxygen substituents in the terminal ring does not affect the hydroxylation procedure.



21

The success of the final oxygenation step in this project may help in determining the mechanism of this important reaction. It is of particular note that when the naphthopyran ring system to be oxygenated at C-4 carries a substituent at C-5

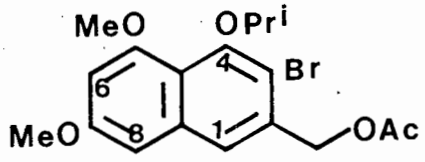
(in all experiments investigated in this Department so far, this substituent has been methoxy), two C-4 alcohols were derived. The major product was the *pseudo*-equatorial alcohol (e.g. (28) from (26)) and the minor product the epimeric *pseudo*-axial alcohol (e.g.(29) from (26)). On the other hand, in the conversion of naphthopyran (36) to the alcohol (21) in this project, only the *pseudo*-equatorial epimer (21) was obtained. This would seem to suggest that the *peri*-methoxy substituent at C-5 in previous cases provided some steric hindrance, leading to the formation of some *pseudo*-axial substitution where interaction with the methoxy group is minimised. Removal of the methoxy substituent at C-5 also removed the *peri*-interactions, giving rise entirely to the *pseudo*-equatorial alcohol as that with the preferred configuration.

These findings made the oxygenation reaction extremely useful in that the synthesis of quinone A (12) and A' (13), when oxygen is present at C-5, both epimers are produced, enabling the ultimate assembly of both these quinones. On the other hand, in the formation of the glucoside B model, the only configuration observed was that found in the naturally derived glucoside. These observations in the synthetic pathway may assist in the rationalisation of the biosynthesis of the protoaphins, in which parallel observations are found on the stereoselectivity of the alcohol function at C-4 in both the quinone and the glucoside moieties.

2.3 The Synthesis of 4-hydroxy-7,9-dimethoxy-1,3 dimethyl-10-(2-propyloxy)-1*H*-naphtho[2,3-*c*]pyran, a Fully Oxygenated Analogue of Glucoside B.

In view of the successful synthesis of the 7,9-dideoxy glucoside B analogue (21) using the series of base-promoted cyclisation and oxygenation reactions pioneered in this Department,[21,22] it was decided to devise an alternative synthesis of a model with the correct oxygenation pattern as required by glucoside B, using the same methodology for the construction of the substituted pyran ring. In the previous synthesis described, the approach used was to take a precursor of a derivative of quinone A and modify it by removal of the oxygen substituent at C-5 as the mesylate derivative by hydrogenolysis with Raney nickel catalyst. However, in the synthesis to be described in this section, it was planned to construct the pyran ring without a C-5 oxygen substituent, hence eliminating the need to remove this group at a later stage.

Thus a suitable hydroxyalkenylnaphthalene, with oxygen substituents at carbons 4, 5, and 7 was needed. A potential starting material was presented in the form of the naphthalene (61), which had been synthesised in this Department[33] for another purpose.

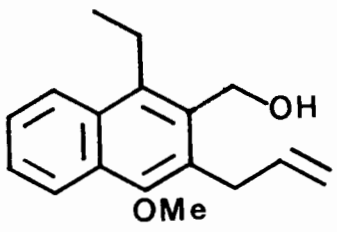


61

This compound had the required oxygenation pattern, as well as being unsubstituted at C-1 of the naphthalene nucleus, this being the carbon atom which would become C-5 of the target naphthopyran.

Compound (61) possesses a number of useful features. First, the presence of bromine at C-3 offers the possibility of activating the naphthalene unit as an aryl lithium species, subsequent reaction of which with acetaldehyde would yield the required hydroxyethyl group in this position. Secondly, the acetoxymethyl group at C-2 can be elaborated to an aldehyde, through which an olefinic function could be introduced *via* a Wittig reaction with ethyltriphenylphosphonium bromide. Both conjugated and non-conjugated *ortho*-propenyl naphthyl alcohols have been shown to ring close giving a *trans*-dimethylpyran as the major product.[21,22]

Furthermore, the stereochemistry of the resultant olefin would be immaterial, since independent work done in this Department[34] found that when the *ortho*-allyl hydroxyalkylnaphthalene (62) was cyclised to afford the naphthopyran (63), work-up of the reaction mixture prior to completion of the reaction showed the non-cyclised material to consist of a mixture of the *E*- and *Z*-olefins (64).



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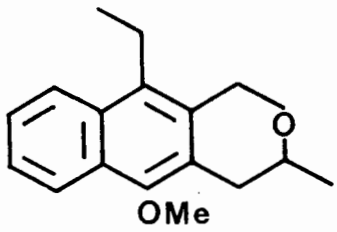

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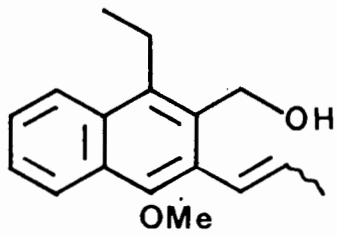
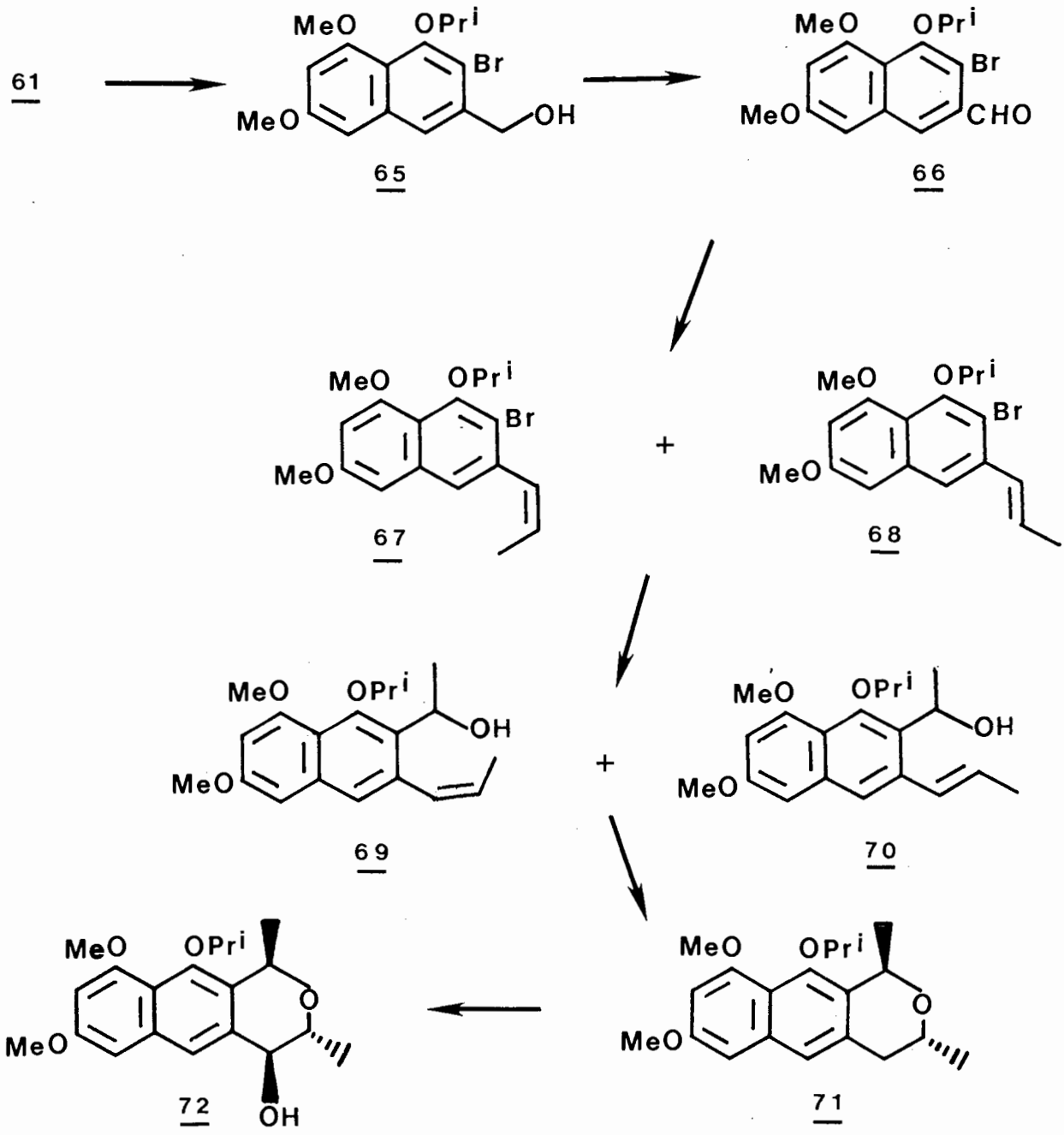


64

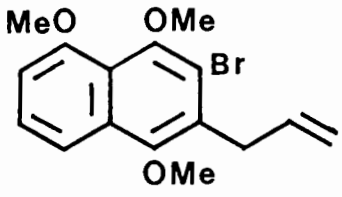
When this mixture of olefins was resubjected to the base-induced cyclisation reaction, it was entirely converted into the naphthopyran (63).

Using the 3-bromo-acetate (61) as the starting material, the planned reaction sequence is as presented in Scheme 4.



SCHEME 4

It was decided to introduce the alkenyl side chain at C-2 prior to the hydroxyethyl group at C-3, since a precedent for this was provided by Yoshii *et al.*[35] in their synthesis of nanaomycin A (7). In that reaction sequence, the trimethoxy-naphthalene (73) was reacted with *n*-butyl lithium followed by acetaldehyde to give the naphthylcarbinol (74).



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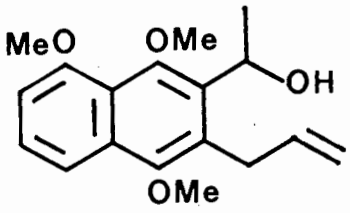


74

It was thought that the proposed base-induced ring closure of the naphthylcarbinols (69) and (70), to afford the *trans*-dimethylpyran (71), might proceed in low yield since there is no substituent *ortho* to the alkenyl side chain.[34] As mentioned earlier, (p 80), those alcohols where both the hydroxyalkyl and alkenyl side chains are flanked by methoxy groups, such as the benzyl alcohol (32), cyclise readily and in high yields. On the other hand, the benzyl alcohols (30) and (34) gave respectively no pyran and pyran in low yield. The compounds (69) and (70) to be cyclised in this project, would be structurally analogous to the latter compound (34), without a substituent *ortho* to the alkenyl group, and might well also give a low yield on cyclisation under the basic conditions.

However, no ring closures of naphthopyrans of type (30) or (34) have been attempted with alkoxy substituents other than methoxy. It is therefore possible that in the intended cyclisation of the naphthalenes (69) and (70) to naphthopyran (71), the isopropoxy group at C-4 may exert a greater steric effect than a methoxy group, and thereby compensate to some extent for the lack of a C-1 substituent *ortho* to the alkenyl group.

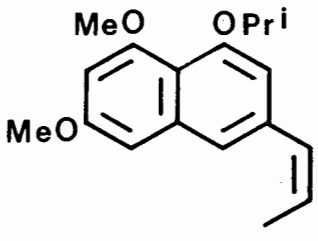
The project described in Chapter 2.2 showed that the oxygenation reaction proceeds well in spite of the lack of the C-5 oxygen substituent. Provided therefore, that the addition of the oxygen substituents on the terminal ring of the naphthalene nucleus does not affect this reaction, the oxygenation of the naphthopyran (71) to the target molecule (72) should proceed without any problems.

Acetate (61) was treated with a 1% w/v solution of potassium hydroxide in methanol to give the the alcohol (65), as evidenced by the loss of the acetyl singlet at δ 2.16 in the ^{1}H n.m.r spectrum. This was accompanied by the appearance of a broad singlet at δ 2.43 for the hydroxy group. The mass spectrum showed a pair of molecular ion peaks at *m/z* 356 and 354 as expected for the bromine-containing product.

The alcohol (65) was boiled with activated manganese dioxide in benzene to produce the aldehyde (66) in a yield of 88%. The infrared spectrum of this product showed an absorption band at 1681 cm^{-1} due to the aldehyde carbonyl group. The ^{1}H n.m.r. spectrum showed the aldehydic proton at δ 10.50.

A Wittig reaction between aldehyde (66) and ethyltriphenylphosphonium bromide was carried out in dry tetrahydrofuran. The ^{1}H n.m.r. spectrum of the product after chromatography to remove the triphenylphosphine oxide, indicated that a stereochemical mixture of the *Z*-olefin (67) and *E*-olefin (68) had been formed in a ratio of 1:2. The spectrum showed a doublet of doublets at δ 1.85 (*J* 6.8 and 1.7 Hz) coupled to a doublet of quartets at δ 5.91 (*J* 11.4 and 6.8 Hz) indicating the presence of the *Z*-olefin (67). The presence of a doublet of doublets at δ 1.94 (*J* 6.7 and 1.7 Hz) coupled to a doublet of quartets at δ 6.24 (*J* 15.5 and 6.7 Hz) showed the presence of the *E*-olefin (68). The accepted coupling constant for a pair of *Z*-protons is in the range 7 - 12 Hz, whereas the range for a pair of *E*-olefinic protons is 13 - 18 Hz.[36]

Earlier research done in this Department has established a method for the conversion of isomeric alkenes into a single stereoisomer.[33] In this work, a transition metal catalyst, palladiumdichloride-bisacetonitrile, was used to isomerise the *Z*-component of a mixture of *Z*- and *E*-olefins (75) and (76) respectively, to afford solely the *E*-olefin (76) in very good yield.



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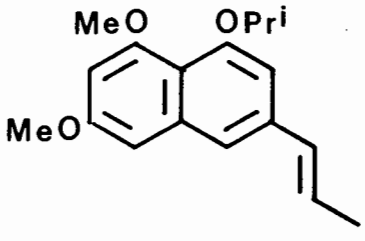


76

Although for the purposes of this project, a stereochemically pure olefin was not essential, it was nevertheless decided to isomerise the mixture of olefins (67) and (68) in order to report the less complex n.m.r spectral data of a pure stereoisomer. This mixture was therefore treated with the palladium(II) catalyst in methylene chloride for three hours to yield the pure *E*-olefin (68). The ^{1}H n.m.r. spectrum of the product showed the disappearance of signals due to the *Z*-olefin (67).

The stereochemically pure *E*-olefin (68) was treated with *n*-butyl lithium and subsequently with acetaldehyde to yield two products. The minor product, (10%), was identified by comparison with the ^{1}H n.m.r. and infrared spectra of the unbrominated *E*-olefin (76) mentioned previously,[33] and this comparison showed these compounds to be identical.

The major product (58%) was the required naphthylcarbinol (70) with *E*-stereochemistry. The ^{1}H n.m.r. spectrum showed a doublet at δ 1.58 (*J* 6.8 Hz) coupled to a quartet (*J* 6.8 Hz) at δ 5.76, confirming the addition of the hydroxyethyl substituent. The coupling constant between the olefinic protons was 15.5 Hz. The mass spectrum showed the presence of a molecular ion at *m/z* 330. Furthermore, the characteristic pattern of a compound possessing a bromine atom was no longer displayed. The infrared spectrum showed a broad absorption band at 3419 cm^{-1} due to the hydroxy group.

The naphthalene (70) was heated at 75°C with a large excess of potassium *t*-butoxide in dimethylformamide under nitrogen.

A single product was obtained after two hours. The molecular ion in the mass spectrum of the product showed it to be isomeric with the starting material (70). This product was identified by inspection of the ^{1}H n.m.r. spectrum as the *trans*-dimethylpyran (71). This spectrum showed *inter alia* two three-proton doublets at δ 1.30 and 1.55 for the C-3 and C-1 methyl groups respectively, a multiplet for 3-H in the range δ 4.01 - 4.20 and the 1-H quartet at δ 5.34. These values are entirely consistent with the ranges specified for the *trans*-dimethylpyrans (51) and (52).[21] The 4-H *pseudo*-axial and *pseudo*-equatorial protons appeared as a multiplet at δ 2.72 - 2.84.

The yield of this product was 83%, which was significantly higher than expected, considering the fact that there was no substituent *ortho* to the alkenyl group of naphthalene (70). Presumably the isopropoxy group at C-4 of naphthalene (70) exerts a considerable steric effect, large enough to bring the alkenyl and hydroxyalkyl groups into close proximity as required for ring closure to occur, thereby increasing the yield. However, other factors may also be operating in view of the structural differences between naphthalene (70) and the monocyclic compound (34).

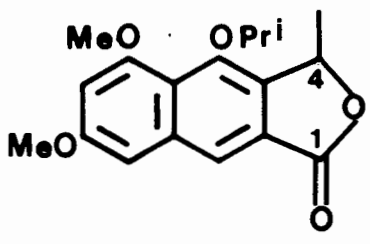
As mentioned earlier, it was anticipated that a stereochemically pure naphthylcarbinol was not necessary for the success of the cyclisation step. This was confirmed when a mixture of the *Z*-and *E*-naphthylcarbinols (69) and (70), obtained by reaction of a mixture of the corresponding bromonaphthyl olefins (67) and (68) with *n*-butyl lithium and

acetaldehyde, gave solely the *trans*-dimethylpyran (71) upon treatment with potassium *t*-butoxide in dimethylformamide. The yield of this reaction was 83%.

The remaining step in the planned reaction sequence was the introduction of the hydroxyl group in the *pseudo*-equatorial configuration at C-4 of the pyran ring to yield the target molecule (72), an analogue of glucoside B.

The pyran (71) was treated with potassium *t*-butoxide in dry dimethyl sulphoxide at room temperature with oxygen bubbling through the solution. After two hours, the reaction was quenched and the mixture yielded two products, together with starting material (30%).

The major product, (30%), a bright fluorescent compound by t.l.c., was identified by ^{1}H n.m.r. spectroscopy as the lactone (77). The relevant signals indicating the presence of a lactone ring were a three-proton doublet (J 6.6 Hz) at δ 1.74, coupled to a one-proton quartet (J 6.6 Hz) at δ 5.71. The infrared spectrum showed a carbonyl absorption at 1757 cm^{-1}, typical for a γ-lactone. The molecular ion in the mass spectrum of this product appeared at m/z 316.



77

The mass spectrum of the minor product, (20%), showed the molecular ion at *m/z* 346 and the infrared spectrum showed a broad hydroxy absorption band at 3413 cm^{-1}. These facts suggested that this product was the C-4 hydroxylated naphthalene (72).

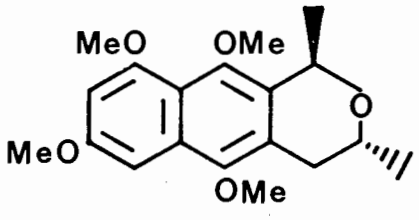
Further confirmation for the formation of the naphthopyran (72), was provided by the ^1H n.m.r. spectrum which showed *inter alia* two three-proton doublets at δ 1.37 (*J* 6.1 Hz) and 1.63 (*J* 6.5 Hz) and a one-proton quartet at δ 5.27 (*J* 6.5 Hz). A broad singlet was noted at δ 4.45. This singlet became a doublet of coupling constant 7.8 Hz upon deuterium oxide exchange. These signals were due to the C-3 and C-1 methyls, 1-H and 4-H respectively. The doublet of quartets for 3-H was partially obscured by the methoxy signals in the spectrum. The doublet at δ 1.37 was ascribed to the C-3 methyl, as irradiation of the 3-H multiplet effected its collapse. Two further three-proton doublets were observed at δ 1.07 and 1.44 (*J* 6.1 Hz). These signals were assigned to the isopropyl methyls as irradiation of the isopropyl methine septet at δ 4.35 caused their collapse.

The stereochemistry of the pyran ring was determined as follows. The large coupling constant between 3-H and 4-H (7.8 Hz) clearly indicates the large dihedral angle between these protons. This large dihedral angle requires that 3-H and 4-H must be axial and *pseudo*-axial respectively. The former follows since the C-3 methyl will retain the less crowded equatorial configuration. The C-4 hydroxy group in pyran (72) is therefore *pseudo*-equatorial. The C-1 methyl

would remain *pseudo*-axial in order to minimise *peri*-interactions with the neighbouring isopropoxy group.

When the temperature of this reaction was raised to 45°C, the pyran (71) was completely converted to the lactone (77). The formation of lactone (77) was unexpected since this C-4 oxygenation reaction had been successfully performed on a number of related systems, including the dimethoxy, tetramethoxy, and dibenzyloxy dimethoxy compounds (26), (78), and (79) respectively. These conversions were undertaken in dimethyl sulphoxide which gave high combined yields of the two possible products of C-4 hydroxylation (the *pseudo*-equatorial isomer predominating in each case).

In addition, the naphthopyran (36) without a C-5 oxygen substituent, was successfully hydroxylated at C-4 to give the product (21) in good yield.



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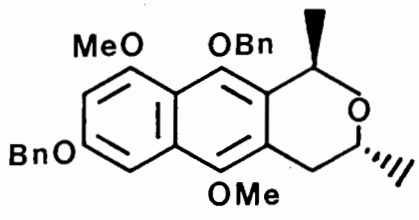

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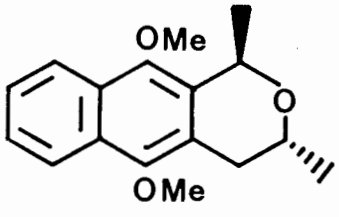

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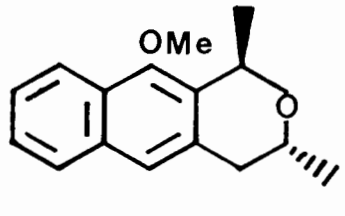


36

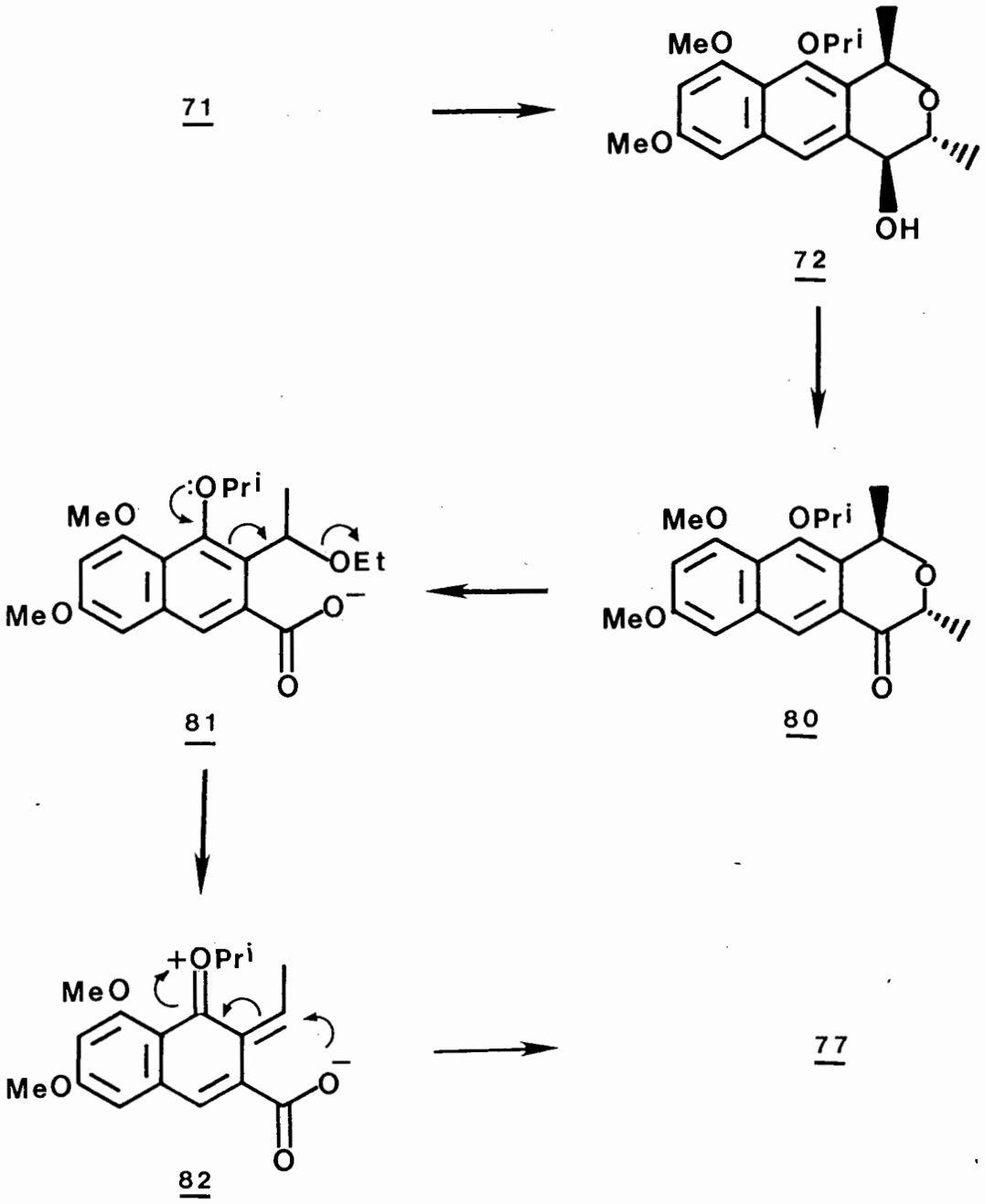
The difference in behaviour of the naphthopyrans (26), (78), (79), and (36) towards oxygenation with potassium *t*-butoxide and air in dimethyl sulphoxide on the one hand, and the behaviour of the naphthopyran (71) under identical conditions on the other, may be caused by a number of factors.

The fact that the reaction proceeds much more smoothly for compound (36) than for the analogue (71) may be due to the latter compound being more electron rich, by virtue of the additional two oxygen substituents on the terminal aromatic ring. This factor might well promote more ready subsequent oxidation of the alcohol product (72) than of compound (21). Such over-oxidation may be discouraged by the presence of the C-5 oxygen in compounds (26), (78), and (79), either on steric or electronic grounds.

Alternatively, the difference in reactivity between naphthalenes (71) and (36) may be occasioned by the greater bulk of the isopropoxy protecting group, compressed as it is between the *peri*-methoxy (at C-9) and *peri*-methyl (at C-1), finding steric relief in the conversion of compound (72) to lactone (77), since in the latter compound the C-1 methyl may be held further from the isopropoxy group as it is attached to a five-membered ring. However, there might well be other factors responsible.

A possible mechanism for the formation of the lactone (77) is outlined in Scheme 5. It was proposed that the hydroxy pyran (72) is initially formed, which is further oxidised to form the ketone (80). There is a precedent for such an oxidation,

since benzyl alcohol is known to undergo oxidation in high yield to give benzaldehyde (but not benzoic acid) under similar conditions.[37]

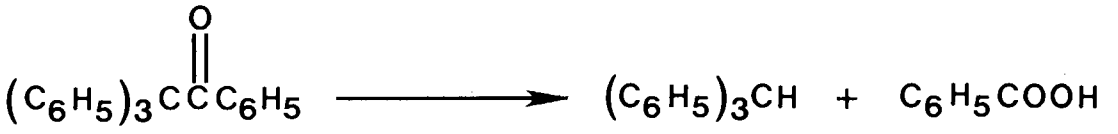


SCHEME 5

It is possible that the ketone (80) could be cleaved by the butoxide anion to give eventually the intermediate (81)

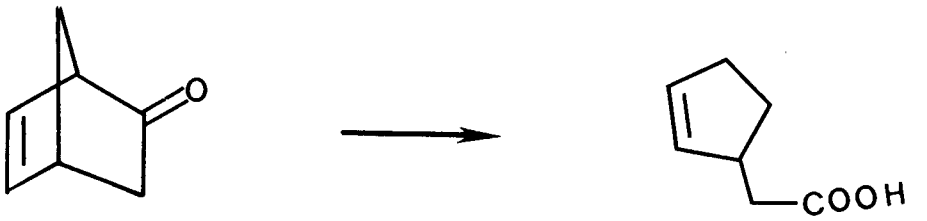
containing an acid and an ether moiety. The water added in the overall conversion of ketone (80) to (81) may be adventitious, or could arise on work-up. Compound (81) might then ring close to eliminate ethanol, thereby accounting for the formation of the lactone. This displacement of ethoxide, which is a benzylic substituent, would presumably take place readily, and is likely to be further facilitated through activation by the isopropoxy substituent as well as both methoxy groups in the other ring.

Gassman and Zalar[38] noted the ability of potassium *t*-butoxide to cleave the non-enolisable benzpinacolone (83) in dimethyl sulphoxide at room temperature, to give triphenylmethane (84) and benzoic acid (85).



83 84 85

However, of even greater significance is that Gassman and Zalar also reported the cleavage of the enolisable ketone norborn-5-ene-2-one (86) to afford cyclopentenyl acetic acid (87) in high yield. These reactions support the reaction mechanism proposed in Scheme 5.



86 87

The use of dimethylformamide as solvent for the oxygenation reaction may inhibit the formation of the lactone (77), since the dimethyl sulphoxide could be aiding the oxidation of the initially formed alcohol (72) to the ketone (80). However, the yield of this reaction would be low, as has been reported for other oxygenations in this solvent.[21,22]

The pyran (71) was therefore treated with potassium *t*-butoxide in dimethylformamide at room temperature with dry air continuously bubbling through the solution. After one hour the hydroxy pyran (72), identical in all respects to the product obtained earlier, was obtained in a yield of 33%. The lactone (77) (8%) was also formed and starting material (30%) was recovered.

The yield of this product was not very good, as was expected, although it had been improved by comparison with the reaction in dimethyl sulphoxide.

One suggestion offered in order to account for the formation of lactone (77) in the base catalysed benzylic hydroxylation reaction of pyran (71), was the presence of the bulky isopropoxy group at C-10. If there is any substance to this suggestion, then replacement of the isopropoxy group by a smaller protecting group, *viz*. methoxy, might allow the hydroxylation procedure to be more successful. The reaction could then be performed in dimethyl sulphoxide, which is a better yielding solvent for this reaction.

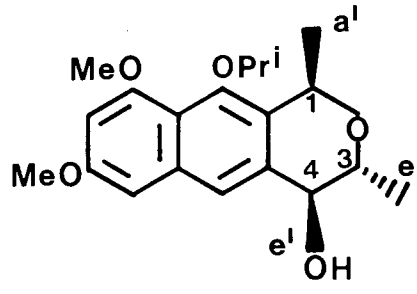
A possibility would be to remove the isopropyl group from the *trans*-dimethyl pyran (71) with the Lewis acid boron trichloride. The naphthol formed could then be methylated with dimethyl sulphate and potassium carbonate in boiling acetone.

However, if the alternative suggestion considered, i.e. the increased electron density of the pyran (71) caused by the presence of the substituents on the terminal aromatic ring, is the reason for the formation of the lactone, changing the protecting group at C-10 will have no significant effect on the oxygenation reaction.

In conclusion, it appears that a synthetic route of the type described in this section to a glucoside B analogue is feasible, although the yield of the final reaction is low. Further work in investigating the reasons for the formation of the lactone (77) from the *trans*-dimethyl pyran (71) is currently being carried out in this Department.

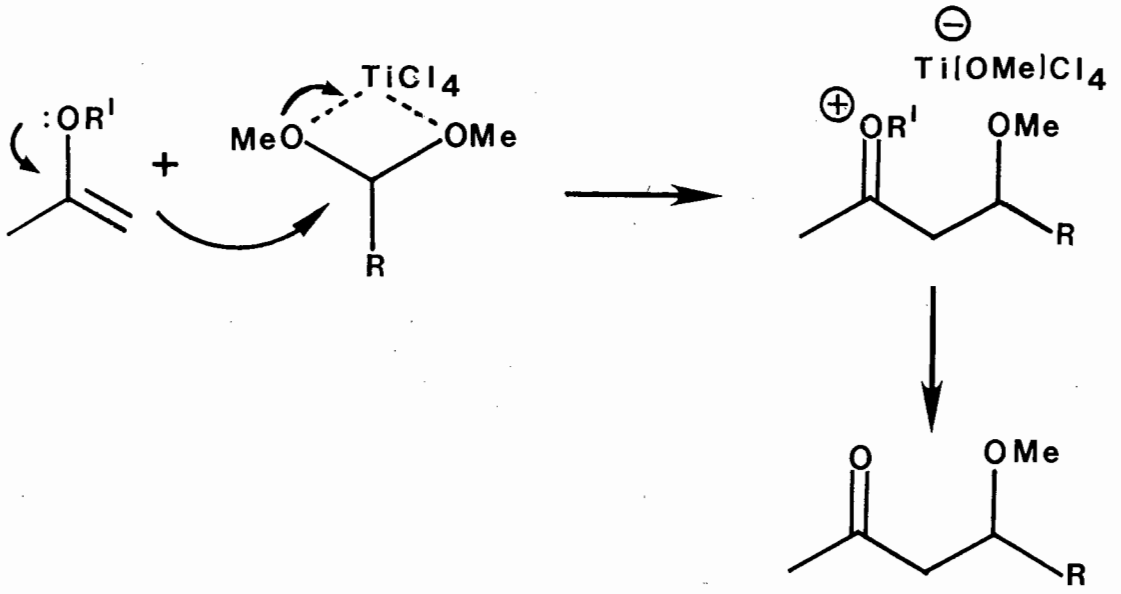
2.4 The Synthesis of naphtho[1,2-c]pyrans Related to Glucoside B *via* an Intramolecular Version of the Mukaiyama Reaction.

The project to be described involves an entirely novel approach toward the construction of the pyran ring on the glucoside B analogue (72). This procedure has, as its key step, the use of an intramolecular version of the Mukaiyama reaction.[23]



72

Mukaiyama and co-workers found that enol ethers, enol esters, and enol acetates will react with an acetal or carbonyl compound in the presence of Lewis acids such as titanium tetrachloride to give the corresponding aldol-type addition product in good yield. It is assumed that titanium tetrachloride initially activates the carbonyl compound, or acetal, toward nucleophilic attack by forming a complex. Regiospecific addition then occurs exclusively at the activated olefinic carbon of the enol. This postulate is depicted in Scheme 6.



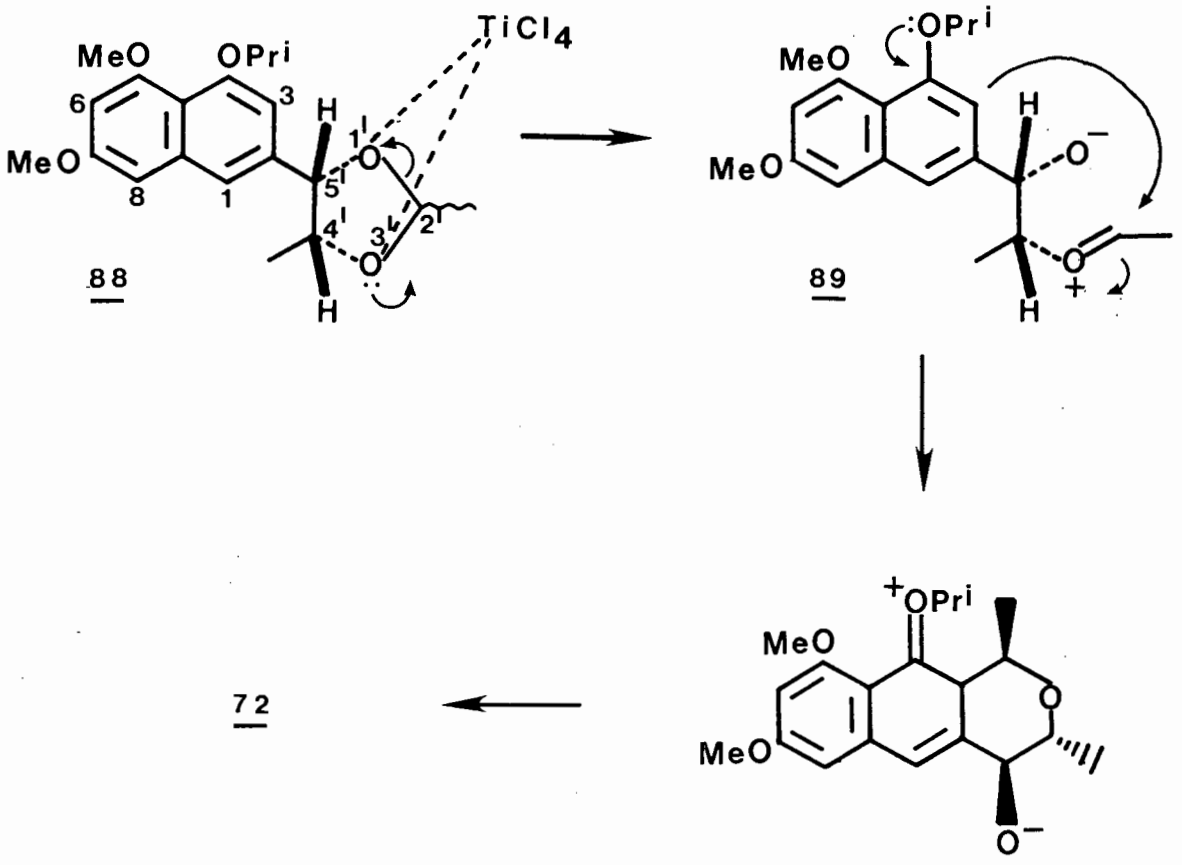
SCHEME 6

It was proposed that this reaction could be applied to the synthesis of naphthopyran (72) by the mechanism outlined in Scheme 7.

The proposed reaction sequence involved the intramolecular isomerisation of a naphthyl substituted dioxolane ring. It was hoped that titanium tetrachloride would ring open the 2-dioxolanyl naphthalene (88) at the O-1′ to C-2′ bond, forming the planar acylium intermediate (89). This intermediate could possibly then be attacked by the nucleophilic carbon C-3, *ortho* to the isopropoxy group, to afford the required naphtho[2,3-*c*]pyran (72).

The stereochemistry at positions C-3 and C-4 of the pyran ring in the product would be determined by the stereochemistry of the dioxolane precursor. Construction of a Dreiding model of dioxolane (88) followed by isomerisation as proposed in the scheme, showed that the C-3 methyl group would assume

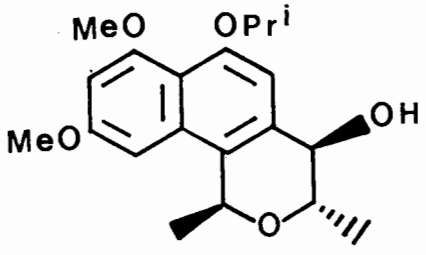
an equatorial position while the C-4 hydroxy group becomes *pseudo*-equatorial.



SCHEME 7

However, the stereochemistry of the C-1 methyl of the product of isomerisation would be determined by *peri*-interactions with the neighbouring oxygen substituent and would thus be *pseudo*-axial.[20] The stereochemistry of the C-2′ methyl of the dioxolane would therefore be immaterial, especially since the reaction is proposed to proceed *via* the planar acylium ion (89).

Thus, if the reaction proceeds *via* the mechanism outlined in Scheme 7, the product would have the correct relative stereochemistry of the three chiral centres of the pyran ring, as required by glucoside B. However, cyclisation of the planar intermediate (89) may also occur at C-1 of the naphthalene nucleus as opposed to C-3, to give an angular naphthopyran. In this case, both naphthalenes (90) and (91) could be formed, with the C-1 methyl *pseudo*-axial and *pseudo*-equatorial respectively. This would be a consequence of the absence of any influence of a neighbouring oxygen substituent in the aromatic nucleus. The stereochemistry of the C-3 methyl and C-4 hydroxy groups would be equatorial and *pseudo*-equatorial respectively, as determined before for ring closure at C-3.



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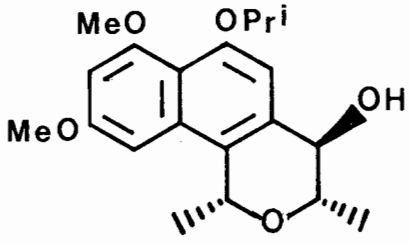
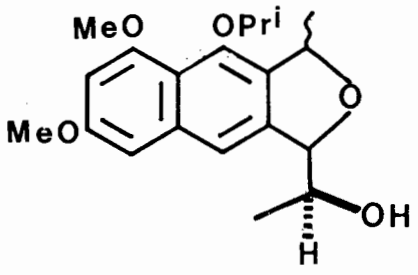


91

A further uncertainty would be which of the two acetal bonds of the dioxolane would cleave during the reaction. Cleavage of the alternate C-2′ to O-3′ bond would result in the formation of a furan of type (92) or (93), depending on the direction of nucleophilic attack. The stereochemistry at C-1 would be uncertain, but might well be determined by the factors already discussed for the isomeric pyrans (72) and (90).



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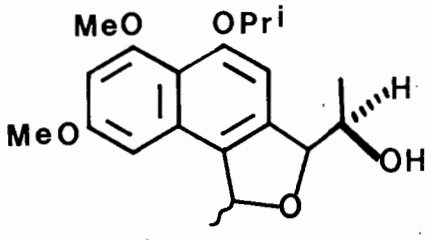
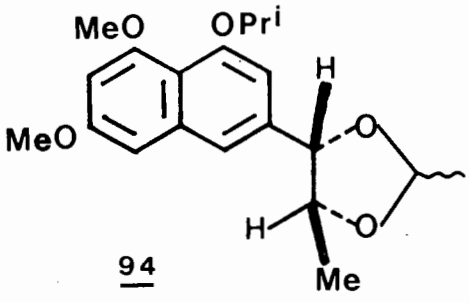


93

These proposals were initially investigated in this Department by a co-worker.[33] This research showed that treatment of the 2-dioxolanyl naphthalene (94) results in the formation of angular naphthopyrans, two isomeric products (95) (10%) and (96) (32%) being formed. In other words, the dioxolane ring was cleaved at the O-1′ to C-2′ bond, and the resultant acylium ion intermediate ring closed at C-1 of the aromatic nucleus. The structures of these compounds were confirmed by X-ray crystallography.



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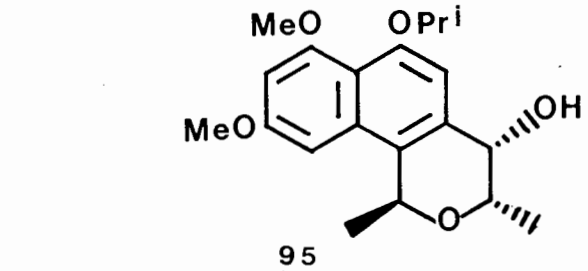

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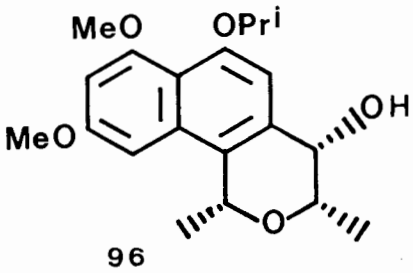


96

It should be noted that the dioxolane stereochemistry in compound (94) was not as required in order to obtain the

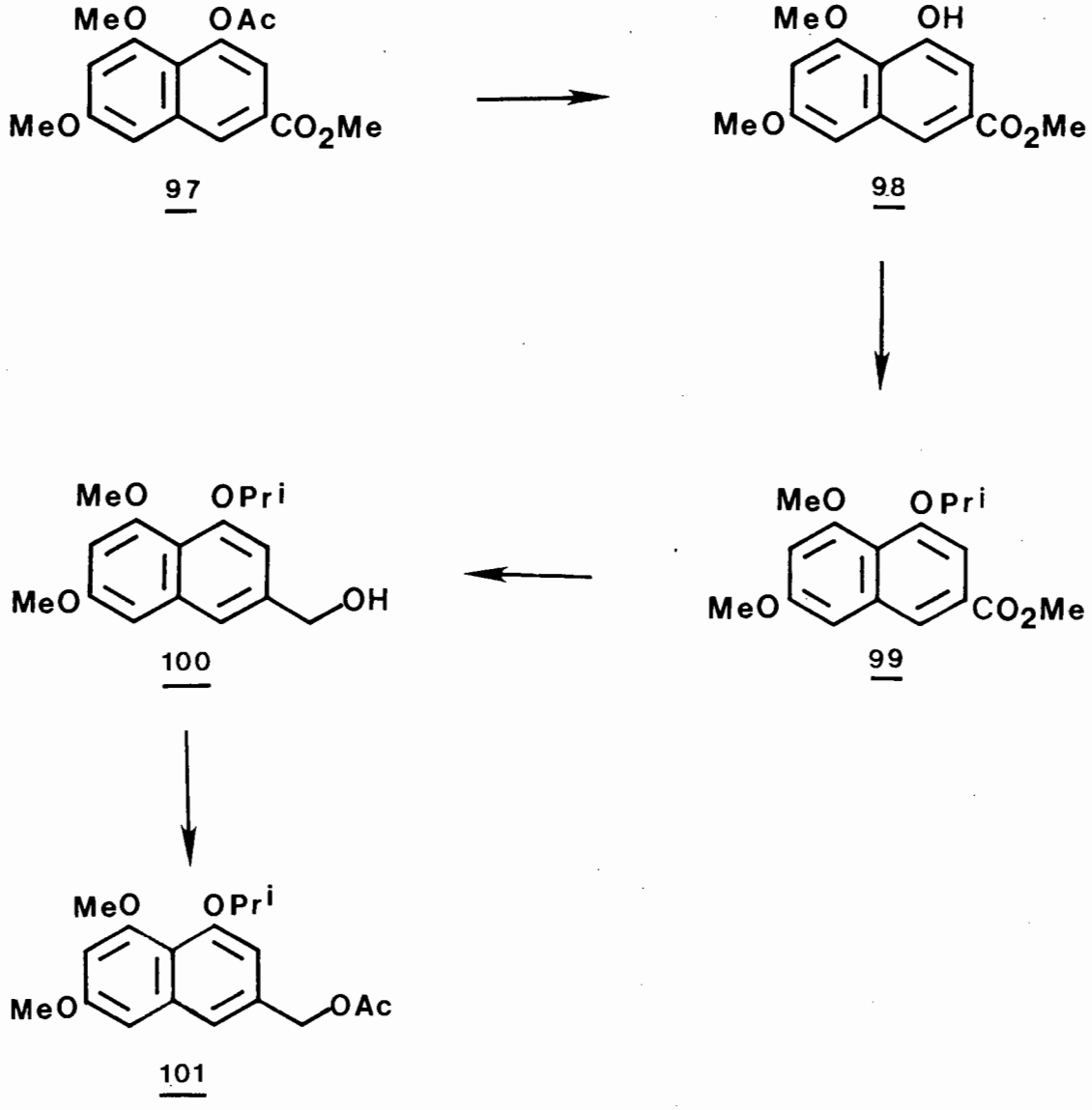
correct relative stereochemistry at C-3 and C-4 of the pyran ring. However, the formation of these two products was as anticipated for ring closure of the dioxolane in an angular fashion according to the postulates discussed earlier.

Two recommendations were made at the conclusion of this work. The first was that a dioxolane of the correct stereochemistry be synthesised so that the product of isomerisation would have the correct relative stereochemistry at C-3 and C-4. Secondly, the naphthalene nucleus should be suitably blocked at position C-1 at some time prior to cyclisation, in order to inhibit the formation of the angular naphthopyrans and promote the formation of the alternative linear naphthopyrans.

The first phase in the project to be described, concerned the choice of a suitable blocking group at position C-1 of the naphthalene nucleus. It was decided to use bromine in this context since work has been done in this Department to establish conditions for the selective bromination of the naphthalene (101).[33]

Naphthalene (101) was obtained as depicted in Scheme 8. A Stobbe reaction using 3,5-dimethoxybenzaldehyde and dimethyl succinate, followed by cyclisation, yielded the 4-acetoxy-5,7-dimethoxy-2-naphthoate (97).[39] Deacetylation of this compound with methanolic potassium hydroxide gave the naphthol (98) which was treated with isopropyl bromide and potassium carbonate in dimethylformamide to yield the isopropyl ether (99). Reduction of compound (99) with

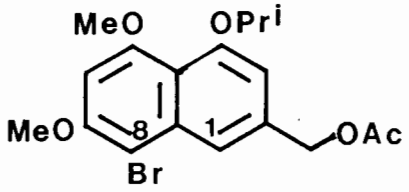
lithium aluminium hydride gave the alcohol (100). Acetylation of this alcohol with acetic anhydride and pyridine afforded the acetate (101).



SCHEME 8

It was shown[33] that electrophilic substitution of the naphthalene ring by bromonium (and acylium) ions occurs preferentially at position C-8. The 8-bromo acetate (102) is thus directly derived from compound (101) by treatment with

bromine in acetic acid in the presence of sodium acetate buffer. Treatment of compound (102) with trifluoroacetic acid yielded the 1-bromo acetate (103), presumably *via* the cationic intermediate (104). Intermediate (104) then loses a bromonium ion either inter- or intramolecularly and this ion subsequently attacks the naphthalene nucleus at C-1 forming compound (103). Alternatively, omission of the sodium acetate buffer in treating acetate (101) with bromine also leads to high yields of 1-bromo naphthalene (103).



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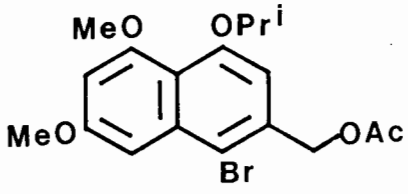

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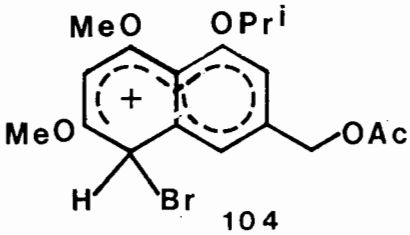
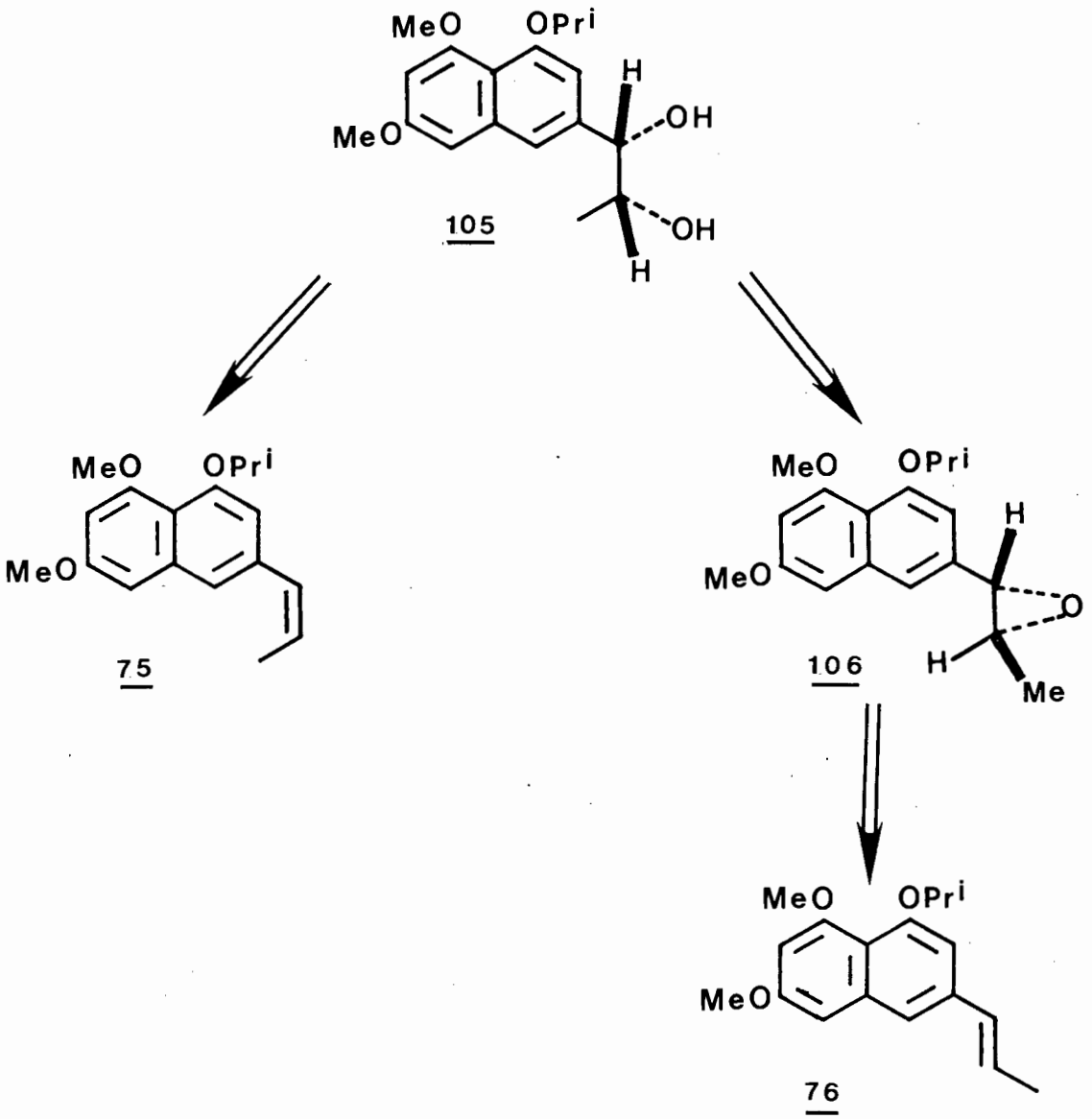


104

Using this methodology, it was therefore possible to use bromine as a blocking group at either the C-1 or C-8 position of the naphthalene nucleus. It was decided to block the C-1 position first. The next step was to plan carefully the reaction sequence in order to obtain the dioxolane with the correct stereochemistry, as shown in structure (88). The precursors of this 2-dioxolanyl naphthalene would thus have to be formed stereospecifically. It was envisaged that a dioxolane of type (88) be obtained *via* an *erythro* diol such

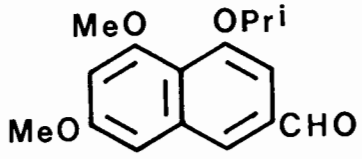
as (105). This diol can be derived *via cis* hydroxylation of the *Z*-olefin (75). Alternatively, diol (105) can be obtained *via* cleavage of the epoxide (106) formed from the *E*-olefin (76) (Scheme 9).



SCHEME 9

A stock of *E*-olefin (76)[33] was available, so it was decided to use this olefin as a model to investigate the epoxidation reaction. The blocking group at C-1 had not been introduced at that stage.

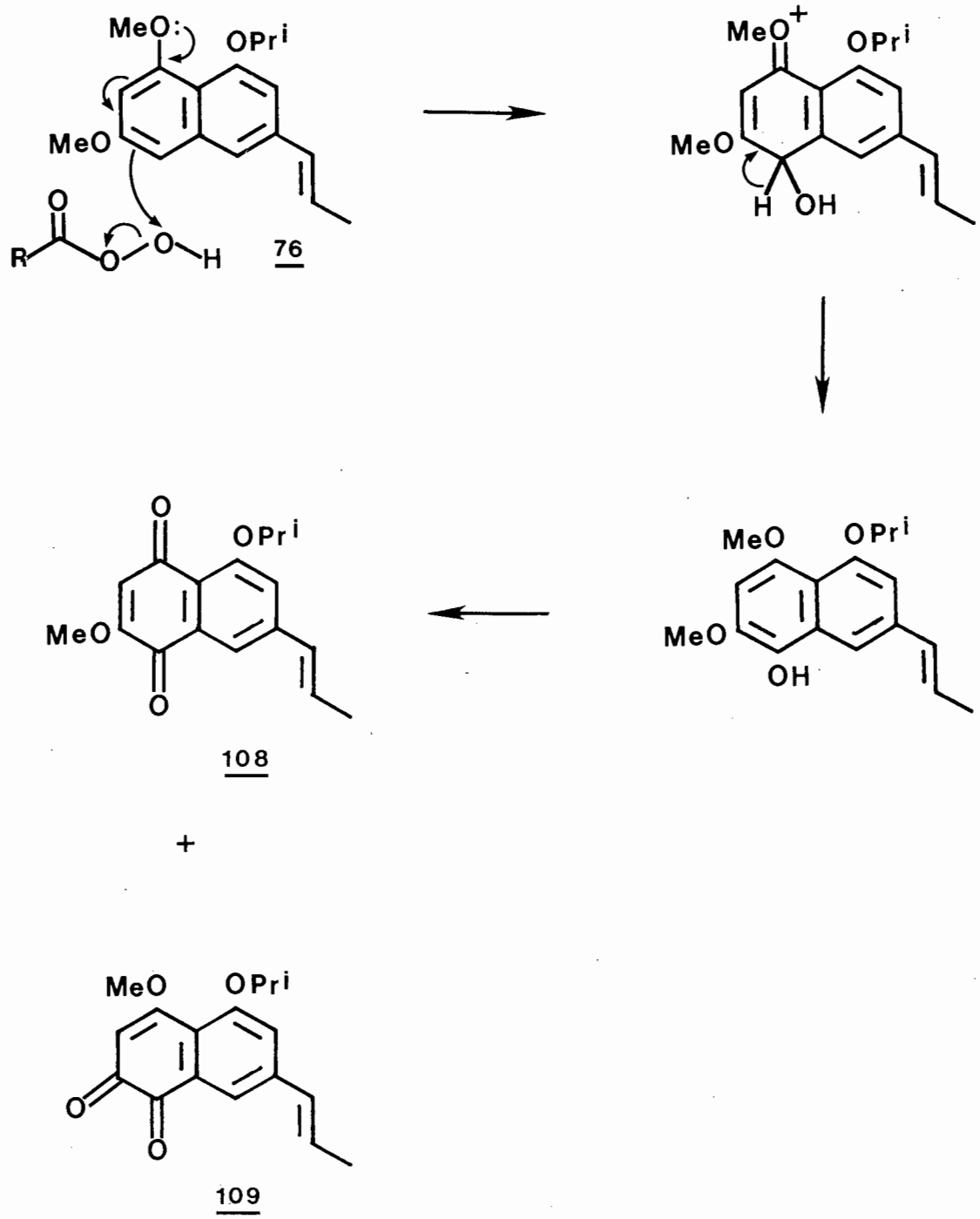
E-olefin (76) is readily obtainable *via* the alcohol (100). Oxidation of this alcohol with manganese dioxide gives the aldehyde (107). Subsequent Wittig reaction of this aldehyde and ethyltriphenylphosphonium bromide affords a mixture of the *Z*- and *E*-olefins (75) and (76) respectively. As was discussed earlier (p 100), the transition metal catalyst palladiumdichloride-bisacetonitrile has been shown to isomerise the *Z*-component of this mixture to yield solely the *E*-olefin (76) in good yield.



107

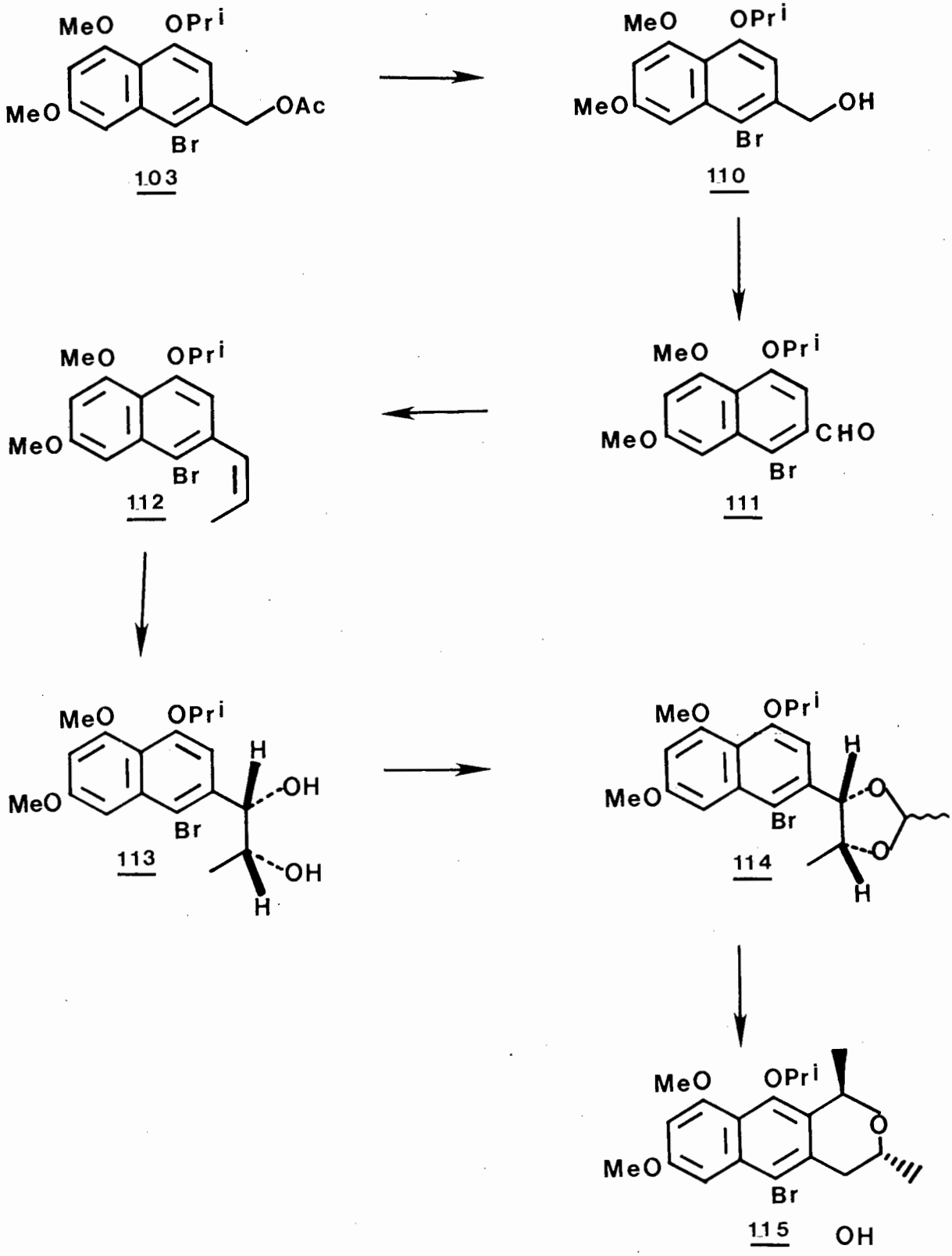
Olefin (76) was thus treated with *meta*-chloroperbenzoic acid, but the desired epoxide (106) was not obtained. A number of products were formed, two of which were identified by ^{1}H n.m.r. and mass spectroscopy as the quinones (108) and (109). These quinones were presumably derived by oxidation of the aromatic ring bearing the two methoxy substituents (Scheme 10).

This finding is consistent with the observation mentioned earlier that electrophilic substitution by bromonium and acylium ions occurs preferentially at C-8 of the naphthalene ring.[33] Thus it was considered that the best strategy to adopt at this stage would be to obtain the desired *erythro* diol *via* a *Z*-olefin.



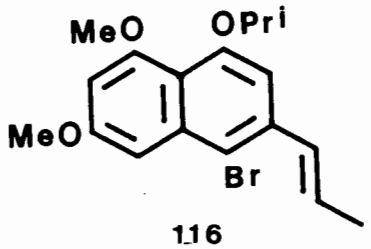
SCHEME 10

The reaction scheme involving blocking the naphthalene nucleus at C-1 and proceeding *via* a *Z*-olefin is depicted in Scheme 11.


MeO
OPr^i
MeO
OAc
Br
103
MeO
OPr^i
MeO
OH
Br
110
MeO
OPr^i
MeO
CHO
Br
111
MeO
OPr^i
MeO
Br
112
MeO
OPr^i
MeO
H
OH
Br
OH
H
113
MeO
OPr^i
MeO
H
O
Br
O
H
114
MeO
OPr^i
MeO
O
Br
115
OH

SCHEME 11

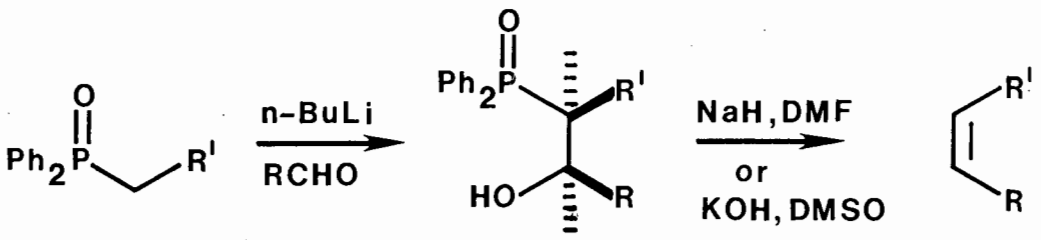
The successful execution of this approach depended on the preparation of the stereochemically pure *Z*-olefin (112). The Wittig olefin synthesis generally gives good yields of predominantly one isomer, *E* or *Z*, but lacks full stereochemical control. Furthermore, the chromatographic separation of alkenes from each other and triphenylphosphine oxide can be difficult to achieve. Thus a Wittig reaction between the aldehyde (111) and ethyltriphenylphosphonium bromide may yield a mixture of the *Z*-olefin (112) and the *E*-olefin (116), or even predominantly the *E*-olefin (116). However, a method has been reported whereby pure *Z*-olefins can be obtained with high material conversion *via* a version of the Horner-Wittig reaction.[40]



116

In this reaction, the diphenylphosphinoyl group in phosphine oxides such as (117) is used to effect 80 - 90% stereochemically pure synthesis of the *erythro* adduct (118) in good yield. The adduct is purified by flash chromatography and/or recrystallisation. Elimination of diphenylphosphinate follows to give pure *Z*-olefin (119).

Thus it should be possible to obtain the stereochemically pure *Z*-olefin (112) *via* either the Wittig or Horner-Wittig reaction.



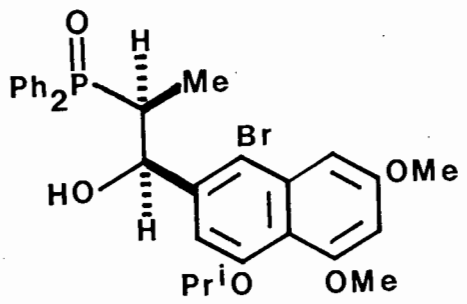
117 118 119

1-Bromo acetate (103) was treated with a 1% w/v methanolic potassium hydroxide solution to cleave the acetoxy group. The formation of compound (110) was confirmed by the ^{1}H n.m.r. spectrum which clearly indicated the appearance of a triplet and a doublet (J 5.5 Hz) at δ 2.18 and 4.88 for the hydroxy and methylene protons respectively of the hydroxymethyl side chain. The infrared spectrum no longer showed the carbonyl band at 1733 cm^{-1} but had a hydroxy absorption band at 3389 cm^{-1}.

Alcohol (110) was subsequently oxidised to the aldehyde (111) with activated manganese dioxide. The Wittig reaction of this aldehyde with ethyltriphenylphosphonium bromide afforded a mixture of the *Z*-olefin (112) and *E*-olefin (116). The ^{1}H n.m.r. spectrum of the product confirmed a stereochemical mixture by showing a doublet of doublets (J 6.5 and 1.7 Hz) at δ 1.97 coupled to a doublet of quartets (J 15.5 and 6.5 Hz) at δ 6.24, supporting the presence of the *E*-isomer. The *Z*-isomer was indicated by a doublet of doublets (J 7 and 1.5 Hz) at δ 1.80 coupled to a doublet of quartets at δ 5.91 (J 11.5 and 1.5 Hz). The accepted coupling constant for a pair

of *Z*-protons is in the range 7 - 12 Hz, and for *E*-protons is 13 - 18 Hz.[36] Integration of the ^{1}H n.m.r. signals at δ 1.80 and 1.97 showed that the *Z*- and *E*-isomers were formed in approximately equal amounts.

The alternative strategy for the synthesis of the *Z*-olefin (112) was to utilise the conditions of the Horner-Wittig reaction. Ethyldiphenylphosphine oxide was thus reacted with the 1-bromo aldehyde (111) according to the conditions stipulated for *erythro* selectivity.[40] The *erythro* adduct (120) was obtained in 45% yield from the aldehyde (111) after repeated recrystallisation in order to seperate the *threo* adduct formed simultaneously.

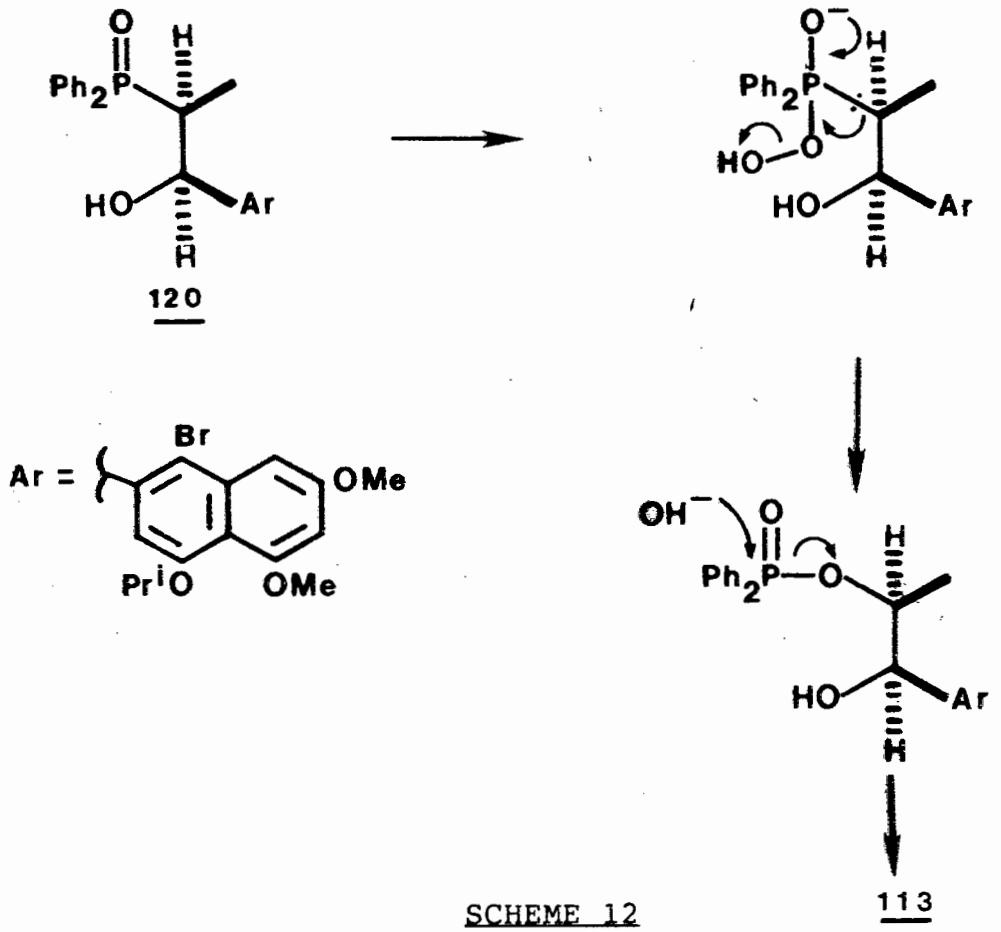


120

It proved difficult to obtain optimum conditions for formation of pure *Z*-olefin (112) from adduct (120). Elimination of diphenylphosphinate with two molar equivalents of sodium hydride in dry dimethylformamide at 50°C under nitrogen for twenty minutes, was found to yield the maximum stereospecificity, producing *Z*-olefin (112) in 82% yield from the *erythro* adduct (120). Small quantities (< 10%) of the *E*-olefin (116) were also produced. The product was assigned *Z*-stereochemistry according to the ^{1}H n.m.r. spectrum, which

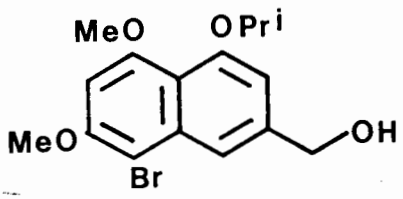
showed a doublet of quartets for 2'-H at δ 5.91 with the coupling constant between the olefinic protons being 11.5 Hz. As mentioned earlier, this value is in accordance with the value anticipated for *Z*-protons.[36]

It was thought that treatment of the *erythro* adduct (120) with alkaline hydrogen peroxide might replace the diphenylphosphinoyl group with a hydroxy group (Scheme 12) to yield the *erythro* diol (113) directly. This would eliminate two steps, namely the sodium hydride elimination and the subsequent hydroxylation to form the diol. Unfortunately no reaction occurred on treatment of adduct (120) with alkaline hydrogen peroxide.

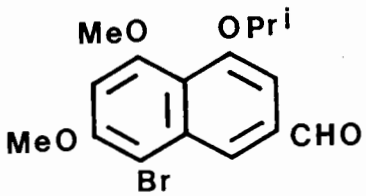


SCHEME 12

At this stage, it was decided to investigate formation of a C-8 blocked *Z*-olefin. The 8-bromo acetate (102) was thus converted into the alcohol (121) by treatment with a 1% methanolic potassium hydroxide solution. This alcohol was oxidised with activated manganese dioxide in boiling benzene to give the aldehyde (122).



121



122

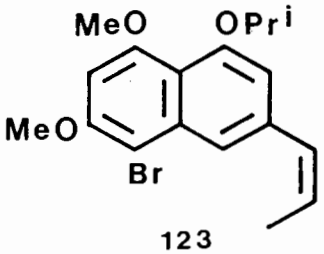
The formation of the aldehyde was indicated clearly by the presence of a low field singlet at δ 10.08 for the aldehydic proton in the ^{1}H n.m.r. spectrum. The ^{13}C n.m.r. spectrum showed a singlet for the aldehyde carbon at δ 192.29. The infrared spectrum showed a strong carbonyl absorption band at 1685^{-1}.

Although a Wittig reaction of the aldehyde (111) with ethyltriphenylphosphonium bromide had yielded a mixture of *Z*- and *E*-isomers, it was nevertheless decided to undertake a similar Wittig reaction of the 8-bromo aldehyde (122).

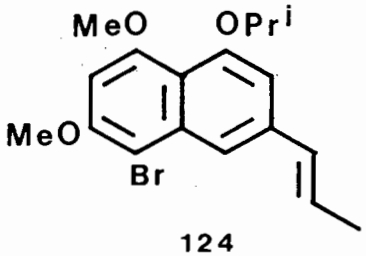
The ^{1}H n.m.r. spectrum of the product from this reaction suggested it to be mostly one isomer, contaminated by approximately 8% of the alternate isomer. A three-proton doublet of doublets (J 1.8 and 8 Hz) appeared at δ 1.92

coupled to a doublet of quartets at δ 5.86 (J 13 and 8 Hz) for the 2'-H olefinic proton. No definitive assignment of the stereochemistry of this product could be made, since the coupling of 13 Hz for the olefinic protons could be interpreted as a moderately large coupling constant for a pair of *Z*-protons, or a moderately small coupling for a pair of *E*-protons.

In order to assign the stereochemistry of this product, it was treated with the transition metal catalyst, palladiumdichloride-bisacetonitrile in chloroform and the reaction monitored by ^{1}H n.m.r. spectroscopy. This catalyst has been shown to isomerise the *Z*-component of a mixture of *Z*- and *E*-isomers to yield the *E*-isomer.[33] Thus if the Wittig product was the *Z*-olefin (123) required, the ^{1}H n.m.r. spectrum would show the relevant changes expected for isomerisation to the *E*-olefin (124). However, if the product was the *E*-olefin (124), no change would be expected in the spectrum.



123



124

After two hours, the ^{1}H n.m.r. spectrum showed a doublet of doublets at δ 1.84 (J 6 and 1.8 Hz) and a doublet of quartets

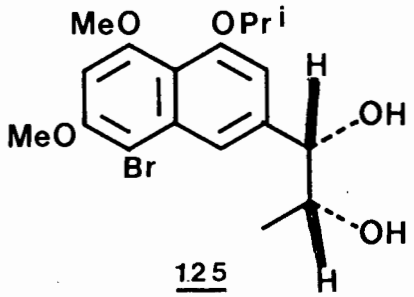
at δ 6.29 (J 15.6 and 6 Hz). This compound was thus the *E*-olefin (124), the assignment being corroborated by the large coupling constant (J 15.6 Hz) for the *trans*-olefinic protons. Isomerisation had thus taken place, implying that the original Wittig reaction product was the *Z*-olefin (123) as required.

If the isomerisation of olefin (123) with the palladium(II) catalyst was left for a longer period, the product obtained was the 1-bromo *E*-olefin (116), a bromine migration having occurred. The same result was obtained if the neat *Z*-olefin (123) was left standing in sunlight for three to four days, isomerisation to the *E*-olefin (124) taking place first, followed by the radical migration of bromine from C-8 to C-1. The *Z*-olefin (123) was thus photochemically unstable. It was also noted that chromatography of this olefin on silica or alumina, caused isomerisation to take place to some extent, larger amounts of the *E*-olefin (124) being formed. Thus, if further work was to be done in this series, the *Z*-olefin (123) would have to be converted into the diol before isomerisation could occur, to ensure optimum stereochemical purity.

It was decided to continue this project in the 8-bromo series for two reasons. Firstly, since the *Z*-olefin can be obtained directly from the aldehyde without having to isolate the intermediate *erythro* phosphine adduct and secondly, since bromine in this position will cause less steric hindrance in the dioxolane while still sufficiently blocking the C-1 position. There is a possibility that a blocking group at

C-1 of the naphthalene dioxolane (88) might prevent ring closure from occurring even at C-3 as a consequence of too much steric crowding.

The conversion of *Z*-olefin (123) to the *erythro* diol (125)* by treatment with osmium tetroxide was highly successful. After purification, a 59% yield of the diol from aldehyde (122) was obtained. In particular, the ^{1}H n.m.r. spectrum showed no sign of duplication of the signals due to a diastereomeric mixture. The benzylic proton resonated as a doublet (J 4.5 Hz) at δ 4.71.



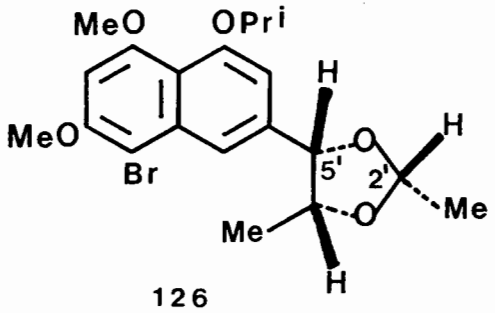
125

Diol (125) was then treated with acetaldehyde dimethyl acetal in the presence of *para*-toluenesulphonic acid in benzene. After thirty minutes a single product was obtained. The ^{1}H n.m.r. spectrum of this compound showed the presence of two methyl substituents on the dioxolane ring, two sets of three-proton doublets appearing at δ 0.86 (J 6.4 Hz) and δ 1.59 (J 4.6 Hz). The proton at C-5′ resonated at δ 5.09 as a doublet

* Structures represented as single enantiomers are in fact racemic.

(*J* 7.1 Hz). The stereochemistry at C-2′ was undetermined at this stage, but it was clear from the spectrum that only one diastereomer had been formed.

A one-dimensional nuclear Overhauser effect (n.O.e.) difference spectrum obtained on this product strongly suggested that the structure of the dioxolane ring was *cis-syn* (i.e. all three substituents were on the same side of the ring, as drawn in structure (126)). The methyl groups are thus *cis* to each other.



126

The n.O.e. difference spectrum (see figure 1) obtained by irradiation at δ 4.41, the signal for 4′-H, showed a 10% enhancement for the signal due to 2′-H, as well as a 13% enhancement for the 5′-H doublet. Alternative n.O.e. difference spectra were obtained upon irradiation of each of the other two dioxolane ring protons. The results of these spectra again supported the assigned relative configuration made above.

This isomer is presumably favoured for the following reason. Since the vicinal methyl and naphthyl substituents are *cis* to each other, two possible configurations of the dioxolane ring

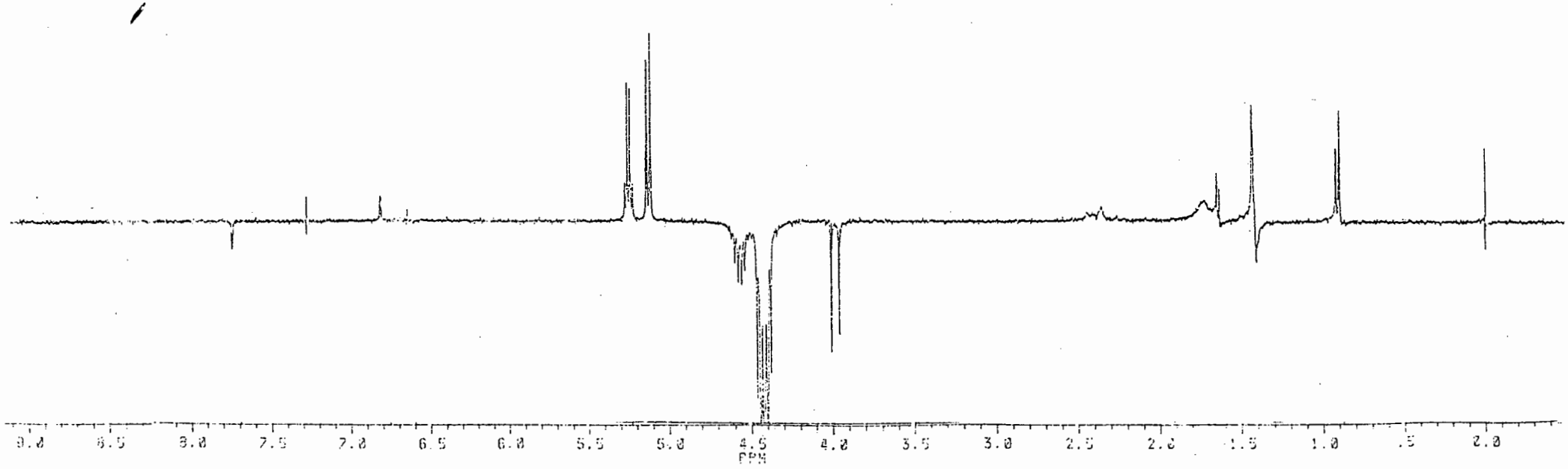
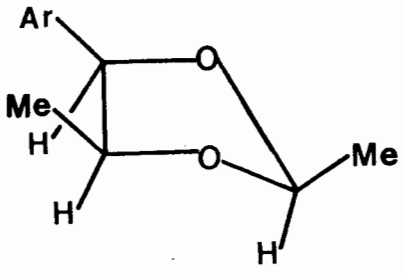
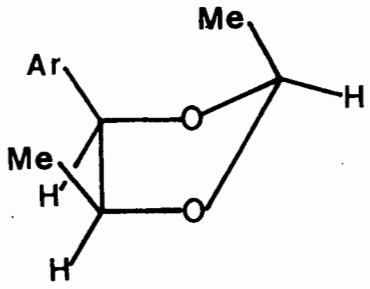


figure 1

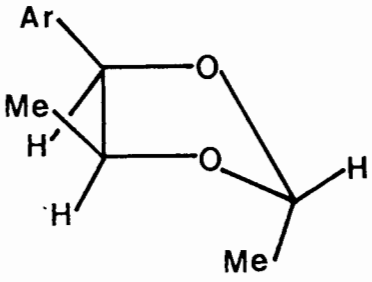
are possible, namely *cis-syn* (A) or *cis-anti* (B). Each configuration would have two limiting conformations, 1 and 2. Of these four possibilities, clearly the least strained and therefore the most favourable arrangement would be A-1, in which the 1,3-"diaxial" type interactions are minimised.



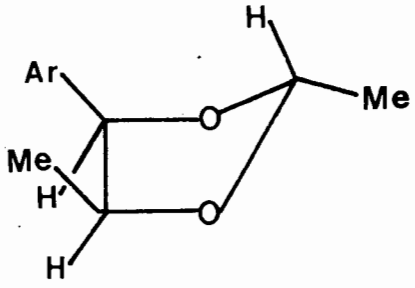
A-1



A-2



B-1



B-2

Having obtained the C-8 brominated dioxolane with the correct stereochemistry, it was possible to proceed with the intramolecular version of the Mukaiyama reaction. The dioxolanyl naphthalene (126) was treated with ten molar equivalents of titanium tetrachloride in methylene chloride at -78°C. At this temperature, thin layer chromatography indicated the formation of a small amount of the diol (125), but no new product. As the temperature was raised, a single compound of

lower R_f than starting material began forming. The reaction was quenched after one hour.

Work-up and chromatography of the reaction mixture yielded dioxolane (126) (12%), diol (125) (14%), alcohol (100) (4%), and two new products of similar R_f values. The single product observed during the course of the reaction was not isolated, and neither of the new products had the same R_f value. For purposes of identification, the major product (of lower R_f), was designated product A, while the minor product (of higher R_f) was designated product B.

The mass spectrum of A showed a molecular ion at *m/z* 346, implying the loss of bromine, whereas product B still had the typical pattern of a compound possessing one bromine atom, the ratio of peaks for the molecular ion at *m/z* values 426 and 424 being 1:1. The yields of products A and B based on these masses, were 40% and 15% respectively.

The ^1H n.m.r spectra of these two products were very similar. The ^1H n.m.r. spectra are shown in figure 2 (product A) and figure 3 (product B), and their spectra after deuterium oxide exchange are shown in figures 4 and 5. The aromatic region of product A showed two singlets at δ 6.50 and 6.97 for two protons and one proton respectively. The aromatic region of product B however, showed a pair of *meta*-coupled protons at δ 6.55 and 6.60. This information was consistent with product A not having a bromine on the naphthalene nucleus and product B still possessing bromine. Furthermore, due to the presence of the *meta*-coupled signals for product B, the

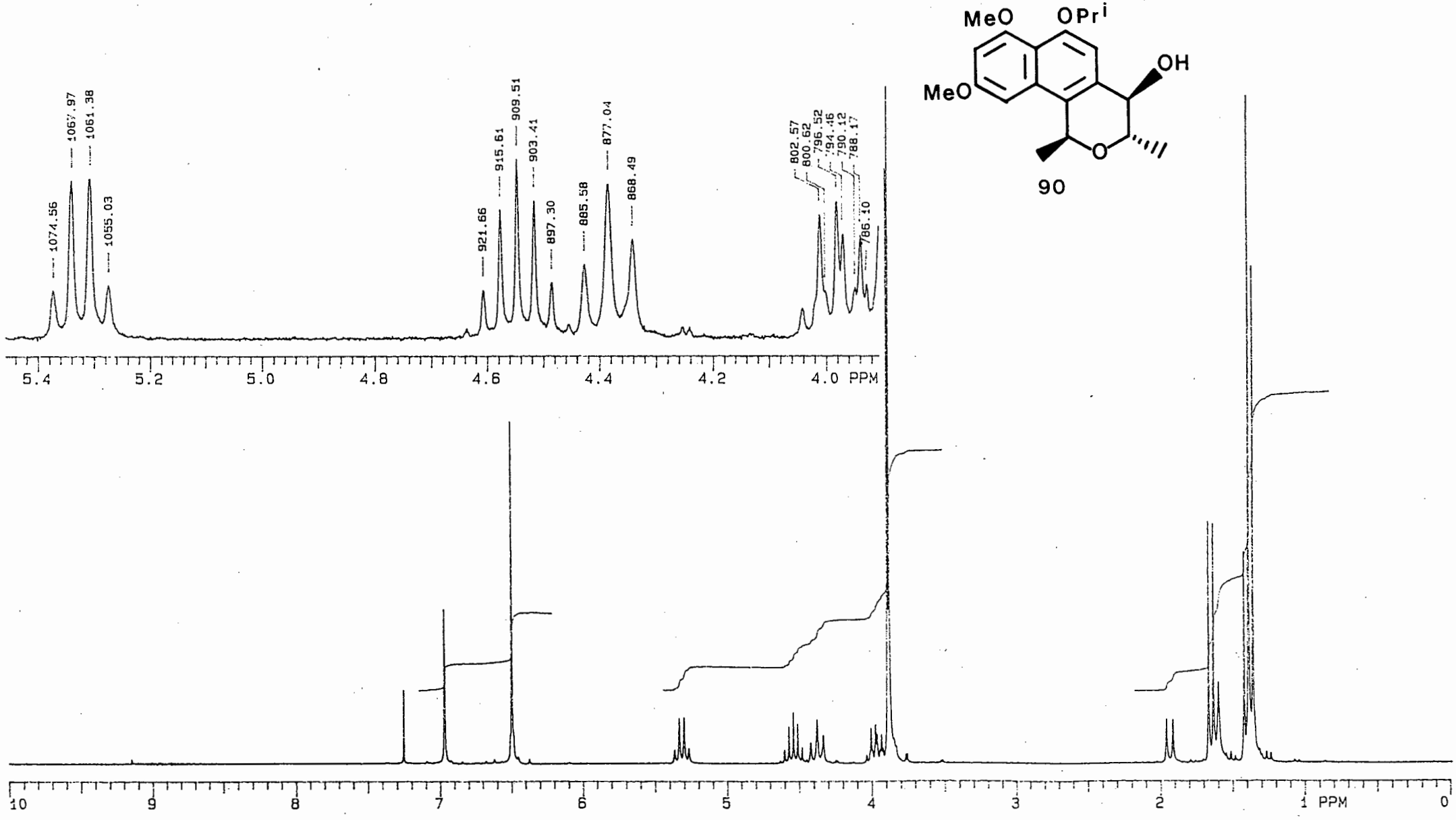
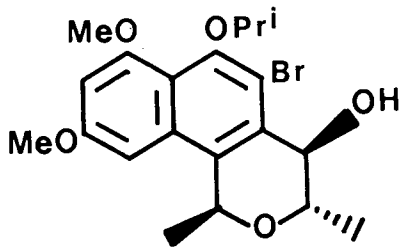

MeO
OPr^i
OH
MeO
O
90
1074.56
1067.97
1061.38
1055.03
921.66
915.61
909.51
903.41
897.30
885.58
877.04
868.49
802.57
800.62
796.52
794.46
790.12
788.17
786.10
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0 PPM
10
9
8
7
6
5
4
3
2
1 PPM
0

figure 2


MeO
OPr^i
Br
OH
MeO
O

130

632.45
627.95
3.932
3.898
1319.26
1317.25
1315.30
1310.17
1307.97
6.65
6.60
6.55
6.50 PPM
1079.93
1073.34
1066.75
1060.40
947.11
942.96
938.38
901.45
895.35
892.61
889.25
886.32
882.90
880.21
876.79
862.39
856.77
850.67
844.51
5.4
5.2
5.0
4.8
4.6
4.4
4.2 PPM
10
9
8
7
6
5
4
3
2
1 PPM
0

figure 3

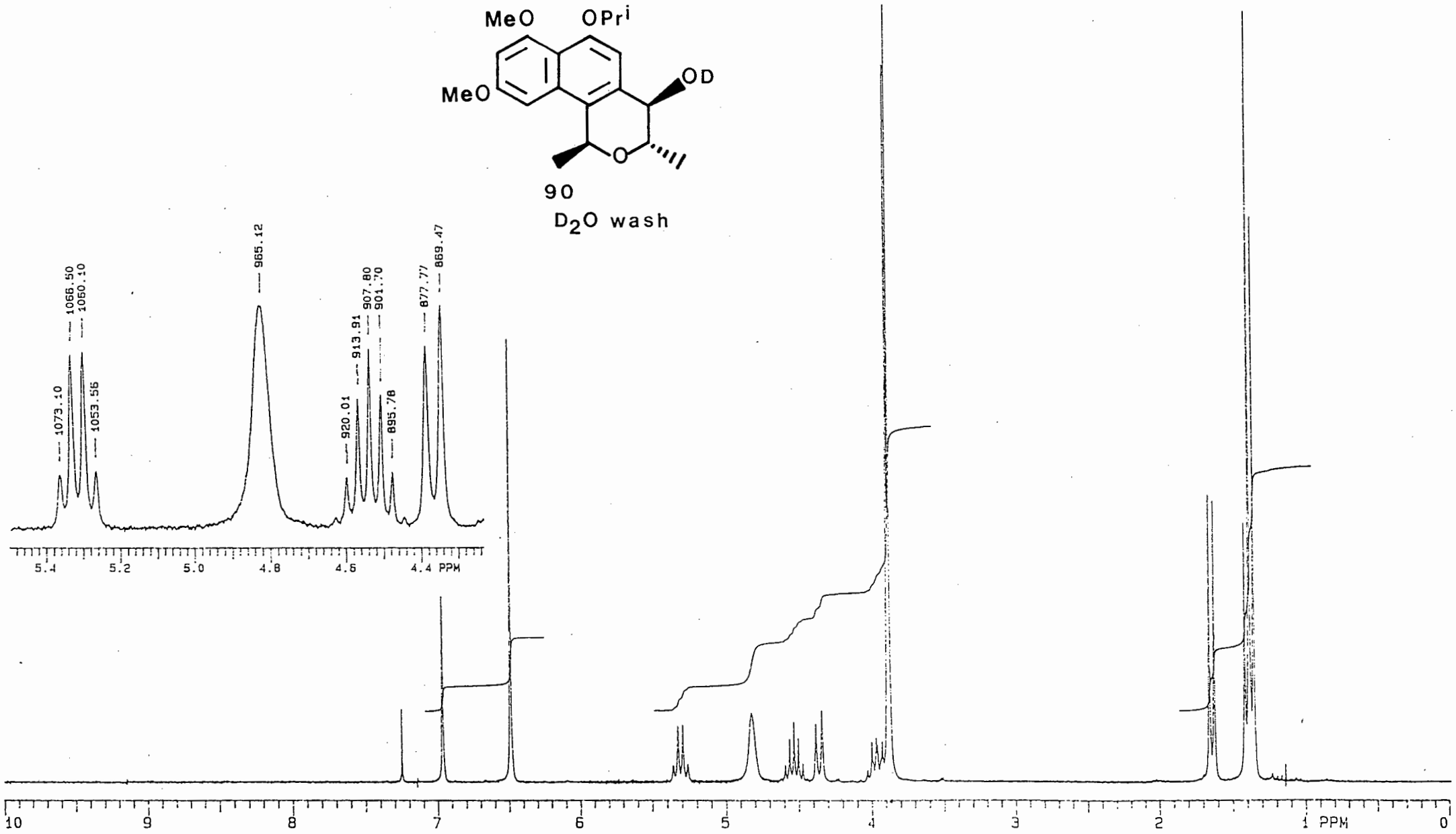

MeO
OPr^i
MeO
OD
O
90
D_2O wash
1073.10
1066.50
1060.10
1053.56
965.12
920.01
913.91
907.80
901.70
895.78
877.77
869.47
5.4
5.2
5.0
4.8
4.6
4.4 PPM
10
9
8
7
6
5
4
3
2
1 PPM
0

figure 4

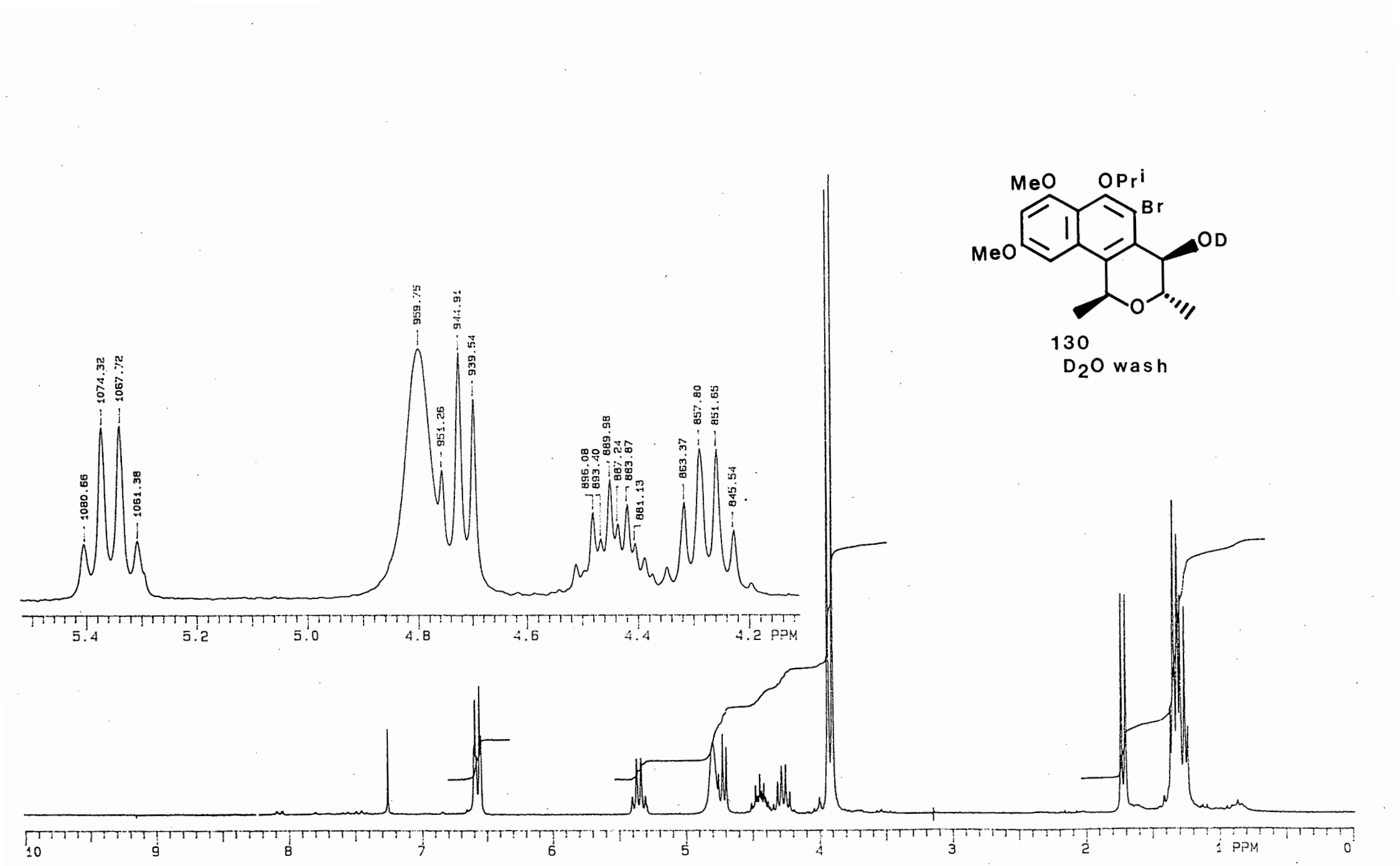
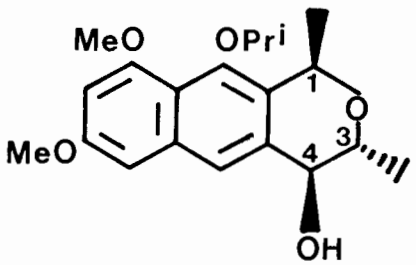

MeO
OPr^i
Br
MeO
OD
O
130
D_2O wash
1080.66
1074.32
1067.72
1061.38
959.75
951.26
944.91
939.54
896.08
893.40
889.98
887.24
883.87
881.13
863.37
857.80
851.65
845.54
5.4
5.2
5.0
4.8
4.6
4.4
4.2 PPM
10
9
8
7
6
5
4
3
2
1 PPM
0

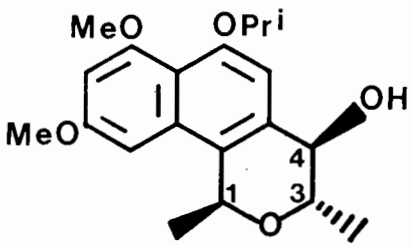
figure 5

bromine atom could no longer be at position C-8, similarly position C-6 was also excluded.

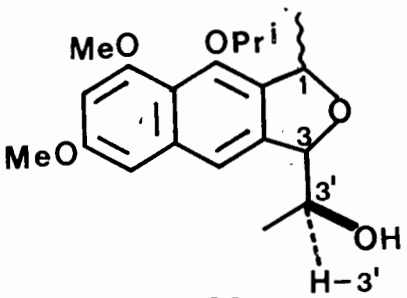
Both spectra showed the signals associated with an isopropoxy grouping as well as the methoxy signals. In addition, three one-proton signals for each compound were observed. For product A, after deuterium oxide exchange, these were a doublet of quartets at δ 3.89 (J 8.3 and 6.3 Hz), a doublet at δ 4.38 (J 8.3 Hz), and a quartet at δ 5.32 (J 6.5 Hz). The corresponding signals for product B, assigned on the basis of a COSY experiment (figure 6), were a sextet at δ 4.27 (J 6.1 Hz), a doublet at δ 4.71 (J 5.4 Hz) and a quartet at δ 5.25 (J 6.6 Hz). This information suggested that products A and B were either naphthopyrans of type (72) or (90), or naphthofurans of type (92) or (93).



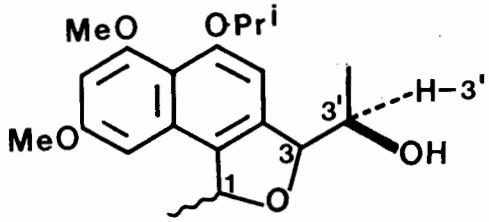
72



90



92



93

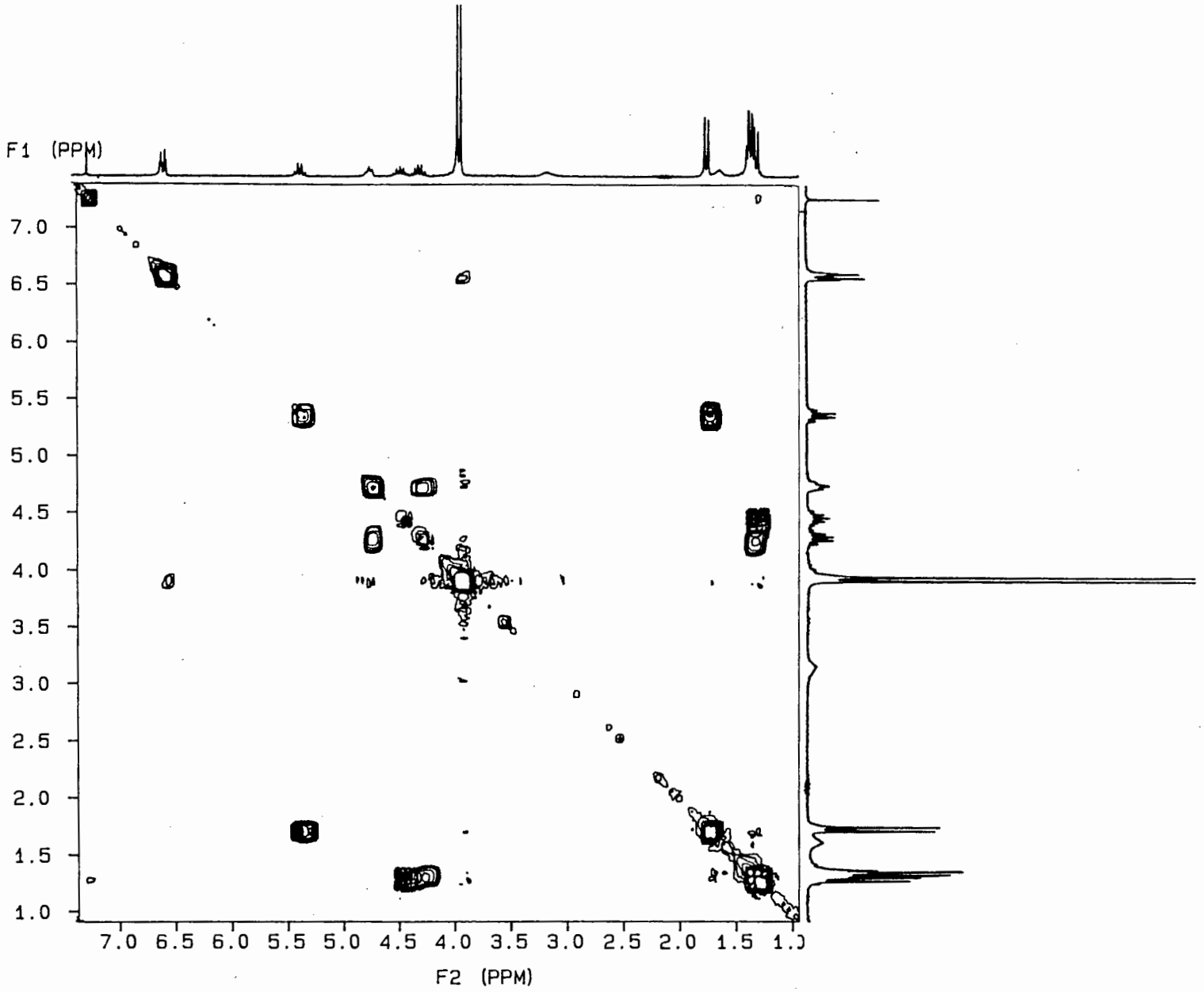

F1 (PPM)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
F2 (PPM)

figure 6

For naphthopyrans, the three one-proton signals would be due to 3-H, 4-H, and 1-H respectively. For naphthofurans they would be due to 3'-H, 3-H, and 1-H respectively.

In order to establish the ring size, product A was acetylated with acetic anhydride and pyridine. This resulted in a large deshielding of the observed doublet (δ 4.38) of the starting material to δ 5.82 in the acetate. Figure 7 shows the ^{1}H n.m.r. spectrum. Product A was thus a naphthopyran and not a naphthofuran, since acetylation of the latter would result in deshielding of the doublet of quartets. Structures such as (92) or (93) could therefore be excluded for product A.

The acetate of product B was synthesised in the same manner. The ^{1}H n.m.r. spectrum (figure 8) of the product showed a similar large deshielding of the doublet at δ 4.71 of the starting material, as observed for product A. However, the signals due to the acetyl, C-1, C-3, and isopropyl methyls, as well as the signal for 4-H were duplicated, suggesting that product B possibly consisted of a mixture of two naphthopyrans.

In order to clarify the uncertainty surrounding this issue, it was decided to remove the bromine atom of product B. This was achieved by treatment of product B with *n*-butyl lithium in dry tetrahydrofuran at -78°C. Only one compound was obtained. This product was indistinguishable both chromatographically and spectroscopically (^{1}H n.m.r., m.s., and i.r.) from product A. It was therefore proposed that the acetate of product B must exist as two conformations, presumably

1309.74
1305.78
1302.85
1300.65
1170.27
1162.70
1082.67
1076.03
1069.68
1062.90
902.92
896.81
890.71
884.61
878.69
850.67
844.57
838.22
837.00
830.65
3.893
2.194
344.34
337.81
275.68
269.58
263.72
257.48
MeO
MeO
OPri
OAc
132
PPM
4.5 PPM

figure 7

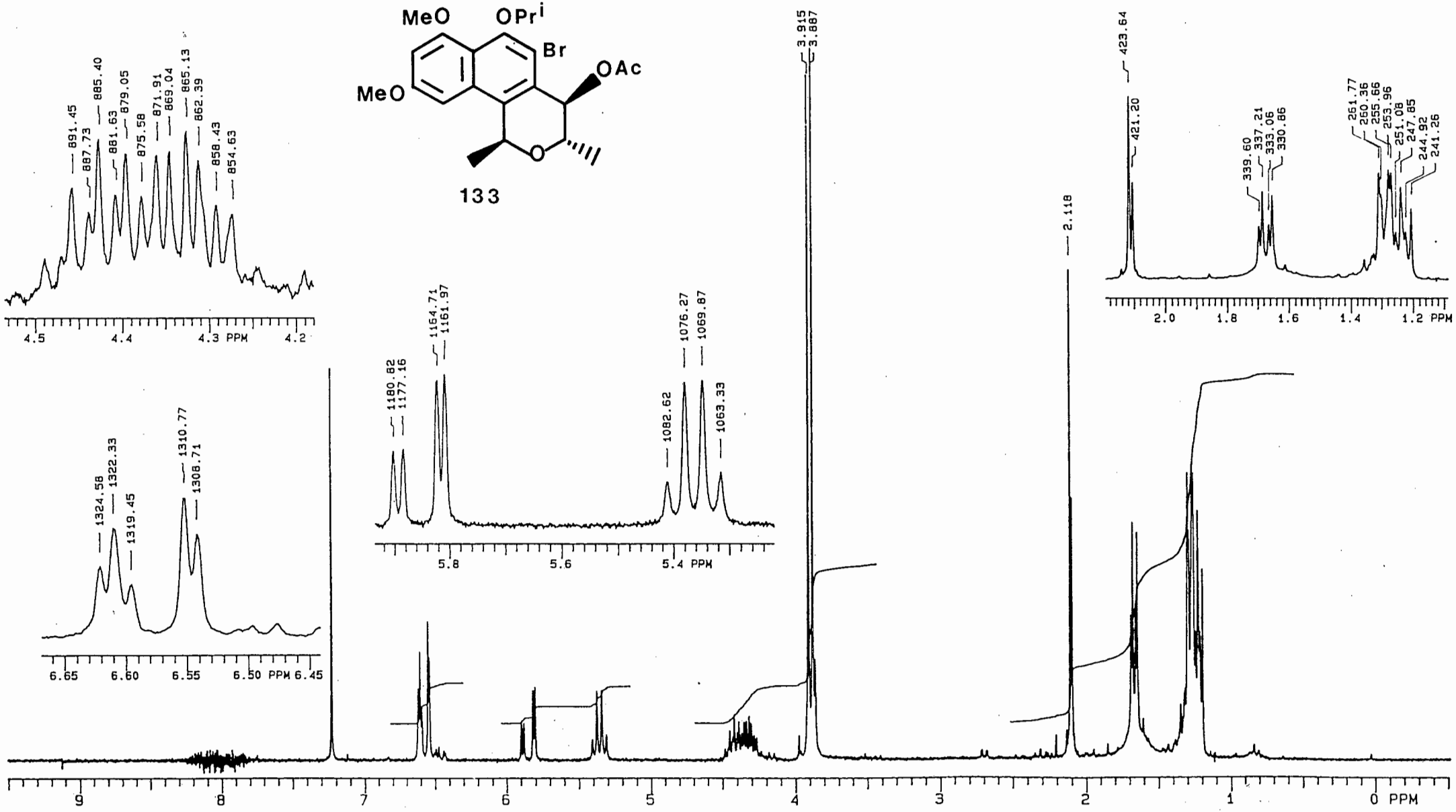

MeO
OPr^i
Br
OAc
MeO
133
891.45
887.73
885.40
881.63
879.05
875.58
871.91
869.04
865.13
862.39
858.43
854.63
4.5
4.4
4.3 PPM
4.2
1324.58
1322.33
1319.45
1310.77
1308.71
6.65
6.60
6.55
6.50 PPM 6.45
1180.82
1177.16
1164.71
1161.97
1082.62
1076.27
1069.87
1063.33
5.8
5.6
5.4 PPM
3.915
3.887
2.118
423.64
421.20
339.60
337.21
333.06
330.86
261.77
260.36
255.66
253.96
251.08
247.85
244.92
241.26
2.0
1.8
1.6
1.4
1.2 PPM
9
8
7
6
5
4
3
2
1
0 PPM

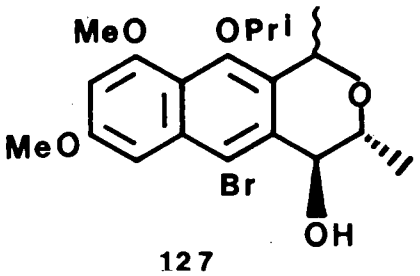
figure 8

caused by the steric crowding effect of bromine on the naphthalene nucleus. This postulate will be discussed at a later stage, when the stereochemistry and form of the pyran ring has been established. The fact that products A and B were identical, except for the presence of bromine on the naphthalene nucleus, was useful in the determination of their structures, since any conclusion derived for the one product would be applicable to the other.

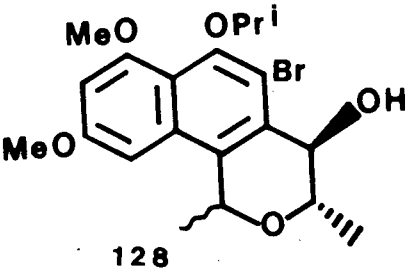
Analysis of the ^{1}H n.m.r. spectrum of A allowed the relative stereochemistry at C-3 and C-4 to be established. The doublet (J 8.3 Hz) at δ 4.38 and the doublet of quartets (J 8.3 and 6.3 Hz) at δ 3.89, are due to 4-H and 3-H respectively. The large coupling constant of 8.3 Hz between these two protons indicates a dihedral angle of close to 180°, implying an arrangement close to *trans*-diaxial between them. This necessitates that the C-3 methyl and C-4 hydroxy groups would have to be equatorial and *pseudo*-equatorial respectively. The bulky methyl group at C-3 would prefer the less crowded equatorial configuration, thus forcing the C-4 hydroxy group to be *pseudo*-equatorial. This result was anticipated by construction of the Dreiding model to investigate isomerisation in Scheme 7. The Dreiding model thus fully supports the predicted course of reaction prior to its execution.

The aromatic region of the ^{1}H n.m.r. spectrum of B, showed a pair of *meta*-coupled protons, a fact which suggested this compound could be either naphthopyran (127) or (128). The chemical shifts of these signals, at δ 6.55 and 6.60 however, ruled out the former compound (127) as a possibility since

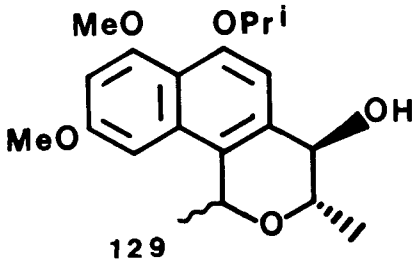
for this product the chemical shift of 6-H would be expected at *ca.* δ 7.30, due to the deshielding effect of the *peri*-bromine. This effect was originally noted in the ^{1}H n.m.r. spectrum of the 3-bromo acetate (103) where 6-H and 8-H appear at δ 6.52 and 7.24 respectively. In contrast, the signals for 6-H and 8-H in the non-bromo derivative (101) appear at δ 6.45 and 6.67 respectively.[33] Thus, from this information, the bromine atom must be at C-5 of the naphthalene nucleus, implying product B was the naphtho[1,2-*c*]pyran (128) with the stereochemistry at C-1 still to be determined. Product A was therefore the naphtho[1,2-*c*]pyran (129) with no bromine at C-5.



127



128



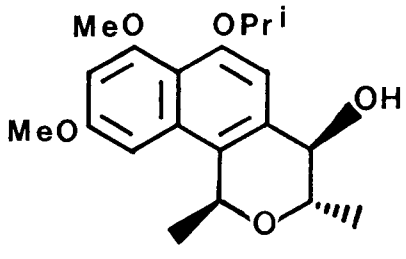
129

Further evidence that products A and B were angular naphthopyrans was provided by a comparison of the chemical shift for 5-H in the ^{1}H n.m.r. spectrum of product A with the chemical shift of the same proton in the spectrum of the linear

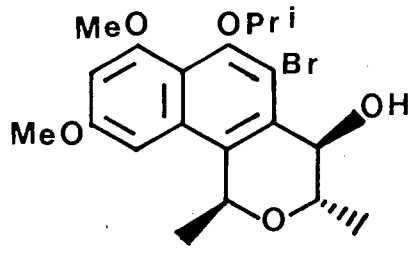
glucoside B analogue (72). In product A this proton appears at δ 6.97 whereas in compound (72) it appears at δ 7.61.

A one-dimensional n.O.e. difference spectrum was obtained on product A. This spectrum strongly suggested that the C-1 methyl was *pseudo*-axial. Irradiation at δ 1.64, the signal for the C-1 methyl, showed enhancement of the signals due to 1-H, 3-H, and 4-H (figure 9). The largest enhancement was for 3-H, showing the proximity of the C-1 methyl to this proton. It therefore follows, as far as this experiment is concerned, that the C-1 methyl group must be *pseudo*-axial, as 3-H had already been determined as axial. The enhancement of the signal for 4-H is probably due to irradiation of the hydroxy signal at δ 1.89 occurring simultaneously.

Furthermore, it was noted that irradiation of the C-1 methyl also showed an enhancement of the signal due to 8-H and 10-H. Irradiation of the 4-H signal at δ 4.38, (figure 10), showed enhancement at the 5-H signal. These results supported the assignment of product A as an angular naphtho[1,2-*c*]pyran. The products A and B can therefore be assigned structures (90) and (130) respectively.



90



130

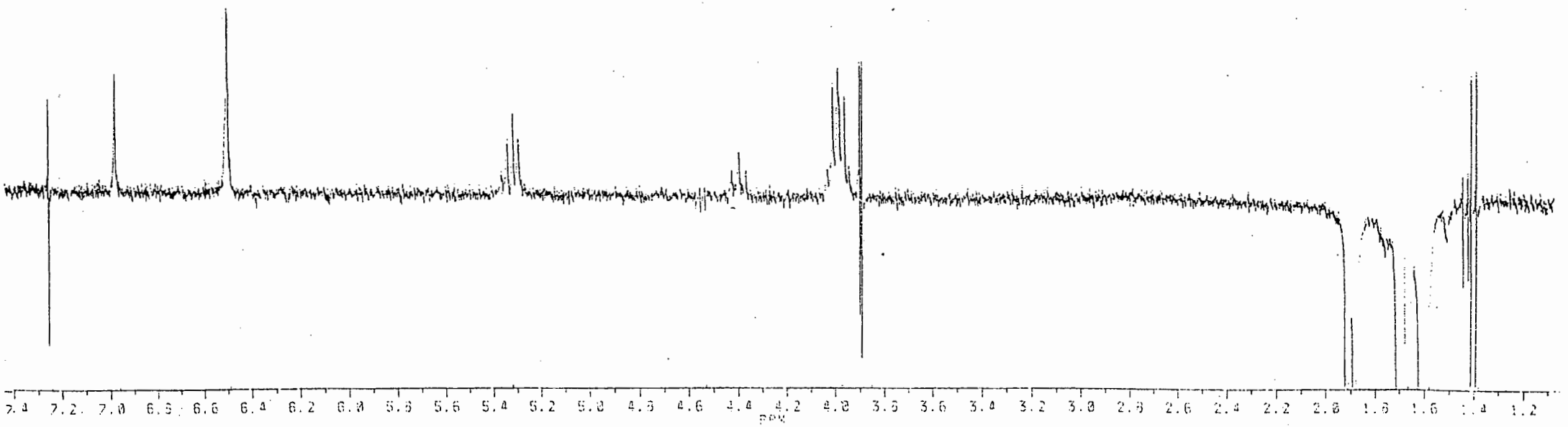

7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
ppm

figure 9

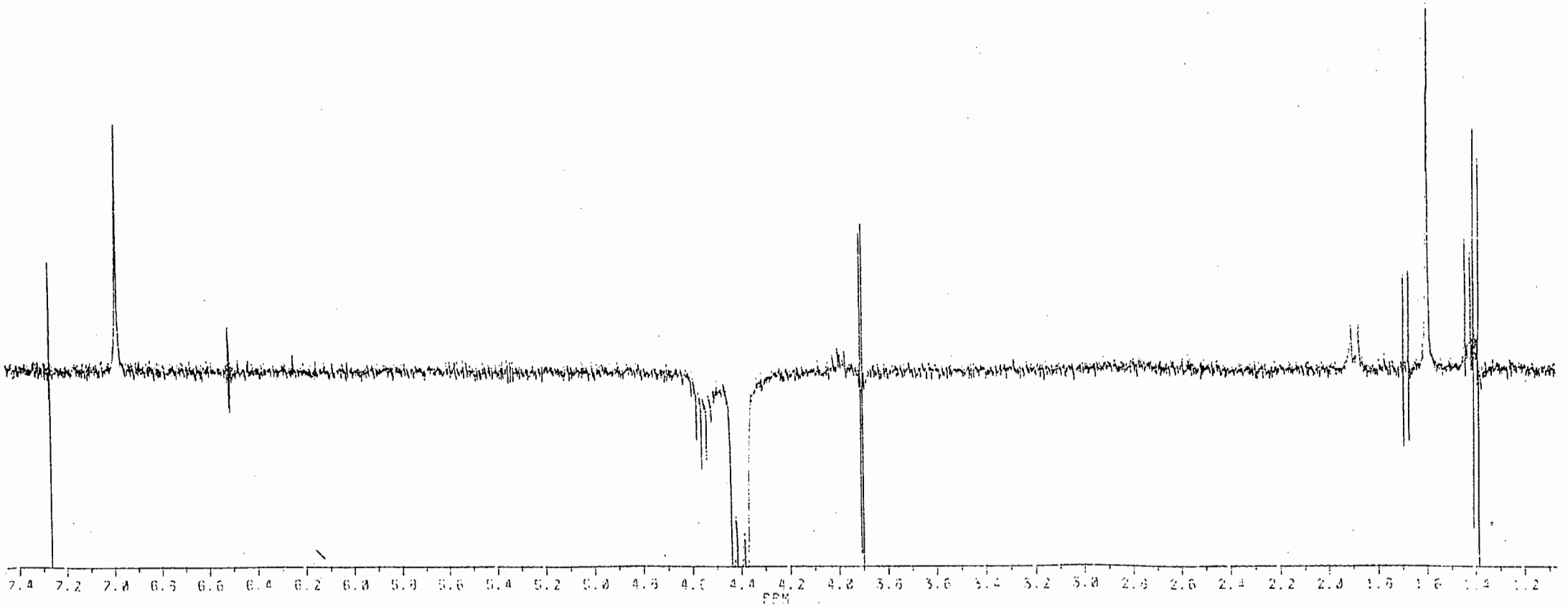
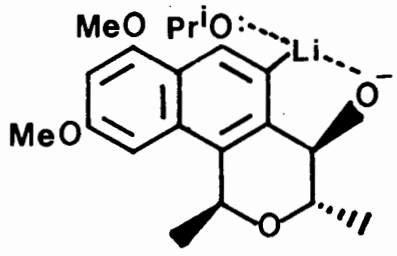

7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
PPM

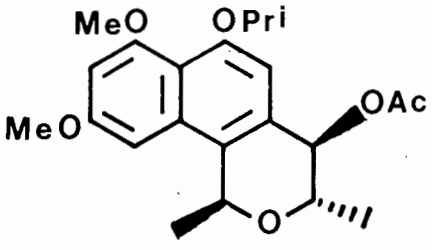
figure 10

The fact that the bromo derivative (130) was readily converted into naphthopyran (90) is easily understood in terms of the stabilisation of the lithio derivative of compound (130) by the *ortho* isopropoxy and *peri*-alcohol substituents, as shown in structure (131).

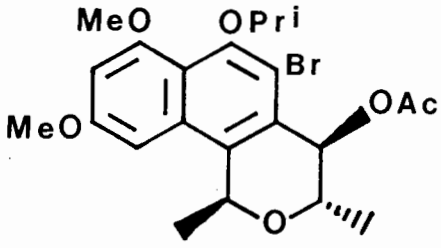


131

Similarly, the acetates of the alcohols (90) and (130) will be represented by structures (132) and (133) respectively.



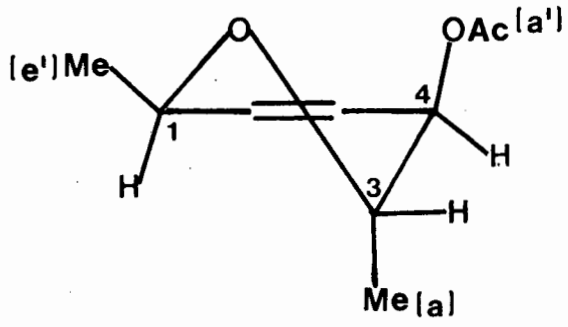
132



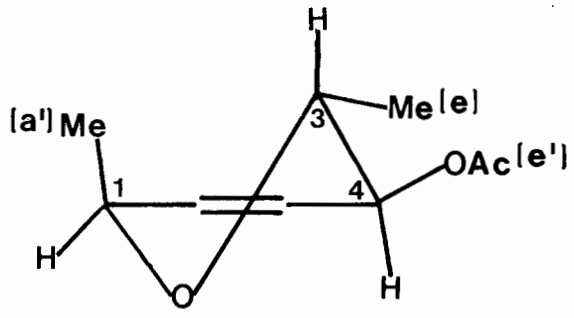
133

The ^{1}H n.m.r. spectra of the acetates (132) and (133) of compounds (90) and (130) are shown in figures 7 and 8. The spectrum of acetate (132) shows the deshielding of 4-H on acetylation (compare figures 7 and 4). However, a comparison of figures 8 and 5 shows, in addition to similar deshielding of 4-H, the doubling of the 4-H signal to give two signals of unequal intensity with rather smaller coupling constants (2.7

and 3.7 Hz). This doubling can be explained in terms of two conformations of the pyran ring of the acetate (133), *viz.* (134) and (135).



134



135

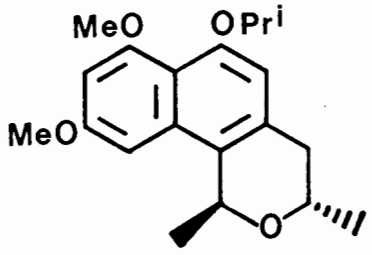
Presumably the *pseudo*-equatorial configuration of the C-4 acetate, as shown in structure (135), is correspondingly less favoured relative to the possible *pseudo*-axial alternative (134), which could be achieved by conformational inversion of the *pseudo*-chair form of the dihydropyran ring. This conformational change would, however, be achieved at the expense of the C-3 methyl group assuming an axial configuration, which would be energetically less favourable because of the derived *pseudo*-1,3-diaxial interaction. At the same time the C-1 methyl would be changed from *pseudo*-axial to *pseudo*-

equatorial, a change which might well be energetically favoured. Earlier studies studies had shown that, in the corresponding conversion of dioxolane (94) into naphthopyrans (95) and (96), the isomer (96) with the C-1 methyl *pseudo*-equatorial was favoured in yield over that of compound (95) in which the C-1 methyl was *pseudo*-axial, in a ratio of approximately three to one.[33]

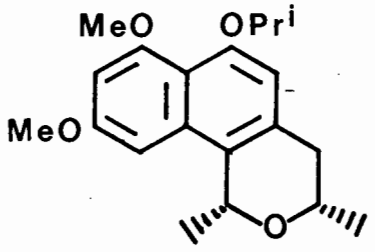
In compound (134) therefore, the smaller dihedral angle between the equatorial 3-H and *pseudo*-equatorial 4-H, would give rise to a smaller coupling constant. For conformer (135) however, the *pseudo*-equatorial acetate may well be sterically compressed by the neighbouring bromine into minimising these *peri*-interactions. This would have the effect of reducing the dihedral angle between the almost antiperiplanar 3-H and 4-H, and would in turn lessen the coupling constant between them.

At this point it was imperative to establish beyond doubt the stereochemistry at C-1 in compounds (90) and (130), as the only evidence for the *pseudo*-axial orientation of the methyl at this position was provided by a n.O.e. difference spectrum.

Naphtho[1,2-*c*]pyrans (95) and (96) have the C-1 methyl *pseudo*-axial and *pseudo*-equatorial respectively. The structures of these compounds were determined by X-ray crystallography. Removal of the benzylic hydroxy group at C-4 of each of these would result in the formation of the *trans*- and *cis*-dimethylpyrans (136) and (137) respectively.



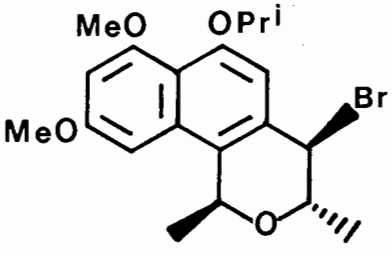
136



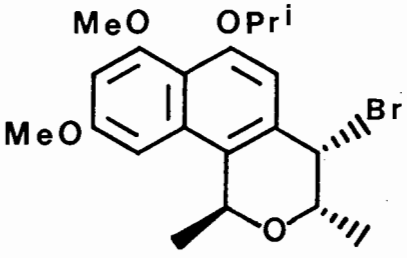
137

If the assignment of structure (90) for the major product obtained upon isomerisation of dioxolane (126) was correct, removal of the C-4 hydroxy from this pyran should result in the formation of the same *trans*-dimethylpyran (136) as obtained from compound (95). Therefore, a comparison of the two dimethylpyrans would confirm the C-1 stereochemistry, and at the same time would also prove that the products (90) and (130) possessed the naphtho[1,2-*c*]pyran ring system.

Compound (95) was thus treated with phosphorous tribromide in benzene at room temperature. After thirty minutes, two products of higher R_f were obtained which were shown by ^1H n.m.r. spectroscopy to be the two bromopyrans (138) and (139).



138



139

The C-4 bromine of compound (138) was *pseudo*-equatorial, as indicated by the large coupling constant of 8.5 Hz between 3-H and 4-H, the signal for 4-H being a doublet (J 8.5 Hz) at δ 5.06. The corresponding signal for 4-H of compound (139) was a doublet (J 2 Hz) at δ 5.11, thus implying that the C-4 bromine was *pseudo*-axial.

The singlet for the aromatic 5-H of compound (138) appeared at δ 6.92, whereas for compound (139) it was at δ 6.65. This difference in chemical shift is due to the effect of the bromine at C-4. In naphthalene (138), where the bromine is *pseudo*-equatorial, its close proximity will deshield the adjacent 5-H.

Treatment of the mixture of these isomers with an aqueous ethanolic solution of Raney nickel catalyst yielded a single product, expected to be the *trans*-dimethylpyran (136). The loss of bromine was confirmed by the mass spectrum of the product, which showed a molecular ion at m/z 330.

The ^{1}H n.m.r. spectrum (figure 11) showed an apparent doublet (J 7.2 Hz) at δ 2.71 for the *pseudo*-equatorial and *pseudo*-axial 4-H protons and an apparent sextet at δ 4.25 (J *ca.* 6.5 Hz) for 3-H. A sharp quartet (J 6.6 Hz) at δ 5.40 appeared for 1-H.

The chemical shifts for the 3-H and 1-H protons of dimethyl-naphthopyrans have been reported,[21] and were used to assign the *trans*-stereochemistry of the dimethylpyrans (36) and (71). The 3-H multiplets appear in the range δ 3.9 - 4.3 for

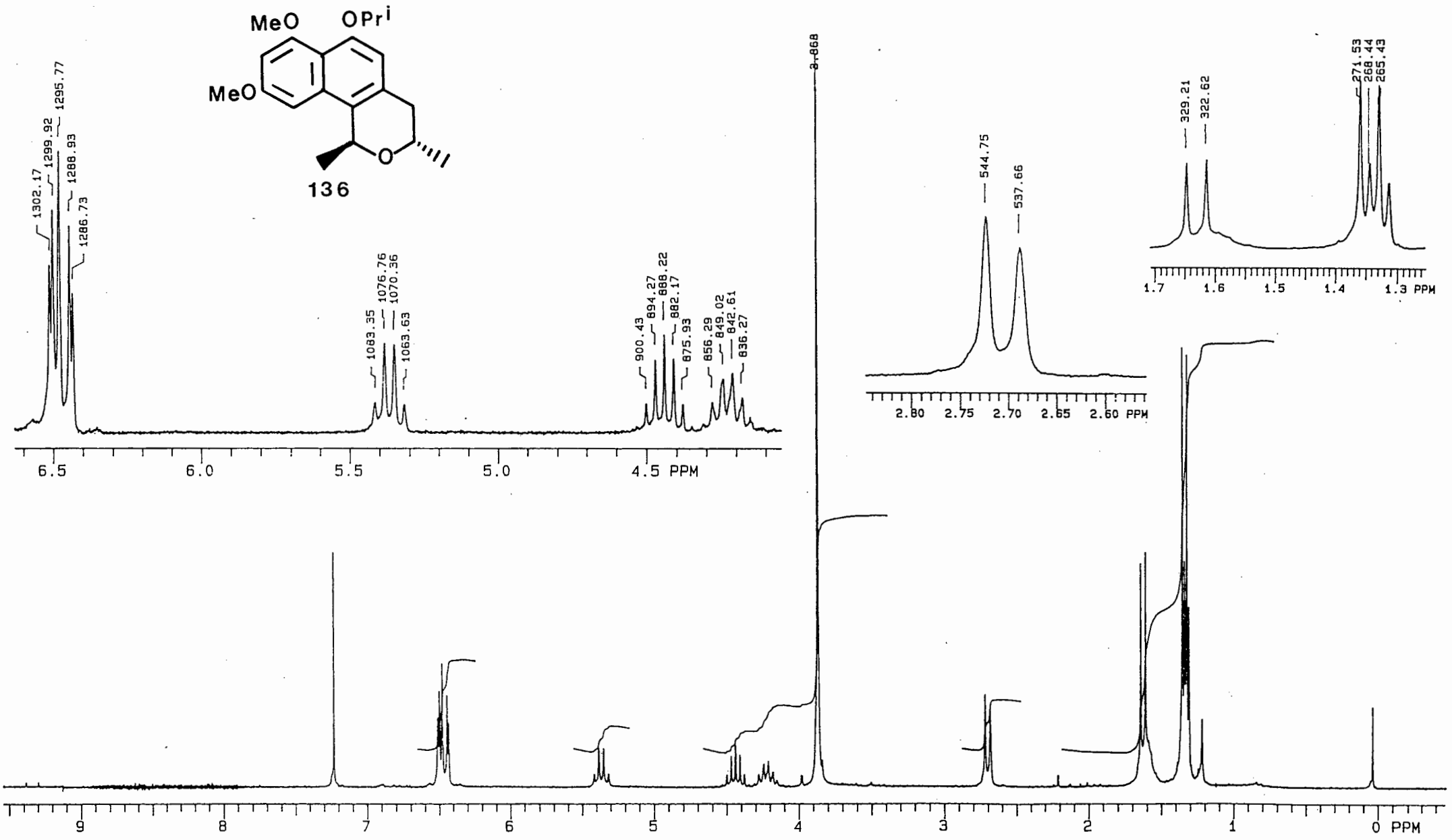
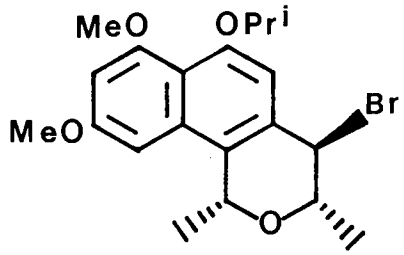

MeO
OPr^i
MeO
136
1302.17
1299.92
1295.77
1288.93
1286.73
1083.35
1076.76
1070.36
1063.63
900.43
894.27
888.22
882.17
875.93
856.29
849.02
842.61
836.27
3.868
544.75
537.66
329.21
322.62
271.53
268.44
265.43
6.5
6.0
5.5
5.0
4.5 PPM
2.80
2.75
2.70
2.65
2.60 PPM
1.7
1.6
1.5
1.4
1.3 PPM
9
8
7
6
5
4
3
2
1
0 PPM

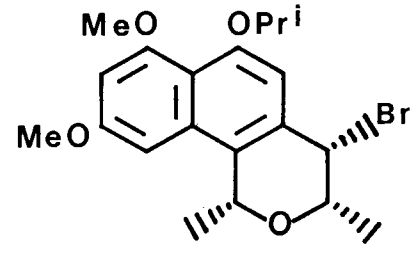
figure 11

trans-isomers, whereas for *cis*-isomers they appear at δ 3.5 - 3.8. The 1-H quartet for *trans*-compounds is at *ca.* δ 5.3, whereas for *cis*-compounds it appears at *ca.* δ 5.2. It is noteworthy that the value for the 3-H multiplet of the *trans*-dimethylnaphthopyran (136) appears in the reported region.

Naphthopyran (96) was treated with phosphorous tribromide to yield the bromopyrans (140) and (141). The stereochemistry of the bromine at C-4 was again suggested by the coupling constant for the 4-H signal in the ^{1}H n.m.r. spectrum. For compound (140), this signal was a doublet (J 8.5 Hz) at δ 5.10, consistent with the fact that 3-H and 4-H in this bromopyran are axial and *pseudo*-axial respectively. On the other hand, for the bromopyran (141), 4-H appears as a broad singlet at δ 4.79, reflecting the fact that the corresponding dihedral angle is much smaller with 4-H *pseudo*-equatorial and 3-H axial.



140



141

Furthermore, a comparison of the ^{1}H n.m.r. spectra of the bromopyrans (140) and (141) showed the deshielding effect of the *pseudo*-equatorial bromine, over that in the corresponding *pseudo*-axial configuration.

A mixture of both isomers was treated with Raney nickel catalyst to yield a single product (137), the *cis*-dimethylnaphthopyran. The mass spectrum showed a molecular ion at *m/z* 330 confirming the loss of bromine.

The ^{1}H n.m.r. spectrum (figure 12) showed the *pseudo*-equatorial 4-H as a broad doublet (*J* 15.6 Hz) at δ 2.56 and the *pseudo*-axial 4-H as a doublet of doublets (*J* 15.6 and 10 Hz) at δ 2.79. The assignment of these signals was based on the coupling constant between 3-H (axial) and 4-H (*pseudo*-axial) which is normally in the range 10 - 15 Hz, and the coupling constant between 3-H (axial) and 4-H (*pseudo*-equatorial) which should be in the range 2 - 5 Hz. The chemical shifts of the 4-Ha'and 4-He' are unusual, since the most deshielded proton is normally 4-He'.

A doublet of doublet of quartets (*J* 2.2, 10, and 6.1 Hz) appeared at δ 3.74 for 3-H, in the range reported for *cis*-dimethylnaphtho[2,3-*c*]pyrans. The 1-H quartet appeared at δ 5.44.

It can be seen that the differences in the ^{1}H n.m.r. spectra of the *trans*- and *cis*-dimethylnaphtho[1,2-*c*]pyrans are obvious enough to be used to differentiate between them. Furthermore, the position of the 3-H multiplet seems to be general for both linear and angular naphthopyrans, and could therefore be used to identify the relative stereochemistry of the methyls on the pyran ring. It follows therefore, that inspection of the ^{1}H n.m.r. spectrum obtained on the product derived by removal of the C-4 benzylic hydroxy of compound

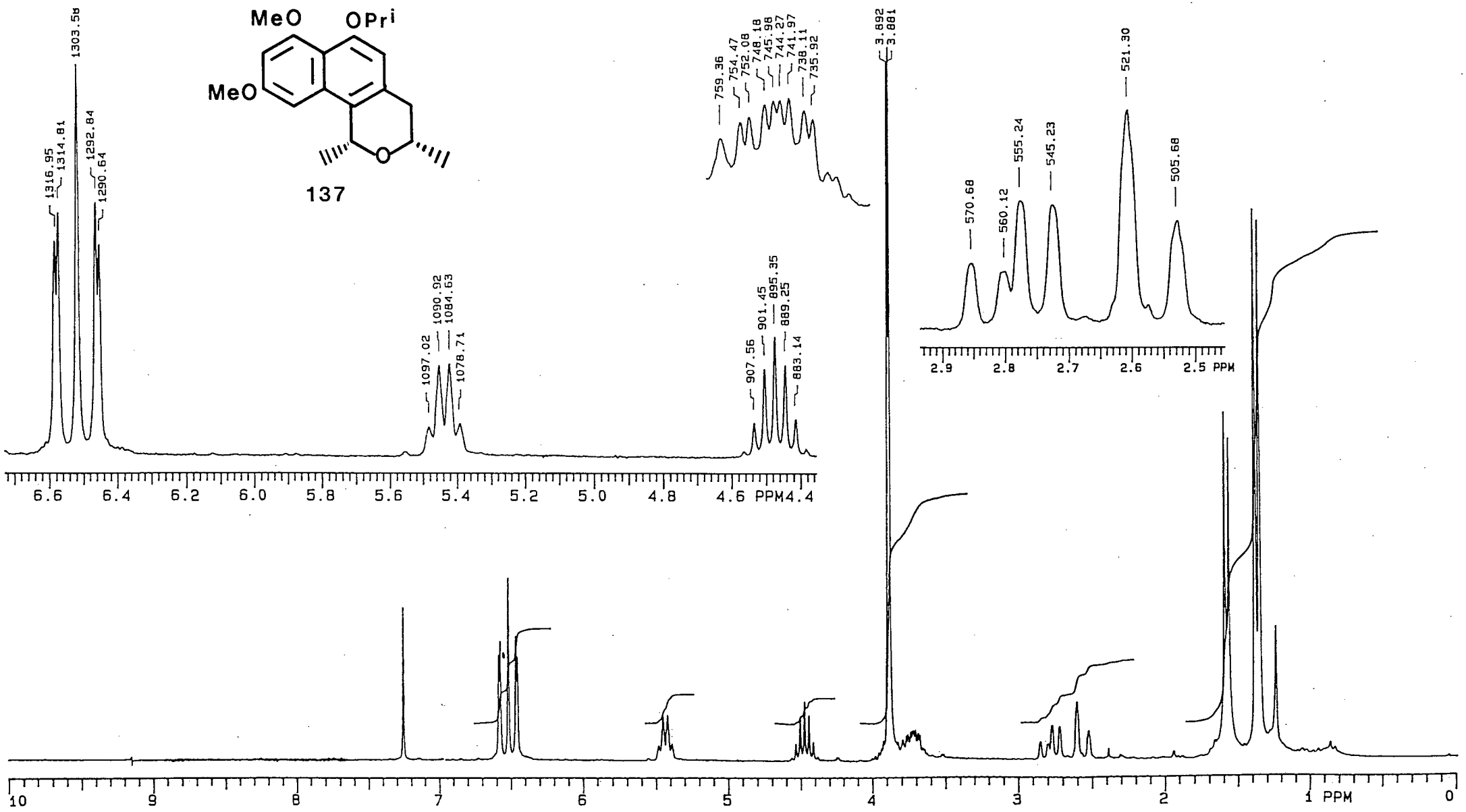

MeO
OPr^i
MeO
137
1316.95
1314.81
1303.56
1292.84
1290.64
1097.02
1090.92
1084.63
1078.71
907.56
901.45
895.35
889.25
883.14
759.36
754.47
752.08
748.18
745.98
744.27
741.97
738.11
735.92
3.892
3.881
570.68
560.12
555.24
545.23
521.30
505.68
6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 PPM4.4
2.9 2.8 2.7 2.6 2.5 PPM
10 9 8 7 6 5 4 3 2 1 PPM 0

figure 12

(90), would determine easily whether the assignment of the C-1 methyl stereochemistry was correct.

Naphthopyran (90) was treated with phosphorous tribromide to yield two bromopyrans. These products were identical (^{1}H n.m.r. and mass spectroscopy) to the bromopyrans (138) and (139) obtained from naphthopyran (95). Removal of the C-4 bromine was accomplished by reaction of the mixture of products with Raney nickel catalyst in an aqueous ethanolic solution. The product obtained was compared with compound (136) *via* infrared, ^{1}H n.m.r., and mass spectroscopy, as well as by melting point. The two compounds were found to be identical by all these criteria.

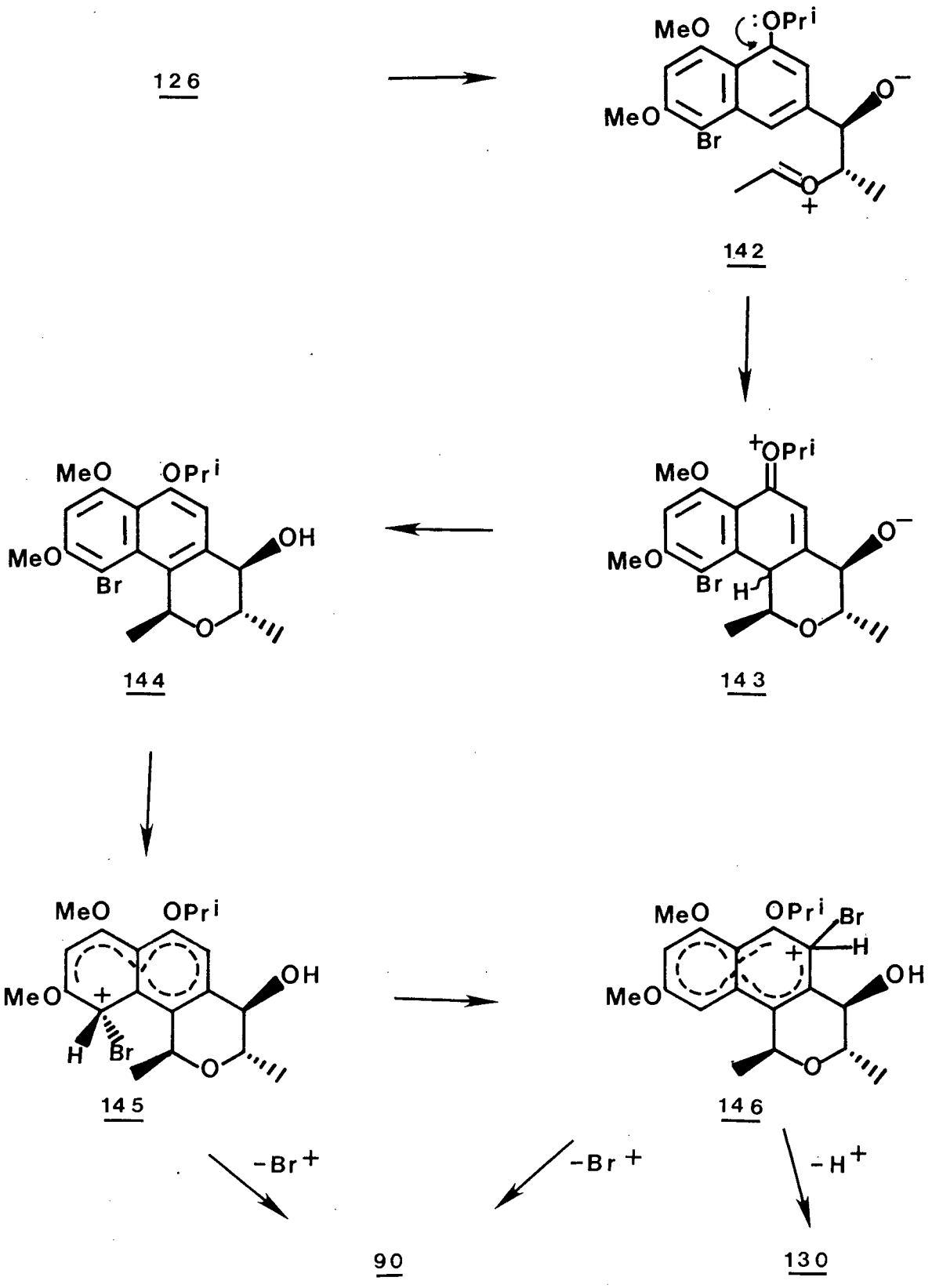
This finding therefore provided final proof that the C-1 methyl of compound (90) was *pseudo*-axial as was implied by the n.O.e. difference spectrum of this compound. Furthermore, ring closure had definitely occurred in an angular fashion. The assigned structures (90) and (130) for the major and minor products respectively of isomerisation of dioxolane (126) with titanium tetrachloride, were thus fully confirmed.

A significant difference in the course of the earlier isomerisation of dioxolane (94) to pyrans (95) and (96),[33] compared with the present conversion of dioxolane (126) into the pyrans (90) and (130), is that the former product pair are epimeric at C-1, whereas both products (90) and (130) have the same stereochemistry for the C-1 methyl.

The observation that the C-1 methyl adopts solely the *pseudo*-axial configuration must reflect the fact that the bromine at C-8 remains at its original site on the naphthalene ring until after isomerisation of the dioxolane to the naphthopyran. The bulk of the bromine atom causes the acylium ion (142) to close in such a way that the C-1 methyl adopts the least crowded configuration, yielding the intermediate (143) (Scheme 13).

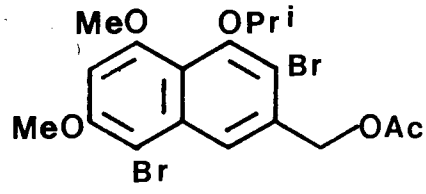
Intermediate (143) can then lose a proton directly to the alkoxide ion generated in the reaction, to afford the naphthopyran (144). This intermediate (144), could be the compound observed by thin layer chromatography during the course of the reaction, but which was different to both of the products (90) or (130) obtained upon work-up of the reaction mixture. Presumably the compound (144) is very crowded, and protonation of it would lead to the intermediate (145), analogous to intermediate (104) proposed earlier for bromine migrations. It might be speculated that in structure (145), bromine would choose to adopt the less crowded environment obtained by protonation of the naphthalene face from the same side as the C-1 methyl, as drawn.

The alternative possibility is that the proton lost from intermediate (143) directly protonates the carbon carrying bromine. Although this suggestion is reasonable, it would not explain the intermediate product observed, but not isolated, during the reaction process. It is perhaps more likely that protonation of compound (144) to afford products (90) and (130) would occur on work-up and chromatography.



SCHEME 13

Product (90) could arise directly from intermediate (144) by loss of bromine, or alternatively, indirectly from the intermediate (146). The fact that the released bromonium ion attaches itself to C-5 of the naphthopyran is consistent with the fact that dibromination of naphthalene (101), or monobromination of its bromo derivative (102) affords the dibromo compound (147).[33]



147

It is also notable that no naphthofuran of type (92) or (93) was observed on isomerisation of dioxolane (126). It is assumed that either of the dioxolane ring C-O bonds can, and presumably do, break but that the pyran ring is formed as it is energetically favoured. Dreiding models of the naphthofurans suggest that they are more strained than the observed naphthopyrans.

The aim of this project was to synthesise the linear naphtho-[2,3-*c*]pyran (72) *via* the novel cyclisation of a dioxolanyl naphthalene. It appears however, that even blocking the C-8 position of the dioxolane is not sufficient to prevent the formation of an angular naphtho[1,2-*c*]pyran. A possibility is that the steric bulk of the isopropoxy group at C-4 of the dioxolanyl naphthalene nucleus is governing the formation of

this naphthopyran, by preventing ring closure from occurring at C-3. Thus an alternative would be to decrease the size of the protecting group at C-4.

The isopropyl group may be removed from the diol (125) by the Lewis acid boron trichloride, thereby permitting substitution of a methyl or any other protecting group at the subsequent dioxolane stage. The reaction sequence may even be continued with C-4 as an hydroxy group. These possibilities are currently being investigated in this Department at the University of Cape Town.

EXPERIMENTAL

General procedures:

The same as described for Chapter 1.

Synthesis of 4-hydroxy-10-methoxy-1,3-dimethyl-1*H*-naphtho-[2,3-*c*]pyran.

1-*Acetoxy*-3-*acetyl*-4-*methoxynaphthalene* (44).- Naphthol (43)[31] (3.00 g, 12.3 mmol) was dissolved in dry acetone (50 ml). Potassium carbonate (4.4 g, 30.75 mmol) and dimethyl sulphate (3.87 g, 30.75 mmol) were added and the mixture stirred vigorously and boiled for 1.5 h under nitrogen. The mixture was cooled, filtered, and the solvent evaporated. The residue was taken up in ether and washed with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the product (44) (2.65 g, 84%) as white rhomboids, m.p. 92 - 93°C (methanol) (Found: C, 69.7; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%); $\nu_{max.}$ 1756 (OAc), 1671 (C=O), and 1602 (C=C) cm^{-1}; δ_H (90 MHz) 2.45 (3 H, s, $OCOCH_3$), 2.78 (3 H, s, $COCH_3$), 3.99 (3 H, s, OCH_3), 7.55 (1 H, s, 2-H), 7.55 - 7.66 (2 H, m, 6- and 7-H), 7.70 - 7.90 (1 H, m, 8-H), and 8.14 - 8.34 (1 H, m, 5-H); *m/z* 258 (M^+, 17%), 216 (100), 201 (68), 173 (28), and 160 (65).

3-Acetyl-4-methoxy-1-naphthol (45).-
Compound (44) (700 mg, 2.71 mmol) was dissolved in a 1% w/v methanolic solution of potassium hydroxide (227 mg, 4.0 mmol). This solution was stirred at room temperature for 10 min before quenching by addition of dilute hydrochloric acid. The organic material was extracted into methylene chloride and the extract washed with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the naphthol (45) (510 mg, 87%) as pale yellow plates, m.p. 137 - 138°C (light petroleum-methylene chloride) (Found: C, 72.3; H, 5.65. $C_{13}H_{12}O_3$ requires C, 72.2; H, 55.5%); $\nu_{max.}$ 3423 (OH), 1652 (C=O), 1623 and 1595 (C=C) cm^{-1}; δ_H (90 MHz) 2.82 (3 H, s, $COCH_3$), 3.94 (3 H, s, OCH_3), 7.38 (1 H, s, 2-H), 7.41 (1 H, br. s, partially obscured by 2-H and chloroform, OH, D_2O exchangeable), 7.48 - 7.67 (2 H, m, 6- and 7-H), and 8.04 - 8.36 (2 H, m, 5- and 8-H); *m/z* 216 (M^+, 100%), 201 (68), 186 (15), and 173 (42).

3-Acetyl-4-methoxy-1-prop-2'-enyloxynaphthalene (46).-
Naphthol (45) (500 mg, 2.31 mmol) was dissolved in dry acetone (50 ml) and treated with potassium carbonate (810 mg, 5.87 mmol) and allyl bromide (710 mg, 5.87 mmol). The mixture was boiled with vigorous stirring for 12 h under nitrogen. The solution was cooled, filtered, and the solvent evaporated to give a residue which was dissolved in methylene chloride. This solution was washed with water and dried over magnesium sulphate, filtered, and the solvent evaporated to give a residue which was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the product (46) (510 mg,

86%) as a pale yellow oil (Found: C, 75.1; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.25%); $\nu_{max.}$ (film) 1669 (C=O), 1622 and 1595 (C=C) cm^{-1}; δ_H (90 MHz) 2.58 (3 H, s, $COCH_3$), 3.92 (3 H, s, OCH_3), 4.72 (2 H, br. d, *J* 5 Hz, OCH_2), 5.20 - 5.40 (2 H, m, vinyl CH_2), 5.64 - 6.38 (1 H, m, vinyl CH), 7.04 (1 H, s, 2-H), 7.44 - 7.68 (2 H, m, 6- and 7-H), and 8.02 - 8.38 (2 H, m, 5- and 8-H); *m/z* 256 (M^+, 25%), 215 (100), 183 (34), and 155 (30).

3-Acetyl-4-methoxy-2-prop-2'-enyl-1-naphthol (47).-
Compound (46) (143 mg, 0.56 mmol) was heated at 160 - 165°C for 5 h as a neat oil under nitrogen. The black gummy oil was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the unstable naphthol (47) (127 mg, 89%) as an oil. δ_H 2.58 (3 H, s, $COCH_3$), 3.42 (2 H, br. d, *J* 6 Hz, $ArCH_2$), 3.83 (3 H, s, OCH_3), 4.98 - 5.28 (2 H, m, vinyl CH_2), 5.60 (1 H, br. s, OH, D_2O exchangeable), 5.78 - 6.20 (1 H, m, vinyl CH), 7.38 - 7.42 (2 H, m, 6- and 7-H), and 7.70 - 8.08 (2 H, m, 8-H). This oil was immediately converted to the isopropoxy derivative (48) or the benzyl derivative (57).

3-Acetyl-4-methoxy-2-prop-2'-enyl-1-(2-propyloxy)naphthalene (48).-
Naphthol (47) (160 mg, 0.63 mmol) was dissolved in dry dimethylformamide (4 ml). Isopropyl bromide (190 mg, 1.58 mmol) and potassium carbonate (218 mg, 1.58 mmol) were added to the solution which was then heated at 60°C under nitrogen for 18 h. The mixture was cooled, filtered, and then

extracted with ether. The residue obtained upon work-up was chromatographed (eluant 5% ethyl acetate-light petroleum) to yield compound (48) (150 mg, 80%) as a yellow oil (Found: C, 76.3; H, 7.3. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%); $\nu_{max.}$ (film) 1697 (C=O) and 1564 (C=C) cm^{-1}; δ_H (90 MHz) 1.34 (6 H, d, *J* 7 Hz, $CH(C\underline{H}_3)_2$), 2.58 (3 H, s, $COCH_3$), 3.62 (2 H, dt, *J* 5 and 2 Hz, $ArCH_2$), 3.84 (3 H, s, OCH_3), 4.20 - 4.28 (1 H, septet, *J* 7 Hz, $C\underline{H}(CH_3)_2$), 4.80 - 5.08 (2 H, vinyl CH_2), 5.64 - 6.08 (1 H, m, vinyl CH), 7.42 - 7.62 (2 H, m, 2- and 7-H), and 7.92 - 8.20 (2 H, m, 5- and 8-H); *m/z* 298 (M^+, 30%), 256 (46), 241 (100), and 226 (22).

3-(1-*Hydroxyethyl*)-4-*methoxy*-2-*prop*-2'-*enyl*-1-(2-*propyloxy*)-*naphthalene* (49).-

To a stirred suspension of lithium aluminium hydride (427 mg, 2.82 mmol) in dry ether (50 ml), was added the ketone (48) (840 mg, 2.82 mmol) in dry ether (20 ml) at a rapid drip rate. The reaction was stirred for 10 min after the addition was complete, by which time t.l.c. indicated the consumption of starting material. The reaction was quenched by the addition of saturated aqueous ammonium chloride, followed by magnesium sulphate. The solid material was filtered off and the filtrate evaporated to give a residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford compound (49) (744 mg, 88%) as a yellow oil (Found: C, 76.0; H, 7.9. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.0%); $\nu_{max.}$ (film) 3429 (OH), 1635 and 1584 (C=C) cm^{-1}; δ_H (90 MHz) 1.29 and 1.36 (each 3 H, d, *J* 6 Hz, $CH(C\underline{H}_3)_2$),1.42 (3 H, d, *J* 7 Hz, $CH(OH)C\underline{H}_3$), 3.54 - 3.98 (3 H, m, $ArCH_2$ and $C\underline{H}(OH)CH_3$), 4.03

(3 H, s, OCH_3),4.20 - 4.50 (1 H, septet, *J* 7 Hz, C<u>H</u>$(CH_3)_2$), 4.80 - 5.34 (3 H, m, vinyl CH_2 and OH), 5.78 - 6.18 (1 H, m, vinyl CH), 7.32 - 7.56 (2 H, m, 6- and 7-H), and 7.84 - 8.16 (2 H, m, 5- and 8-H); *m/z* 300 (M^+, 87%), 282 (18), 258 (100), 249 (38), and 224 (78).

trans-3,4-*Dihydro*-10-*methoxy*-1,3-*dimethyl*-5-(2-*propyloxy*)-1H-*naphtho*[2,3-c]*pyran* (<u>50</u>).-

Compound (<u>49</u>) (244 mg, 0.81 mmol) was dissolved in dry dimethylformamide (10 ml) and dry nitrogen was passed through the solution for 10 min. Potassium *t*-butoxide (555 mg, 4.86 mmol) was added and this solution stirred at room temperature under nitrogen for 30 min. The reaction was quenched by the addition of water and the mixture was extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant 5% ethyl acetate-light petroleum to afford the <u>naphthopyran</u> (<u>50</u>) (187 mg, 77%) as white needles, m.p. 54 - 55°C (light petroleum-methylene chloride) (Found: C, 75.9; H, 7.8. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.0%); $\nu_{max.}$ 1589 (C=C) cm^{-1}; δ_H (90 MHz) 1.31 (3 H, d, *J* 8 Hz, 3-CH_3), 1.36 (6 H , d, *J* 7 Hz, $CH(C\underline{H}_3)_2$), 1.59 (3 H, d, *J* 7 Hz, 1-CH_3), 2.56 (1 H, dd, *J* 11 and 18 Hz, *pseudo*-axial 4-H), 3.12 (1 H, dd, *J* 4 and 18 Hz, *pseudo*-equatorial 4-H), 3.88 (3 H, s, OCH_3), 3.80 - 4.30 (1 H, m, 3-H), 4.30 - 4.54 (1 H, septet, *J* 7 Hz, C<u>H</u>$(CH_3)_2$), 5.32 (1 H, q, *J* 7 Hz, 1-H), 7.32 - 7.55 (2 H, m, 7- and 8-H), and 7.88 - 8.12 (2 H, m, 6- and 9-H); *m/z* 300 (M^+, 50%), 258 (38), 243 (100), 228 (20), and 213 (40).

3-Acetyl-1-benzyloxy-4-methoxy-2-prop-2'-enylnaphthalene (57).-

Naphthol (47) (2.28 g, 8.91 mmol) and benzyl bromide (3.85 g, 22.5 mmol) were dissolved in dry acetone (100 ml). Potassium carbonate (3.09 g, 22.5 mmol) was added and the solution boiled under nitrogen for 18 h. The solution was cooled, filtered and evaporated to dryness. The residue was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield compound (57) (2.87 g, 93%) as white needles, m.p. 62 - 63°C (light petroleum-methylene chloride) (Found: C, 79.95; H, 6.45. $C_{23}H_{22}O_3$ requires C, 79.8; H, 6.4%); $\nu_{max.}$ 1700 (C=O) and 1583 (C=C) cm^{-1}; δ_H (90 MHz) 2.60 (3 H, s, $COCH_3$), 3.62 (2 H, br. d, *J* 5 Hz, $ArC\underline{H}_2$), 3.88 (3 H, s, OCH_3), 4.80 - 5.14 (2 H, m, vinyl CH_2), 4.96 (2 H, s, $OC\underline{H}_2Ph$), 5.70 - 6.14 (1 H, m, vinyl CH), 7.30 - 7.66 (7 H, m, $OCH_2\underline{Ph}$, 6- and 7-H), and 7.96 - 8.18 (2 H, m, 5- and 8-H); *m/z* 346 (M^+, 40%), 255 (100), 240 (55), 213 (35), and 91 (84).

1-Benzyloxy-3-(1-hydroxyethyl)-4-methoxy-2-prop-2'-enyl-naphthalene (58).-

Naphthalene (57) (2.91 g, 8.41 mmol) in dry ether (20 ml) was added to a stirred suspension of lithium aluminium hydride (1.12 g, 33.6 mmol) in dry ether (20 ml). After 20 min, t.l.c. showed that all starting material had been consumed and the reaction was quenched by the addition of saturated aqueous ammonium chloride followed by magnesium sulphate. Evaporation of the filtrate gave a residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield

the product (58) (2.45 g, 83%) as a pale yellow cubes, m.p. 45 - 46°C (light petroleum) (Found: C, 79.5; H, 6.95. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.0%); $\nu_{max.}$ (film) 3375 (OH) and 1586 (C=C) cm^{-1}; δ_H (90 MHz) 1.60 (3 H, d, *J* 8 Hz, CH(OH)C$\underline{H}_3$), 3.59 - 4.03 (3 H, m, C$\underline{H}$(OH)CH_3 and ArC$\underline{H}_2$), 4.07 (3 H, s, OCH_3), 4.97 (2 H, s, OC$\underline{H}_2$Ph), 4.81 - 5.43 (3 H, m, vinyl CH_2 and OH), 5.85 - 6.31 (1 H, m, vinyl CH), 7.35 - 7.65 (7 H, m, $OCH_2\underline{Ph}$, 6- and 7-H), and 7.95 - 8.19 (2 H, m, 5- and 8-H); *m/z* (M^+, 24%), 257 (100), 239 (20), 213 (20), and 91 (47).

trans-5-*Benzyloxy*-3,4-*dihydro*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* (59).-

Compound (58) (50 mg, 0.14 mmol) was dissolved in dry dimethylformamide (3 ml), and dry nitrogen passed through the solution for 10 min. Potassium *t*-butoxide (96 mg, 0.86 mmol) was added and the solution stirred under nitrogen at room temperature for 20 min. The mixture was then thrown into water and extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the naphthopyran (59) (36 mg, 72%) as white needles, m.p. 106 - 107°C (light petroleum-methylene chloride) (Found: C, 79.5; H, 6.85. $C_{23}H_{24}O_2$ requires C, 79.3; H, 6.9%); $\nu_{max.}$ 1592 (C=C) cm^{-1}; δ_H (90 MHz) 1.35 (3 H, d, *J* 6 Hz, 3-CH_3), 1.63 (3 H, d, *J* 6 Hz, 1-CH_3), 2.56 (1 H, dd, *J* 10 and 17 Hz, *pseudo*-axial 4-H), 3.10 (1 H, dd, *J* 3.5 and 17 Hz, *pseudo*-equatorial 4-H), 3.92 (3 H, s, OCH_3), 4.01 - 4.20 (1 H, m, 3-H), 4.94 and 5.04 (each 1 H, d, *J* 10 Hz, OC$\underline{H}_2$Ph), 5.35 (1 H, q, *J* 6 Hz, 1-H), 7.32 - 7.61

(7 H, m, OCH_2Ph, 7- and 8-H), and 7.98 - 8.15 (2 H, m, 6- and 7-H); *m/z* (M^+, 10%), 257 (54), 213 (100), and 91 (30).

trans-3,4-*Dihydro*-10-*methoxy*-1,3-*dimethyl*-5-*methylsulphoxy*-1H-*naphtho*[2,3-c]*pyran* (37).-

Compound (59) (51 mg, 0.15 mmol) was dissolved in dry methylene chloride (5 ml) at -78°C. Boron trichloride (35 mg, 0.30 mmol) in methylene chloride was added and the solution stirred at -78°C for 10 min. The reaction was quenched by the addition of water, and the organic layer separated and washed with more water. The residue obtained upon work-up containing naphthol (60) was immediately dissolved in dry pyridine (6 ml) and methylsulphonyl chloride (0.1 ml, 1.35 mmol) added. This solution was stirred at room temperature for 3 h. Dilute hydrochloric acid was added to quench the reaction acid and the organic material was extracted into methylene chloride and washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl actetate-light petroleum) to afford the product (37) (41 mg, 81%) as white needles, m.p. 115 - 116°C (methanol) (Found: C, 60.5; H, 5.95. $C_{17}H_{20}O_5S$ requires C, 60.7; H, 5.95%); $\nu_{max.}$ 1594 (C=C), 1339 and 1167 (OSO_2CH_3) cm^{-1}; δ_H (90 MHz) 1.36 (3 H ,d, *J* 7 Hz, 3-CH_3), 1.62 (3 H, d, *J* 7 Hz, 1-CH_3), 2.74 (1 H, dd, *J* 11 and 18 Hz, *pseudo*-axial 4-H), 2.94 (1 H, dd, *J* 4 and 18 Hz, *pseudo*-equatorial 4-H), 3.38 (3 H, s, OSO_2CH_3), 3.92 (3 H, s, OCH_3), 3.96 - 4.30 (1 H, m, 3-H), 5.33 (1 H, q, *J* 7 Hz, 1-H), 7.42 - 7.64 (2 H, m, 7- and 8-H), and 7.92 - 7.98 (2 H, m, 6- and 9-H); *m/z* 336 (M^+, 15%), 257 (32), and 213 (100).

trans-3,4-*Dihydro*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]-*pyran* (36).-

Compound (37) (50 mg, 0.15 mmol) was dissolved in ethanol (7.5 ml) and water (2.5 ml) and the solution was boiled for 2 h with Raney nickel catalyst (400 mg, 50% in water). The catalyst was filtered off and washed exhaustively with methylene chloride. The organic layer was washed with water and dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the product (36) (24 mg, 66%) as colourless rhomboids, m.p. 85 - 86°C (methanol) (Found: C, 79.1; H, 7.45. $C_{16}H_{18}O_2$ requires C, 79.3; H, 7.4%); $\nu_{max.}$ 1631 and 1559 (C=C) cm^{-1}; δ_H (90 MHz) 1.21 (3 H, d, *J* 7 Hz, 3-CH_3), 1.62 (3 H, d, *J* 7 Hz, 1-CH_3), 2.80 (1 H dd, *J* 10.5 and 17 Hz, *pseudo*-axial 4-H), 2.94 (1 H, dd, *J* 5 and 17 Hz, *pseudo*-equatorial 4-H), 3.90 (3 H, s, OCH_3), 3.98 - 4.36 (1 H, m, 3-H), 5.34 (1 H, q, *J* 7 Hz, 1-H), 7.30 - 7.50 (2 H, m, 7- and 8-H), 7.38 (1 H, s, 5-H), 7.60 - 7.80 (1 H, m, 6-H), and 7.90 - 8.06 (1 H, m, 9-H); *m/z* 242 (M^+, 25%), 227 (100), and 212 (30).

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* (21) *and its enantiomer*.-

Naphthopyran (36) (140 mg, 0.58 mmol) was dissolved in dry dimethyl sulphoxide (30 ml) and dry air passed through the solution for 15 min. Potassium *t*-butoxide (250 mg, 2.23 mmol) was added and the solution stirred at room temperature for 20 min under a stream of dry air. Another quantity of potassium *t*-butoxide (130 mg, 1.16 mmol) was added and the

mixture stirred for a further 20 min. The reaction was quenched by the addition of water and the mixture extracted exhaustively with ether. The ether layer was washed several times with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to yield the product (21) (100 mg, 67%) as white cubes, m.p. 141 - 142°C (*n*-hexane) (Found: M^+, 258.1240. $C_{16}H_{18}O_3$ requires *M*, 258.1255); $\nu_{max.}$ 3410 (OH), 1631 and 1598 (C=C) cm^{-1}; δ_H 1.41 (3 H, d, *J* 6.5 Hz, 3-CH_3), 1.68 (3 H, d, *J* 6.6 Hz, 1-CH_3), 2.04 (1 H, br. s, OH, D_2O exchangeable), 3.43 (3 H, s, OCH_3), 3.89 - 4.06 (1 H, m, partially obscured by OCH_3, 3-H), 4.50 (1 H, br. d, *J* 5 Hz, becomes d on D_2O exchange, *J* 8 Hz, 4-H), 5.28 (1 H, q, *J* 6.6 Hz, 1-H), 7.48 - 7.52 (2 H, m, 7- and 8-H), 7.84 (1 H, s, 5-H), and 7.80 - 8.08 (2 H, m, 6- and 9-H); *m/z* 258 (M^+, 68%), 243 (100), 225 (18), and 214 (70).

Synthesis of 4-hydroxy-7,9-dimethoxy-1,3-dimethyl-10-(2-propyloxy)-1*H*-naphtho[2,3-*c*]pyran.

3-Bromo-2-hydroxymethyl-5,7-dimethoxy-4-(2-propyloxy)naphthalene (65).-

Acetate (61) (100 mg, 0.25 mmol) was dissolved in a 1% w/v solution of potassium hydroxide (21 mg, 0.38 mmol) in methanol. The solution was stirred at room temperature for 10 min and the reaction quenched by the addition of dilute hydrochloric acid. The organic material was extracted into ether and washed with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the product (65) (82 mg, 92%) as white grains, m.p. 126 - 127°C (light petroleum-ethyl acetate) (Found: C, 54.4; H, 5.6. $C_{16}H_{19}O_4Br$ requires C, 54.1; H, 5.35%); $\nu_{max.}$ 3467 (OH), 1621 and 1575 (C=C) cm^{-1}; δ_H 1.29 (6 H, d, *J* 6.2 Hz, $CH(C\underline{H}_3)_2$), 2.43 (1 H, br. s, OH, D_2O exchangeable), 3.83 and 3.89 (each 3 H, s, OCH_3), 4.46 (1 H, septet, *J* 6.2 Hz, $C\underline{H}(CH_3)_2$), 4.79 (2 H, s, CH_2), 6.46 and 6.61 (each 1 H, d, *J* 2.2 Hz, 6- and 8-H), and 7.47 (1 H, s, 1-H); δ_C 21.92 ($CH(\underline{C}H_3)_2$), 55.25 and 55.66 (2 X OCH_3), 65.22 (CH_2), 77.82 ($\underline{C}H(CH_3)_2$), 98.90 (C-6), 99.22 (C-1)[a], 113.76 (C-4a)[b], 116.64 (C-8a)[b], 121.59 (C-8)[a], 136.63 (C-3), 138.67 (C-2), 150.79 (C-4)[c], 156.54 (C-5)[c], and 158.21 (C-7)[c] (Assignments with identical superscripts are interchangeable); *m/z* 356 (M^+ {^{81}Br}, 18%), 354 (M^+ {^{79}Br}, 18%), 314 (100), 312 (100), 271 (22), and 269 (22).

3-Bromo-5,7-dimethoxy-4-(2-propyloxy)-2-naphthaldehyde (66).- Compound (65) (330 mg, 0.93 mmol) was dissolved in dry benzene (40 ml) and boiled with activated manganese dioxide[41] (1.5 g) for 2 h. The solution was cooled, filtered and evaporated to yield a residue which was chromatographed (eluant 20% ethyl acetate-light petroleum) affording the aldehyde (66) (290 mg, 88%) as yellow needles, m.p. 80 - 81°C (light petroleum) (Found: C, 54.5; H, 4.7. $C_{16}H_{17}O_4Br$ requires C, 54.4; H, 4.8%); $\nu_{max.}$ 1681 (C=O), 1615 and 1573 (C=C) cm^{-1}; δ_H 1.33 (6 H, d, *J* 6.2 Hz, $CH(C\underline{H}_3)_2$), 3.89 and 3.95 (each 3 H, s, OCH_3), 4.51 (1 H, septet, *J* 6.2 Hz, $C\underline{H}(CH_3)_2$), 6.62 and 6.81 (each 1 H, d, *J* 2.2 Hz, 6- and 8-H), 8.01 (1 H, s, 1-H), and 10.50 (1 H, s, CHO); δ_C 21.91 ($CH(\underline{C}H_3)_2$), 55.44 and 55.88 (2 X OCH_3), 77.64 ($\underline{C}H(CH_3)_2$), 100.44 (C-6), 102.14 (C-1)[a], 114.16 (C-4a)[b], 120.47 (C-8a)[b], 125.28 (C-8)[a], 131.77 (C-2), 135.87 (C-3), 151.71 (C-4)[c], 156.49 (C-5)[c], 158.77 (C-7)[c], and 192.89 (CHO); *m/z* 354 (M^+ {^{81}Br}, 19%), 352 (M^+ {^{79}Br}, 19%), 312 (100), 310 (100), 297 (9), 295 (9), 269 (25), and 267 (26).

Z- and E-3-Bromo-5,7-dimethoxy-2-prop-1'-enyl-4-(2-propyloxy)naphthalene (67) *and* (68).- Ethyltriphenylphosphonium bromide[42] (673 mg, 1.81 mmol) was added to dry tetrahydrofuran (30 ml) under nitrogen at 0°C. *n*-Butyl lithium (1.81 mmol, 1.6 mol equiv.) was added and the solution stirred at 0°C for 15 min and then cooled to -78°C. The aldehyde (66) (400 mg, 1.13 mmol) in dry tetrahydrofuran (5 ml) was added and the mixture stirred at -78°C for 15 min and warmed to room temperature over 1 h. The reaction was

quenched by the addition of water, and the mixture extracted with methylene chloride and washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluant 5% ethyl acetate-light petroleum) to afford the olefins (67) and (68) (297 mg, 72%) as an oil. δ_H 1.32 and 1.34 (each 6 H, d, *J* 6.2 Hz, $CH(C\underline{H}_3)_2$ of both isomers), 1.85 (3 H, dd, *J* 6.8 and 1.7 Hz, 3'-CH_3 of isomer (67)), 1.94 (3 H, dd, *J* 6.7 and 1.7 Hz, 3'-CH_3 of isomer (68)), 3.90 and 3.94 (each 6 H, s, OCH_3 of both isomers), 4.51 and 4.52 (each 1 H, septet, *J* 6.2 Hz, $C\underline{H}(CH_3)_2$ of both isomers), 5.91 (1 H, dq, *J* 11.4 and 6.8 Hz, 2'-H of isomer (67)), 6.24 (1 H, dq, *J* 15.5 and 6.7 Hz, 2'-H of isomer (68)), 6.49 and 6.51 (each 1 H, d, *J* 2.2 Hz, 6-H of both isomers), 6.62 (1 H, dq, *J* 11.4 and 1.7 Hz, 1'-H of isomer (67)), 6.69 (2 H, d, *J* 2.2 Hz, 8-H of both isomers), 6.87 (1 H, dq, 15.5 and 1.7 Hz, 1'-H of isomer (68)), 7.37 (1 H, s, 1-H of isomer(67)), and 7.54 (1 H, s, 1-H of isomer (68)).

E-3-*Bromo*-5,7-*dimethoxy*-2-*prop*-1'-*enyl*-4-(2-*propyloxy*)-*naphthalene* (68).-

A mixture of *Z*- and *E*-olefins (67) and (68) (100 mg, 0.27 mmol) was dissolved in dry methylene chloride (10 ml) and palladiumdichloride-bisacetonitrile[43] (20 mg) added. This reaction mixture was stirred for 3 h at room temperature. The solution was filtered and the residue obtained upon evaporation of the solvent chromatographed (eluant 5% ethyl acetate-light petroleum) to yield the product (68) (90 mg, 90%) as a yellow oil (Found: C, 59.4; H, 6.1. $C_{18}H_{21}O_3Br$ requires C, 59.2; H, 5.75%); $\nu_{max.}$ (film) 1617 and 1571 (C=C)

cm^{-1}; δ_H 1.32 (6 H, d, *J* 6.2 Hz, $CH(C\underline{H}_3)_2$), 1.94 (3 H, dd, *J* 6.7 and 1.7 Hz, 3'-CH_3), 3.90 and 3.94 (each 3 H, s, OCH_3), 4.51 (1 H, septet, *J* 6.2 Hz, $C\underline{H}(CH_3)_2$), 6.24 (1 H, dq, *J* 15.5 Hz and 6.7 Hz, 2'-H), 6.49 and 6.69 (each 1 H, d, *J* 2.2 Hz, 6- and 8-H), 6.87 (1 H, dq, *J* 15.5 and 1.7 Hz, 1'-H), and 7.54 (1 H, s, 1-H); δ_C 18.65 (3'-CH_3), 21.95 ($CH(\underline{C}H_3)_2$), 55.26 and 55.70 (2 X OCH_3), 76.36 ($\underline{C}H(CH_3)_2$), 98.61 (C-6), 99.03 (C-1)[a], 115.55 (C-4a)[b], 120.02 (C-8)[a], 124.15 (C-8a)[b], 128.76 (C-1')[c], 130.92 (C-2')[c], 136.55 (C-2)[d], 137.35 (C-3)[d], 151.94 (C-4)[e], 156.63 (C-5)[e], and 158.13 (C-7)[e]; *m/z* 366 (M^+ {^{81}Br}, 24%), 364 (M^+ {^{79}Br}, 24%), 324 (100), 322 (100), 281 (8), 279 (8), and 243 (15).

E-3-(1-*Hydroxyethyl*)-5,7-*dimethoxy*-2-*prop*-1'-*enyl*-4-(2-*propyloxy*)*naphthalene* (70).-

E-Olefin (68) (80 mg, 0.22 mmol) was dissolved in dry tetrahydrofuran (15 ml) at -78°C under nitrogen. *n*-Butyl lithium (0.31 mmol, 1.4 mol equiv.) was added. The solution was stirred for 30 min at this temperature under nitrogen. An excess of acetaldehyde (0.5 ml) was added and the solution stirred for a further 15 min. The reaction was quenched by the addition of water and the mixture extracted with ether. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the product (70) (42 mg, 58%) as an oil (Found: C, 72.3; H, 8.2. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); $\nu_{max.}$ (film) 3419 (OH), 1618 and 1571 (C=C) cm^{-1}; δ_H 1.24 and 1.32 (each 3 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.58 (3 H, d, *J* 6.8 Hz, $C\underline{H}_3(CH)OH$), 1.92 (3 H, dd, *J* 6.6 and 1.7 Hz, 3'-CH_3), 2.32 (1 H, br. s, OH, D_2O

exchangeable), 3.87 and 3.92 (each 3 H, s, OCH_3), 4.28 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.76 (1 H, q, *J* 6.8 Hz, $CH_3(C\underline{H})OH$), 6.13 (1 H, dq, *J* 15.5 and 6.6 Hz, 2'-H), 6.42 and 6.66 (each 1 H, d, *J* 2.2 Hz, 6- and 8-H), 7.24 (1 H, dq, *J* 15.5 and 1.7 Hz, partially obscured by chloroform, 1'-H), and 7.47 (1 H, s, 1-H); δ_C 18.74, 21.55, 22.38, and 23.36 (4 X CH_3), 55.23 and 55.69 (2 X OCH_3), 65.16 and 77.00 (2 X CH), 98.54 (C-1)[a], 98.69 (C-6)[a], 114.69 (C-4a)[b], 121.49 (C-8)[a], 127.69 (C-1')[c], 130.29 (C-2')[c], 130.49 (C-8a)[b], 137.11 (C-2)[d], 137.40 (C-3)[d], 150.09 (C-4)[e], 157.09 (C-5)[e], and 157.93 (C-7)[e]; *m/z* 330 (M^+, 40%), 315 (37), 300 (35), 272 (55), and 254 (100). A further compound isolated from the mixture was the *E*-olefin (76) (6 mg, 10%), identical with authentic material.[33]

Z- and E-3-(1-*Hydroxyethyl*)-5,7-*dimethoxy*-2-*prop*-1'-*enyl*-4-(2-*propyloxy*)*naphthalene* (69) *and* (70).-
A mixture of the *Z*-olefin (67) and *E*-olefin (68) (100 mg, 0.28 mmol) was dissolved in dry tetrahydrofuran (20 ml) at -78°C under nitrogen. *n*-Butyl lithium (0.39 mmol, 1.4 mol equiv.) was added and the solution stirred for 30 min at this temperature. An excess of acetaldehyde (0.8 ml) was added and the solution stirred for a further 15 min at -78°C. The reaction was quenched by the addition of water and the mixture extracted with ether. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the products (69) and (70) (53 mg, 57%) as an oil. δ_H 1.22 and 1.30 (each 3 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$ of isomer (69)), 1.24 and 1.32 (each 3 H, d, *J* 6.1 Hz,

$CH(C\underline{H}_3)_2$ of isomer (70)), 1.52 (3 H, d, *J* 6.8 Hz, $C\underline{H}_3(CH)OH$ of isomer (69)), 1.58 (3 H, d, *J* 6.8 Hz, $C\underline{H}_3(CH)OH$ of isomer (70)), 1.76 (3 H, dd, *J* 6.9 and 1.8 Hz, 3'-CH_3 of isomer (69)), 1.92 (3 H, dd, *J* 6.6 and 1.7 Hz, 3'-CH_3 of isomer (70)), 2.32 (1 H, br. s, OH of isomer (70)), 2.71 (1 H, br. s, OH of isomer (69)), 3.87, 3.90, 3.92, and 3.95 (each 3 H, s, OCH_3 of both isomers), 4.25 and 4.28 (each 1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$ of both isomers), 5.62 (1 H, q, *J* 6.8 Hz, $CH_3(C\underline{H})OH$ of isomer (69)), 5.76 (1 H, q, *J* 6.8 Hz, $CH_3(C\underline{H})OH$ of isomer (70)), 5.92 (1 H, dq, *J* 11.4 and 6.9 Hz, 2'-H of isomer (69)), 6.13 (1 H, dq, *J* 15.5 and 6.6 Hz, 2'-H of isomer (70)), 6.42 and 6.49 (each 1 H, d, *J* 2.2 Hz, 6-H of both isomers), 6.64 and 6.66 (each 1 H, d, *J* 2.2 Hz, 8-H of both isomers), 6.94 (1 H, dq, *J* 11.4 and 1.8 Hz, 1'-H of isomer (69)), 7.21 (1 H, s, 1-H of isomer (69)), 7.24 (1 H, dq, *J* 15.5 and 1.7 Hz, partially obscured by chloroform, 1'-H of isomer (70)), and 7.47 (1 H, s, 1-H of isomer (70)). A mixture of olefins (75) and (76) (10 mg, 13%), identical with authentic material was also isolated.

trans-3,4-*Dihydro*-7,9-*dimethoxy*-1,3-*dimethyl*-10-(2-*propyl*-*oxy*)-1H-*naphtho*[2,3-c]*pyran* (71).-

Compound (70) (40 mg, 0.12 mmol) was dissolved in dry dimethylformamide (5 ml) and dry nitrogen was passed through the solution for 15 min. Potassium *t*-butoxide (148 mg, 1.32 mmol) was added and the solution stirred under nitrogen for 2 h at 75°C. The reaction was quenched by the addition of water and the mixture extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant

10% ethyl acetate-light petroleum) to yield product (71) (33 mg, 83%) as white cubes, m.p. 133 -134°C (light petroleum) (Found: C, 72.7; H, 7.6. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); $\nu_{max.}$ 1626 and 1572 (C=C) cm^{-1}; δ_H 1.06 and 1.41 (each 3 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.30 (3 H, d, *J* 6.3 Hz, 3-CH_3), 1.55 (3 H, d, *J* 6.6 Hz, 1-CH_3), 2.72 - 2.84 (2 H, m, *pseudo*-axial and *pseudo*-equatorial 4-H), 3.85 and 3.90 (each 3 H, s, OCH_3), 4.01 - 4.20 (1 H, m, 3-H), 4.28 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.34 (1 H, q, *J* 6.6 Hz, 1-H), 6.39 and 6.59 (each 1 H, d, *J* 2.3 Hz, 8- and 6-H), and 7.12 (1 H, s, 5-H); δ_C 20.51, 21.21, 21.78, and 22.95 (4 X CH_3), 36.15 (CH_2), 55.17 and 55.70 (2 X OCH_3), 62.56, 69.68, and 76.91 (3 X CH), 97.95 (C-5)[a], 98.03 (C-6)[a], 114.84 (C-4a)[b], 121.68 (C-8)[a], 128.89 (C-5a)[b], 133.29 (C-9a)[b], 136.57 (C-10a)[b], 149.06 (C-7)[c], 156.78 (C-9)[c], and 157.36 (C-10)[c]; *m/z* 330 (M^+, 20%), 315 (9), and 273 (100).

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-7,9-*dimethoxy*-1,3-*dimethyl*-10-(2-*propyloxy*)-1H-*naphtho*[2,3-c]*pyran* (72) *and its enantiomer*.-

Naphthopyran (71) (50 mg, 0.15 mmol) was dissolved in dry dimethylformamide (15 ml) and dry air passed through the solution for 15 min. Potassium *t*-butoxide (135 mg, 1.20 mmol) was added and the solution stirred at room temperature with dry air bubbling through. After 1 h the reaction was quenched by the addition of water and the organic material extracted into ether and washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the lactone (77) (3

mg, 8%) as an oil. $\nu_{max.}$ (film) 1757 (C=O) and 1619 (C=C) cm^{-1}; δ_H 1.18 and 1.44 (each 3 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.74 (3 H, d, *J* 6.6 Hz, 3-CH_3), 3.94 and 3.99 (each 3 H, s, OCH_3), 4.44 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.71 (1 H, q, *J* 6.6 Hz, 3-H), 6.65 and 6.88 (each 1 H, d, *J* 2.2 Hz, 6- and 8-H), and 8.02 (1 H, s, 9-H); *m/z* 316 (M^+, 25%), 274 (59), 259 (100), 231 (38), and 203 (19). The second fraction afforded <u>naphthopyran</u> (<u>72</u>) (17 mg, 33%) as a yellow oil (Found: M^+, 346.1799. $C_{20}H_{26}O_5$ requires *M*, 346.1780); $\nu_{max.}$ (film) 3413 (OH), 1624 and 1575 (C=C) cm^{-1}; δ_H 1.07 and 1.44 (each 3 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.37 (3 H, d, *J* 6.1 Hz, 3-CH_3), 1.63 (3 H, d, *J* 6.5 Hz, 1-CH_3), 1.94 (1 H, br. s, OH, D_2O exchangeable), 3.89 and 3.95 (each 3 H, s, OCH_3), 3.90 (1 H, dq, *J* 7.8 and 6.1 Hz, partially obscured by OCH_3, 3-H), 4.35 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 4.45 (1 H, br. s, becomes d on D_2O exchange, *J* 7.8 Hz, 4-H), 5.27 (1 H, q, *J* 6.5 Hz, 1-H), 6.49 and 6.74 (each 1 H, d, *J* 2.3 Hz, 8- and 6-H), and 7.61 (5-H); *m/z* 346 (M^+, 28%), 289 (100), and 271 (28). Starting material (15 mg, 30%) was recovered.

Synthesis of naphtho[1,2-c]pyrans related to Glucoside B.

E-2-Methoxy-7-prop-1'-enyl-5-(2-propyloxy)-1,4-naphtho-quinone (108) *and* E-*4-Methoxy-7-prop-1'-enyl-5-(2-propyloxy)-1,2-naphthoquinone* (109).-

Olefin (76) (68 mg, 0.24 mmol) was dissolved in methylene chloride (20 ml) and a solution of saturated sodium hydrogen carbonate (1 ml) added. *m*-Chloroperbenzoic acid (144 mg, 0.96 mmol) was added to this solution over 20 min and the solution was stirred vigorously at room temperature. The colour of the reaction mixture became dark red. After 24 h t.l.c. of the reaction mixture indicated that a number of products had been formed. Water was thus added and the reaction mixture extracted with methylene chloride. The residue obtained upon work-up was chromatographed (20% ethyl acetate-light petroleum) and the two major products were isolated. The product of higher R_f was quinone (108) (7 mg, 10%); δ_H 1.42 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.93 (3 H, d, *J* 6 Hz, 3'-CH_3), 3.84 (3 H, s, OCH_3), 4.65 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 6.03 (1 H, s, 3-H), 6.35 - 6.59 (2 H, m, 1'- and 2'-H), 7.18 and 7.71 (each 1 H, d, *J* 2 Hz, 6- and 8-H); *m/z* 286 (M^+, 95%), 271 (100), and 244 (80). The product of lower R_f was quinone (109) (9 mg, 13%); δ_H 1.37 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.92 (3 H, d, *J* 6 Hz, 3'-CH_3), 3.91 (3 H, s, OCH_3), 4.59 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.90 (1 H, s, 3-H), 6.30 - 6.50 (2 H, m, 1'- and 2'-H), 7.14 and 7.82 (each 1 H, d, *J* 2 Hz, 6- and 8-H); *m/z* 286 (M^+, 92%), 271 (100), and 244 (79).

1-Bromo-2-hydroxymethyl-5,7-dimethoxy-4-(2-propyloxy)naphthalene (110).-

The acetate (103) (200 mg, 0.50 mmol) was dissolved in a 1% w/v solution of potassium hydroxide (42 mg, 0.75 mmol) in methanol and the mixture stirred for 10 min at room temperature. Dilute hydrochloric acid was added to quench the reaction and the organic material was extracted into ether and washed with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford product (110) (142 mg, 80%) as white feather-like needles, m.p. 106 - 107°C (light petroleum) (Found: C, 53.9; H, 5.35. $C_{16}H_{19}O_4Br$ requires C, 54.1; H, 5.35%); $\nu_{max.}$ 3389 (OH), 1619 and 1599 (C=C) cm^{-1}; δ_H 1.39 (6 H, d, *J* 6.2 Hz, $CH(C\underline{H}_3)_2$), 2.18 (1 H, t, *J* 6.4 Hz, OH, D_2O exchangeable), 3.91 and 3.94 (each 3 H, s, OCH_3), 4.57 (1 H, septet, *J* 6.2 Hz, $C\underline{H}(CH_3)_2$), 4.88 (1 H, d, *J* 6.4 Hz, CH_2), 6.51 (1 H, d, *J* 2.4 Hz, 6-H), 7.23 (1 H, d, *J* 2.4 Hz, 8-H), and 7.26 (1 H, s, 3-H); δ_C 22.06 (2 X CH_3), 55.22 and 56.11 (2 X OCH_3), 65.72 (CH_2), 73.25 (CH), 98.20 (C-6)[a], 99.14 (C-3)[a], 110.31 (C-8)[a], 112.42 (C-4a)[b], 115.29 (C-8a)[b], 135.99 (C-1), 139.05 (C-2), 154.80 (C-4)[c], 158.31 (C-5)[c], and 158.88 (C-7)[c]; *m/z* 356 (M^+ {^{81}Br}, 35%), 354 (M^+ {^{79}Br}, 35%), 314 (100), 312 (100), 271 (12), and 269(12).

1-Bromo-5,7-dimethoxy-4-(2-propyloxy)-2-naphthaldehyde (111).-

A solution of alcohol (110) (125 mg, 0.35 mmol) was dissolved in benzene (10 ml) and boiled with activated manganese dioxide[41] (1 g) for 1 h. The reaction mixture was cooled,

filtered and concentrated. The residue was purified by chromatography (eluant 10% ethyl acetate-light petroleum) to afford the aldehyde (111) (100 mg, 81%) as yellow needles, m.p. 111 - 112°C (light petroleum) (Found: C, 54.5; H, 4.85. $C_{16}H_{17}O_4Br$ requires C,54.4; H, 4.8%); $\nu_{max.}$ 1680 (C=O), 1617 and 1593 (C=C) cm^{-1}; δ_H 1.42 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.92 and 3.98 (each 3 H, s, OCH_3), 4.70 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 6.68 (1 H, d, *J* 2.3 Hz, 6-H), 7.20 (1 H, s, 3-H), 7.42 (1 H, d, *J* 2.3 Hz, 8-H), and 10.60 (1 H, s, CHO); δ_C 21.95 (2 X CH_3), 55.37 and 56.41 (2 X OCH_3), 72.24 (CH), 99.22 (C-6), 102.29 (C-3)[a], 105.37 (C-8)[a], 118.41 (C-4a)[b], 120.42 (C-8a)[b], 131.98 (C-2), 136.32 (C-1), 155.49 (C-4)[c], 158.49 (C-5)[c], 9.82 (C-7)[c], and 193.07 (CHO); *m/z* 354 (M^+ {^{81}Br}, 34%), 352 (M^+ {^{79}Br}, 34%), 312 (100), 310 (100), 269 (24), and 267 (24).

Z- and E-1-*Bromo*-5,7-*dimethoxy*-2-*prop*-1'-*enyl*-4-(2-*propyl*-*oxy*)*naphthalene* (112) and (116).-

To a stirred suspension of ethyltriphenylphosphonium bromide[42] (400 mg, 1.10 mmol) in dry tetrahydrofuran (10 ml) under nitrogen at 0°C, was added *n*-butyl lithium (1.10 mmol, 1.3 mol equiv.). The orange solution was stirred at 0°C for 5 min, and then cooled to -78°C. The aldehyde (111) (300 mg, 0.85 mmol) dissolved in dry tetrahydrofuran (2 ml) was slowly dripped in so that the temperature of the solution did not rise above -78°C. The solution was stirred at -78°C for 15 min and then allowed to warm to room temperature over 1 h. The reaction was quenched by the addition of water. Ether was added and the organic layer washed several times with

aqueous sodium chloride. The residue obtained upon work-up was chromatographed on alumina (eluant 15% ethyl acetate-light petroleum) to afford a mixture of the olefins (112) and (116) (248 mg, 80%) as a yellow oil. δ_H 1.34 and 1.36 (each 6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$ of both isomers), 1.80 (3 H, dd, *J* 7 and 1.5 Hz, 3'-CH_3 of isomer (112)), 1.97 (3 H, dd, *J* 6.5 and 1.7 Hz, 3'-CH_3 of isomer (116)), 3.90, 3.91, 3.95, and 3.99 (each 3 H, s, OCH_3 of both isomers), 4.50 and 4.54 (each 1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$ of both isomers), 5.91 (1 H, dq, *J* 11.5 and 7 Hz, 2'-H of isomer (112)), 6.24 (1 H, dq, *J* 15.5 and 6.5 Hz, 2'-H of isomer (116)), 6.51 (1 H, d, *J* 1.5 Hz, 6-H of isomer (112)), 6.54 (1 H, d, *J* 1.5 Hz, 6-H of isomer (116)), 6.65 (1 H, dq, 11.5 and 1.5 Hz, 1'-H of isomer (112)), 6.72 (1 H, s, 3-H of isomer (112)), 6.94 (1 H, s, 3-H of isomer (116)), 6.98 (1 H, dq, *J* 15.5 and 1.7 Hz, 1'-H of isomer (116)), 7.29 (1 H, d, *J* 1.5 Hz, 8-H of isomer (112)), and 7.34 (1 H, d, *J* 1.5 Hz, 8-H of isomer(116)).

2-Diphenylphosphinoyl-1-[8-bromo-4,6-dimethoxy-3-(2-propyl-oxy)naphthalene]propan-1-ol (120).-

To ethyldiphenylphosphine oxide (131 mg, 0.57 mmol) in dry tetrahydrofuran (4 ml) at 0°C under nitrogen, was added *n*-butyl lithium (0.57 mmol, 1 mol equiv.). The dark orange solution was immediately cooled to -78°C and aldehyde (111) (200 mg, 0.57 mmol) in dry tetrahydrofuran (2 ml) added dropwise at such a rate that the temperature of the solution did not rise above -78°C. The solution was allowed to warm to room temperature over 1 h and the reaction was quenched by addition of water. The organic material was extracted into

ether and flash chromatography (eluant 70% ethyl acetate-light petroleum) of the residue obtained upon work-up yielded a mixture of *erythro* and *threo* adducts (212 mg, 63%). Recrystallisation (light petroleum) afforded the <u>*erythro* adduct</u> (<u>120</u>) (140 mg, 42%) as white needles, m.p. 204 - 205°C (light petroleum) (Found: C, 61.65; H, 5.4. $C_{30}H_{32}O_5PBr$ requires C, 61.7; H, 5.5%); $\nu_{max.}$ 3190 (OH), 1615 and 1593 (C=C) cm^{-1}; δ_H 1.05 (3 H, dd, *J* 16.1 and 7.1 Hz, $CHC\underline{H}_3$), 1.37 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 2.94 (1 H, quintet, *J* 7.1 Hz, $C\underline{H}CH_3$), 3.91 (6 H, s, 2 X OCH_3), 4.62 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.01 (1 H, s, OH), 5.59 (1 H, d, *J* 8.3 Hz, $C\underline{H}OH$), 6.51 and 7.19 (each 1 H, d, *J* 2 Hz, 5- and 7-H), 7.22 (1 H, s, 2-H), and 7.50 - 8.14 (10 H, m, Ph_2PO); *m/z* 584 (M^+ {^{81}Br}, 8%), 582 (M^+ {^{79}Br}, 8%), 503 (100), and 461 (65).

Z-1-Bromo-5,7-dimethoxy-2-prop-1'-enyl-4-(2-propyloxy)-naphthalene (<u>112</u>).-

Erythro adduct (<u>120</u>) (29 mg, 0.05 mmol) was dissolved in dry dimethylformamide (3 ml) at 55°C under nitrogen. Sodium hydride (0.1 mmol) was added in one portion and this solution stirred at 55°C for 20 min. Water was added and the organic material extracted into ether and backwashed with an aqueous sodium chloride solution. The residue obtained upon work-up was chromatographed on alumina (eluant 15% ethyl acetate-light petroleum) to afford the <u>*Z*-olefin</u> (<u>112</u>) (15 mg, 82%) as an oil (Found: C, 59.3; H, 5.6. $C_{18}H_{21}O_3Br$ requires C, 59.2; H, 5.75%); $\nu_{max.}$ (film) 1615 and 1590 (C=C) cm^{-1}; δ_H 1.36 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.80 (3 H, dd, *J* 7 and 1.5 Hz, 3'-CH_3), 3.90 and 3.95 (each 3 H, s, OCH_3), 4.50 (septet, *J*

6.1 Hz, C<u>H</u>$(CH_3)_2$), 5.91 (1 H, dq, *J* 11.5 and 7 Hz, 2'-H), 6.51 (1 H, d, *J* 1.5 Hz, 6-H), 6.65 (1 H, dq, *J* 11.5 and 1.5 Hz, 1'-H), 6.72 (1 H, s, 3-H), and 7.29 (1 H, d, *J* 1.5 Hz, 8-H); *m/z* 366 (M^+ {^{81}Br}, 42%), 364 (M^+ {^{79}Br}, 42%), 324 (100), 322 (100), 285 (20), and 243 (80).

8-Bromo-2-hydroxyethyl-5,7-dimethoxy-4-(2-propyloxy)naphthalene (<u>121</u>).-

Acetate (<u>101</u>) (500 mg, 1.25 mmol) was dissolved in a 1% w/v methanolic solution of potassium hydroxide (105 mg, 1.88 mmol) and the solution stirred for 10 min at room temperature. The reaction was quenched by the addition of dilute hydrochloric acid and the organic material extracted into ether and backwashed with water. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to afford the <u>product</u> (<u>121</u>) (399 mg, 90%) as white needles, m.p. 97 - 98°C (light petroleum) (Found: C, 54.0; H, 5.15. $C_{16}H_{19}O_4Br$ requires C, 54.1; H, 5.35%); $\nu_{max.}$ 3419 (OH), 1622 and 1596 (C=C) cm^{-1}; δ_H 1.38 (6 H, d, *J* 6.1 Hz, CH(C<u>H</u>$_3)_2$), 2.23 (1 H, t, *J* 6.1 Hz, OH, D_2O exchangeable), 3.98 and 4.03 (each 3 H, s, OCH_3), 4.55 (1 H, septet, *J* 6.1 Hz, C<u>H</u>$(CH_3)_2$), 5.77 (1 H, d, *J* 6.1 Hz, CH_2), 6.62 (1 H, s, 6-H), 6.82 (1 H, d, *J* 1.5 Hz, 3-H), and 7.71 (1 H, s, 1-H); δ_C 22.04 (2 X CH_3), 56.47 and 56.72 (2 X OCH_3), 65.39 (CH_2), 72.96 (CH), 95.28 (C-6), 99.75 (C-4a)[a], 109.44 (C-3)[b], 114.80 (C-8a)[a], 116.81 (C-1)[b], 135.26 (C-8), 140.87 (C-2), 153.88 (C-4)[c], 155.16 (C-5)[c], and 159.84 (C-7)[c]; *m/z* 356 (M^+ {^{81}Br}, 38%), 354 (M^+ {^{79}Br}, 38%), 314 (100), 312 (100), 299 (16), 297 (16), 271 (19), and 269 (20).

8-Bromo-5,7-dimethoxy-4-(2-propyloxy)-2-naphthaldehyde (122).-

The alcohol (121) (150 mg, 0.42 mmol) was dissolved in benzene (10 ml) and boiled with activated manganese dioxide (1 g) for 1 h. The reaction mixture was cooled, filtered, concentrated, and the residue chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the aldehyde (122) (127 mg, 85%) as yellow needles, m.p. 127 - 128°C (light petroleum-methylene chloride) (Found: C, 54.2; H, 4.85. $C_{16}H_{17}O_4Br$ requires C, 54.4; H, 4.8%); $\nu_{max.}$ 1685 (C=O) and 1595 (C=C) cm^{-1}; δ_H 1.43 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.96 and 4.03 (each 3 H, s, OCH_3), 4.74 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 6.75 (1 H, s, 6-H), 7.19 and 8.31 (each 1 H, d, *J* 1.5 Hz, 3- and 1-H), and 10.08 (CHO); δ_C 21.99 (2 X CH_3), 56.82 and 56.93 (2 X OCH_3), 71.99 (CH), 98.27 (C-6), 101.21 (C-4a)[a], 102.53 (C-3)[b], 118.18 (C-8a)[a], 126.42 (C-1)[b], 135.25 (C-2)[c], 135.74 (C-8)[c], 154.79 (C-4)[d], 156.49 (C-5)[d], 158.49 (C-7)[d], and 192.29 (CHO); *m/z* 354 (M^+ {^{81}Br}, 40%), 352 (M^+ {^{79}Br}, 40%), 312 (100), 310 (100), 297 (19), 295 (19), 269 (36), and 267 (36).

E-*8-Bromo-5,7-dimethoxy-2-prop-1'-enyl-4-(2-propyloxy)-naphthalene* (124).-

A solution of methylene chloride (5 ml) containing palladium-dichloride-bisacetonitrile[43] (25 mg) and *Z*-olefin (123) (200 mg, 0.55 mmol) was stirred at room temperature for 2 h. The solution was filtered and concentrated. The residue was chromatographed (eluant 5 % ethyl acetate-light petroleum) to afford the *E*-olefin (124) (170 mg, 85%) as an oil. $\nu_{max.}$

(film) 1615 and 1590 (C=C) cm^{-1}; δ_H 1.30 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.84 (3 H, dd, *J* 6 and 1.8 Hz, 3'-CH_3), 3.87 and 3.92 (each 3 H, s, OCH_3), 4.49 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 6.29 (1 H, dq, *J* 15.6 and 6 Hz, 2'-H), 6.47 (1 H, dq, *J* 15.6 and 1.8 Hz, partially obscured by 6-H, 1'-H), 6.51 (1 H, s, 6-H), 6.84 and 7.65 (each 1 H, d, *J* 1.5 Hz, 3- and 1-H); *m/z* 366 (M^+ {^{81}Br}, 44%), 364 (M^+ {^{79}Br}, 44%), 324 (100), 322 (100), 285 (22), and 243 (80).

(1'S,2'R)-8-*Bromo*-2-(1',2'-*dihydroxypropyl*)-5,7-*dimethoxy*-4-(2-*propyloxy*)*naphthalene* (125) *and its enantiomer*.-
To a stirred suspension of ethyltriphenylphosphonium bromide (400 mg, 1.10 mmol) in dry tetrahydrofuran (10 ml) cooled to 0°C, was added *n*-butyl lithium (1.08 mmol, 1.3 mol equiv.) under nitrogen. The orange solution was stirred at 0°C for 5 min and then cooled to -78°C. Aldehyde (122) (300 mg, 0.85 mmol) dissolved in dry tetrahydrofuran (3 ml) was slowly dripped in at such a rate that the temperature of the solution did not rise above -78°C. After 15 min at this temperature, the reaction mixture was warmed to room temperature and the reaction monitored by t.l.c. When no starting material remained (*ca.* 1.5 h) water was added and the organic material extracted into ether. The organic layer was washed several times with aqueous sodium chloride. The residue obtained upon work-up contained *Z*-8-Bromo-5,7-dimethoxy-2-prop-1'-enyl-4-(2-propyloxy)-naphthalene (123) together with triphenylphosphine oxide. This mixture was immediately converted to the diol (124). δ_H (on chromatographed olefin) 1.38 (6 H, d, *J* 6.5 Hz, $CH(C\underline{H}_3)_2$), 1.92 (3 H, dd, *J* 8 and 1.8

Hz, 3'-CH_3), 3.92 and 3.98 (each 3 H, s, OCH_3), 5.54 (1 H, septet, *J* 6.5 Hz, C<u>H</u>$(CH_3)_2$), 5.86 (1 H, dq, *J* 13 and 8 Hz, 2'-H), 6.54 (1 H, dq, *J* 13 and 1.8 Hz, 1'-H), 6.58 (1 H, s, 6-H), 6.72 and 7.75 (each 1 H, d, *J* 2 Hz, 3- and 1-H). To the solution of crude *Z*-olefin (<u>122</u>) in dry pyridine (4 ml), was added a solution of osmium tetroxide (250 mg, 0.98 mmol) in dry ether (6 ml). The dark black solution was stirred at room temperature for 30 min. Sodium metabisulphite (1.2 g), water (10 ml), and pyridine (10 ml) were added and the solution stirred for 10 min. The reaction mixture was acidified with dilute hydrochloric acid and the organic material extracted with methylene chloride. The residue obtained upon work-up was purified by chromatography (eluant 30% ethyl acetate-light petroleum) to yield the <u>diol</u> (<u>125</u>) (200 mg, 59% from aldehyde (121)) as off-white needles, m.p. 128 - 129°C (light petroleum-ethyl acetate) (Found: C, 54.1; H, 5.8. $C_{18}H_{23}O_5Br$ requires C, 54.1; H, 5.8%); $\nu_{max.}$ 3346 (OH), 1616 and 1596 (C=C) cm^{-1}; δ_H 1.06 (3 H, d, *J* 6.4 Hz, C<u>H</u>$_3$CH), 1.32 (6 H, d, *J* 6.2 Hz, CH(C<u>H</u>$_3$)$_2$), 1.89 and 2.61 (each 1 H, br. s, OH, D_2O exchangeable), 3.89 and 3.94 (each 3 H, s, OCH_3), 4.15 (1 H, dq, *J* 4.6 and 6.4 Hz, partially obscured by OCH_3, CH_3C<u>H</u>), 4.48 (1 H, septet, *J* 6.2 Hz, C<u>H</u>$(CH_3)_2$), 4.71 (1 H, d, *J* 4.6 Hz, ArC<u>H</u>), 6.54 (1 H, s, 6-H), 6.78 and 7.27 (each 1 H, s, 3- and 1-H); δ_C 17.55 (CH_3), 22.13 (CH(<u>C</u>H$_3$)$_2$), 56.68 and 56.92 (2 X OCH_3), 71.26 (2 X CH), 72.99 (<u>C</u>H$(CH_3)_2$), 95.65 (C-6), 96.02 (C-4a)[a], 109.07 (C-3)[b], 110.05 (C-8a)[a], 117.26 (C-1)[b], 135.28 (C-8), 140.42 (C-2), 154.17 (C-4)[c], 155.24 (C-5)[c], and 158.51 (C-7)[c]; *m/z* 400 (M^+ {^{81}Br}, 79%), 398 (M^+ {^{79}Br}, 79%), 354 (19), 352 (19), 313 (100), 311 (100), 285 (41), 283 (39), 232 (28), and 204 (76).

(2'R,4'R,5'S)-8-Bromo-5,7-dimethoxy-4-(2-propyloxy)-2-(2',4'-dimethyl-1',3'-dioxolan-5'-yl)naphthalene (126) *and its enantiomer.-*

To a solution of the diol (125) (60 mg, 0.15 mmol) in benzene (20 ml) was added acetaldehyde dimethyl acetal (40 mg, 0.45 mmol) and a catalytic amount of *p*-toluenesulphonic acid. The solution was boiled for 30 min in a Dean Stark apparatus. The cooled solution was washed with sodium hydrogen carbonate and water. The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate-light petroleum) to yield the dioxolane (126) (47 mg, 74%) as colourless cubes, m.p. 89 - 90°C (light petroleum) (Found: C, 56.2; H, 5.65. $C_{20}H_{25}O_5Br$ requires C, 56.5; H, 5.9%); $\nu_{max.}$ 1620 and 1597 (C=C) cm^{-1}; δ_H 0.86 (3 H, d, *J* 6.4 Hz, 4'-CH_3), 1.36 (6 H, d, *J* 6 Hz, $CH(C\underline{H}_3)_2$), 1.59 (3 H, d, *J* 4.6 Hz, 2'-CH_3), 3.93 and 3.96 (each 3 H, s, OCH_3), 4.41 (1 H, dq, *J* 7.1 and 6.4 Hz, 4'-H), 4.54 (1 H, septet, *J* 6 Hz, $C\underline{H}(CH_3)_2$), 5.09 (1 H, d, *J* 7.1 Hz, 5'-H), 5.21 (1 H, q, *J* 4.6 Hz, 2'-H), 6.61 (1 H, s, 6-H), 6.74 and 7.70 (each 1 H, s, 3- and 1-H); δ_C 16.29 and 19.96 (2 X CH_3), 22.14 ($CH(\underline{C}H_3)_2$), 56.75 and 56.93 (2 X OCH_3), 72.73 ($\underline{C}H(CH_3)_2$), 77.00 and 81.02 (2 X CH), 95.67 (C-6), 100.22 (CH), 101.01 (C-4a)[a], 109.49 (C-3)[b], 115.41 (C-8a)[a], 117.45 (C-1)[b], 135.29 (C-8), 138.77 (C-2), 154.06 (C-4)[c], 155.02 (C-5)[c], and 158.12 (C-7)[c]; *m/z* 426 (M^+ {^{81}Br}, 100%), 424 (M^+ {^{79}Br}, 100%), 384 (18), 382 (18), 340 (90), 338 (90), 325 (39), 323 (40), 259 (22), and 72 (50).

(1S,3S,4R)-5-*Bromo*-4-*hydroxy*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]*pyran* (130) *and* (1S,3S,4R)-4-*Hydroxy*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naptho*-[1,2-c]*pyran* (90) *and their enantiomers*.-

To a stirred solution of dioxolane (126) (113 mg, 0.26 mmol) in dry methylene chloride (10 ml) at -78°C under nitrogen, was added titanium tetrachloride (0.3 ml, 2.6 mmol). The darkened solution was immediately warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of a saturated sodium hydrogen carbonate solution, and the organic layer extracted with methylene chloride and washed with water. The residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate-light petroleum) to afford product (130) (18 mg, 15%) as a yellow oil (Found: M^+, 424.0866. $C_{20}H_{25}O_5Br$ requires M, 424.0886); $\nu_{max.}$ (film) 3413 (OH), 1618 and 1594 (C=C) cm^{-1}; δ_H 1.28 (3H, d, J 6.1 Hz, 3-CH_3), 1.32 (6 H, d, J 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.72 (3 H, d, J 6.6 Hz, 1-CH_3), 3.14 (1 H, br. s, OH, D_2O exchangeable), 3.89 and 3.93 (each 3 H, s, OCH_3), 4.27 (1 H, sextet, J 6.1 Hz, 3-H), 4.43 (1 H, dseptet, J 2.8 and 6.1 Hz, $C\underline{H}(CH_3)_2$), 4.71 (1 H, br. s, becomes d on D_2O exchange, J 5.4 Hz, 4-H), 5.25 (1 H, q, J 6.6 Hz, 1-H), 6.55 (1 H, d, J 2.1 Hz, 8-H), and 6.60 (1 H, t, J 2.1 Hz, 10-H); m/z 426 (M^+ {^{81}Br}, 20%), 424 (M^+ {^{79}Br}, 20%), 384 (21), 382 (20), 369 (94), 367 (94), and 323 (100). Compound (90) with lower R_f was obtained as white needles (36 mg, 40%), m.p. 128 - 129°C (light petroleum) (Found: C, 69.4; H, 7.3. $C_{20}H_{26}O_5$ requires C, 69.4; H, 7.5%); $\nu_{max.}$ 3393 (OH), 1616 and 1594 (C=C) cm^{-1}; δ_H 1.35 (6 H, d, J 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.41 (3 H, d, partially obscured by $CH(CH_3)_2$, J 6.3 Hz, 3-CH_3), 1.64 (3 H, d, J 6.5

Hz, 1-CH_3), 1.89 (1 H, d, *J* 3.3 Hz, OH, D_2O exchangeable), 3.86 and 3.88 (each 3 H, s, OCH_3), 3.89 (1 H, dq, partially obscured by OCH_3, *J* 8.3 and 6.3 Hz, 3-H), 4.38 (1 H, t, *J* 8.3 Hz, collapses to d on D_2O exchange, *J* 8.3 Hz, 4-H), 4.54 (1 H, septet, *J* 6.1 Hz, C<u>H</u>$(CH_3)_2$), 5.32 (1 H, q, *J* 6.5 Hz, 1-H), 6.50 (2 H, s, 8- and 10-H), and 6.97 (1 H, s, 5-H); δ_C 18.78 and 20.22 (2 X CH_3), 22.16 ($CH(\underline{C}H_3)_2$), 55.20 and 56.20 (2 X OCH_3), 68.90, 69.43, and 71.26 (3 X CH), 72.79 ($\underline{C}H(CH_3)_2$), 95.25 (C-5)[a], 98.25 (C-8)[a], 108.43 (C-10)[a], 114.56 (C-6a)[b], 126.58 (C-10a)[b], 133.65 (C-1a)[b], 134.32 (C-4a)[b], 154.75 (C-6)[c], 158.17 (C-7)[c], and 159.04 (C-9)[c]; *m/z* 346 (M^+, 47%), 331 (32), 289 (100), 271 (25), and 245 (30). A further three compounds isolated from the mixture were the dioxolane (<u>126</u>) (14 mg, 12%), diol (<u>125</u>) (14 mg, 14%), and alcohol (<u>100</u>) (3 mg, 4%), each identical with original material.

(1S,3S,4R)-4-*Acetoxy*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyl*-*oxy*)-1H-*naphtho*[1,2-c]*pyran* (<u>131</u>) *and its enantiomer*.- A solution of compound (<u>90</u>) (41 mg, 0.12 mmol) in acetic anhydride (2 ml) and pyridine (0.5 ml) was stirred at 55°C for 1 h. Methylene chloride and water were added to the mixture, and this solution was washed with dilute hydrochloric acid and then finally with water. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate-light petroleum) to yield <u>acetate</u> (<u>131</u>) (45 mg, 97%) as colourless rhomboids, m.p.135 - 136°C (light petroleum) (Found: C, 67.85; H, 7.0. $C_{22}H_{28}O_5$ requires C, 68.0; H, 7.2%); $\nu_{max.}$ 1733 (C=O), 1616 and 1593 (C=C) cm^{-1}; δ_H (3 H, d, *J* 6.2 Hz, 3-CH_3), 1.37 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.70

(3 H, d, *J* 6.5 Hz, 1-CH_3), 2.19 (3 H, s, $COCH_3$), 3.89 (6 H, s, 2 X OCH_3), 4.18 (1 H, dq, *J* 7.6 and 6.2 Hz, 3-H), 4.45 (1 H, septet, *J* 6.1 Hz, C<u>H</u>$(CH_3)_2$), 5.36 (1 H, q, *J* 6.5 Hz, 1-H), 5.82 (1 H, d, *J* 7.6 Hz, 4-H), 6.48 - 6.53 (2 H, m, 8- and 10-H), and 6.55 (1 H, s, 8-H); *m/z* 388 (M^+, 30%), 373 (12), 313 (21), and 271 (100).

<u>Conversion of Compound (130) to (90)</u>.-
Naphthopyran (<u>130</u>) (51 mg, 0.12 mmol) was dissolved in dry tetrahydrofuran (20 ml) at -78°C under nitrogen. *n*-Butyl lithium (0.59 mmol, 5 mol equiv.) was added. The solution was stirred for 1 h at -78°C and then allowed to warm to room temperature over 15 min. The reaction was quenched by the addition of water. The mixture was extracted with ether and washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate-light petroleum) to afford the <u>naphthopyran</u> (<u>90</u>) (33 mg, 81%) whose t.l.c. behaviour, ^{1}H n.m.r., m.s., and i.r. spectra were identical with original material described above.

(1S,3S,4R)-4-*Bromo*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]*pyran* (<u>138</u>) *and* (1S,3S,4S)-4-*Bromo*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]-*pyran* (<u>139</u>) *and their enantiomers*.-
Naphthopyran (<u>95</u>) (50 mg, 0.14 mmol) was dissolved in dry benzene (5 ml) and treated with phosphorus tribromide (0.05 ml, 0.53 mmol). The solution was stirred at room temperature for 30 min, and the reaction quenched by addition of a solution of dilute sodium hydrogen carbonate. The organic

material was extracted into methylene chloride and the residue obtained upon work-up chromatographed (eluant 10% ethyl acetate-light petroleum) to afford two products. The first fraction yielded compound (138) (22 mg, 38%); δ_H 1.40 (6 H, d, *J* 6 Hz, $CH(C\underline{H}_3)_2$), 1.49 (3 H, d, *J* 6 Hz, 3-CH_3), 1.73 (3 H, d, *J* 6.5 Hz, 1-CH_3), 3.89 (6 H, s, 2 X OCH_3), 4.32 (1 H, dq, partially obscured by $C\underline{H}(CH_3)_2$, *J* 8.5 and 6.1 Hz, 3-H), 4.51 (1 H, septet, *J* 6 Hz, $C\underline{H}(CH_3)_2$), 5.06 (1 H, d, *J* 8.5 Hz, 4-H), 5.37 (1 H, q, *J* 6.5 Hz, 1-H), 6.51 (2 H, s, 8- and 10-H), and 6.92 (1 H, s, 5-H); *m/z* 410 (M^+ {^{81}Br}, 45%), 408 (M^+ {^{79}Br}, 45%), 395 (20), 393 (20), 353 (72), 351 (72), 329 (25), 314 (38), 287 (56), 271 (100), and 257 (46). The second fraction contained compound (139) (22 mg, 39%); δ_H 1.39 (6 H, d, *J* 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.46 (3 H, d, *J* 6.1 Hz, 3-CH_3), 1.64 (3 H, d, *J* 6.6 Hz, 1-CH_3), 3.89 (6 H, s, 2 X OCH_3), 4.17 (1 H, dq, *J* 2 and 6.1 Hz, 3-H), 4.53 (1 H, septet, *J* 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.11 (1 H, d, *J* 2 Hz, 4-H), 5.49 (1 H, q, *J* 6.6 Hz, 1-H), 6.54 (2 H, s, 8- and 10-H), and 6.65 (1 H, s, 5-H); *m/z* 410 (M^+ {^{81}Br}, 45%), 408 (M^+ {^{79}Br}, 45%), 395 (20), 393 (20), 353 (75), 351 (75), 329 (27), 314 (38), 287 (57), 271 (100), and 257 (43).

trans-3,4-*Dihydro*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]*pyran* (136).-

A mixture of compounds (138) and (139) (44 mg, 0.11 mmol) were dissolved in ethanol (7.5 ml) and water (2.5 ml). To this mixture was added Raney nickel catalyst (100 mg, 50% in water) and the solution stirred at 60°C for 15 min. The reaction was quenched by filtering off the catalyst and

washing exhaustively with methylene chloride. The organic layer was washed with water, dried over magnesium sulphate, filtered and evaporated to dryness. The residue was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the naphthopyran (136) (25 mg, 69%) as white cubes, m.p. 84 - 84°C (light petroleum) (Found: C, 72.5; H, 7.75. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); $\nu_{max.}$ 1616 (C=C) cm^{-1}; δ_H 1.35 (3 H, d, *J* 6.1 Hz, 3-CH_3), 1.37 (6 H, d, *J* 6.1 Hz, CH(C$\underline{H}_3$)$_2$), 1.66 (3 H, d, *J* 6.6 Hz, 1-CH_3), 2.71 (2 H, apparent d, *J* 7.2 Hz, *pseudo*-equatorial and *pseudo*-axial 4-H), 3.89 (6 H, s, 2 X OCH_3), 4.25 (1 H, apparent sextet, *J* 6.5 Hz, 3-H), 4.48 (1 H, septet, *J* 6.1 Hz, C$\underline{H}$(CH_3)$_2$), 5.40 (1 H, q, *J* 6.6 Hz, 1-H), 6.46 (1 H, d, *J* 2.2 Hz, 8-H), 6.50 (1 H, s, 5-H), and 6.54 (1 H, d, *J* 2.2 Hz, 10-H); δ_C 20.35 and 21.94 (2 X CH_3), 22.13 (CH(C$\underline{H}_3$)$_2$), 36.69 (CH_2), 55.15 and 56.11 (2 X OCH_3), 62.46 and 69.80 (2 X CH), 72.95 (C$\underline{H}$(CH_3)$_2$), 94.79 (C-5)[a], 97.67 (C-8)[a], 112.28 (C-10)[a], 114.05 (C-4a)[b], 126.17 (C-6a)[b], 131.64 (C-10a)[b], 134.02 (C-1a)[b], 153.68 (C-6)[c], 157.93 (C-7)[c], and 158.89 (C-9)[c]; *m/z* 330 (M^+, 39%), 315 (29), and 273 (100).

(1R,3S,4R)-4-*Bromo*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[2,3-c]*pyran* (140) *and* (1R,3S,4S)-4-*Bromo*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]*pyran* (141) *and their enantiomers*.-

Naphthopyran (96) (40 mg, 0.12 mmol) dissolved in dry benzene (5 ml) was treated with phosphorus tribromide (0.04 ml, 0.45 mmol). The solution was stirred at room temperature for 30 min and a dilute solution of sodium hydrogen carbonate added.

The organic material was extracted with methylene chloride and the residue obtained upon work-up chromatographed (eluant 10% ethyl acetate-light petroleum) to afford two products. Compound (140) (15 mg, 30%) of higher R_f; δ_H 1.40 (6 H, d, *J* 6 Hz, $CH(C\underline{H}_3)_2$), 1.54 (3 H, d, *J* 6.1 Hz, 3-CH_3), 1.56 (3 H, d, *J* 6.1 Hz, 1-CH_3), 3.87 (1 H, dq, partially obscured by OCH_3, *J* 8.5 and 6.1 Hz, 3-H), 3.88 and 3.94 (each 3 H, s, OCH_3), 4.54 (1 H, septet, *J* 6 Hz, $C\underline{H}(CH_3)_2$), 5.10 (1 H, d, *J* 8.5 Hz, 4-H), 5.42 (1 H, q, *J* 6.1 Hz, 1-H), 6.50 and 6.56 (each 1 H, d, *J* 2.2 Hz, 8- and 10-H), and 7.00 (1 H, s, 5-H); *m/z* 410 (M^+ {^{81}Br}, 46%), 408 (M^+ {^{79}Br}, 46%), 395 (20), 393 (21), 353 (75), 351 (75), 329 (24), 314 (38), 287 (55), 271 (100), and 257 (40). Compound (141) (17 mg, 35%) of lower R_f; δ_H 1.40 (6 H, d, *J* 6 Hz, $CH(C\underline{H}_3)_2$), 1.42 (3 H, d, partially obscured by $CH(C\underline{H}_3)_2$, *J* 6 Hz, 3-CH_3), 1.69 (3 H, d, *J* 6.1 Hz, 1-CH_3), 3.76 (1 H, q, *J* 6 Hz, 3-H), 3.88 and 3.89 (each 3 H, s, OCH_3), 4.58 (1 H, septet, *J* 6 Hz, $C\underline{H}(CH_3)_2$), 4.79 (1 H, br. s, 4-H), 5.58 (1 H, q, *J* 6.1 Hz, 1-H), 6.51 and 6.58 (each 1 H, d, *J* 2.2 Hz, 8- and 10-H), and 6.62 (1 H, s, 5-H); *m/z* 410 (M^+ {^{81}Br}, 45%), 408 (M^+ {^{79}Br}, 45%), 395 (20), 393 (20), 353 (76), 351 (76), 329 (25), 314 (38), 287 (55), 271 (100), and 257 (42).

cis-3,4-*Dihydro*-7,9-*dimethoxy*-1,3-*dimethyl*-6-(2-*propyloxy*)-1H-*naphtho*[1,2-c]*pyran* (137).-

A mixture of compounds (140) and (141) (32 mg, 0.08 mmol) was dissolved in ethanol (7.5 ml) and water (2.5 ml). To this mixture was added Raney nickel catalyst (100 mg, 50% in water) and the solution was stirred at 60°C for 15 min. The

reaction was quenched by filtering off the catalyst and washing exhaustively with methylene chloride. The organic layer was washed with water, dried over magnesium sulphate, and filtered. The residue obtained upon evaporation of the solvent was chromatographed (eluant 10% ethyl acetate-light petroleum) to yield the naphthopyran (137) (17 mg, 64%) as white cubes, m.p. 74 - 75°C (light petroleum) (Found: M^+, 330.1835 $C_{20}H_{26}O_4$ requires M, 330.1831); $\nu_{max.}$ 1617 (C=C) cm^{-1}; δ_H 1.81 (9 H, d, J 6.1 Hz, $CH(C\underline{H}_3)_2$ and 3-CH_3), 1.59 (3-H, d, J 6.1 Hz, 1-CH_3), 2.56 (1 H, br. d, J 15.6 Hz, *pseudo*-equatorial 4-H), 2.79 (1 H, dd, J 15.6 and 10 Hz, *pseudo*-axial 4-H), 3.74 (1 H, ddq, J 2.2, 10, and 6.1 Hz, 3-H), 3.88 and 3.89 (each 3 H, s, OCH_3), 4.48 (1 H, septet, J 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.44 (1 H, q, J 6.1 Hz, 1-H), 6.46 (1 H, d, J 2.1 Hz, 6-H), 6.51 (1 H, s, 5-H), and 6.58 (1 H, d, J 2.1 Hz, 10-H); m/z 330 (M^+, 37%), 315 (29), and 273 (100).

REFERENCES

1. R.H. Thomson, "Naturally Occurring Quinones", 2nd ed. (1971), Academic Press, London, pp 597 - 622.

2. H. Duewell, J.P.E. Human, A.W. Johnson, S.F. Macdonald, and A.R. Todd, *Nature*, London, 1948, 162, 759.

3. H.J. Banks and D.W. Cameron, *Aust. J. Chem.*, 1972, 25, 2199.

4. H. Schmid, A. Ebnöther, and T.M. Maijer, *Helv. Chim. Acta*, 1950, 33, 1751.

5. H. Schmid and A. Ebnöther, *Helv. Chim. Acta*, 1951, 34, 561.

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

7. A. Zeeck, H. Zähner, and M. Mardin, *Justus Liebigs Ann. Chem.*, 1974, 1101.

8. S. Omura, H.Tanoka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 1976, 320.

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

10. H.W. Moore, *Science*, 1977, 197, 527.

11. D.W. Cameron and A.R. Todd, "Oxidative Coupling of Phenols", W.I. Taylor and A.R. Battersby eds., Marcel Decker, New York, 1967, pp 203 - 241.

12. J.P.E. Human, A.W. Johnson, S.F. Macdonald, and A.R. Todd, *J. Chem. Soc.*, 1950, 477.

13. H.J. Banks and D.W. Cameron, *Aust. J. Chem.*, 1972, 25, 2199.

14. D.W. Cameron, R.I.T. Cromartie, D.G.I. Kingston, and A.R. Todd, *J. Chem. Soc.*, 1964, 51.

15. D.W. Cameron and H.W.-S. Chan, *J. Chem. Soc. (C)*, 1966, 1825.

16. K.S. Brown, D.W. Cameron, and U. Weiss, *Tetrahedron Lett.*, 1969, 471.

17. (a) D.W. Cameron, D.G.I. Kingston, N. Sheppard, and A.R. Todd, *J. Chem. Soc.*, 1964, 98.
(b) D.W. Cameron, S.R. Hall, C.L. Raston, and A.H. White, *Aust. J. Chem.*, 1977, 30, 2705.

18. D.W. Cameron and J.C.A. Craik, *J. Chem. Soc (C)*, 1968, 3068.

19. J.H. Bowie and D.W. Cameron, J. Chem. Soc. (C), 1967, 712.

20. T.A. Chorn, R.G.F. Giles, I.R. Green, and P.R.K. Mitchell, *J. Chem. Soc., Perkin Trans. I*, 1983, 1249.

21. R.G.F. Giles, I.R. Green, V.I. Hugo, P.R.K. Mitchell, and S.C. Yorke, *J. Chem. Soc., Perkin Trans. I*, 1983, 2309.

22. R.G.F. Giles, I.R. Green, V.I. Hugo, P.R.K. Mitchell, and S.C. Yorke, *J. Chem. Soc., Perkin Trans. I*, 1984, 2383.

23. T. Mukaiyama, T.I. Zawa, and K. Saigo, *Chem. Lett.*, 1974, 323 - 326.

24. J. Rhamdohr, M.Sc. thesis, University of Cape Town, 1987.

25. R.G.F. Giles, I.R. Green, and J.A.X. Pestana, *J. Chem. Soc., Perkin Trans. I*, 1984, 2389.

26. E.C. Taylor and G.E. Jagdmann, Jr., *J. Org. Chem.*, 1978, 43, 4385.

27. L.M. Harwood, *J. Chem. Soc., Perkin Trans. I*, 1984, 2577.

28. Y. Naruta, H. Uno, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1981, 1277.

29. T. Sala and M.V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1979, 2593.

30. I.R. Green, *J. Chem. Ed.*, 1982, 59, 698.

31. G. Read and V.M. Ruiz, *J. Chem. Soc., Perkin Trans. I*, 1973, 235.

32. G.W. Kenner and M.A. Murray, *J. Chem. Soc.*, 1949, S 178.

33. V. Lee Son, M.Sc. thesis, University of Cape Town, 1986.

34. J.A.X. Pestana, Ph.D. thesis, University of Cape Town, 1985.

35. T. Kometani, Y. Takeuchi, and E. Yoshii, *J. Chem. Soc., Perkin Trans. I*, 1981, 1197.

36. J. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hill Inc., Englewood Cliffs, N.J. 1965, p 99.

37. V.J. Traynelis and W.L. Hergenrother, *J. Am. Chem. Soc.*, 1964, 86, 298.

38. P.G. Gassman and F.V. Zalar, *Tetrahedron Lett.*, 1964, 3031.

39. D.W. Cameron, G.I. Feutrill, and L.J.H. Pannan, *Aust. J. Chem.*, 1980, 33, 2531.

40. A.D. Buss and S. Warren, *J. Chem. Soc., Perkin Trans. I*, 1985, 2307.

41. O. Mancera, G. Rosenkrantz, and F Sondheimer, *J. Chem. Soc.*, 1953, 2190.

42. Chemical Abstracts, Vol. 53, p 151186.

43. S.J. Danishefsky, B.J. Uang, and G. Quallich, *J. Am. Chem. Soc.*, 1985, 107, 1285 - 1293.
