SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME QUINONOID SYSTEMS

by

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CAPE TECHNIKON

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STATEMENT

I, Victor Ignatius Hugo, hereby declare that the contents of this thesis represent my own ideas and that all synthetic routes (except where acknowledgment is given) were devised by the undersigned. Furthermore, this thesis has not previously been submitted to any Institution for academic examination towards any qualification.

SIGNATURE: .....

DATE: .....

CONTENTS

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PREFACE

Several bioactive quinonoid compounds are obtained from Nature but then only in minute quantities so that laboratory experiments with the aim of establishing their mode of action or bioactivity are severely restricted. Thus their laboratory synthesis became a particular challenge to several synthetic organic chemistry groups world-wide.

In view of the above the author started on a project in 1982 which was aimed at the laboratory synthesis of such compounds or their derivatives which would make them more readily available for biological studies. The results of this work, which was performed mainly at the Cape Technikon, were published in a series of papers in international Journals and in a thesis entitled, *Syntheses related to some naturally occurring naphthopyranquinones*, submitted in 1986 to the University of Cape Town for the PhD degree in Organic Chemistry. This thesis described *inter alia* the synthesis of some 90 new compounds.

During 1990 the Chemical Technology Research Unit and an antimicrobial evaluation facility were established by the author in the Department of Chemistry at the Cape Technikon and up to date some 50 potential antibiotic compounds were synthesised and evaluated. Some of these synthetic compounds show promising antibiotic properties indeed.

It was envisaged that by preparing a variety of these compounds and then comparing their biological properties and activities, a better insight or understanding would be gained into a molecular structure - activity relationship. Thus the target compounds were being chosen on the basis of specific potential structure-activity relationships.

Our Research Unit at the Cape Technikon is the first in the RSA to have embarked on a systematic bio-evaluation programme of several synthetic quinones and some of their precursors. As a direct result of this work, the pharmaceutical company Glaxo in England requested the provision of some of the new synthetic compounds for studies in their anti-bacterial activity programme. The Unit has also now reached the stage where internationally recognised chemists from overseas (Dr M Brimble, University of Sydney; Prof R G F Giles, University of Murdoch, Perth, and others) are collaborating by providing samples for bioactivity screening.

With respect to the expected impact of the expertise developed as a consequence of this project, and the national need, the author wishes to mention that (in general) the RSA is lacking behind the rest of the world as far as bio-evaluation of new compounds is concerned - an aspect which should be urgently addressed.

As there is an ongoing search for cheaper and more efficient medicines, especially antibiotics, it is sincerely hoped that this work and its possible spin-offs may contribute eventually to this need.

ABSTRACT

A new general synthetic strategy for the synthesis of benzo[*c*]pyranquinones, with a view to making the route more generally applicable to the synthesis of naturally occurring naphtho[2,3-*c*]pyranquinones of potential importance as antimicrobial agents, has been developed. This synthetic approach afforded, *inter alia*, the natural products, isoeleutherin and hongconin (as their racemates) in good overall yield.

A new high-yielding synthetic route for the synthesis of 1,5-dimethoxy-4-naphthol, 2-allyl-5-methoxy-1,4-naphthoquinone and 3-acetyl-5-methoxy-1,4-naphthoquinone, all of which are key intermediates in several laboratory routes to naturally occurring naphtho[2,3-*c*]pyranquinones, has also been developed. A key-step in their formation is respective methylation, allylation or acetylation of a common intermediate Diels-Alder adduct.

A feasible route to a naphtho[2,3-*c*]pyranone was developed. This model route is envisaged to be generally applicable for the synthesis of higher oxygenated naphtho[2,3-*c*]pyranones by virtue of the nature of the conditions and reagents used in this synthetic route.

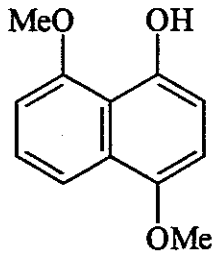
The target quinones and some of their precursors were evaluated for antimicrobial activity and specificity *in vitro*. This showed that the benzo[*c*]pyranquinones have a broader specificity spectrum than their naphtho[2,3-*c*] or naphtho[2,3-*b*] analogues.

INTRODUCTION

The objectives of this study were:

(i) to develop a new general synthetic strategy for the synthesis of benzo[*c*]pyranquinones with a view to making the route more generally applicable to the synthesis of naturally occurring naphtho[2,3-*c*]pyranquinones and other quinones of potential importance as antimicrobial or antineoplastic agents.

(ii) to develop a new general synthetic route for the synthesis of 1,5-dimethoxy-4-naphthol (**1**),[1] 2-allyl-5-methoxy-1,4-naphthoquinone (**2**)[2] and 3-acetyl-5-methoxy-1,4-naphthoquinone (**3**).[3, 4]



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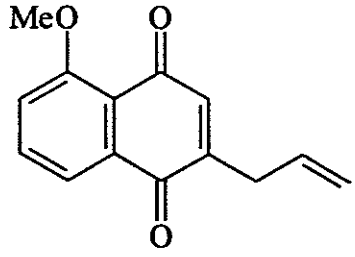

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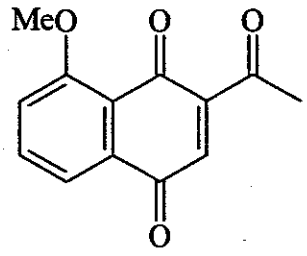

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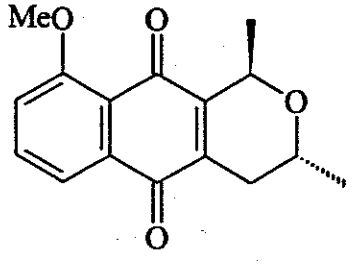
These naphthalene derivatives are key intermediates in laboratory routes to some important naturally occurring naphtho[2,3-*c*]pyranquinones. For example, naphthol (**1**) has been used in the synthesis of isoeleutherin (**4**)[5], and quinone (**2**) was employed as starting material in a route[6] to nanaomycins A (**5**) and D (**6**) which are potent antimicrobial agents.[7]

In addition, bromination of compound (**1**) afforded the bromo derivative (**7**) which could be oxidised to the corresponding quinone (**8**) used by Yoshii *et al.* in their synthesis of nanaomycin A (**5**).[8]



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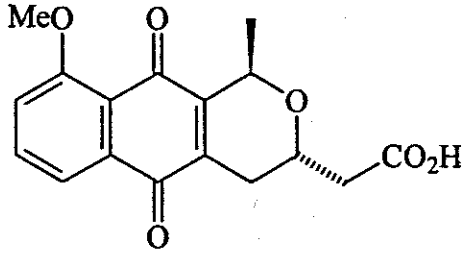

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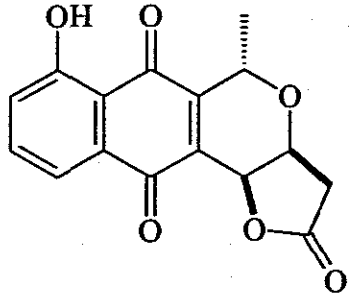

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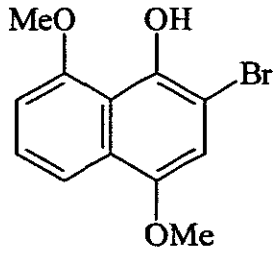

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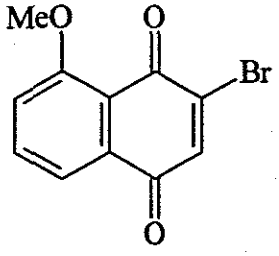

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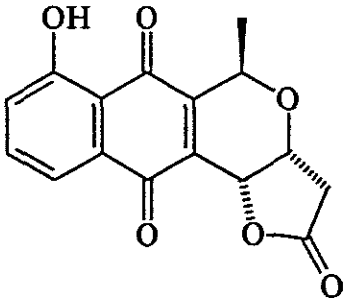
Quinone (3) was also employed as a key intermediate in syntheses of isoeleutherin (4),[5] nanaomycin A (5)[9] and kalafungin (9)[10] [the enantiomer of (6)].



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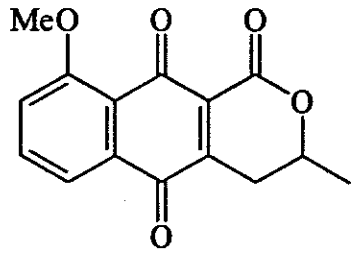
(iii) to evaluate the synthesised target quinones chosen on the basis of specific potential structure-activity relationships and some precursors obtained from the strategies in (i) and (ii) above, for antimicrobial activity. The

main objective in this regard was to screen the synthetic compounds for antibiotic activity and specificity (whether the compound is active against Gram positive and/or Gram negative micro-organisms) *in vitro*, rather than to quantify their bioactivity or establish their mechanism of action. As mentioned earlier it was envisaged that by preparing a variety of these quinonoid compounds and then comparing their antimicrobial specificity, a better insight would hopefully be gained into a molecular structure-activity-specificity relationship.

(iv) to develop a feasible route to the naphtho[2,3-*c*]pyranone (**10**) in order to (from a structural point of view) determine and compare its antimicrobial activity or specificity with that of the naphtho[2,3-*c*]pyran isoeleutherin (**4**).



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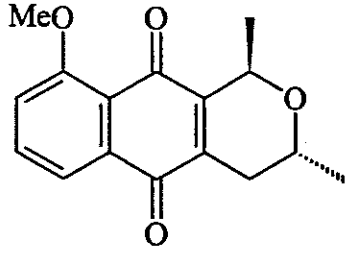
CHAPTER 1

SYNTHETIC ROUTES TO SOME POTENTIAL ANTIMICROBIAL BENZOQUINONES

The biological potential of naturally occurring naphtho[2,3-*c*]pyran-5,10-quinones as antineoplastic agents or antibiotics has been recognised for many years and the synthesis of some of these compounds has been successfully undertaken by several groups.[5, 6, 11] Examples include isoeleutherin (**4**), the nanaomycins A (**5**) and D (**6**),[9] fusarubin (**11**), marticin (**12**)[12] and hongconin (**13**)[13, 14] which is used as a remedy for angina pectoris. This natural product was recently synthesised in our laboratories as its racemate.[15]



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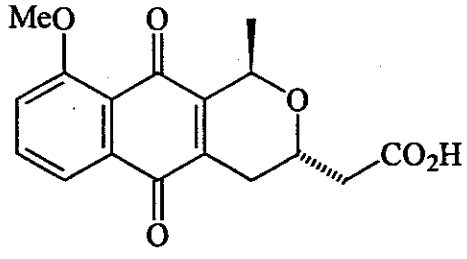

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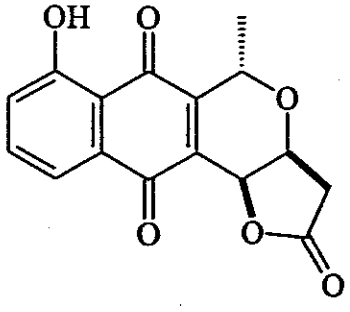

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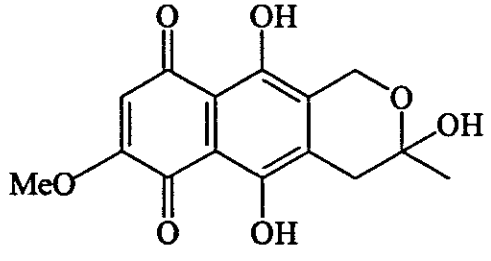

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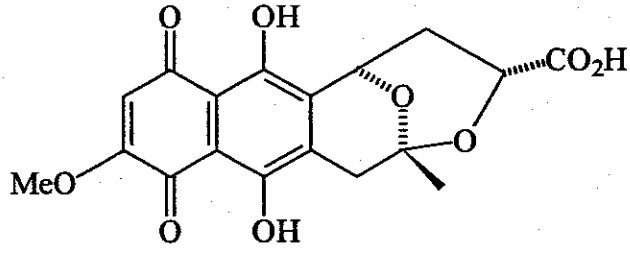

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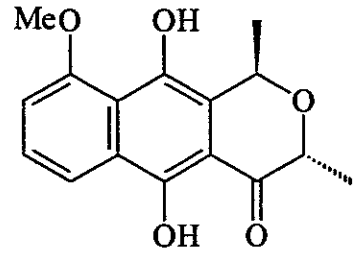

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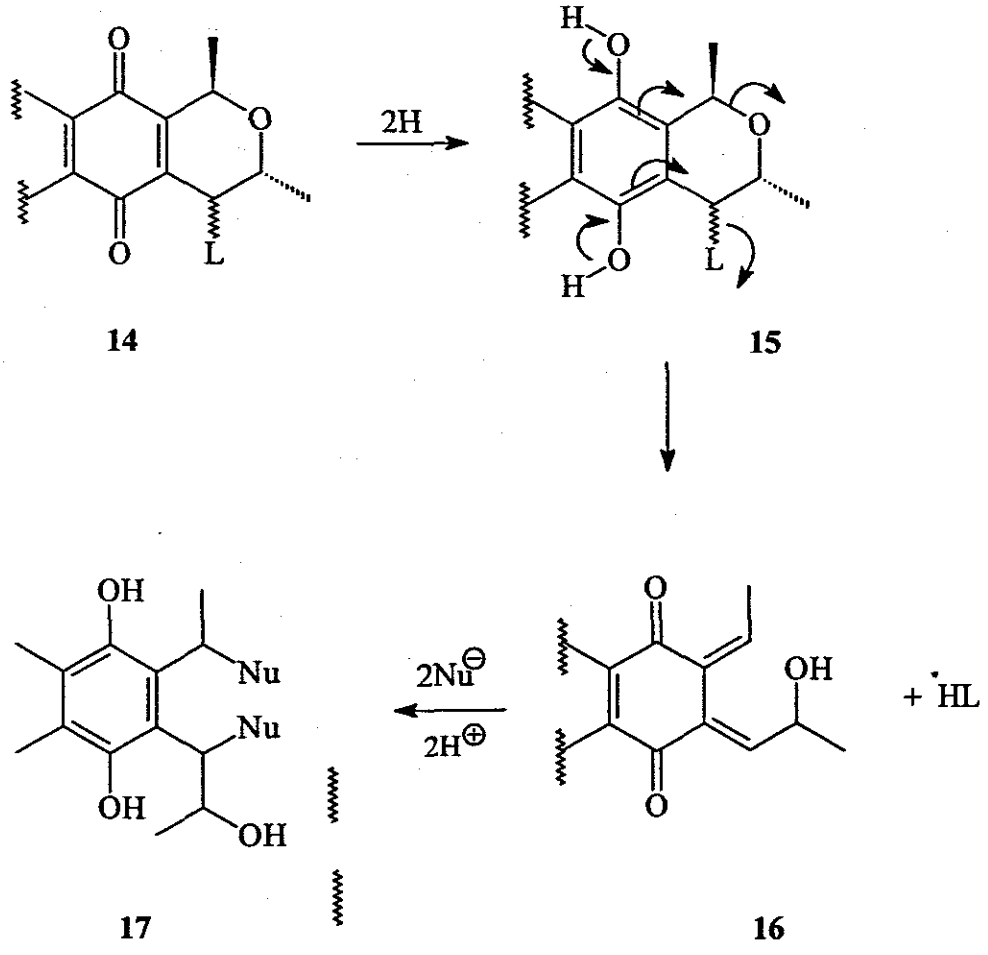
Basing much of his proposed mechanism for the biological activity of these systems on work done by Sartorelli,[16, 17] Moore[18] suggested that a [2,3-*c*]pyranquinone, *viz.* (**14**) first undergoes an *in vivo* reduction to the quinol (**15**) which could ring-open as shown in **Scheme 1** to afford a highly active bisquinone-methine system (**16**). This system could then react with nucleophilic centres in DNA and RNA. Once the natural structures of the nucleic acids have been modified in this way as in (**17**), tumour growth or bacterial multiplication will become inhibited.

In our view the most important structural feature for biological activity in these systems is the aryl[2,3-*c*]pyranquinone nucleus and that a leaving group L at C-4 of the pyran ring would increase the activity (as in **Scheme 1**).

Scheme 1

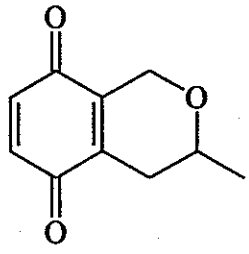


14 **15** **16** **17**

The complex naturally occurring cyclinones (**19**) and (**20**)[19] are inhibitory against Gram positive bacteria and it was suggested that their activity could be partially due to the [2,3-*c*]pyranquinone system as in (**18**).

Thus the initial aim was the synthesis of the benzo[*c*]pyranquinone (**18**)[20, 21] (as its racemate) in order to study the importance of the position of the oxygen

in the pyran ring for antimicrobial activity. Once this was established a leaving group in the form of hydroxyl could be introduced at C-4.



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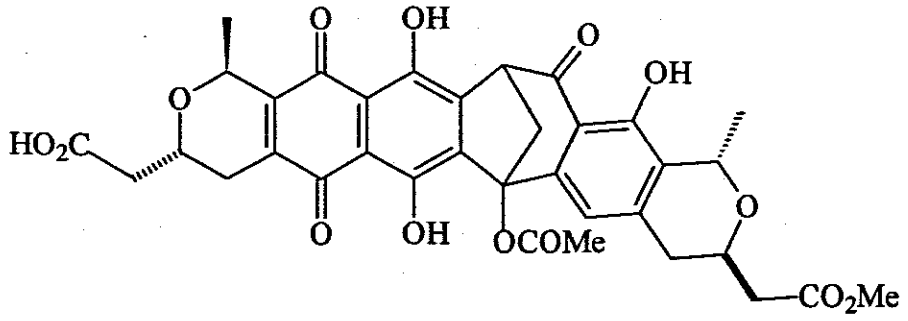

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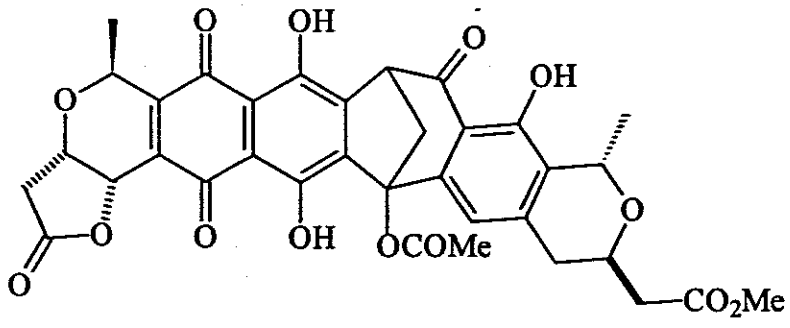

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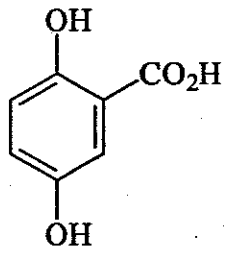
The readily available gentisic acid (**21**) was smoothly converted to the known allyl ester (**22**)[22] in a yield of 65% with some diallyloxyallyl ester (**27**) forming as a by-product (8%).



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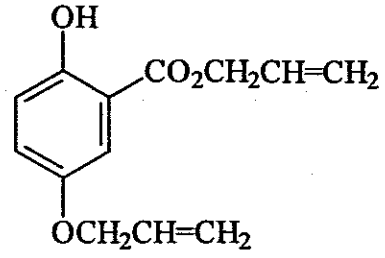

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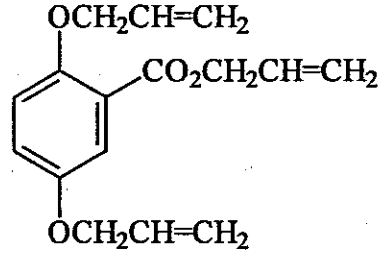

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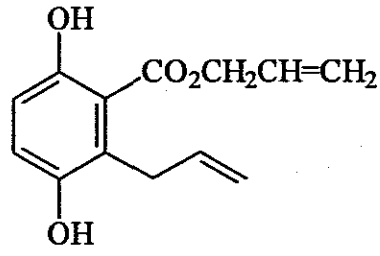
Claisen rearrangement of ester (**22**) gave the quinol (**23**) (69%) as a result of an *ortho* migration of the allyl group to the sterically disfavoured position. Similar regioselectivity in the Claisen rearrangement of esters of 5-allyloxy-2-hydroxybenzoic acid has been noted earlier.[23] Assignment of structure (**23**) to the product of Claisen rearrangement was supported by its ^{1}H nmr spectrum in which the aromatic 4-H and 5-H resonated as *ortho* coupled doublets (J 9 Hz) at δ 7.30 and 6.80 respectively.



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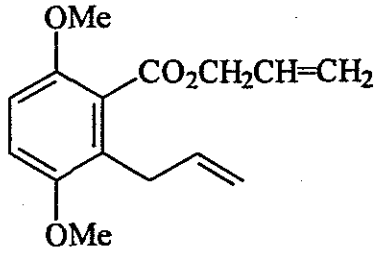
Methylation of quinol (**23**) with iodomethane and potassium carbonate in boiling acetone afforded ether (**24**) in excellent yield (95%) which upon reduction with lithium aluminium hydride yielded the alcohol (**25**) in a yield of 90%.



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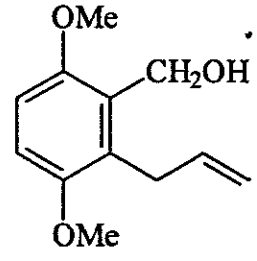

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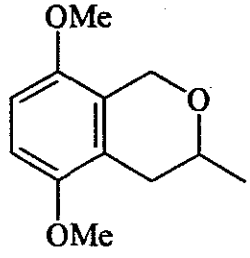
Anaerobic base-induced cyclisation[5] of (**25**) produced the racemic benzo[2,3-*c*]pyran (**26**) which upon oxidative demethylation gave the corresponding racemic benzo[2,3-*c*]pyranquinone (**18**)[21] in good yield.



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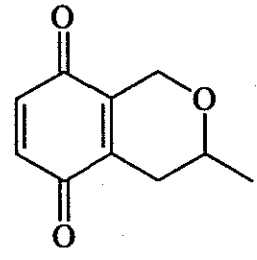

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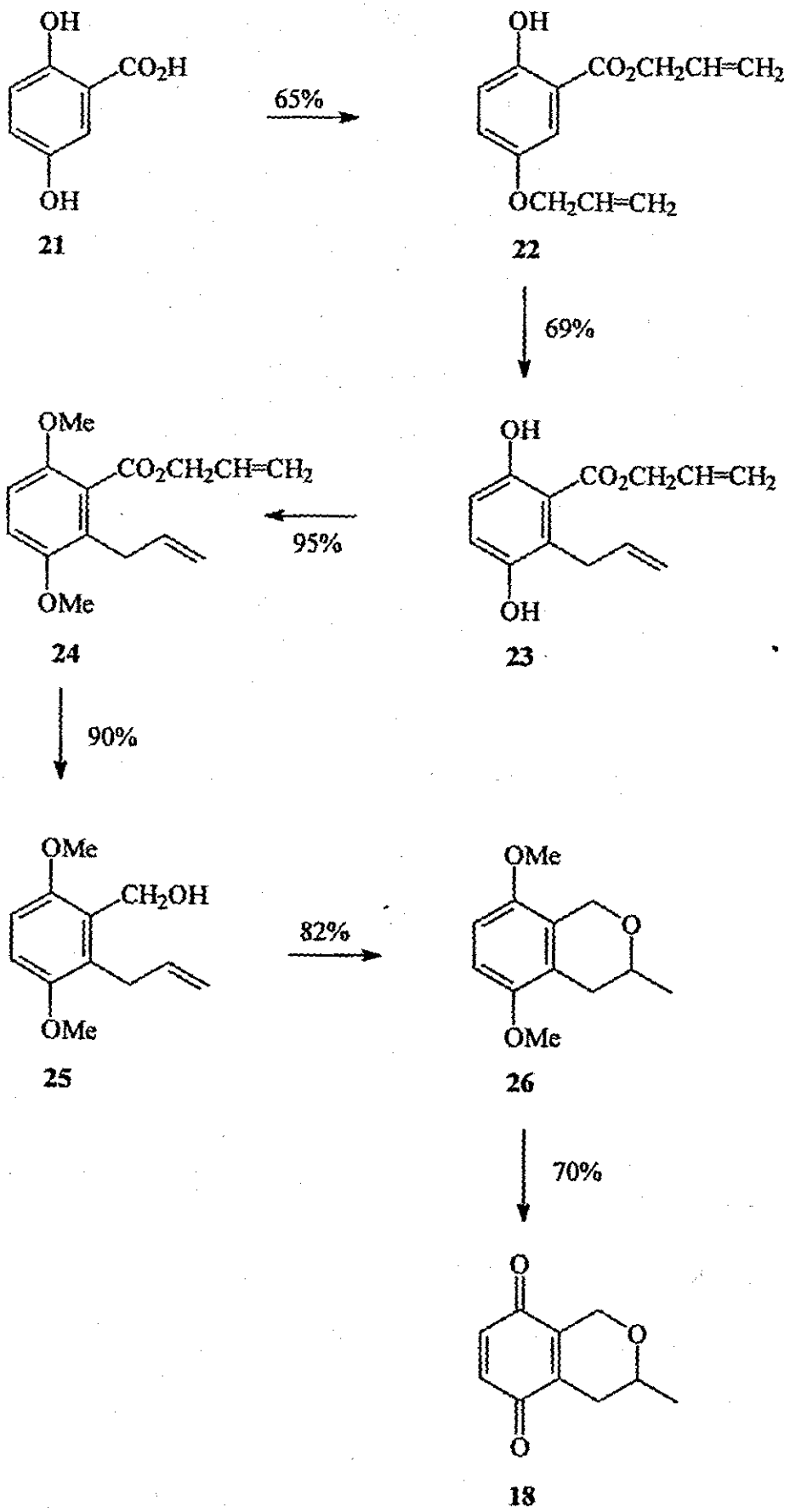
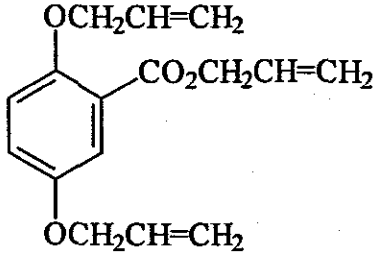
The ^{1}H nmr spectrum of quinone (**18**) showed *inter alia* a complex resonance pattern (dddd) centred at δ 2.08 due to the *pseudo*-axial 4-H of the pyran ring which is geminally coupled (J 19 Hz) to the *pseudo*-equatorial 4-H, vicinally coupled (J 10 Hz) to the axial 3-H and long-range coupled (J 3.5 and 3.0 Hz) to the *pseudo*-axial and *pseudo*-equatorial protons at C-1 respectively. The *pseudo*-equatorial 4-H resonated as a doublet of triplets (J 19 and 3.5 Hz) at δ 2.60 whereas the *pseudo*-axial and *pseudo*-equatorial protons at C-1 resonated as doublet of triplets (J 19 and 3.5 Hz) and a doublet of doublets (J 19 and 3 Hz) at δ 4.35 and 4.75 respectively.

The synthetic route to pyranquinone (**18**) is summarised in **Scheme 2.**

Scheme 2


OH
CO2H
OH
21
65%
OH
CO2CH2CH=CH2
OCH2CH=CH2
22
69%
OH
CO2CH2CH=CH2
OH
23
95%
OMe
CO2CH2CH=CH2
OMe
24
90%
OMe
CH2OH
OMe
25
82%
OMe
O
OMe
26
70%
O
O
O
18

Following the completion of the successful synthesis of quinone (**18**), an extended investigation into the Claisen rearrangement of allyloxy systems particularly of the type (**27**) and (**32**)[21] was sought as a consequence of the formation of quinol (**23**) where a regiospecific migration of the allyl group to the sterically more conjested position was observed.



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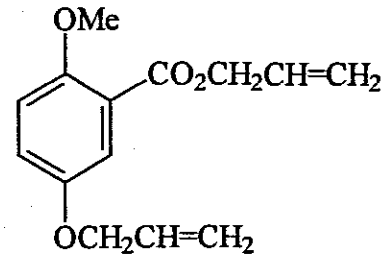

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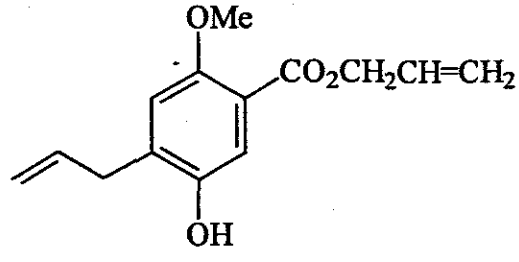
Subjection of ether (**32**) to Claisen conditions yielded phenol (**33**) (32%) as the sole product. The structure of (**33**) is based on the ^{1}H nmr spectrum, which showed the 3- and 6-H signals as singlets at δ 6.75 and 7.40 respectively.



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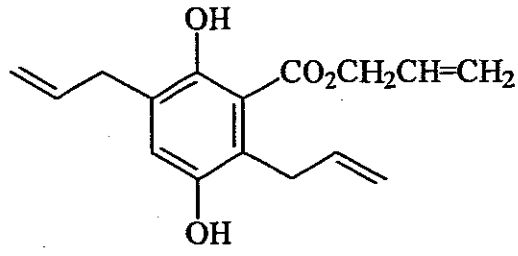
This finding further demonstrated that when hydrogen bonding between the ester carbonyl group and the hydroxyl on C-2 [as in (**22**)] was absent, migration of the allyl group was to the less crowded alternative *ortho* position.

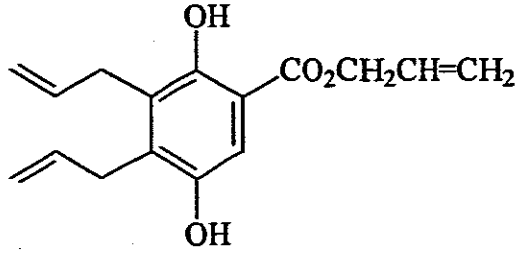
Furthermore, when ester (**27**) was pyrolysed, quinol (**28**) was the sole product isolated, indicating that the allyl group at the C-5 ether position had migrated to the sterically disfavoured position at C-6.



28

In order to account for this apparent anomaly it is proposed that the initial step in the rearrangement is prior migration of the allyl group from the C-2-O to C-3, thereby allowing H-bonding to be re-established as before and thus dictating the migration of the allyl group from C-5-O to C-6.

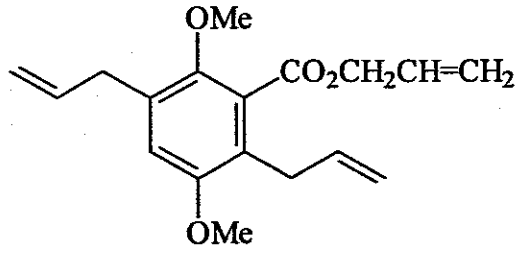
Chemical verification for the assignment of structure (**28**) was considered necessary since the single resonance in the ^1H nmr spectrum at δ 6.85 was in our view not conclusive evidence to discount the alternative isomer (**28a**).



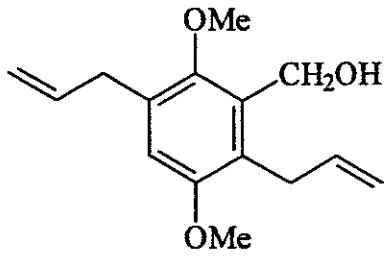
28a

If structure (**28**) assigned to this product was correct, then it would afford pyran (**31**)[21] by employing conditions as for the conversion of (**23**) ⟶

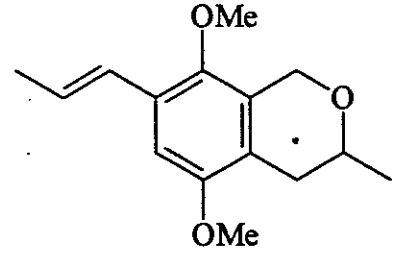
pyran (**26**). This indeed proved to be the case. Thus methylation of (**28**) afforded ether (**29**) (96%), which upon reduction with lithium aluminium hydride gave the alcohol (**30**).



29



30



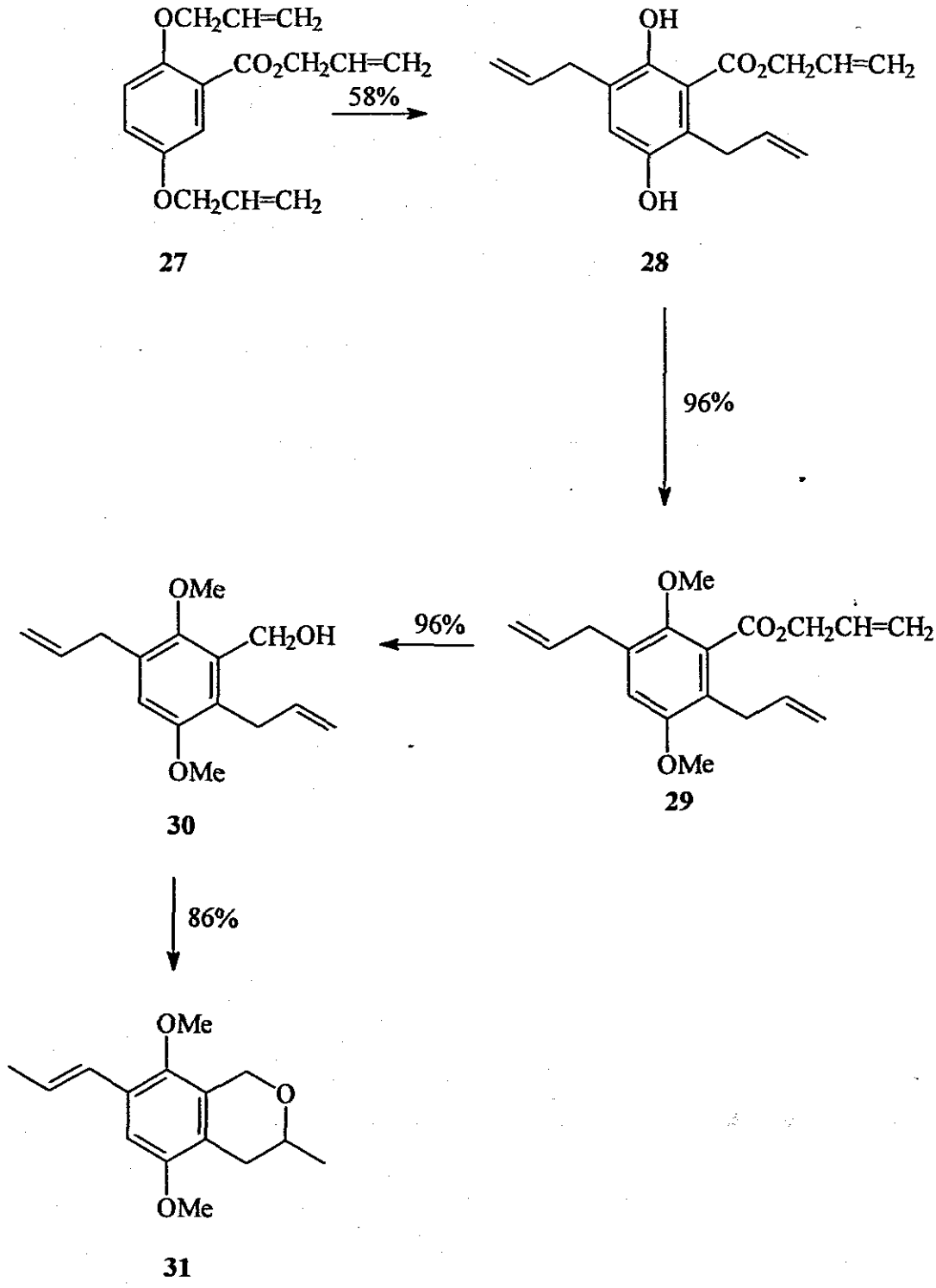
31

Compound (**30**) underwent smooth anaerobic base-catalysed cyclisation to the benzo[*c*]pyran (**31**). During cyclisation of alcohol (**30**), the propenyl group at C-3 underwent conjugation leading to product (**31**), as was evident from the ^{1}H nmr spectrum in which the 3'-CH_3 resonated as a doublet (J 6 Hz) at δ 1.92. The stereochemistry of the olefinic protons was assigned *trans* as indicated by the coupling constant (J 16 Hz).

Oxidation of benzopyran (**31**) using either cerium(IV) ammonium nitrate[24] (CAN) or silver(II) oxide[25] failed to yield any of the corresponding quinone, but led to decomposition products instead.

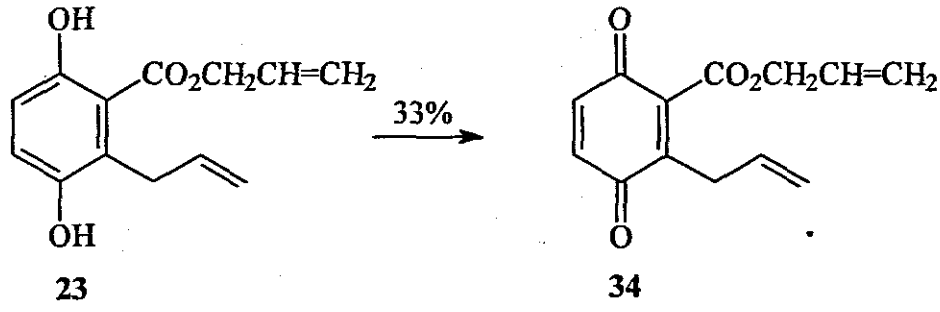
The route to pyran (**31**) is summarised in **Scheme 3**.

Scheme 3

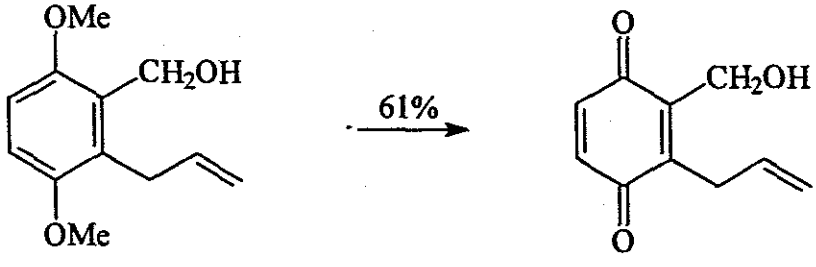


It was next decided to convert some of the precursors of quinone (**18**) to their corresponding quinones in order to compare their antimicrobial activity[20] or specificity (if any) with that of the heterocyclic compound (**18**).

Thus CAN-mediated oxidation of quinol (**23**) and alcohol (**25**) afforded the quinones (**34**) and (**35**) respectively.

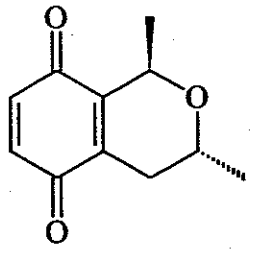


23 **34**

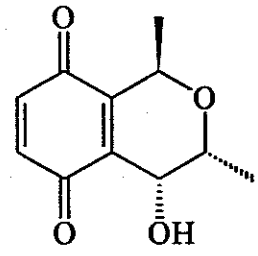


25 **35**

Having now successfully developed an efficient synthetic route to the benzo[2,3-*c*]pyranquinone (**18**), attention was next focused on the synthesis of the related benzopyrans (**36**), (**37**), (**38**) and (**39**),[21] for our comparative antimicrobial structure-activity relationship studies.[26]



36



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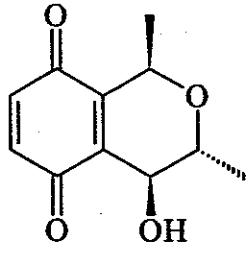
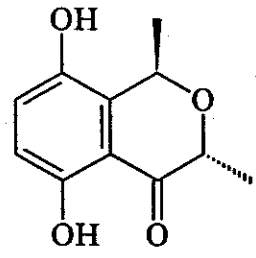
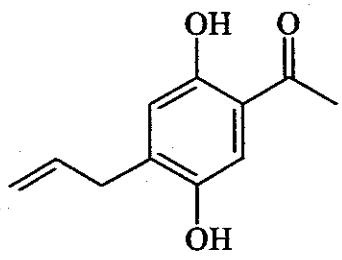


38



39

Pyranquinone (**36**) was synthesised (as in **Scheme 4** on page 21) in good overall yield from 2,5-dihydroxy-acetophenone (**40**) by applying the route as for the synthesis of pyranquinone (**18**). Thus acetophenone (**40**) was monoallylated to afford ketone (**41**)[23] (93%) which underwent a Claisen rearrangement to the quinol (**42**) in a yield of 84%. In this case a small amount (8%) of the alternative isomer (**42a**) was detected in the reaction mixture. Also in this case H-bonding between the hydroxyl group at C-2 and the ketone carbonyl facilitated migration of the allyl group to C-6. The ^{1}H nmr spectrum of (**42**) showed *inter alia* the resonances of the 5-H and 4-H protons as pair of *ortho* coupled doublets (J 9 Hz) at δ 6.78 and 6.98 respectively.

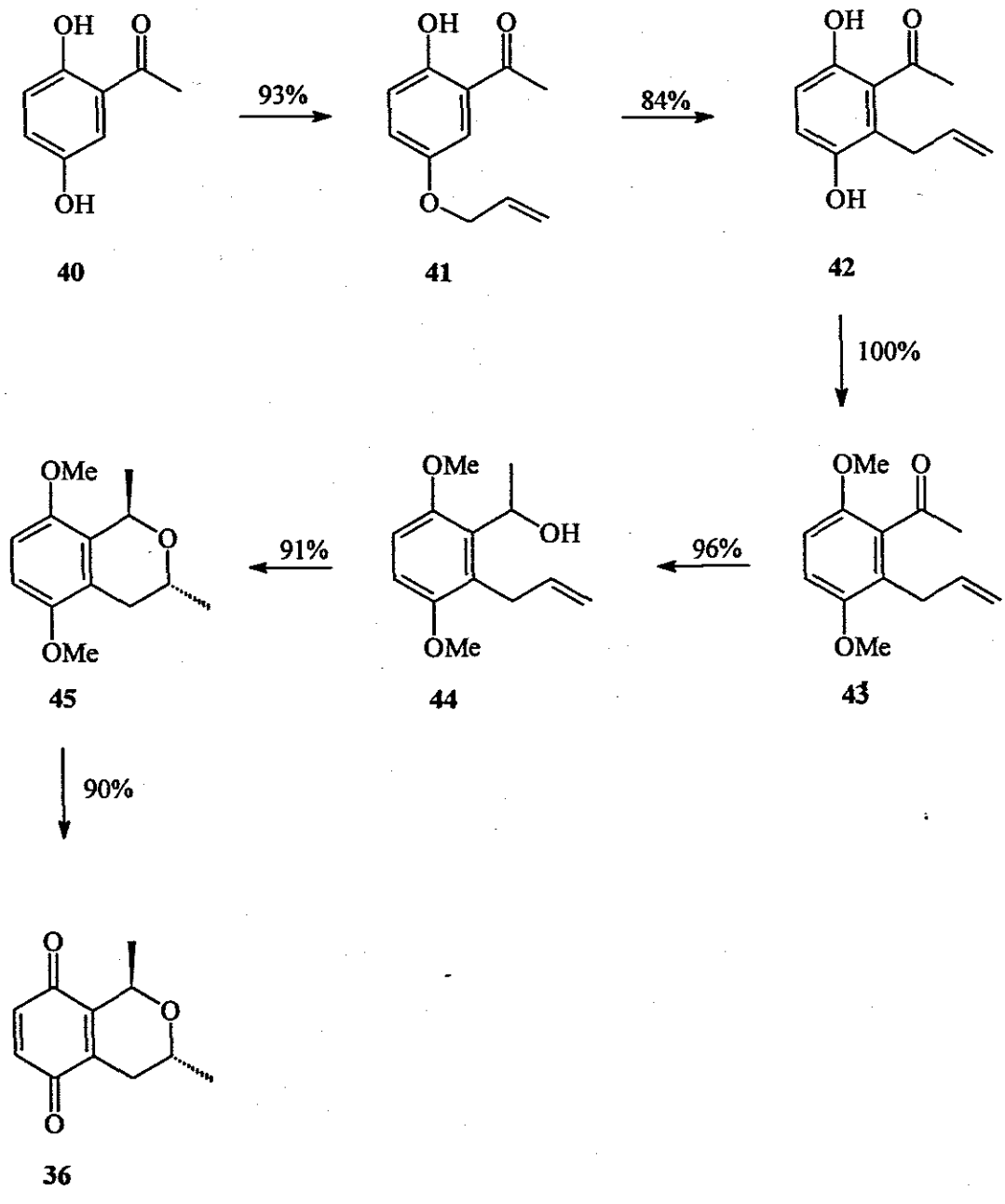


42a

Methylation of quinol (**42**) as before, led to quantitative formation of the dimethyl ether (**43**), which underwent smooth reduction with lithium aluminium hydride to yield the secondary alcohol (**44**) (96%).

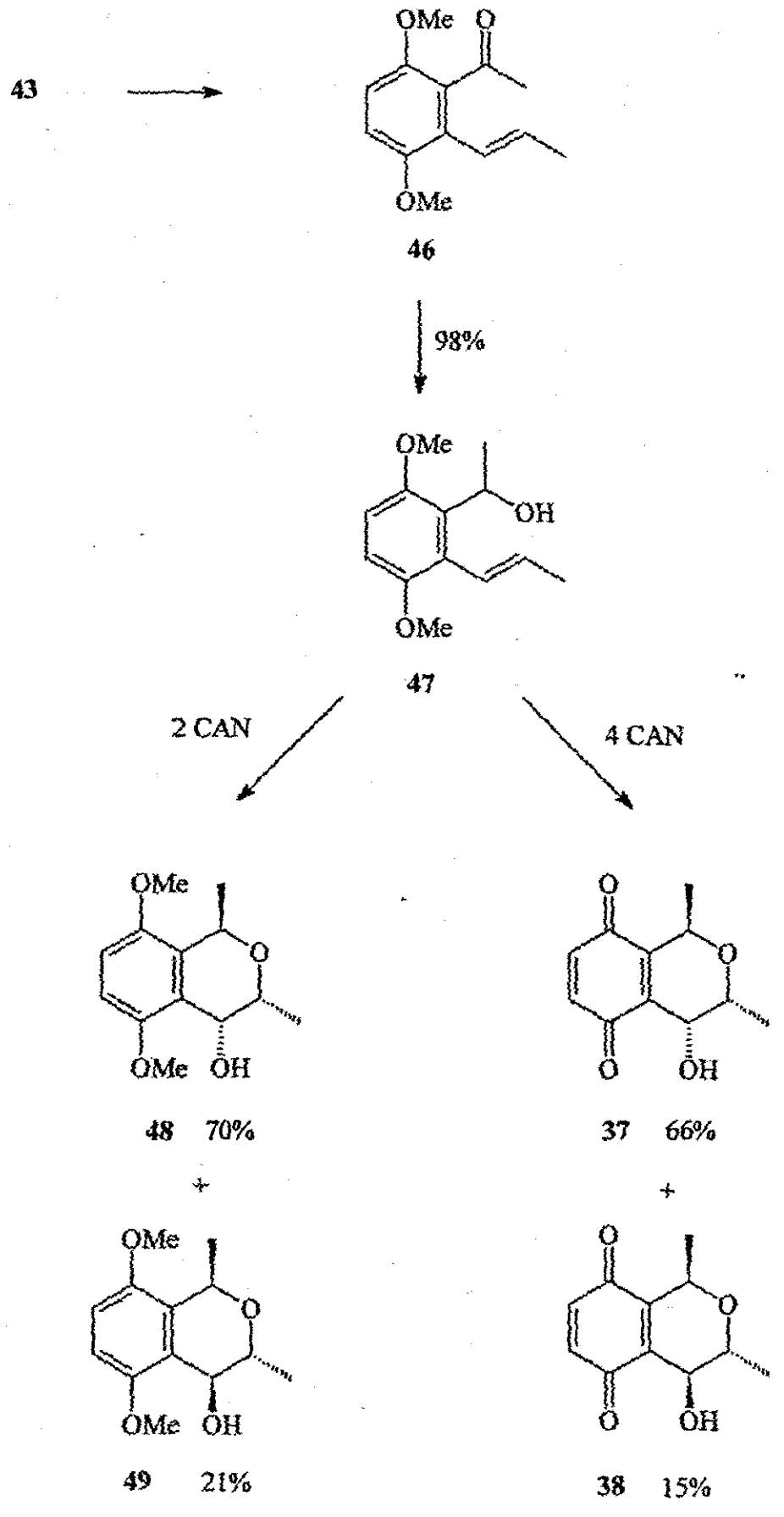
Anaerobic base-induced cyclisation[5] of this alcohol gave the racemic benzopyran (**45**) as the sole product in a yield of 91%. Oxidative demethylation of (**42**) using CAN afforded pyranquinone (**36**) in excellent yield (90%). The relative configuration between the methyl groups at C-1 and C-3 of pyrans (**45**) and (**36**) was confirmed as *trans* by their ^{1}H nmr spectroscopic data.[21]

Scheme 4



Whereas the introduction of a hydroxyl group at C-4 in the naphthopyran series of compounds studied proceeded smoothly,[5, 27, 28] great difficulty was experienced in all our attempts at introducing the hydroxyl group at C-4 in pyran (**45**) and, consequently, an alternative route was sought (**Scheme 5**).

Scheme 5

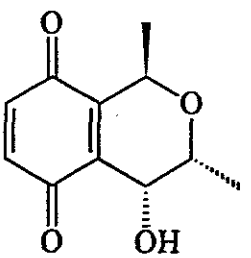

43
OMe
O
OMe
46
98%
OMe
OH
OMe
47
2 CAN
4 CAN
OMe
O
OMe
OH
48 70%
+
O
O
O
OH
37 66%
+
OMe
O
OMe
OH
49 21%
O
O
O
OH
38 15%

Thus, ketone (**43**) was treated with potassium *tert*-butoxide in tetrahydrofuran to produce the *trans*, conjugated analogue (**46**), which was confirmed by (*inter alia*) the 3'-CH_3 group appearing at δ 1.85 as a doublet (J 6 Hz). Reduction of this ketone to the corresponding alcohol (**47**) was smoothly accomplished using lithium aluminium hydride in ether (97%).

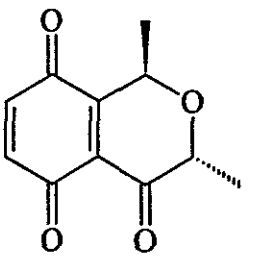
Treatment of (**47**) with 2 molar equivalents of CAN in aqueous acetonitrile[5, 29] produced the 4-hydroxypyran derivatives (**48**) and (**49**) in yields of 70% and 21%, respectively. The infrared spectrum of the major isomeric alcohol (**48**) showed a sharp absorption at 3480 cm^{-1}, which confirmed the presence of the alcohol group, while the molecular ion at *m/z* 238.1184 in the mass spectrum gave support for the molecular formula as the pyran (**48**). Confirmation of the stereochemistry[30, 31] about the pyran ring was evident from the ^1H nmr spectrum, in which the three pyran protons appeared as a doubled of quartets at δ 4.08 (J 2 and 6.5 Hz), a doublet of doublets at δ 4.54 (J 7.4 and 2 Hz) and quartet at δ 5.10 (J 6.7 Hz), assigned to the 3-H, 4-H and 1-H protons, respectively. The relative stereochemistry between the 3-H and 4-H pyran ring protons was established as axial and *pseudo*-equatorial, respectively, by virtue of the common coupling constant of 2 Hz, which confirmed that the C-4 alcohol function for the major isomer (**48**) is *pseudo*-axial. The corresponding coupling constant between the 3-H and 4-H of the minor isomeric alcohol (**49**)

is 7 Hz, confirming the fact that the 4-H is *pseudo*-axial and that the C-4 alcohol function is thus *pseudo*-equatorial.

In a similar way, treatment of (**47**) with 4 molar equivalents of CAN in aqueous acetonitrile resulted in cyclisation and concomitant oxidative demethylation to afford the pyranquinones (**37**) and (**38**) in yields of 66% and 15%, respectively. The infrared spectrum of (**37**) showed sharp bands at 3480 and 1650 cm^{-1} which confirmed the presence of the alcohol and quinone groups, respectively. The ^1H nmr spectrum displayed a close similarity to that of the pyran (**48**) while the ^1H nmr spectra of pyranquinone (**38**) and pyran (**49**) had confirmatory similarities, thereby establishing the assigned relative stereochemistries of the protons at C-1, C-3 and C-4 of the pyran ring. Attempts at oxidising the pyranquinone (**37**) to the ketoquinone (**37a**) using pyridinium dichromate failed in our hands, with the starting material being recovered.

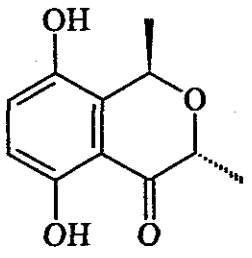


37

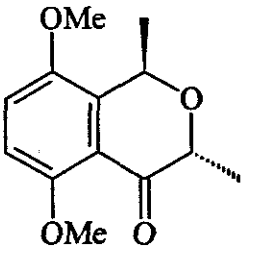


37a

An alternative route investigated (**Scheme 6**) for the synthesis of quinol (**39**) [the aryl [*c*]pyran moiety of hongconin (**13**)] proved to be successful and involved the initial oxidation of the C-4 hydroxypyran (**48**) to the C-4 ketopyran (**50**) with pyridinium dichromate in dichloromethane in fair yield.



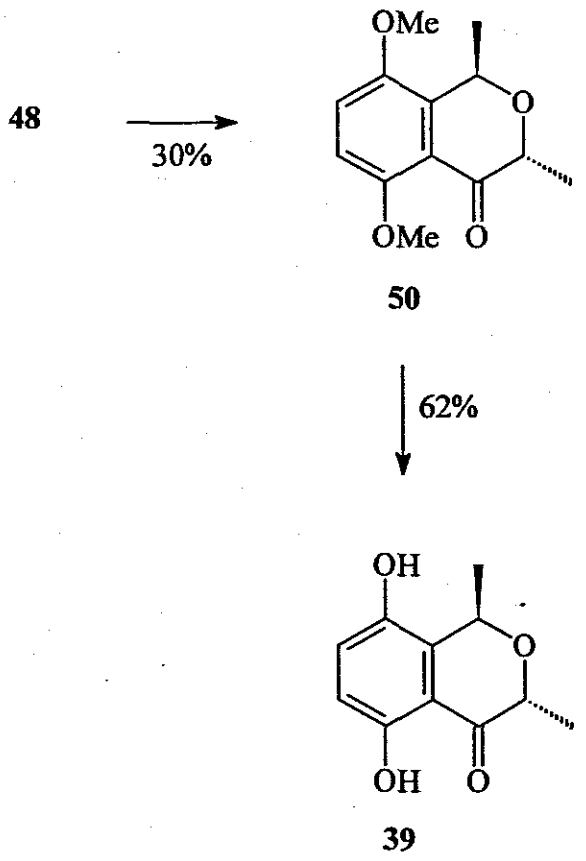
39



50

The absence of bands in the 3400 cm^{-1} region and the appearance of a strong band at 1690 cm^{-1} in the infrared spectrum confirmed that the desired oxidation had occurred. Finally, demethylation of ketopyran (**50**) afforded the pyranquinol (**39**) in a yield of 62%. Assignment of the structure (**39**) to the product is based on a strong band at 3370, a weaker band at 1700 and a strong band at 1650 cm^{-1} in the infrared spectrum, while the molecular ion at *m/z* 208.0742 in the mass spectrum supported the molecular formula of $C_{11}H_{12}O_4$ for pyran (**39**). Confirmation of the two hydroxyl groups was evident from the ^1H nmr spectrum, in which the C-8 hydroxyl group appeared as a D_2O-exchangeable single peak at δ 4.90, while the hydrogen-bonded C-5 hydroxyl group appeared downfield as a sharp D_2O-exchangeable peak at δ 11.32.

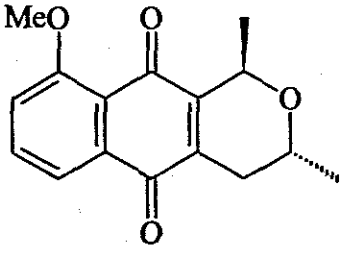
Scheme 6



The reluctance of quinol (**39**) to undergo oxidation to the corresponding quinone (**37a**) under the conditions used is a result of the strong H-bonding stabilisation between the C-5 hydroxyl and C-4 carbonyl groups, since oxidative demethylation of pyran (**45**), in which the C-4 carbonyl is absent, afforded quinone (**36**) in a yield of 90%.

Thus, a general strategy has been developed for the synthesis of benzo[*c*]pyran ring systems which are considered to be appropriate for comparative antimicrobial evaluation. Furthermore these synthetic strategies could now be

applied to the synthesis of some naturally occurring naphtho[2,3-*c*]pyrans such as isoeleutherin (**4**) and hongconin (**13**) as their racemates.



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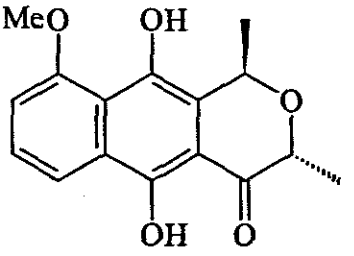


13

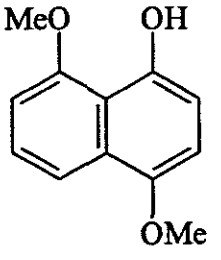
CHAPTER 2

SYNTHETIC STRATEGIES TOWARDS KEY PRECURSORS IN ROUTES TO SOME NATURALLY OCCURRING NAPHTHO[2,3-*C*]PYRANS

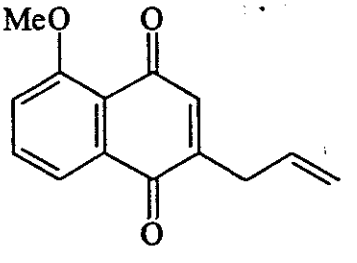
2.1 SYNTHESIS OF 1,5-DIMETHOXY-4-NAPHTHOL (1), 2-ALLYL-5-METHOXY-1,4-NAPHTHOQUINONE (2), AND 3-ACETYL-5-METHOXY-1,4-NAPHTHOQUINONE (3)

2.1.1 EXISTING METHODS

Compounds (1), (2) and (3) are key intermediates in synthetic routes to some naturally occurring naphtho[2,3-*c*]pyranquinones.[5,6,8] Convenient laboratory routes to compounds (1), (2) and (3) would thus constitute an important part in the total synthesis of these natural products.



1



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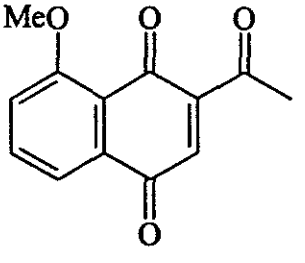
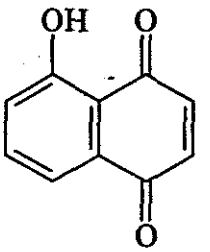


3

Synthesis for compounds (1), (2) and (3) have previously been reported.[1, 2, 3] However, these routes have some synthetic

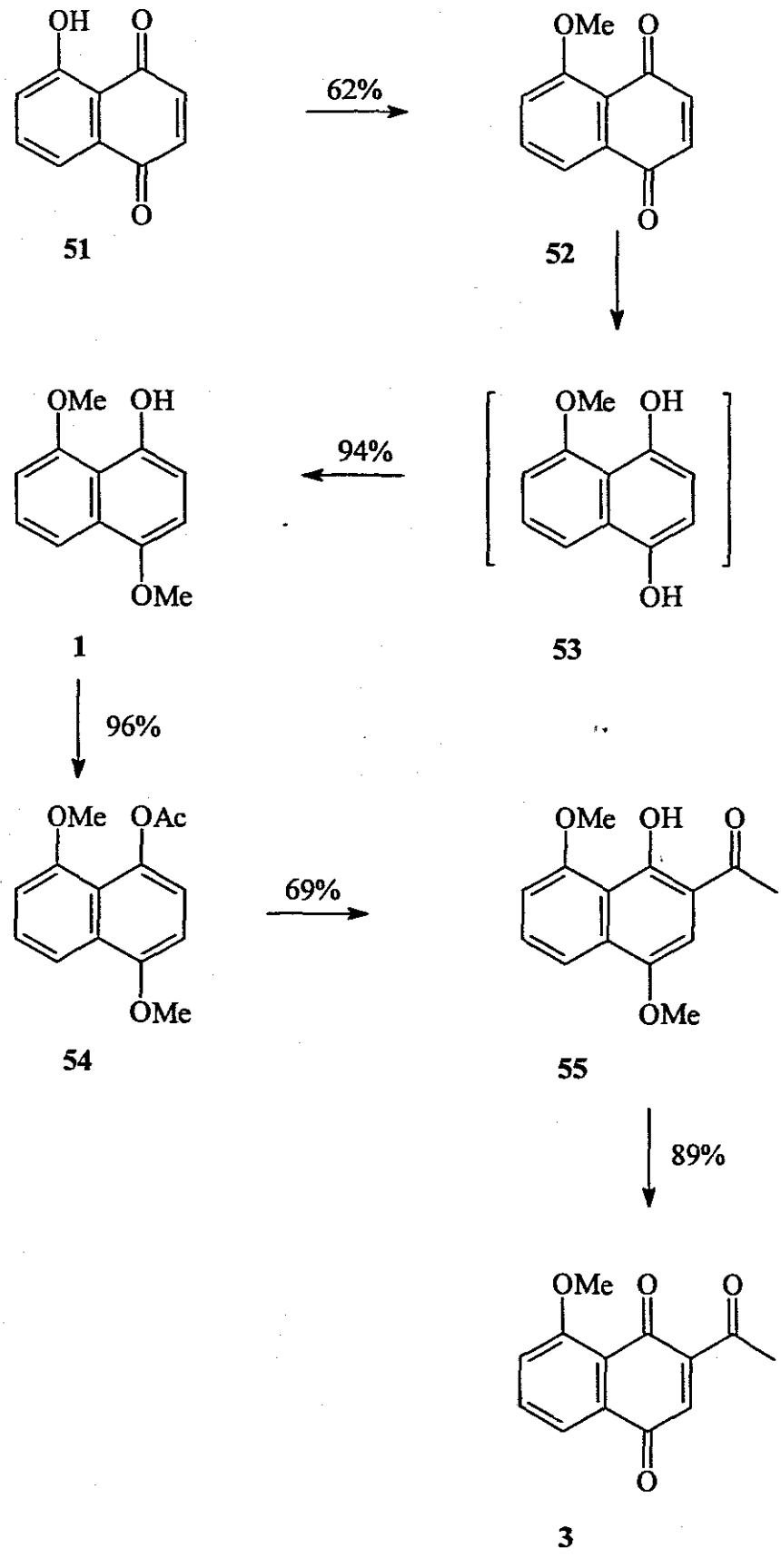
disadvantages. For example, the low yield (34%) in the final step to quinone (**3**) by Bosshard *et al.*[3] made an alternative route desirable for further synthesis.

Thus our group[5] later developed a new route (as in **Scheme 7**) to naphthol (**1**) and quinone (**3**) from the natural product juglone (**51**).[32]



51

Scheme 7

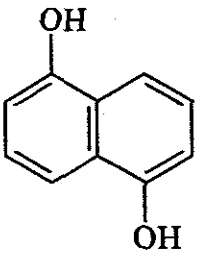

OH
O
O
51
62%
OMe
O
O
52
OMe
OH
OMe
1
94%
OMe
OH
OH
53
96%
OMe
OAc
OMe
54
69%
OMe
OH
O
OMe
55
89%
OMe
O
O
O
3

Juglone (**51**) was methylated using iodomethane and silver(I) oxide to afford juglone methyl ether (**52**) (62%). This gave the diol (**53**) on treatment with sodium dithionite. Compound (**53**) was then monomethylated at the less hindered hydroxyl to afford naphthol (**1**) [94% from (**52**)].

Acetylation of compound (**1**) gave the acetate (**54**) (96%) which underwent a Fries rearrangement upon treatment with boron trifluoride-etherate, to give the acetyl naphthalene (**55**) (69%). Oxidative demethylation using CAN afforded quinone (**3**) in good yield (89%).

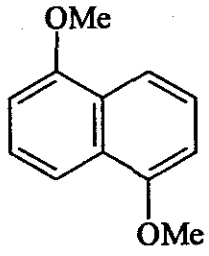
However, a disadvantage of this route is the cost and limited availability (either from natural sources or by inefficient laboratory syntheses[1]) of juglone (**51**).

Naphthol (**1**) has also been prepared by Rapoport[1] from 1,5 dihydroxynaphthalene (**56**).



56

The dimethyl ether (**57**), available from (**56**) by methylation with dimethyl sulphate, was treated with dimethylformamide (DMF) and $POCl_3$ in toluene to afford the naphthaldehyde (**58**) which on Baeyer-Villiger oxidation afforded formate (**59**) which afforded naphthol (**1**) by alkaline hydrolysis.



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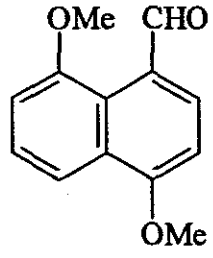
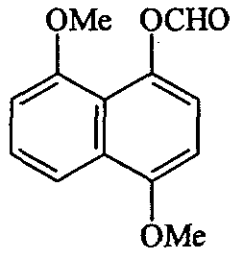
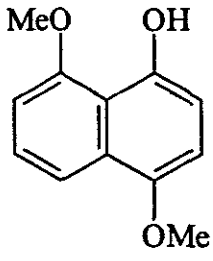


58

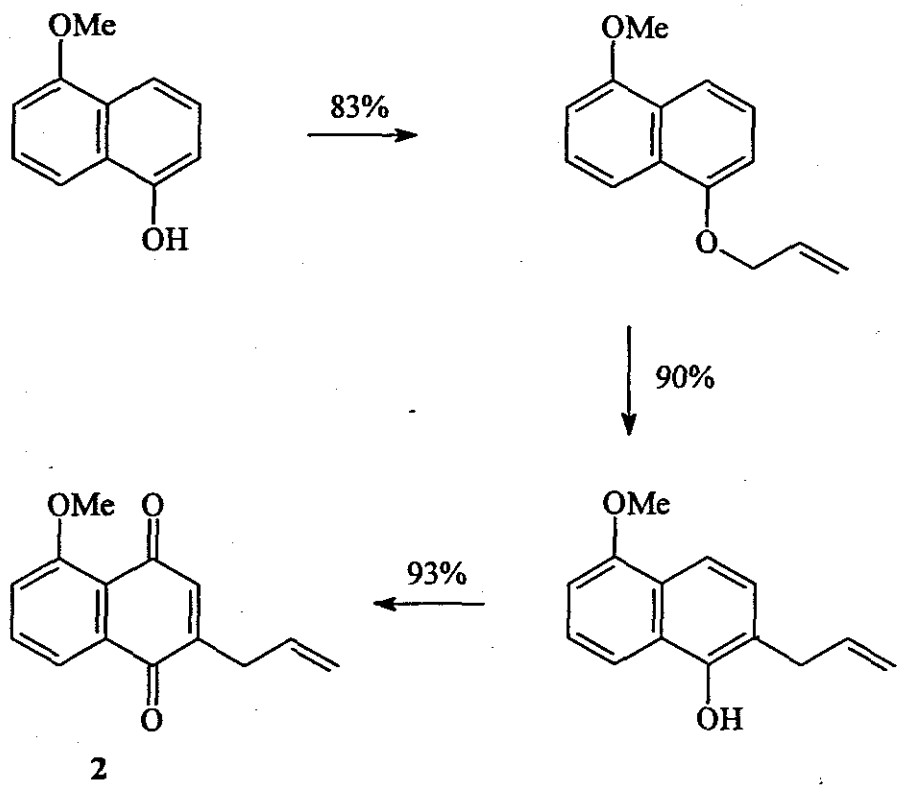


59



1

2-Allyl-5-methoxy-1,4-naphthoquinone (**2**) was earlier prepared *via* the following route[2] and was later used[6] as starting material (as in **Scheme 8**) in the synthesis of nanaomycin A(**5**) and D(**6**).



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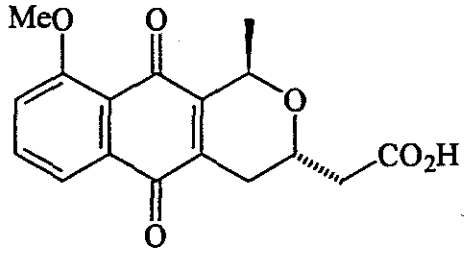
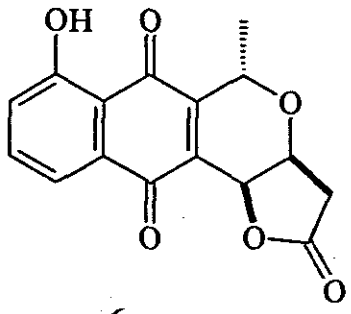
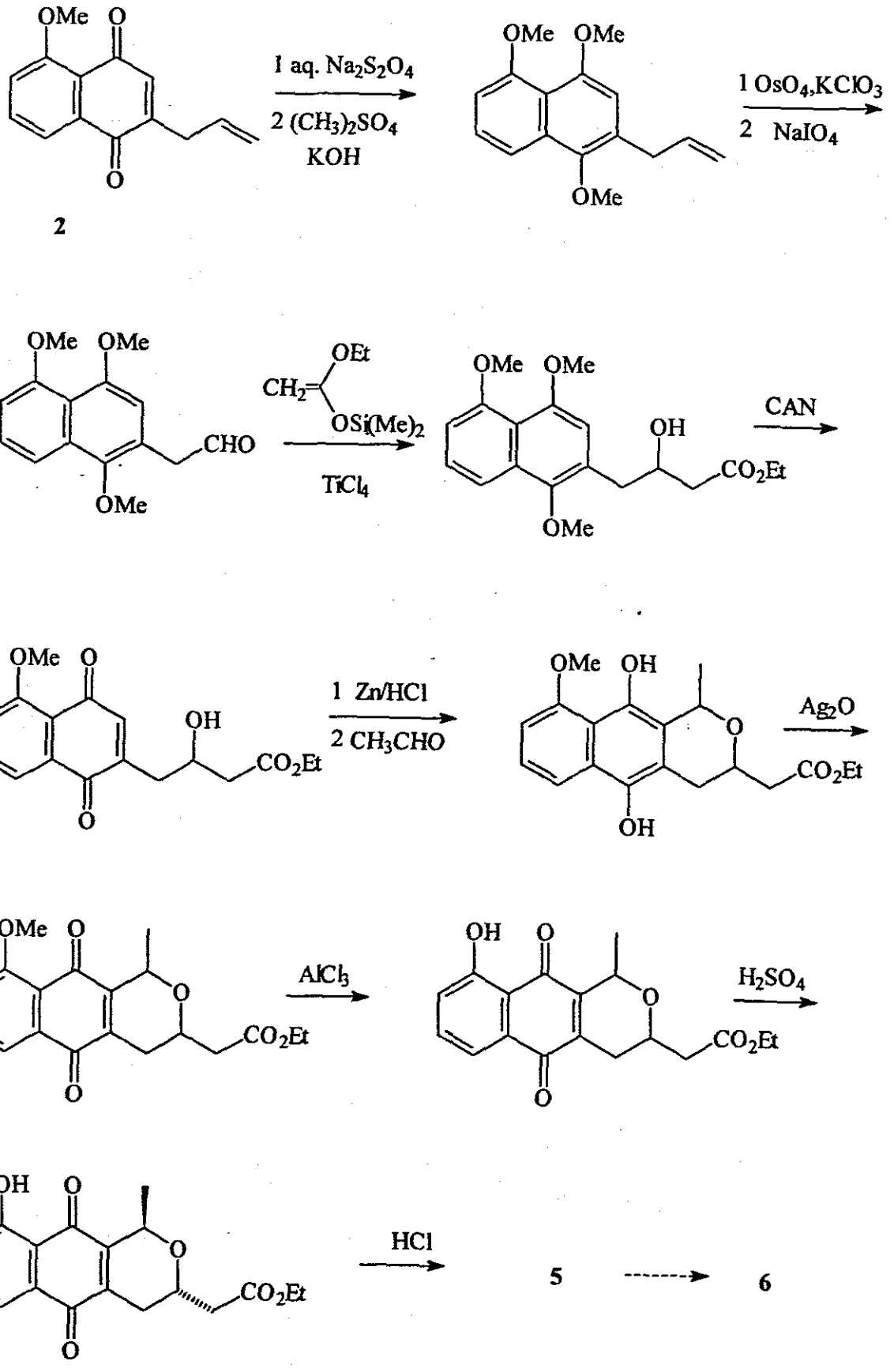


5



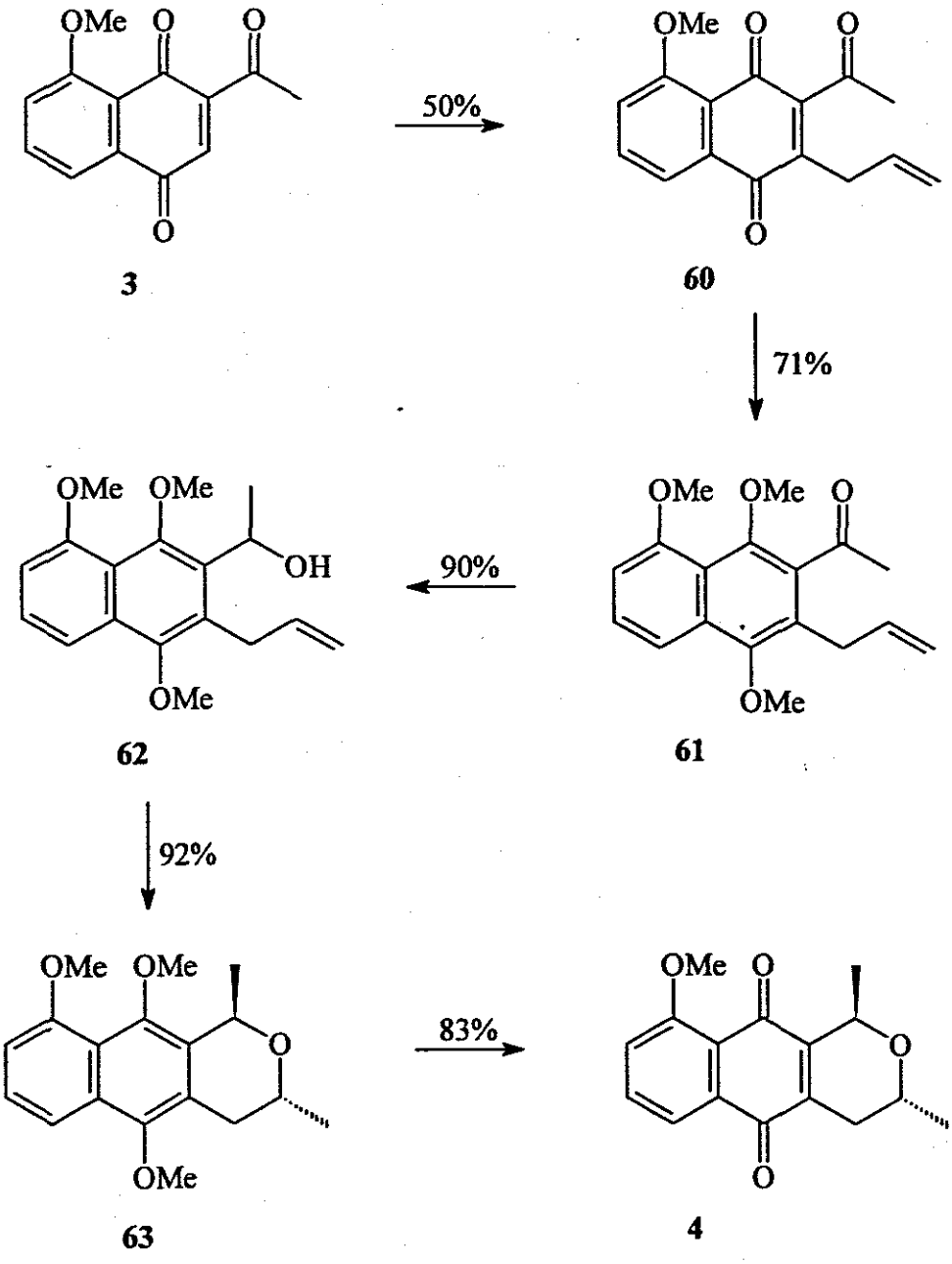
6

Scheme 8


OMe
O
1 aq. $Na_2S_2O_4$
2 $(CH_3)_2SO_4$
KOH
OMe
OMe
OMe
1 OsO_4,$KClO_3$
2 $NaIO_4$
2
OMe
OMe
CHO
OMe
OEt
CH_2
$OSi(Me)_2$
$TiCl_4$
OMe
OMe
OH
CO_2Et
OMe
CAN
OMe
O
OH
CO_2Et
O
1 Zn/HCl
2 CH_3CHO
OMe
OH
O
CO_2Et
OH
Ag_2O
OMe
O
O
CO_2Et
$AlCl_3$
OH
O
O
CO_2Et
O
H_2SO_4
OH
O
O
CO_2Et
O
HCl
5
6

Our group employed quinone (**3**) in a novel synthesis[5] of racemic isoeleutherin (**4**). This route is illustrated in **Scheme 9**.

Scheme 9



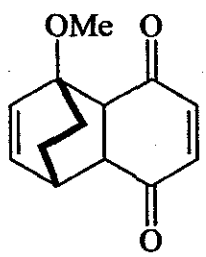
Allylation of compound (**3**) was achieved using vinyl acetic acid in the presence of silver nitrate and potassium persulphate. This Jacobsen-Torssell type reaction[33] gave the quinone (**60**) in a yield of 50%.

Reductive methylation of quinone (**60**) with aqueous sodium dithionite followed by treatment with potassium carbonate and dimethyl sulphate, gave the trimethoxy naphthalene (**61**)[34] in good yield. The secondary alcohol (**62**) was readily available by reduction (using lithium aluminium hydride) of (**61**).

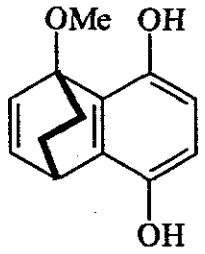
Anaerobic base-induced cyclisation of alcohol (**61**) employing potassium *tert*-butoxide in DMF afforded the *trans* 1,3-dimethylpyran (**63**)[5, 34] which gave isoeleutherin (**4**) on treatment with CAN.

2.1.2 A NEW APPROACH[35, 36] TO THE SYNTHESIS OF 1,5-DIMETHOXY-4-NAPHTHOL (1), 2-ALLYL-5-METHOXY-1,4-NAPHTHOQUINONE (2) AND 3-ACETYL-5-METHOXY-1,4-NAPHTHOQUINONE (3)

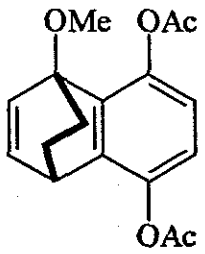
Convenient and efficient syntheses for the target compounds (**1**), (**2**) and (**3**) have now been developed in our laboratories. In the case of compounds (**1**) and (**2**), a key step in their formation involved methylation or allylation of an intermediate enolised Diels-Alder adduct[37] (**67**) while in the case of quinone (**3**), it involved *inter alia* pyrolysis of an acetylated Diels-Alder adduct (**71**) derived from the common adduct (**67**), followed by a regiospecific Fries rearrangement reaction.



66



67



71

The synthetic strategy to compounds (**1**), (**2**) and (**3**), from a common Diels-Alder-type intermediate (**66**) is illustrated in **Schemes 10** and **11**, on pages 40 and 41 respectively.

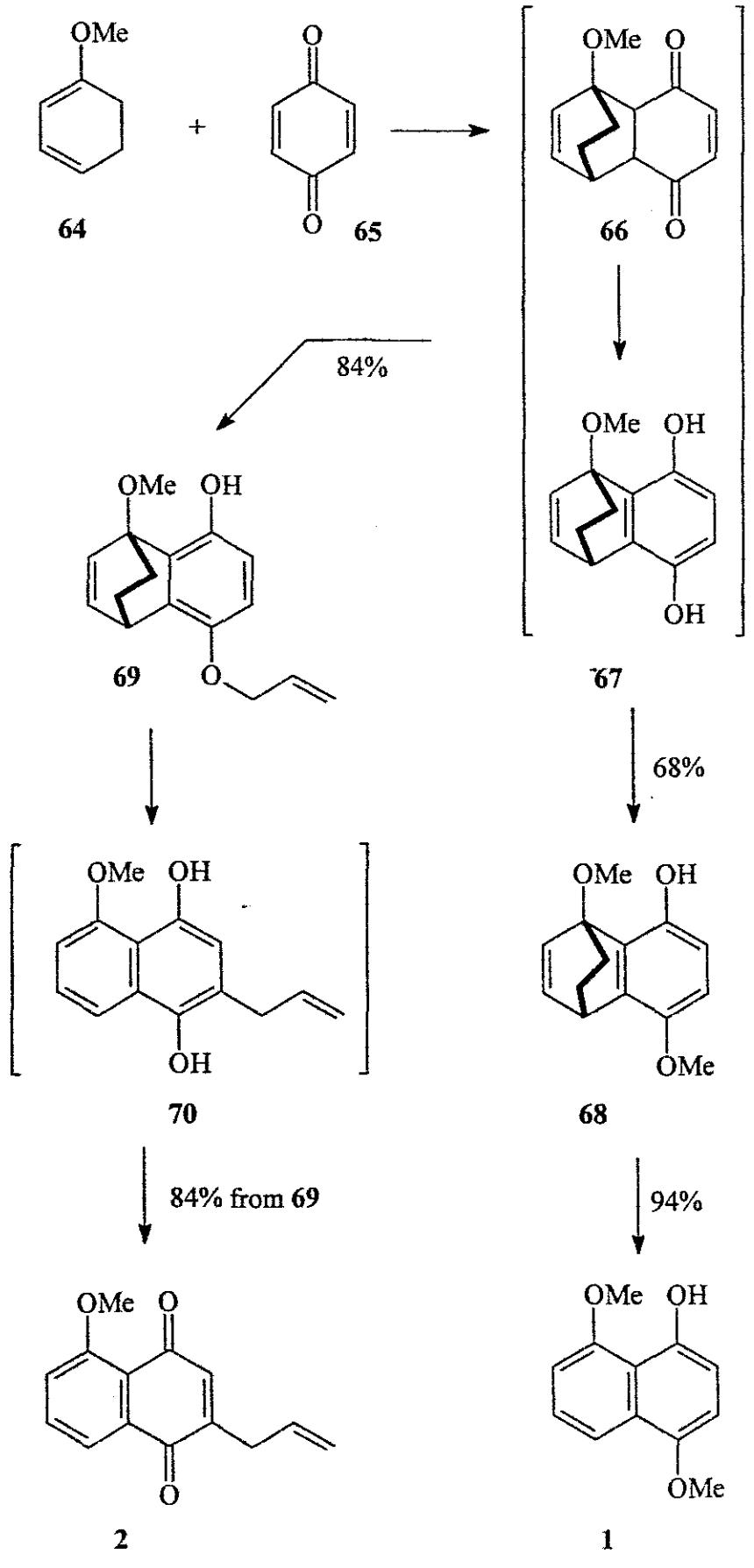
1-Methoxycyclohexa-1,3-diene (**64**) and 1,4-benzoquinone (**65**) afforded the Diels-Alder adduct (**66**), which without isolation, was enolised with potassium carbonate in dry acetone and then treated with either iodomethane or allylbromide to give compounds (**68**) and (**69**) in yields of 68% and 84% respectively.

Thermal elimination of the ethano bridge in (**68**) proceeded smoothly to afford the target naphthol (**1**) in excellent yield (94%).

Brief pyrolysis of compound (**69**) (in a nitrogen atmosphere) resulted in elimination of the 1,4-ethano bridge and concomitant Claisen rearrangement of the allyl group to give the unstable intermediate diol (**70**) - the structure of which was confirmed by ^{1}H nmr analyses of the crude reaction mixture.

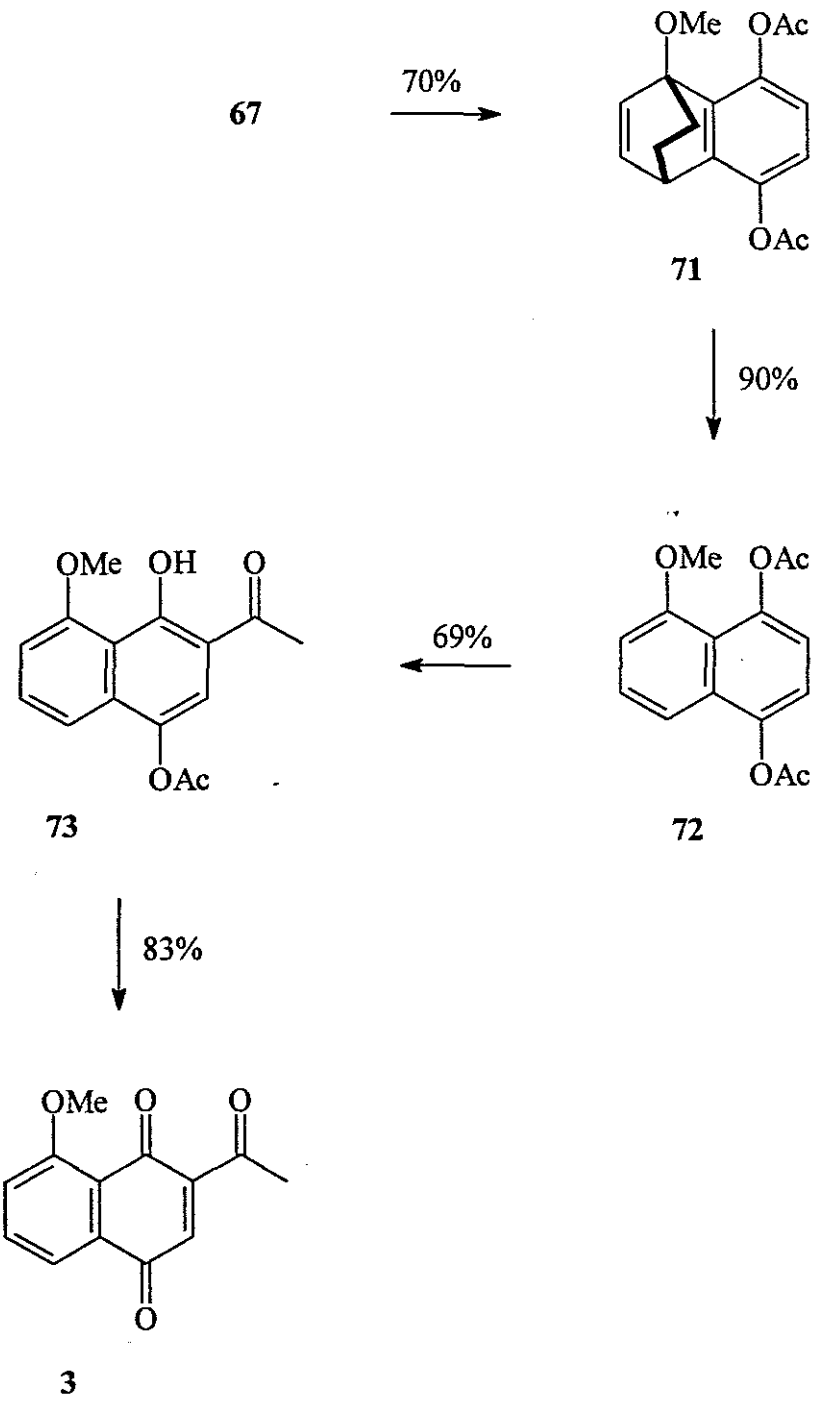
Finally, addition of a suspension of silver(I) oxide in chloroform to (**70**) afforded the allyl quinone (**2**) in high yield [84% from (**69**)] after chromatography.

Scheme 10

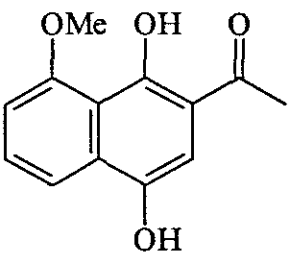


For the synthesis of quinone (**3**) as in **Scheme 11**, the enolised Diels-Alder adduct (**67**) was treated with acetic anhydride and pyridine to afford the diacetate (**71**) in good yield (70%).

Scheme 11



Pyrolysis of diacetate (**71**) resulted as before in elimination of the 1,4-ethano bridge to give the diacetoxy naphthalene (**72**) in excellent yield (90%). The diester underwent a regiospecific Fries rearrangement when treated with boron trifluoride to afford mainly naphthol (**73**)[4] and quinol (**74**) as a minor by-product (*circa* 10%).



74

The structure of compound (**73**) was confirmed by comparing its ^1H nmr spectrum and melting point with that of material obtained *via* another route.[4]

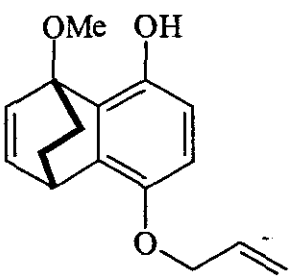
The ^1H nmr spectrum of quinol (**74**) showed *inter alia* two D_2O-exchangeable signals - one at δ 14.4 due to the chelated hydroxyl at C-4 and a broad signal at *circa* δ 6 due to the hydroxyl at C-1.

Quinol (**74**) was readily converted to compound (**73**) by treatment of the crude reaction mixture with acetic anhydride and pyridine in boiling chloroform containing zinc dust [to ensure that any quinone (**3**) present by aerial oxidation of (**74**) was reduced to the hydroquinone level]. This procedure simplified the isolation of products from the reaction

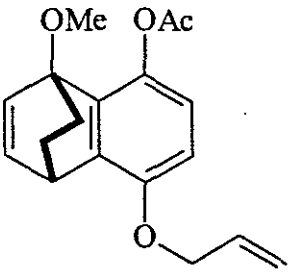
mixture by reducing their number. Finally, oxidation of naphthol (**73**) employing CAN, gave the target quinone (**3**) in a yield of 83%.

2.1.3 CLAISEN AND FRIES REARRANGEMENT STUDIES OF SOME NAPHTHALENE DERIVATIVES[38]

The Claisen- and in particular the Fries rearrangement reactions have been extensively studied in benzene derivatives. [39-47] However, no comprehensive studies on systems of the types (**69**)[35] and (**75**) have been carried out - either thermally or under the influence of Lewis acid catalysis.



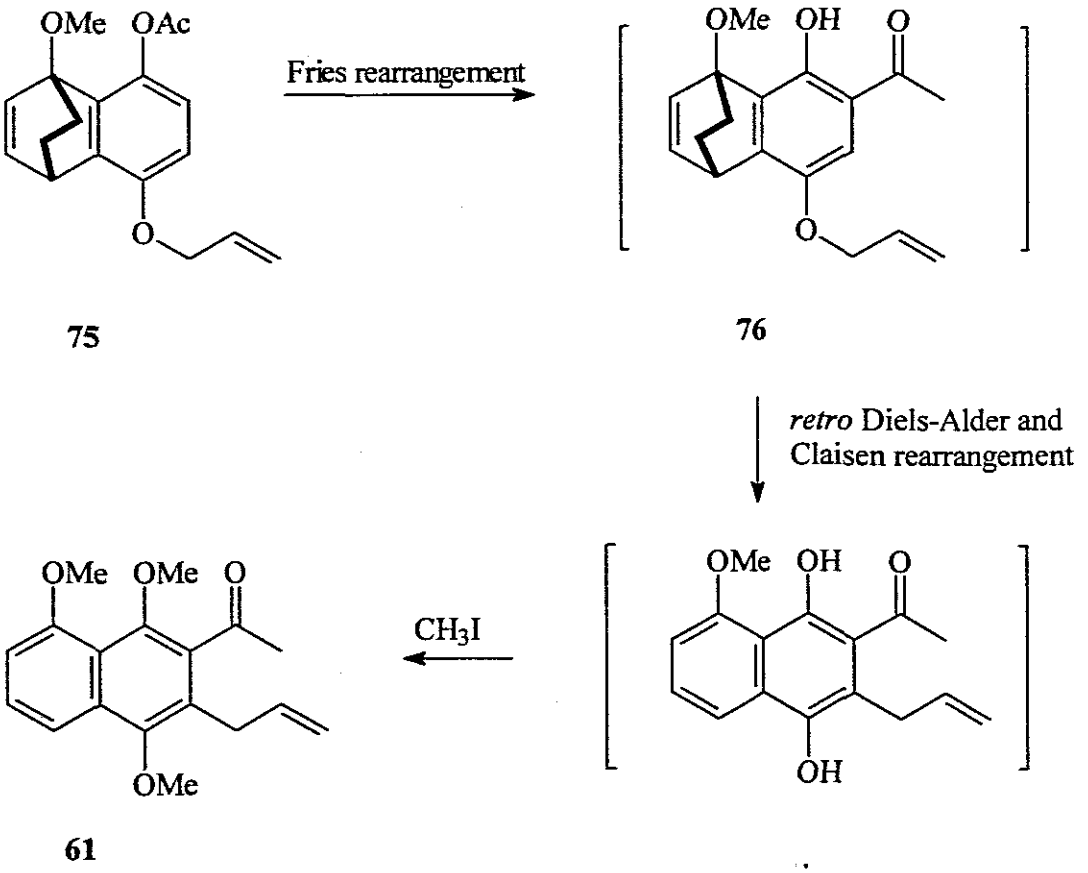
69



75

Compound (**75**),[38] which is readily available from (**69**), was considered by us to be an alternative precursor to the trimethoxynaphthalene (**61**),[34] an important intermediate in the synthesis of isoeleutherin (**4**) (see **Scheme 9** on page 36).

The following transformation was envisaged.



Thus treatment of compound (**75**) with boron trifluoride etherate or aluminium(III) chloride at oil bath temperatures ranging between 50°C to 80°C failed to give the desired product of Fries rearrangement (**76**). Starting material was recovered in all cases.

In an alternative approach, the pyrolytic (Claisen) behaviour of both acetate (**75**) and its precursor (**69**) was investigated.

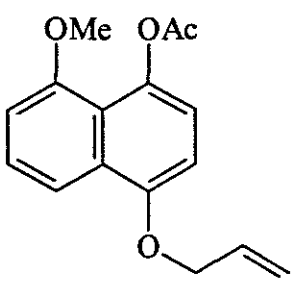
From **Table 2-1** it is clear that the temperature at which the pyrolysis of acetate (**75**) is conducted, plays a major role in the product distribution.

TABLE 2-1

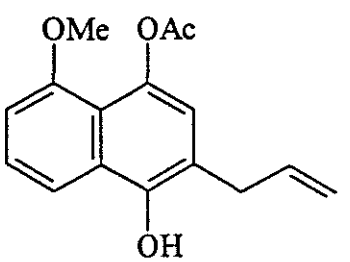
PRODUCT DISTRIBUTION OF PYROLYSIS OF ACETATE (75)

Bath temperature	Pyrolysis time	Compounds isolated after chromatography as %		
°C	min	75	77	78
170	90	100	-	-
180	90	29	9	64
195	90	9	7	88
210	40	2	5	90
220	50	0	5	90

Thus at temperatures below 175°C no rearrangement occurs, whereas at 180°C the spectrum of products comprises starting material (**75**) (29%), acetate (77) (9%) and naphthol (**78**) (64%).



77



78

These findings clearly demonstrate that the first step that occurs during the pyrolysis is the *retro* Diels-Alder reaction involving de-ethylenation affording acetate (77), followed by the Claisen rearrangement to yield

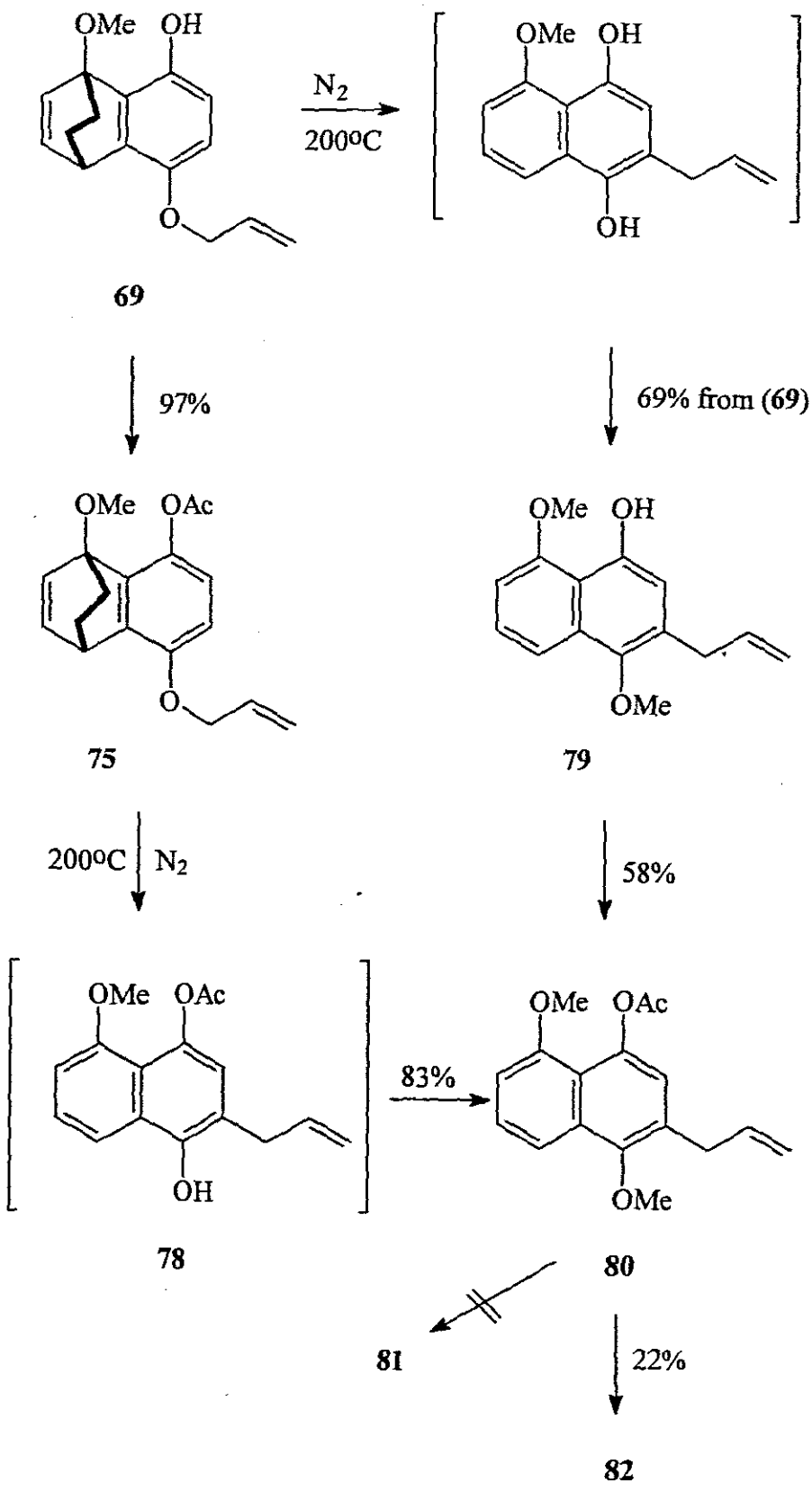
naphthol (**78**). It was not possible, however, to control these processes selectively.

The full aromatisation of compound (**69**) *via* a one-pot *retro* Diels-Alder and concomitant Claisen rearrangement, followed by selective protection of the C-4 hydroxyl by methylation to afford naphthol (**79**), (as in **Scheme 12**) was also investigated.

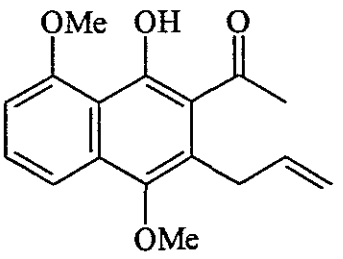
Final acetylation afforded the acetate (**80**) in an overall yield of 40% from (**69**).

The alternative pathway involving the sequence (**69**) → (**75**) → (**78**) → (**80**) proved to be more efficient since the overall yield was higher.

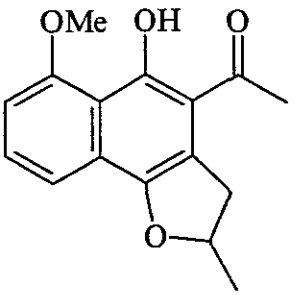
Scheme 12


OMe OH
N_2
200°C
OMe OH
OH
O
69
97%
69% from (69)
OMe OAc
OMe OH
O
OMe
75
79
200°C
N_2
58%
OMe OAc
OMe OAc
83%
OH
OMe
78
80
81
22%
82

Treatment of acetate (**80**) with boron trifluoride etherate did not afford the expected product of Fries rearrangement (**81**). Instead, the only product isolated from the tarry complex mixture was the furan (**82**) in low yield (22%).



81

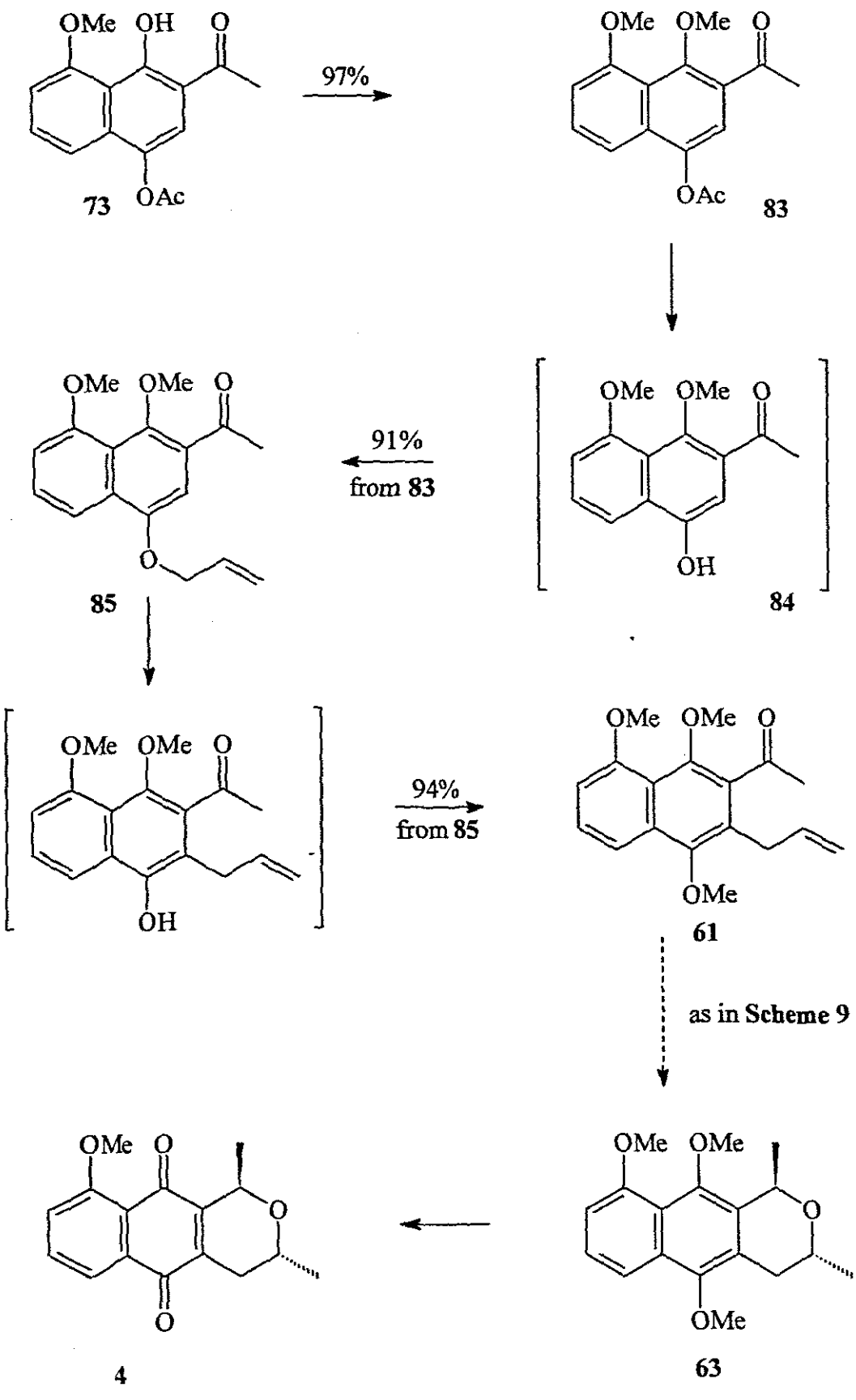


82

2.1.4 A NEW AND EFFICIENT SYNTHESIS OF THE INTERMEDIATE (61) AND HONGCONIN (13)

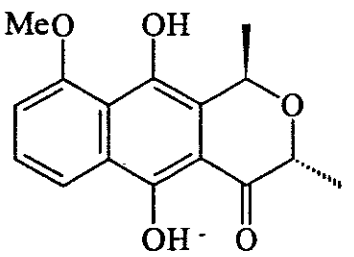
Following the investigations into the Claisen and Fries rearrangement reactions (2.1.3) which unfortunately did not afford a viable route to compound (**61**), an alternative synthetic approach to (**61**) [employing acetate (**73**) as starting material] proved to be successful (**Scheme 13**).

Scheme 13


OMe OH O
OAc
73
97%
OMe OMe O
OAc
83
OMe OMe O
OH
84
91%
from 83
OMe OMe O
O
85
OMe OMe O
OH
94%
from 85
OMe OMe O
OMe
61
as in Scheme 9
OMe O
O
O
4
OMe OMe
O
OMe
63

Thus acetate (**73**), the precursor of quinone (**3**) (as in **Scheme 11**) was methylated to give compound (**83**) in a yield of 97%. Mild alkaline hydrolysis of (**83**) followed by allylation of the intermediate naphthol (**84**) gave the naphthyl ketone (**85**) [91% from (**83**)]. Pyrolysis of (**85**) followed by methylation of the intermediate naphthol afforded the target trimethoxy-naphthalene (**61**) in good yield (94%).

This route proved to be an efficient and overall high-yielding synthesis of (**61**) from which isoeleutherin (**4**) (as in **Scheme 9**) and hongconin (**13**) (**Scheme 14**) were synthesised to be used in our antimicrobial evaluation programme.



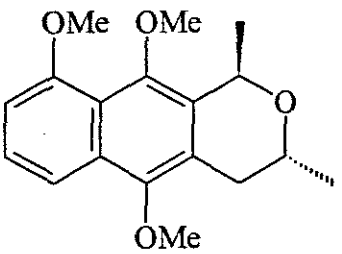
13

Hongconin (**13**) has been used as a folk medicine in southern China especially for coronary disorders. It is isolated from the rhizome of *Eleutherine americana* (Iridaceae) and has been shown to exhibit cardioprotective activity against angina pectoris in clinical trials.[49]

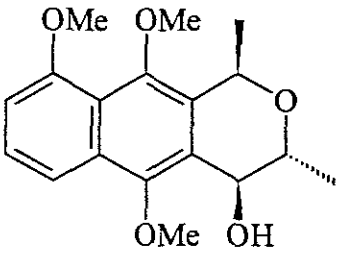
The synthesis of racemic hongconin (**13**) has been reported,[14, 50] but due to some inherent chemoselective and stereochemical problems coupled

with a low overall yield, we sought and developed an efficient alternative route which has now been published.[15] The collaboration of Mr F J Oosthuizen in this regard is gratefully acknowledged.

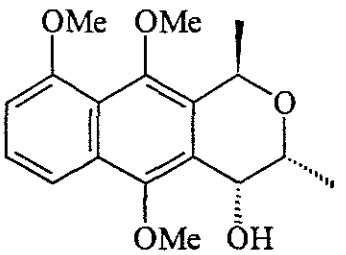
The synthesis of (**13**) (**Scheme 14** on page 53) involved aerobic hydroxylation[5,27,28] at C-4 of the pyran ring of (**63**)[5] to afford the *pseudo* equatorial hydroxypyran (**86**) and its C-4 epimer (**86a**) in a ratio of 4:1.



63

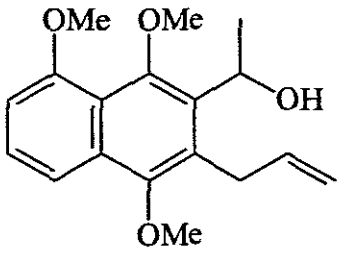


86

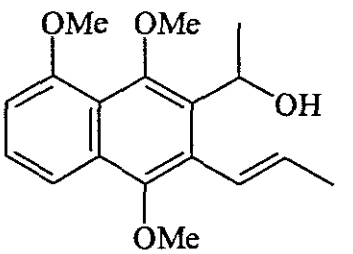


86a

In an alternative route to the epimers (**86**) and (**86a**), alcohol (**62**) was treated with palladium chloride bisacetonitrile[51] and produced the *trans* olefinic alcohol (**62a**) in quantitative yield.



62

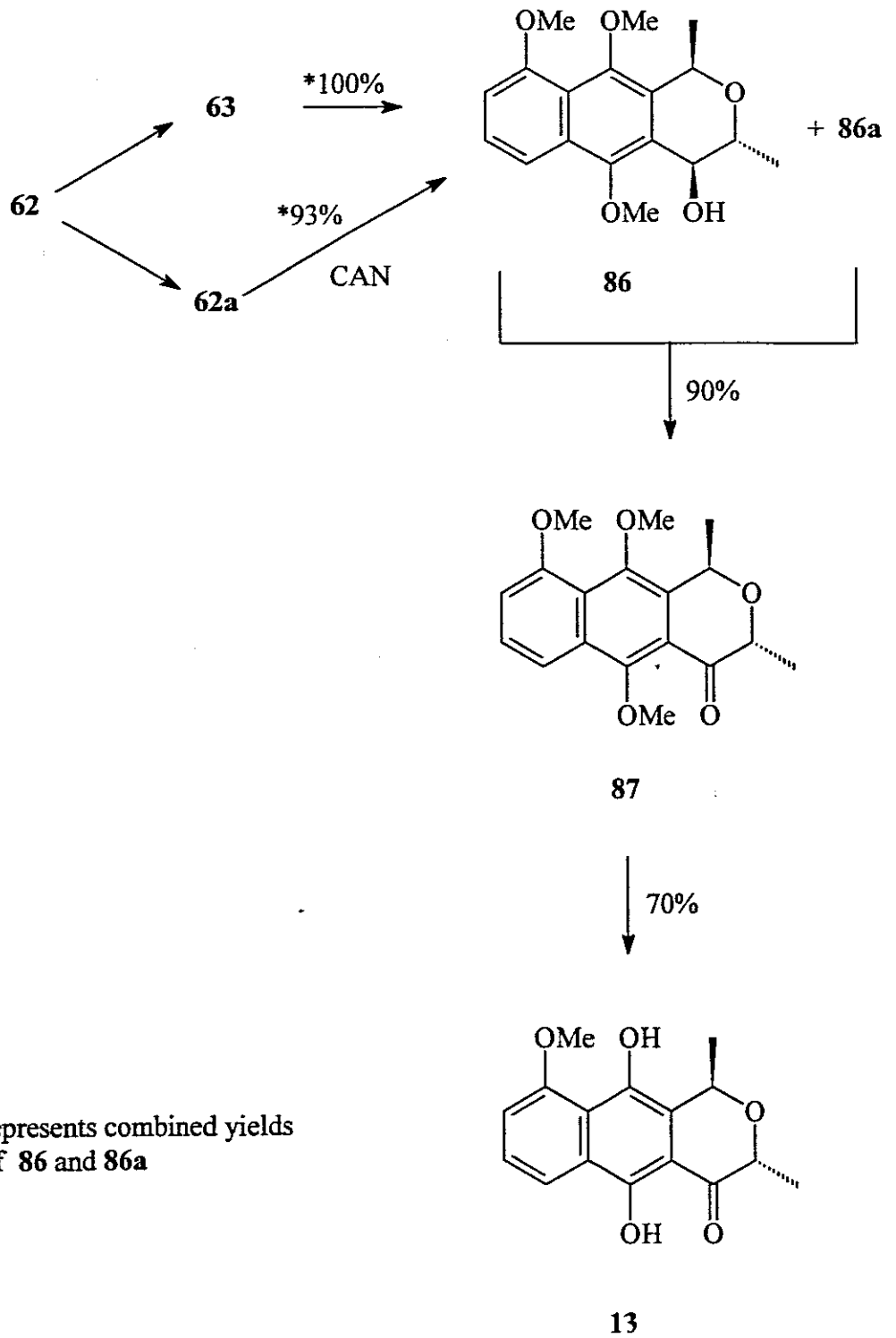


62a

Careful treatment of (**62a**) with 2 molar equivalents of CAN in aqueous acetonitrile gave a high yield of the epimeric pyrans (**86**) and (**86a**) in the reversed ratio of 2:3 as adduced from the ^{1}H nmr spectra.[5, 15]

This mixture was oxidised using pyridinium chlorochromate to the ketopyran (**87**), which upon demethylation, afforded hongconin (**13**) as its racemate.[15]

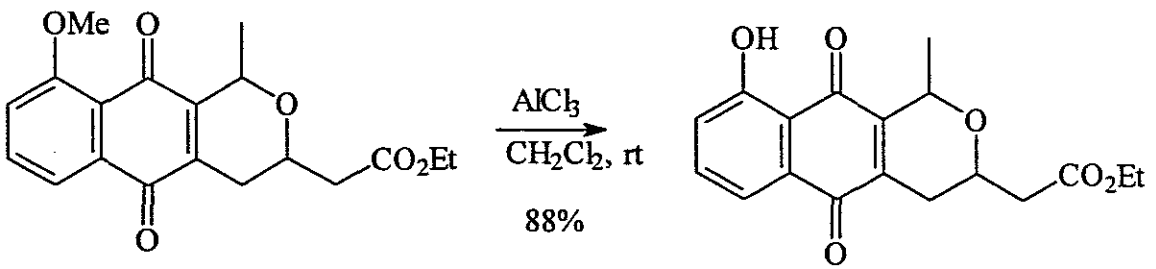
Scheme 14



* represents combined yields of **86** and **86a**

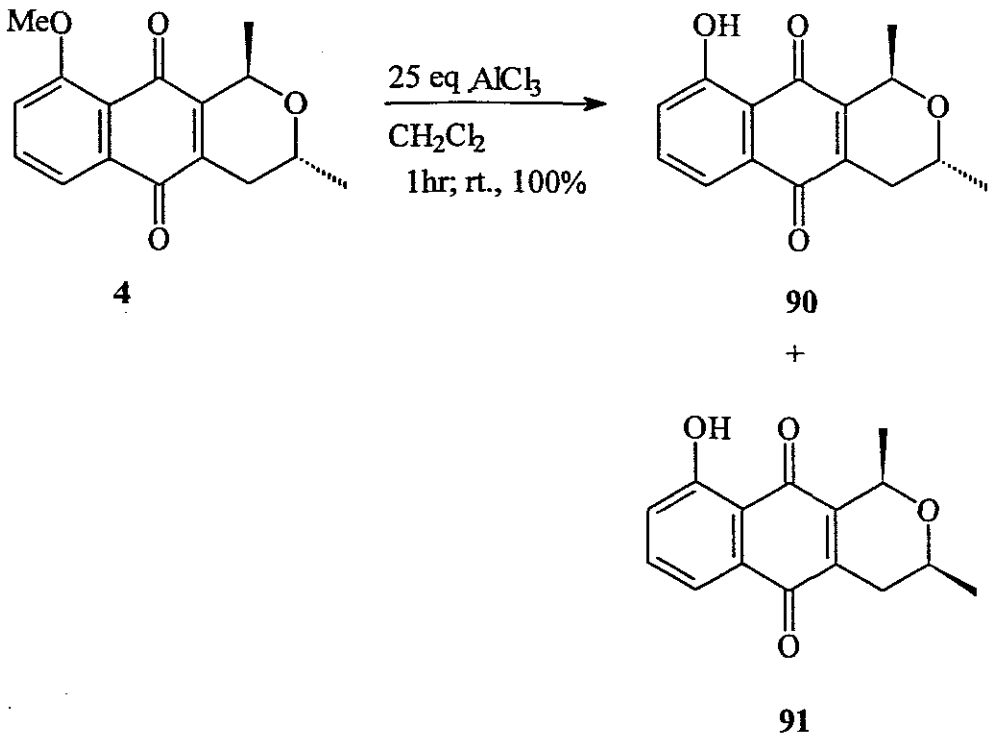
2.1.5 REACTION OF ALUMINIUM CHLORIDE WITH BENZO[*C*]- AND NAPHTHO[2,3-*C*]PYRANS

Aluminium chloride is known to demethylate *peri*-methoxy groups in quinonoid systems to afford the corresponding hydroxy derivatives.[6, 8] One example is the demethylation of pyran (**88**) to afford the 9-hydroxy derivative (**89**) as illustrated in **Scheme 8** earlier.



88 **89**

Employing this methodology in our antibiotics synthesis programme, it was discovered that the Lewis acid not only effected demethylation, but also *trans* - *cis* stereo-isomerisations. For example, isoeleutherin (**4**), when treated with 25 molar equivalents of $AlCl_3$ at room temperature in dichloromethane, afforded a mixture of the 9-hydroxy-*trans*-1,3-dimethylnaphtho[2,3-*c*]pyran (**90**) and the stereoisomeric *cis*-pyran (**91**) in a ratio of [3:2] respectively.

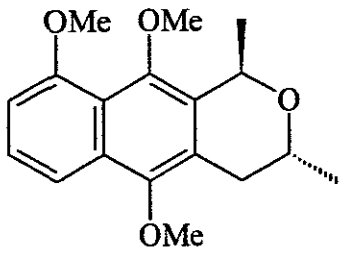


4 **90** + **91**

However, at 0°C compound (**4**) could be converted to the *trans*-pyran (**90**) with none of the *cis*-isomer (**91**) being observed.

Compounds (**90**) and (**91**) have identical R_f values (MERCK Kieselgel 60 F_{254}). Consequently their relative abundance was determined by ^1H nmr. Treatment of compound (**4**) with boron trifluoride etherate at room temperature did not afford any demethylation or isomerisation.

However, treatment of the *trans* pyran (**63**) with aluminium chloride at room temperature also afforded the stereoisomeric mixture of compounds (**90**) and (**91**) in a ratio of [1:1] in a combined yield of 21%.



63

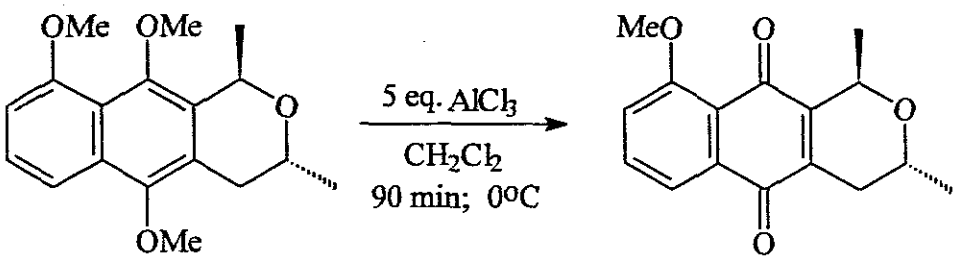
$\xrightarrow[CH_2Cl_2]{25\text{ eq. } AlCl_3}$
20hr; rt

90 + 91

[1:1]

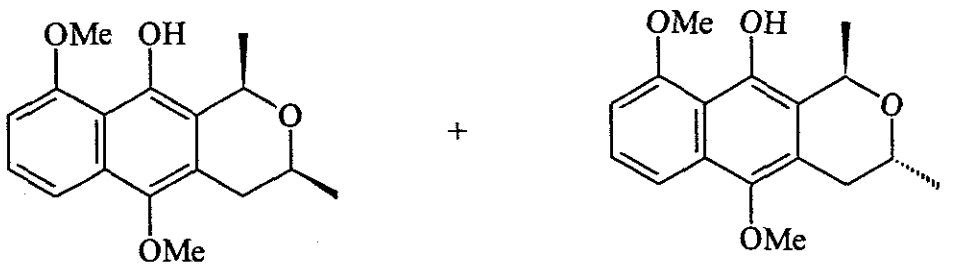
The ^{1}H nmr spectrum confirmed the formation of *cis* and *trans* isomers in the reaction mixture. It allows for definitive distinctions to be made between the *cis* and *trans* isomers. [8, 48] The 3-H multiplets differ substantially in chemical shift; for the *trans* isomer (**90**) it falls in the range at δ 3.90 - 4.05 while that of the *cis* isomer (**91**) appears at δ 3.50 - 3.69. In the case of the 1-H of the *trans* isomer it resonates as a quartet at *ca.* δ 4.99, while that of the *cis* isomer resonates as a multiplet at *ca.* δ 4.83.

When pyran (**63**) was treated with 5 molar equivalents $AlCl_3$ at 0°C for 90 minutes, three major fractions, namely compounds (**4**), (**92**) and (**93**) were obtained in a molar ratio of [1:2:1] respectively.



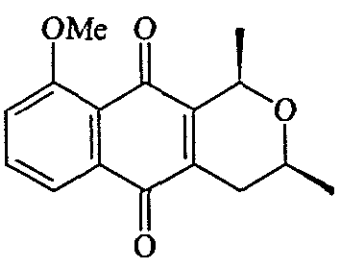
63 **4**

+



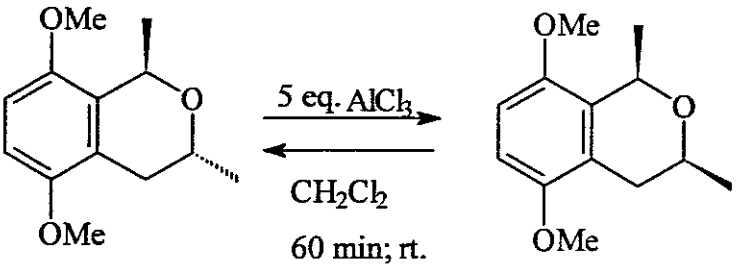
93 **92**

The structures of pyrans (**92**) and (**93**) were confirmed by silver(II) oxide oxidation of these to afford isoeleutherin (**4**) and eleutherin (**94**) respectively.



94

The benzopyran (**45**) was also subjected to the Lewis acid to afford the corresponding *cis*-epimer (**95**) at room temperature. However, at 0°C only traces of the *cis* isomer was observed.



45 **95**

[trans : cis 1:1]

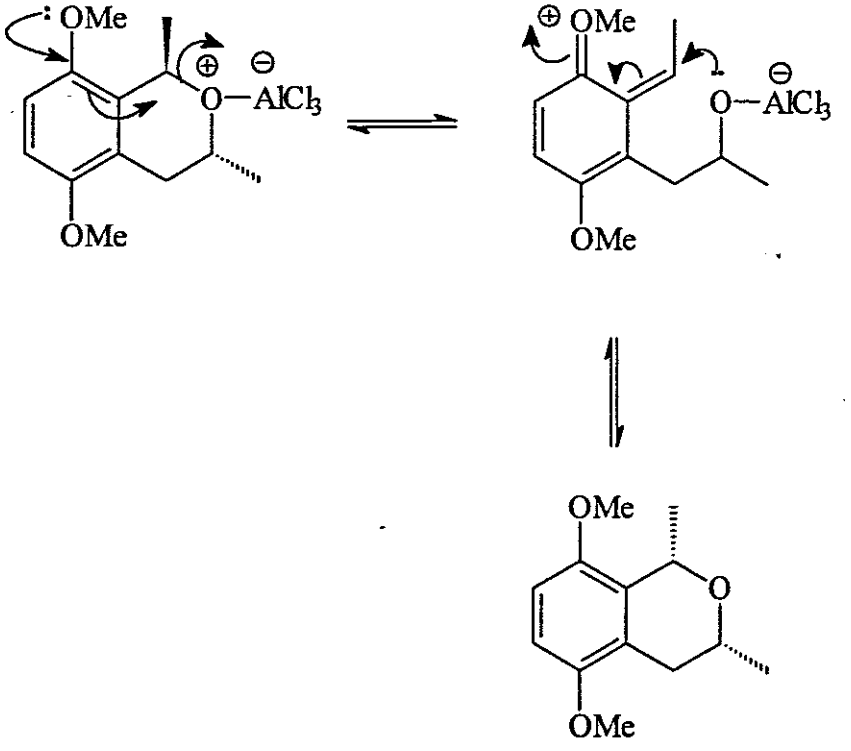
The same ratio [1:1] was obtained with the conversion of the *cis* benzopyran (**95**) to the *trans* isomer (**45**). In both cases no epimerisation was achieved with $AlCl_3$ in tetrahydrofuran (THF) or N,N-dimethylformamide (DMF).

A distinction can also be made between the stereoisomers (**45**) and (**95**). The 3-H multiplets differ substantially in chemical shift; for the *trans* isomer (**45**), 3-H resonates at *ca.* δ 3.98 - 4.15 while that of the *cis* isomer (**95**) falls in the range at δ 3.55 - 3.70. The chemical shift of the 1-H quartet of the *cis* isomer (δ 5.00) also differs from that of the *trans* isomer (δ 5.10).

Other reagents were also investigated (without success) to effect epimerisation of the pyran ring system. These were $PdCl_2$ / CH_2Cl_2 or THF; $ZnCl_2$ / CH_2Cl_2 or THF; conc. HCl / CH_2Cl_2; Et_3N / CH_2Cl_2; TFA / CH_2Cl_2 (all at room temperature).

It is evident that the $AlCl_3$-mediated isomerisation process is reversible at room temperature and highly solvent dependent — presumably due to stabilisation by solvation of a transition state. The Lewis acid no doubt catalyses ring opening of the pyran ring with subsequent ring closing as proposed in **Scheme 15**, to afford the alternative stereoisomer.

Scheme 15

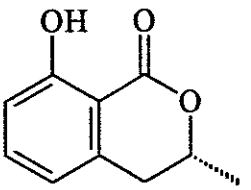


CHAPTER 3

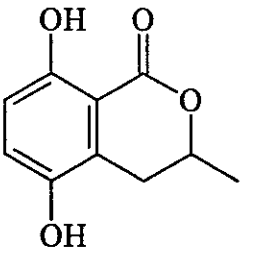
SYNTHESIS OF A QUINONOID NAPHTHO[2,3-*C*]PYRANONE AS A MODEL FOR THE CONSTRUCTION OF THE PYRANONE(LACTONE) RING SYSTEM

3.1 MODEL ROUTES TO NAPHTHO[2,3-C]PYRANONES

Isocoumarins or aryl[2,3-*c*]pyranones are compounds containing a δ-lactone ring moiety as in R-mellein (**96**). They occur wide-spread in Nature and some have been shown to possess bio-activity.



96



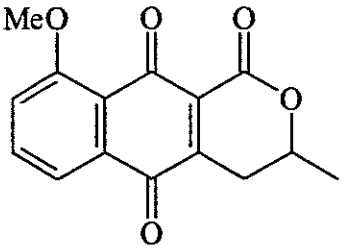
97

For example, R-mellein (**96**)[22,52] is a metabolite of *Aspergillus melleus* and *Septoria nodorum* and has been proposed as the active agent in promoting the stomatal resistance of rice. The structurally similar isocoumarin (**97**)[22] has itself been identified in extracts of Brazilian wood infected by fungi.

Compound (**96**) is also a constituent of the mandibular secretion of carpenter ants (*Componotus*) and is believed to have pheromonal properties.[22]

Our group thus became interested in the synthesis of dihydroisocoumarins and in particular naphtho[2,3-*c*]pyranones of the

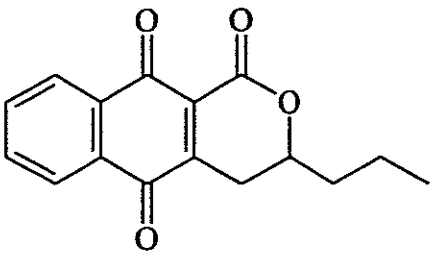
type (**10**) with a view to establishing the antimicrobial activity or specificity (if any) of this class of compounds.



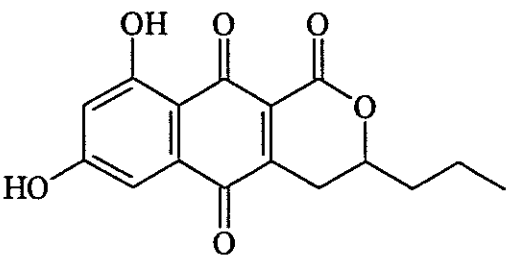
10

3.1.1 SOME EXISTING METHODS FOR THE SYNTHESIS OF [2,3-*C*]PYRANONES

Giles and co-workers[53] synthesised the quinonoid naphtho[2,3-*c*]pyranone (**98**) (as in **Scheme 16** on page 65) with a view to determining a route to its 7,9-dihydroxy-analogue (**99**).



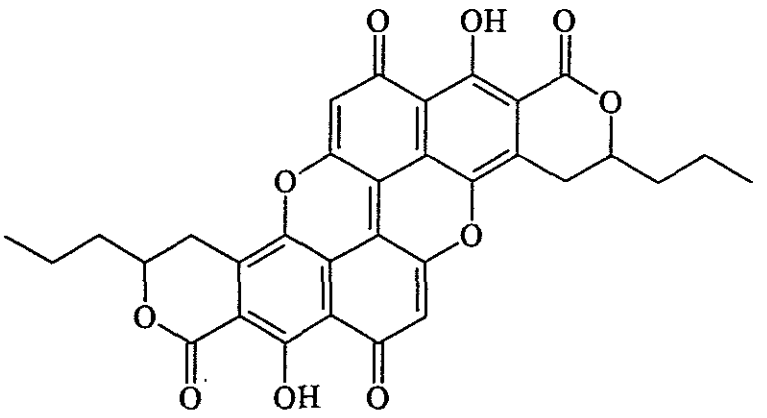
98



99

As a consequence of some anaerobic coupling reactions of aphid degradation products by Blackburn *et al.*,[54] Giles *et al.* postulated that

the lactone (**99**) could be a likely precursor to the naturally occurring quinonoid pigment xylindein (**100**).[32]



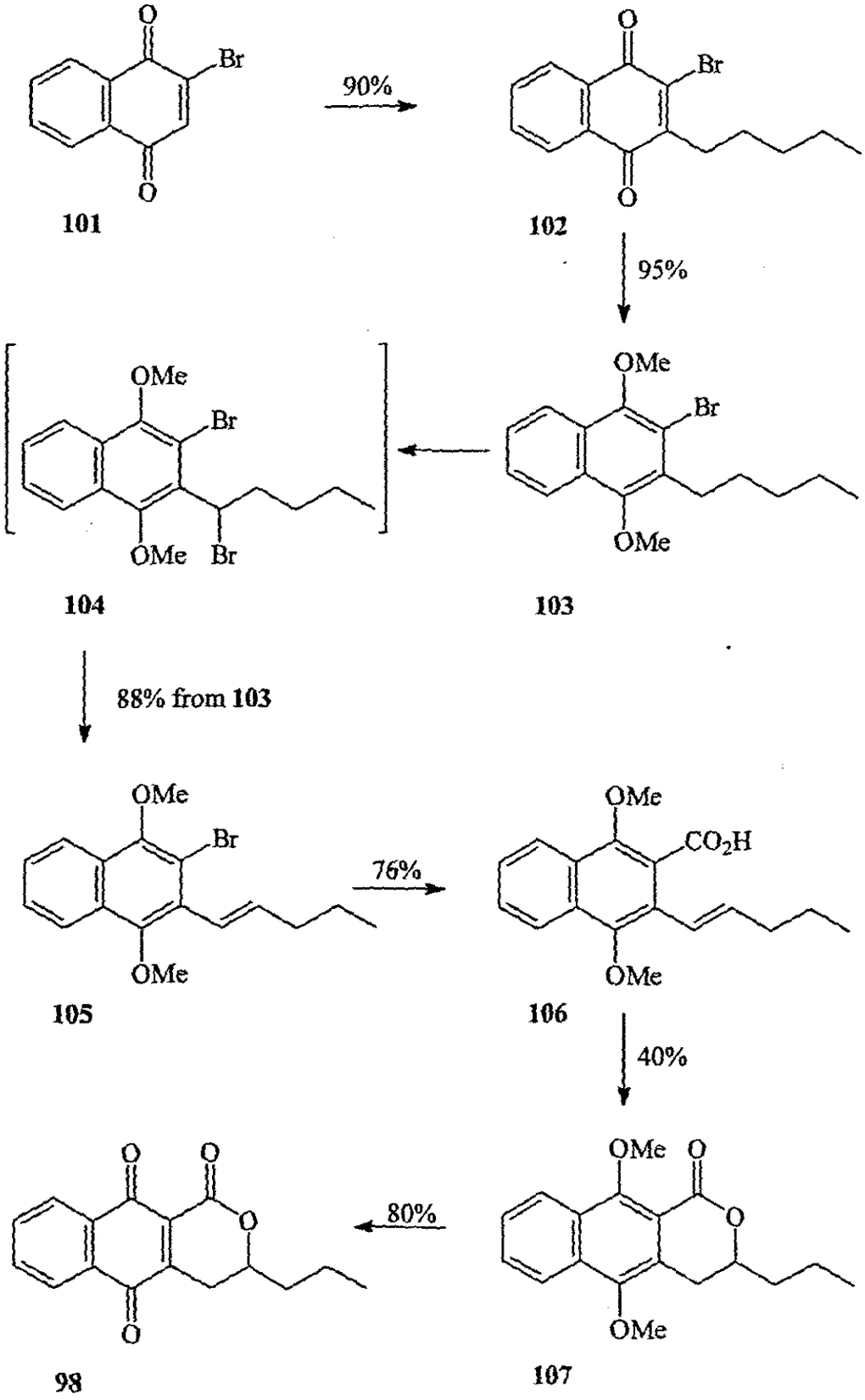
100

Giles' route to (**98**) involved the alkylation of the bromoquinone (**101**)[55] with hexanoic acid employing the experimental conditions of Jacobsen and Torssell,[33] to obtain the quinone (**102**) in excellent yield (90%). This compound was converted to the dimethyl ether (**103**) by reductive methylation with aqueous sodium dithionite, followed by treatment with dimethyl sulphate.

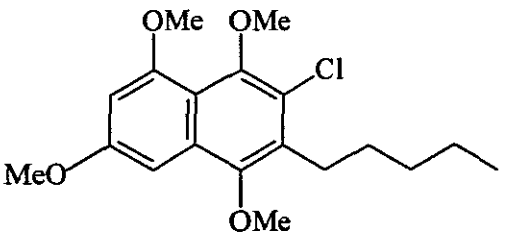
Bromination of (**103**) with *N*-bromosuccinimide in the presence of di-*t*-butyl peroxide afforded the benzylic bromide (**104**) which could be dehydrobrominated by boiling in lutidine to yield the *trans*-olefin (**105**) in good yield. [88% from (**103**)]. Treatment of the olefin (**105**) with butyl-lithium in dry ether followed by carbon dioxide, afforded the acid (**106**).

The formation of the lactone ring system from the olefinic acid (**106**) was accomplished by a novel photochemical ring closure. The acid was irradiated in solution in cyclohexane through quartz and a Vycor filter to afford the lactone (**107**) in a yield of 40%. Oxidative demethylation of compound (**107**) employing silver(II) oxide, gave the quinonoid pyranone (**98**) in a yield of 80%.

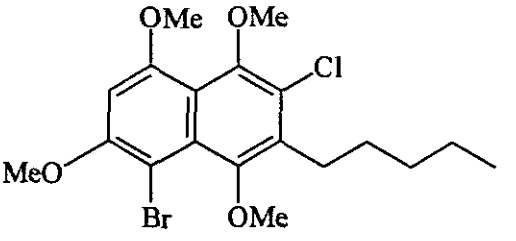
Scheme 16


O
Br
O
90%
101
102
95%
OMe
Br
OMe
Br
OMe
Br
104
103
88% from 103
OMe
Br
OMe
76%
OMe
CO2H
OMe
105
106
40%
O
O
O
O
80%
OMe
O
O
OMe
98
107

It was later shown[56] that higher oxygenated naphthalenes, for example (**108**), underwent bromination of the naphthalene nucleus under a variety of conditions with *N*-bromosuccinimide, to afford mainly (**109**).



108



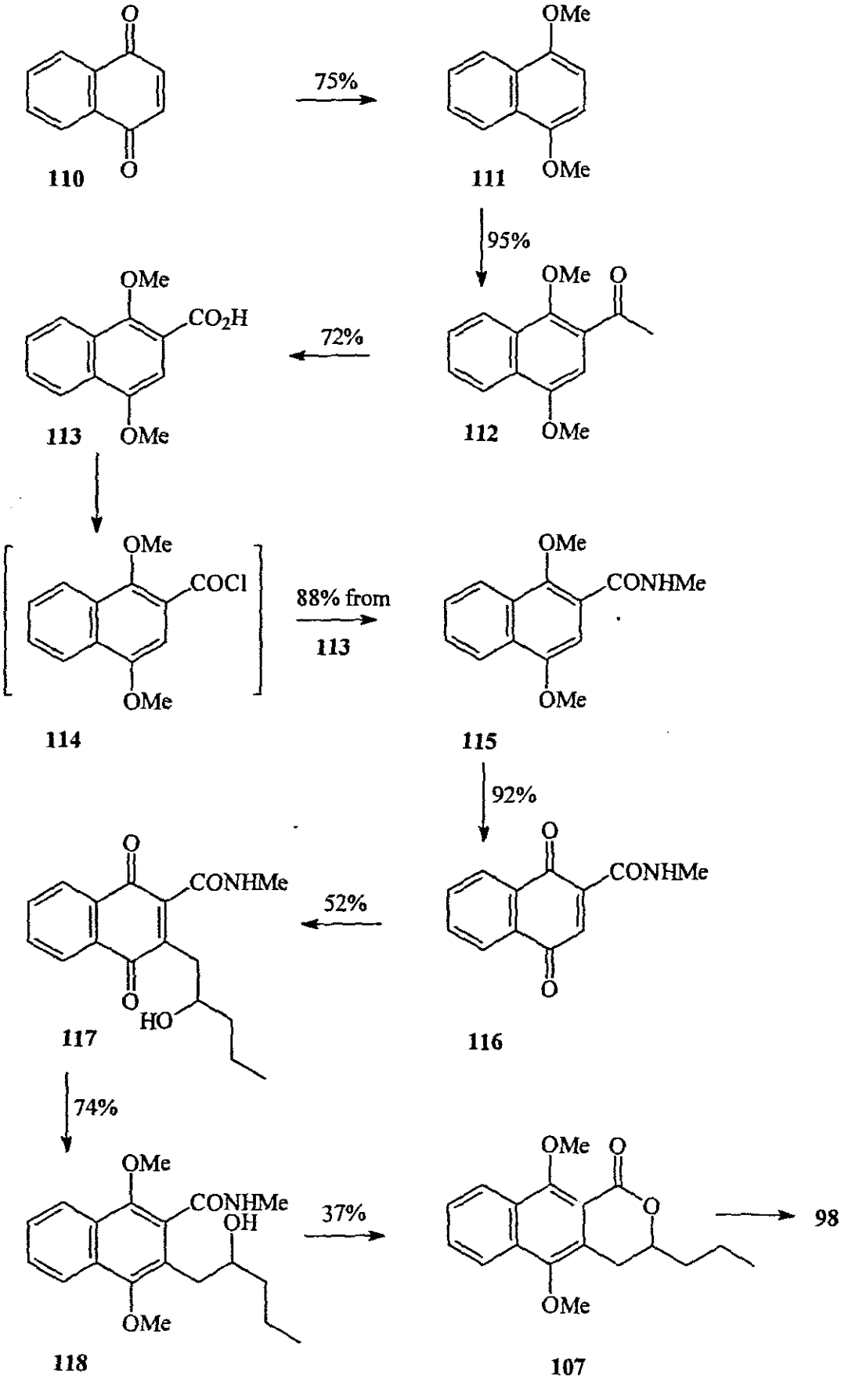
109

All attempts to brominate the benzylic position failed, owing to the competing reactivity of position 8 in the naphthalene nucleus.

In the light of these findings the author earlier developed an alternative model route to the lactone (**98**) by means of which other oxygenated naphthopyranones may be available.[57]

This route to pyranone (**98**) as in **Scheme 17** employed the readily available 1,4-naphthoquinone (**110**) as starting material.

Scheme 17


110
75%
111
OMe
OMe
95%
112
OMe
O
OMe
72%
113
OMe
CO2H
OMe
114
OMe
COCl
OMe
88% from
113
115
OMe
CONHMe
OMe
92%
116
O
CONHMe
O
52%
117
O
CONHMe
O
HO
74%
118
OMe
CONHMe
OH
OMe
37%
107
OMe
O
O
OMe
98

The quinone (**110**) was reductively methylated by employing the usual conditions to afford the naphthalene dimethyl ether (**111**) in a yield of 75% after chromatography. Treatment of (**111**) with premixed trifluoroacetic anhydride and glacial acetic acid[58] afforded the acetyl naphthalene (**112**) (95%) which gave the acid (**113**) in good yield on treatment with aqueous sodium hypochlorite. This acid yielded the amide (**115**) on treatment with thionyl chloride followed by ammonolysis of the intermediate acyl chloride (**114**) with an aqueous methylamine solution.

Oxidative demethylation of the amide using silver (II) oxide, gave the corresponding quinone (**116**) in good yield after chromatography (92%).

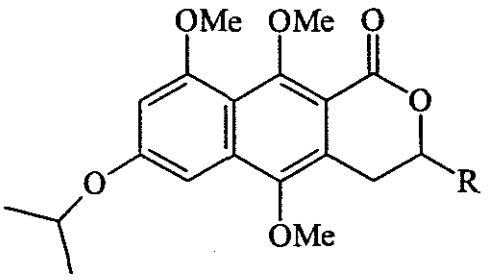
The next step in the synthetic sequence involved the hydroxypentylation[33] of the quinonoid moiety of (**116**) using 3-hydroxyhexanoic acid to afford quinone (**117**). The ^{1}H nmr spectrum of this product showed, *inter alia*, a distorted triplet (J 6 Hz) at δ 0.9 due to the methyl of the hydroxypentyl side-chain, and a broad one-proton signal at δ 5.2 which disappeared on addition of deuterium oxide, due to the hydroxy group. The amido-nitrogen proton resonated as a broad singlet at δ 7.01.

The direct conversion of quinone (**117**) to the lactone (**98**) by pyrolysis was next attempted. Heat treatment of (**117**) under nitrogen gave a mixture of compounds in which the lactone (**98**) was not identified.

It was thus decided to convert quinone (**117**) to the corresponding dimethyl ether (**118**). This was achieved by reductive methylation, employing the usual reagents, in a yield of 74% after chromatography.

Finally, pyrolysis of compound (**118**) under nitrogen afforded the naphthopyranone (**107**) (37%), identical to the material obtained by Giles *et al.*[53] The ^{1}H nmr spectrum of this lactone showed the characteristic doublet of doublets (J 11 and 16 Hz) due to the *pseudo*-axial 4-H at δ 3.37. The axial 3-H resonated as a multiplet at δ 4.42. The 1'- and 2'-methylene groups of the C-3 propyl side-chain resonated as a multiplet at δ 1.4-1.95 while the methyl group appeared as a deformed triplet (J 7 Hz) at δ 0.96.

However, when this methodology was extended to the synthesis of tetraoxygenated systems of the type (**119**), certain major difficulties were encountered.[57] This proved that the methodology as illustrated in **Schemes 16** and **17** on pages 65 and 67 respectively could not be generalised for the synthesis of higher oxygenated systems.



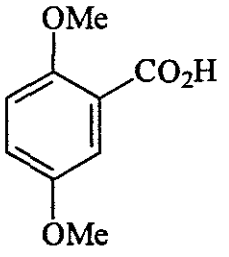
119 R= alkyl chain

In recent years organothallium compounds have become increasingly useful as synthetic intermediates in organic chemical syntheses.[59-65] Thallium(III) trifluoroacetate (T.T.F.A.) in particular has been found to be extremely efficient as a reagent for electrophilic aromatic thallations. The thallium moiety can be substituted by several functional groups affording new routes to many substituted arenes.

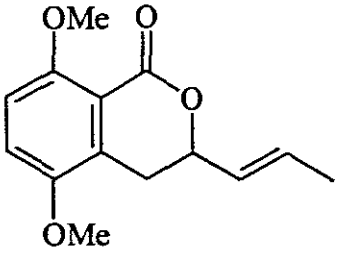
Taylor *et al.*[61] prepared several aromatic iodides *via* thallation of substituted aromatic substrates followed by treatment of the intermediate arylthallium ditrifluoroacetates with aqueous potassium iodide. It was found that *meta* substitution is usually observed under conditions of thermodynamic control, whereas under the conditions of kinetic control *ortho* substitution results as in the case of benzoic acid by means of *ortho* delivery of thallium.

Larock *et al.*[62] have synthesised several 3,4-dihydroisocoumarins from β-phenylethyl alcohols as substrates employing the direct thallation-carbonylation of the substrate alcohols. Larock and co-workers[63] also developed attractive routes to several isocoumarins *via* the thallation-olefination of several benzoic acid derivatives.

In the light of the results obtained by Larock and other groups, the thallation reaction was extended in this laboratory to the dimethoxybenzoic acid (**120**). Treatment of this compound with T.T.F.A. in trifluoroacetic acid followed by palladium(II) chloride and 1,3-pentadiene, afforded the 3,4-dihydroisocoumarin (**121**) in an overall yield of 41%.

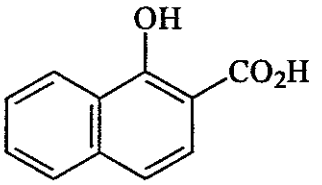


120

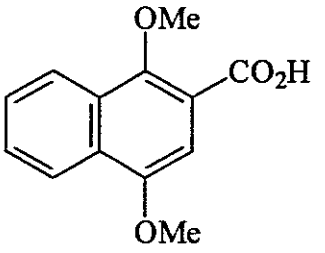


121

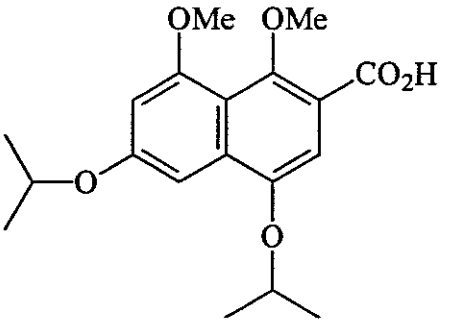
However, when this thallation reaction was repeated with the naphthalenic acids (**122**), (**123**) and (**124**) under the same conditions, none of their corresponding lactones was obtained.[57b]



122



123



124

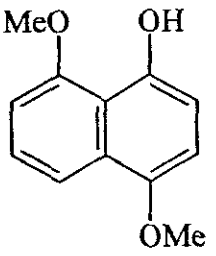
In all these cases a mixture of unreacted starting material and tars was recovered.

These results thus prompted us to investigate an alternative approach (which could be more widely employed) to the synthesis of naphtho[2,3-*c*]pyranones.

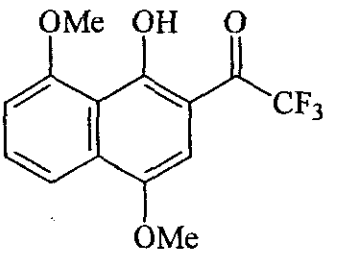
3.1.2 SYNTHESIS OF RACEMIC 3,4-DIHYDRO-9-METHOXY-3-METHYL-1H-NAPHTHO[2,3-*C*]PYRAN-1,5,10-TRIONE (10)

Our model route to pyranone (**10**) employs naphthol (**1**), readily available from our synthetic strategy[35] depicted in **Scheme 10**.

Thus treatment of naphthol (**1**) with trifluoroacetic anhydride under anhydrous conditions gave the trifluoroacetyl naphthol (**125**)[66] which upon treatment with CAN afforded the *gem*-diol quinone (**126**).[66]

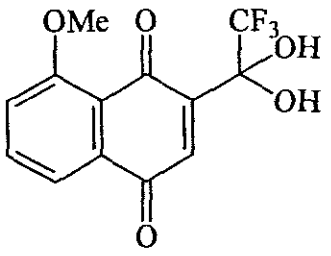


1

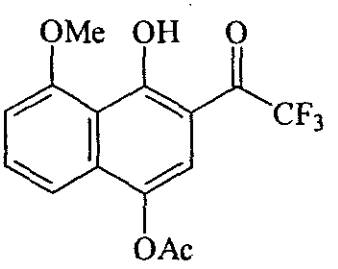


125

This was reductively monoacetylated to afford compound (**127**) in a yield of 89% overall from (**125**). The ^{1}H nmr spectrum of (**127**) showed the chelated hydroxyl as a D_2O-exchangeable singlet at δ 12.53.

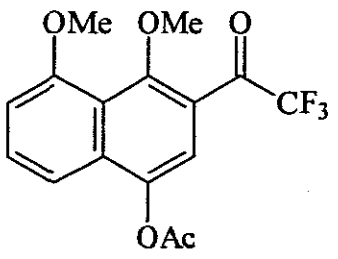


126

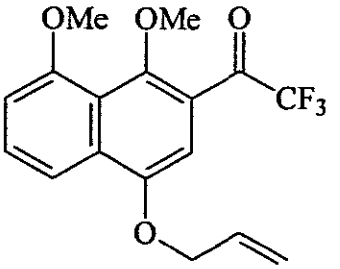


127

Protection of the hydroxyl of (**127**) by methylation using iodomethane, afforded the acetate (**128**) (75%) which was hydrolysed under mild alkaline conditions and then allylated to yield the allyloxynaphthalene (**130**) in a yield of 72% from compound (**128**).



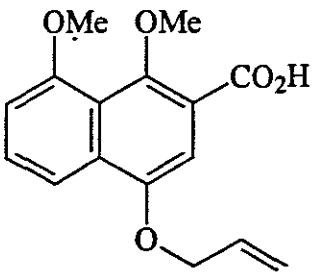
128



130

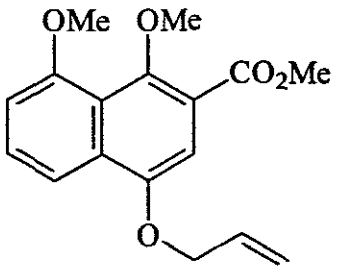
The ^{1}H nmr spectrum (60 MHz) of (**130**) showed the resonances of the propenyl function as a doublet (J 4 Hz) at δ 4.70 due to the methylene protons; a multiplet at δ 5.25 -δ 5.60 due to the olefinic methylenes and another multiplet at δ 5.75 - 6.85 due to the olefinic methine proton.

The naphthalenic acid (**131**) was available from the trifluoroacetyl derivative (**130**) by treatment with a 5% potassium hydroxide - DMSO solution at 60°C.

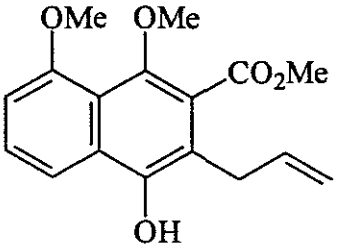


131

Pyrolysis of the acid under Claisen conditions afforded a complex mixture and thus it was decided to convert (**131**) into its methyl ester (**132**) prior to Claisen rearrangement. This was achieved in excellent yield (96%).

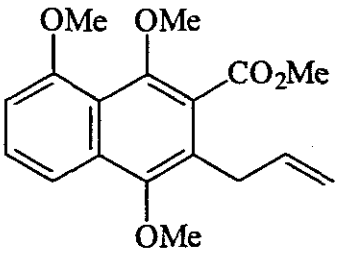


132

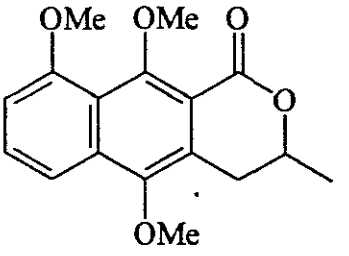


133

Pyrolysis of ester (**132**) followed by methylation of the intermediate naphthol (**133**), gave the trimethoxynaphthalene methyl ester (**134**) in an overall yield of 68% from (**132**).



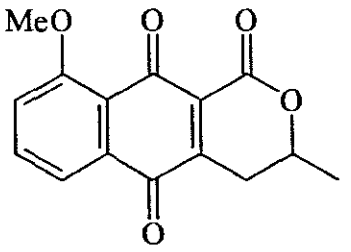
134



135

Treatment of ester (**134**) with hot trifluoroacetic acid gave the naphthopyranone (**135**) in a yield of 34%. Its ^{1}H nmr (200 MHz) spectrum showed, *inter alia*, a doublet of doublets (J 15.7 and 10.9 Hz) at δ 2.79 due to the *pseudo*-axial 4-H; a doublet of doublets at δ 3.29 (J 15.7 and 2.2 Hz) due to the *pseudo*-equatorial 4-H and a multiplet at *ca.* δ 4.4 - 4.6 due to 3-H of the heterocyclic ring.

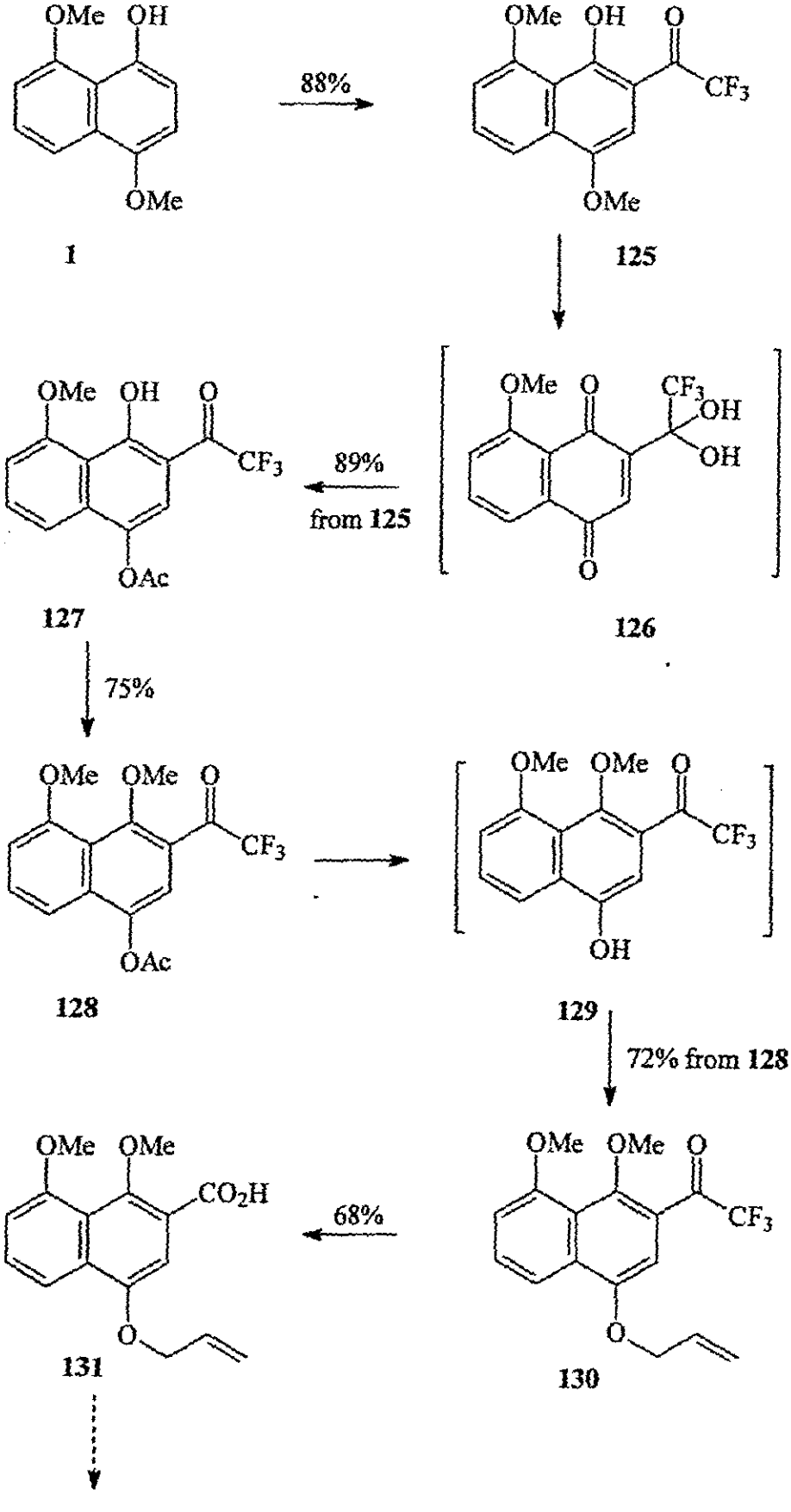
Finally, oxidative demethylation of (**135**), using silver(II) oxide, afforded the quinonoid pyranone (**10**) in good yield (73%).



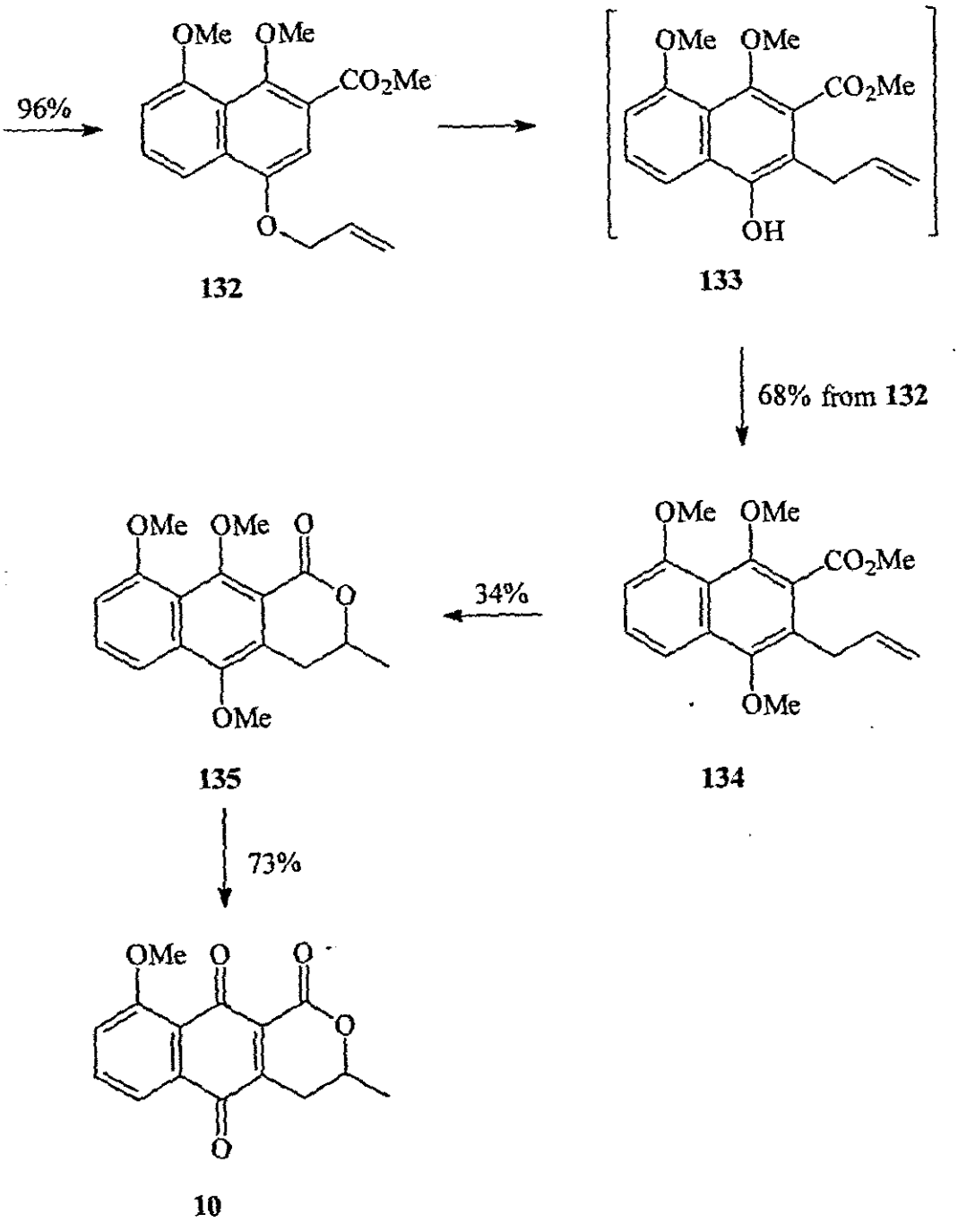
10

It is envisaged that this route should be generally applicable for the synthesis of higher oxygenated naphtho [2,3-*c*]pyranones by virtue of the nature of the conditions and reagents used. The route to lactone **(10)** is summarised in **Scheme 18.**

Scheme 18


OMe OH
OMe
1
88%
OMe OH O
CF3
OMe
125
OMe O CF3
OH
OH
O
126
89%
from 125
OMe OH O
CF3
OAc
127
75%
OMe OMe O
CF3
OAc
128
OMe OMe O
CF3
OH
129
72% from 128
OMe OMe O
CF3
O
130
68%
OMe OMe
CO2H
O
131

Scheme 18 continued



CHAPTER 4

EXPERIMENTAL

4.1 SYNTHESES

GENERAL

^{1}H nmr spectra were recorded using the following instruments: 60 MHz Varian EM-360 and 200 MHz Varian XL-200. Unless otherwise stated, all ^{1}H nmr spectra were recorded at ambient temperature in deuterochloroform using tetramethylsilane as an internal standard and J values are expressed in Hz. High resolution mass spectra were recorded at the Cape Technikon. Unless otherwise stated, infrared spectra were measured for Nujol mulls. Melting points are quoted uncorrected and were recorded on a Fischer-John apparatus. Elemental analyses were performed on a Heraeus CHN-RAPID analyser.

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

Light petroleum refers to the fraction of boiling point 60 - 80°C. Anhydrous magnesium sulphate was used to dry the organic solvents after extraction procedures, and most organic solvents and liquid reagents were distilled immediately before use.

C.A.N. refers to cerium(IV) ammonium nitrate while T.F.A.A. refers to trifluoroacetic anhydride. The phrase "residue obtained upon work-up" refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

1,5-*Dimethoxy-4-naphthol* (**1**)

Compound (**68**) (0.4 g) was heated in a nitrogen atmosphere (oil bath 220°C) for 20 min. Chromatographic purification of the residue using ethyl acetate-light petroleum (1:4) as eluent afforded *naphthol* (**1**) (0.332 g) (94%) identical in all respects to the material obtained *via* an alternative route[4(b)].

2-*Allyl-5-methoxy*-1,4-*naphthoquinone* (**2**)

Compound (**69**) (0.404 g; 1.6 mmol) was heated in a nitrogen atmosphere (oil bath 220°C) for 10 minutes. A ^{1}H nmr spectrum run on the crude mixture had the following features: δ_H 3.44 (2H, dt, *J* 6 and 2, allylic-CH_2), 4.03 (3H, s, OCH_3), 5.0-5.4 (3H, m, =CH_2 and 1-OH, D_2O exchangeable), 5.4-6.3 (1H, m, =CH), 6.5-7.8 (4H, m, 3-, 6-, 7- and 8-H), 8.86 (1H, s, 4-OH, D_2O exchangeable). Silver(I) oxide (0.732 g; 3 mmol) in chloroform was added to the cooled crude material and the mixture was stirred for 20 min, filtered and the residue chromatographed using ethyl acetate-light petroleum (2:3) as eluent to afford *quinone* (**2**) (0.30 g; 84%) m.p. 94-96°C (dichloromethane-light petroleum) (Lit.[2] 96-97°C); δ_H 3.33 (2H, dt, *J* 6 and 2, C*H*$_2$-CH=CH_2), 4.03 (3H, s, OCH_3), 5.0-5.4 (2H, m, =CH_2), 5.6-6.2 (1H, m, =CH), 6.87 (1H, t, *J* 1.5, 3-H), 7.2-7.85 (3H, m, 6- 7- and 8-H).

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

Cerium(IV) ammonium nitrate (0.420 g; 0.77 mmol) in water (2 cm^3) was added dropwise with stirring over a period of 5 min. to a solution of naphthol (**73**) (0.10 g; 0.36 mmol) in acetonitrile (10 cm^3). The solution was stirred for a further 10 min, poured into water (50 cm^3) and extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$) and filtered. Evaporation of the solvent gave *quinone* (**1**) (0.07 g, 83%) m.p. 104°C (dichloromethane-light petroleum) (Lit.[4b] 102-103°C).

3,4-*Dihydro*-9-*methoxy*-3-*methyl*-1H-*naphtho*[2,3-*c*]*pyran*-1,5,10-*trione* (**10**)

Lactone (**135**) (30 mg, 0.1 mmol) in aqueous acetonitrile (10 cm^3) was oxidised in the usual manner with CAN (2.2 mol equivalents) to afford a residue which was briefly treated with silver(I) oxide in hot chloroform to give the *product* (**10**) (20 mg, 73%) m.p. 98-100°C (from light petroleum). ν_{max} 1750 and 1720 cm^{-1}; δ_H (200 MHz) 1.54 (3H, d, *J* 6.3, 3-CH_3), 3.98 (3H, s, OCH_3), 2.5 (1H, dd, *J* 18.7 and 11.5 *pseudo*-axial 4-H), 3.15 (1H, dd, *J* 18.7 and 3, *pseudo*-equatorial 4-H), 4.5-4.7 (1H, m, 3-H), 7.3-7.4 (2H, m, 7-H) and 7.6-7.8 (2H, m, 6- and 8-H) (Found: C, 66.3; H, 4.2%. Calc. for $C_{15}H_{12}O_5$: C, 66.18; H, 4.4%).

(±)(IR,3R)-5,10-*Dihydroxy*-9-*methoxy*-1,3-*dimethyl*-4-*oxo*(1H,3H)*naphtho*[2,3-*c*]*pyran* (**13**)

To a stirred suspension of ketone (**87**) (340 mg; 1.08 mmol) in dioxane (40 cm^3) containing silver(II) oxide (526 mg; 4.28 mmol) was added dropwise a solution of nitric acid (7.0 cm^3 of a 6 M solution) until all the silver (II) oxide completely dissolved. The solution was stirred for an additional 30 min and water (150 cm^3) was added and the resulting solution extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to yield *hongconin* (**13**)[15] (218 mg; 70%) as yellow crystals, m.p. 133-136°C. ν_{max} 3400 and 1635 cm^{-1}; δ_H (200 MHz) 1.53 (3H, d, *J* 6.5, 3-CH_3), 1.69 (3H, d, *J* 6.5, 1-CH_3), 4.07 (3H, s, OCH_3), 4.69 (1H, q, *J* 6.5, 3-H), 5.49 (1H, q, *J* 6.5, 1-H), 7.01 (1H, d, *J* 7.5, 8-H), 7.38 (1H, t, *J* 7.5, 7-H), 8.05 (1H, d, *J* 7.5, 6-H), 8.97 (1H, D_2O exchangeable, 10-OH) and 12.82 (1H, D_2O exchangeable, 5-OH) (Found: C, 66.5; H, 5.4%, M^+, 288.0985. Calc. for $C_{16}H_{16}O_5$: C, 66.6; H, 5.55%, M, 288.0998).

3,4-*Dihydro*-3-*methyl*-1H-*benzo*[*c*]*pyran*-5,8-*dione* (**18**)

To a stirred mixture of pyran (**26**) (59 mg, 0.3 mmol) and silver(II) oxide (176 mg, 2.5 mmol) in dioxan (10 cm^3) was added nitric acid (0.4 cm^3 of a 6 mol dm^{-3} solution) over a period of 5 min. Stirring was continued for a further 10 min, after which the reaction was quenched by the addition of a dichloromethane-water (26:6) mixture. The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to afford the *quinone* (**18**) (35 mg, 70%) as yellow plates, m.p. 94-95°C (from dichloromethane-light petroleum); ν_{max} 1660 cm^{-1}; δ_H (300 MHz) 1.35 (3H, d, *J* 6, 3-CH_3), 2.08 (1H, dddd, *J* 19, 10, 3.5 and 3, *pseudo*-axial 4-H), 2.60 (1H, dt, *J* 19 and 3.5, *pseudo*-equatorial 4-H), 3.35-3.85 (1H, m, 3-H), 4.35 (1H, dt, *J* 19 and 3.5, *pseudo*-axial 1-H), 4.75 (1H, dd, *J* 19 and 3, *pseudo*-equatorial 1-H) and 6.75 (2H, s, 5- and 6-H) (Found: C, 67.2; H, 5.6%; M^+, 178. Calc. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.6%; *M*, 178).

Prop-2′-*enyl* 3,6-*dihydroxy*-2-*prop*-2′-*enylbenzoate* (**23**)

The ester (**22**)[22] (650 mg, 2.8 mmol) was pyrolysed at 210°C under nitrogen for 5 h. The tarry product was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to yield the *Claisen product* (**23**) (453 mg, 69%) as a light brown oil; ν_{max} (film) 3440, 1670 and 1470 cm^{-1}; δ_H 3.75 (2H, dt, *J* 6 and 2, 1′-CH_2), 4,85 (2H, dt, *J* 6 and 2,

CO_2CH_2), 4.87 (1H, s, D_2O exchangeable, 3-OH), 5.10-5.65 (4H, m, 3′-CH_2 and $CO_2CH_2CH{=}CH_2$), 5.65-6.65 (2H, m, 2′-C*H* and $CO_2CH_2CH{=}CH_2$), 6.80 (1H, d, *J* 9, 5-H), 7.30 (1H, d, *J* 9, 4-H) and 10.45 (1H, s, D_2O exchangeable, 6-OH) (Found: C, 66.5; H, 6.2%; M^+, 234. Calc. for $C_{13}H_{14}O_4$: C, 66.7; H, 6.0%; *M*, 234).

Prop-2′-enyl 3,6-*dimethoxy*-2-*prop*-2′-*enylbenzoate* (**24**).

Quinol (**23**) (622 mg, 2.7 mmol) was methylated as for compound (**29**). The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent, to give *product* (**24**) (672 mg, 95%) as an oil; ν_{max} (film) 1735 cm^{-1}; δ_H 3.35 (2H, dt, *J* 6 and 2, CH_2-$CH{=}CH_2$), 3.75 (6H, s, 2 x OCH_3), 4.83 (2H, dt, *J* 6 and 2, $CO_2CH_2CH{=}CH_2$), 5.07-5.40 (4H, m, 2 x $CH_2CH{=}CH_2$), 5.80-6.10 (2H, m, 2 x $CH_2CH{=}CH_2$), 6.70 (1H, d, *J* 9 , 5-H) and 6.90 (1H, d, *J* 9, 4-H) (Found: C, 68.6; H, 6.9%; M^+, 262. Calc. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9%; *M*, 262).

3,6-*Dimethoxy*-1-*hydroxymethyl*-2-*prop*-2′-*enylbenzene* (**25**).

Ester (**24**) (928 mg, 3.54 mmol) in dry ether (20 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (673 mg, 17.7 mmol) in dry ether (50 cm^3) over a 5-min period and the mixture was stirred for 30 min at room temperature. Reduction was halted by

the slow addition of a saturated solution of ammonium chloride (2 cm^3). Dichloromethane (60 cm^3) and magnesium sulphate (5 g) were added and the mixture was filtered. The residue obtained by removal of the solvent from the filtrate was chromatographed using ethyl acetate-light petroleum (1:4) as eluent and gave the *product* (**25**) (660 mg, 90%) as white crystals, m.p. 46-47°C (from light petroleum); ν_{max} 3365 cm^{-1}; δ_H 3.55 (2H dt, *J* 6 and 2, $CH_2CH{=}CH_2$), 3.75 and 3.80 (each 3H, each s, 2 x OCH_3), 4.70 (1H, s, D_2O exchangeable, OH), 4.73 (2H, s, $ArCH_2OH$), 4.94-5.10 (2H, m, $CH_2CH{=}CH_2$), 5.65-6.40 (1H, m, $CH_2CH{=}CH_2$), 6.71 and 6.77 (each 1H, d, *J* 9, 3- and 4-H) (Found: C, 69.1; H, 7.4%; M^+, 208. Calc. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7%; *M*, 208).

3,4-*Dihydro*-5,8-*dimethoxy*-3-*methyl*-1H-*benzo*[*c*]-*pyran* (**26**)

Potassium *tert*-butoxide (602 mg, 5.28 mmol) was added at once to a stirred solution of the alcohol (**25**) (270 mg, 1.30 mmol) in dry dimethylformamide (20 cm^3). The resultant mixture was stirred under nitrogen at 60°C (oil bath) for 15 min. after which it was quenched by the addition of water (60 cm^3). The product was extracted into ether and the residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to afford the *product* (**26**) (220 mg, 82%) as white crystals, m.p. 74-75°C (from dichloromethane-

light petroleum); ν_{max} 1260 and 1135 cm^{-1}; δ_H 1.35 (3H, d, *J* 6, 3-CH_3), 2.35 (1H, dd, *J* 17 and 10, *pseudo*-axial 4-H), 2.85 (1H, dd *J* 17 and 4, *pseudo*-equatorial 4-H), 3.75 and 3.78 (each 3H, each s, 2 x OCH_3), 3.39-4.00 (1H, m, partially obscured by OCH_3 signals, 3-H), 4.56 (1H, d, *J* 15, *pseudo*-axial 1-H), 4.95 (1H, d, *J* 15, *pseudo*-equatorial 1-H), 6.60 and 6.65 (each 1H, d, *J* 9, 6- and 7-H) (Found: C, 69.2; H, 7.6%; M^+, 208. Calc. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7%; *M*, 208).

Prop-2′-enyl 3,6-*dihydroxy*-2,5-*diprop*-2′-*enylbenzoate* (**28**).

The diallyl ether (**27**)[22] (10.02 g, 37 mmol) was pyrolysed as above and the residue was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to afford the *diol* (**28**) (5.81 g, 58%) as white crystals, m.p. 36-37°C (from light petroleum); ν_{max} 3600-3100 and 1660 cm^{-1}; δ_H 3.48[2H, dt, *J* 6 and 2, 5-(1′-C*H*$_2$)], 3.70[2H, dt *J* 6 and 2, 2-(1′-C*H*$_2$)], 4.80 (1H, s, D_2O exchangeable, 3-OH), 4.83 (2H, dt *J* 6 and 2, CO_2CH_2), 5.10-5.60 (6H, m, 3 x $CH_2CH{=}CH_2$), 5.70-6.50 (3H, m, 3 x $CH_2CH{=}CH_2$), 6.85 (1H, s, 4-H) and 10.40 (1H, s, D_2O exchangeable, 6-OH) (Found: C, 70.1; H, 6.7%; M^+, 274.1224. Calc. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%; *M*, 274.1205).

Prop-2'-enyl 3,6-*dimethoxy*-2,5-*diprop*-2'-*enylbenzoate* (**29**).

A mixture of the quinol (**28**) (1.30 g, 4.74 mmol), potassium carbonate (6.5 g, 47.1 mmol) and iodo-methane (6.7 g, 47.2 mmol) in acetone (60 cm^3) was vigorously stirred and heated under reflux for 24 h. The cooled solution was filtered and the filtrate was stripped of solvent to yield an oil which was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to afford the *dimethyl ether* (**29**) (1.39 g, 96%) as an oil; ν_{max} (film) 1720 cm^{-1}; δ_H3.35 and 3.45 (each 2H, each dt, *J* 6 and 2, 5- and 2-$CH_2CH{=}CH_2$), 3.75 and 3.85 (each 3H, s, 2 x OCH_3), 4.85 (2H, dt, *J* 6 and 2, CO_2CH_2), 5.00-5.65 (6H, m, 3 x $CH_2CH{=}CH_2$), 5.75-6.50 (3H, m, 3 x $CH_2CH{=}CH_2$) and 6.80 (1H, s, 4-H) (Found: C, 71.5; H, 7.15%; M^+, 302.1531. Calc. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3%; *M*, 302.1518).

3,6-*Dimethoxy*-2,5-*diprop*-2'-*enylbenzyl alcohol* (**30**).

A solution of the ester (**29**) (1.36 g, 4.5 mmol) in dry ether (30 cm^3) was added dropwise into a slurry of lithium aluminium hydride (1.03 g, 27 mmol) in ether (50 cm^3) over a period of 5 min. Stirring was continued for a further 20 min. and the excess of hydride was destroyed by the addition of aqueous saturated ammonium chloride. Dichloromethane (50 cm^3) and magnesium sulphate (5 g) were added and the mixture was

filtered. Removal of solvents yielded a residue that was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to finally afford the *alcohol* (**30**) (1.07 g, 96%) as an oil; ν_{max} (film) 3500-3140 cm^{-1}; δ_H 3.42 and 3.52 (each 2H, each dt, *J* 6 and 2, 5- and 2-$CH_2CH{=}CH_2$), 3.82 (6H, s, 2 x OCH_3), 4.70 (1H, s, D_2O exchangeable, OH), 4.80 (2H, s, Ar-CH_2OH, 4.85-5.35 (4H, m, 2 x $CH_2CH{=}CH_2$), 5.70-6.40 (2H, m, 2 x $CH_2CH{=}CH_2$) and 6.75 (1H, s, 4-H) (Found: C, 72.6; H, 8.4%; M^+, 248. Calc. for $C_{15}H_{20}O_3$: C, 72.6; H, 8.1%, *M*, 248).

(E)-3,4-*Dihydro*-5,8-*dimethoxy*-3-*methyl*-7-*prop*-1′-*enyl*-1H-*benzo*[*c*]*pyran* (**31**)

Alcohol (**30**) (207 mg, 0.83 mmol) in dry dimethylformamide (15 cm^3) was treated with potassium *tert*-butoxide (561 mg, 5 mmol) under nitrogen and the mixture was stirred and heated at 60°C (oil bath) for 15 min. After quenching the reaction with water (80 cm^3), the aqueous solution was extracted with ether. The residue obtained upon work-up was chromatographed with ethyl acetate-light petroleum (1:9) as eluent to afford the *pyran* (**31**) (178 mg, 86%) as white needles, m.p. 55-56°C (from light petroleum); ν_{max} 1223 and 1135 cm^{-1}; δ_H 1.35 (3H, d, *J* 6, 3-CH_3), 1.92 (3H, d, *J* 6, 3′-CH_3),2.35 (1H, dd, *J* 17 and 10, *pseudo*-axial 4-H), 2.80 (1H, dd, *J* 17 and 4, *pseudo*-equatorial 4-H), 3.62 and

3.85 (each 3H, s, 2 x OCH_3), 3.40-3.90 (1H, m, 3-H partially obscured by OCH_3 signals), 4.65 (1H, d, *J* 15, *pseudo*-axial 1-H), 5.05 (1H, d, *J* 15, *pseudo*-equatorial 1-H), 6.10 (1H, dq, *J* 16 and 6, 2′-H), 6.40 (1H, dq, *J* 16 and 2, 1′-H) and 6.84 (1H, s, 6-H) (Found: C, 72.4; H, 7.9%; M^+, 248. Calc. for $C_{15}H_{20}O_3$: C, 72.6; H, 8.1%; *M*, 248).

Prop-2′-enyl 2-methoxy-5-prop-2′-enyloxybenzoate (**32**)

The ester (**22**)[16] (1.2 g, 5.1 mmol) in dry acetone (60 cm^3) containing iodomethane (7.2 g, 51 mmol) and potassium carbonate (2.15 g, 15.6 mmol) was vigorously stirred under reflux for 24 h. The cooled reaction mixture was filtered and the filtrate stripped of solvent to leave an oily residue which was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to afford the *methoxy ether* (**32**) (775 mg, 61%) as an oil; ν_{max} (film) 1730 and 1505 cm^{-1}; δ_H 3.85 (3H, s, OCH_3), 4.50 (2H, dt, *J* 6 and 2, 5-OCH_2CH=CH_2), 4.83 (2H, dt, *J* 6 and 2, CO_2CH_2), 5.15-5.68 (4H, m, 2 x $OCH_2CH{=}CH_2$), 5.70-6.60 (2H, m, 2 x $OCH_2CH{=}CH_2$), 6.87 (1H, d, *J* 9, 3-H), 7.10 (1H, dd, *J* 9 and 3, 4-H) and 7.37 (1H, d, *J* 3, 6-H) (Found: C, 67.5; H, 6.3%; M^+, 248.1073. Calc. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.45%; *M*, 248.1049).

Prop-2'-enyl 5-*hydroxy*-2-*methoxy*-4-*prop*-2'-*enylbenzoate* (**33**)

Ester (**32**) (775 mg, 3.1 mmol) was pyrolysed as above for (**22**) and the tarry residue was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to yield the *phenol* (**33**) (250 mg, 32%) as an oil; ν_{max} (film) 3400 and 1705 cm^{-1}; δ_H 3.42 (2H, dt, *J* 6 and 2, 1'-CH_2), 3.84 (3H, s, OCH_3), 4.77(2H, dt, *J* 6 and 2, CO_2CH_2), 4.9-5.6 (4H, m, 2 x $CH_2CH{=}CH_2$), 5.68-6.60 (2H, m, 2 x $CH_2CH{=}CH_2$, 6.10 (1H, s, D_2O exchangeable, 5-OH), 6.75 (1H, s, 3-H) and 7.40 (1H, s, 6-H) (Found: C, 67.4; H, 6.25%; M^+, 248. Calc. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.45%; *M*, 248).

Prop-2'-enyl 3-*prop*-2'-*enyl*-1,4-*benzoquinone*-2-*carboxylate* (**34**)

The ester (**23**) (120 mg, 0.56 mmol) was oxidised with cerium(IV) ammonium nitrate (614 mg, 1.12 mmol) as for compound (**25**) with a similar chromatographic procedure to afford the *product* (**34**) (43 mg, 33%) as a yellow oil; ν_{max} (film) 1735 and 1655 cm^{-1}; δ_H 3.14 (2H, dt, *J* 6 and 2, $CH_2CH{=}CH_2$), 4.75-4.95 (2H, m, $CO_2CH_2CH{=}CH_2$), 5.00-5.60 (4H, m, 2 x $CH_2CH{=}CH_2$), 5.63-6.40 (2H, m, 2 x $CH_2CH{=}CH_2$) and 6.74 (2H, s, 4- and 5-H) (Found: C, 67.15; H, 5.3%; M^+, 232. Calc. for $C_{13}H_{12}O_4$: C, 67.2; H, 5.2%; *M*, 232).

2-Hydroxymethyl-3-prop-2'-enyl-1,4-benzoquinone (**35**)

To a stirred solution of alcohol (**25**) (268 mg, 1.29 mmol) in acetonitrile (20 cm^3) was added water (2 cm^3) followed by a solution of cerium(IV) ammonium nitrate (2.83 g, 5.2 mmol) in water (5 cm^3) over 5 min. Stirring was continued for a further 15 min. before the reaction was diluted with water (200 cm^3), extracted with ether (3 x 100 cm^3) and the residue obtained after work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *product* (**35**) (140 mg, 61%) as a red oil; ν_{max} (film) 3460 and 1670 cm^{-1}; δ_H 3.37 (2H, dt *J* 6 and 2, $CH_2CH{=}CH_2$), 4.52 (2H, s, $ArCH_2OH$), 4.65 (1H, s, D_2O exchangeable, OH), 4.90-5.30 (2H, m, $CH_2CH{=}CH_2$), 5.44-6.20 (1H, m, $CH_2CH{=}CH_2$) and 6.82 (2H, s, 5- and 6-H) (Found: C, 67.3; H, 5.3%; M^+, 178.0630. Calc. for $C_{10}H_{10}O_3$: C, 67.4, H, 5.6%; *M*, 178.0620).

trans-3,4-Dihydro-1,3-dimethyl-1H-benzo[c]pyran-5,8-di-one (**36**)

Pyran (**45**) (200 mg, 0.90 mmol) in a solution of acetonitrile-water (9:1) (10 cm^3) was treated over a period of 5 min. with cerium(IV) ammonium nitrate (997 mg, 1.82 mmol) dissolved in water (1 cm^3). Stirring was continued for an additional 15 min. after which water (100 cm^3) was added and the resulting mixture was extracted with dichloromethane. The residue obtained upon work-up was

chromatographed using ethyl acetate-light petroleum (15:85) as eluent to afford the *quinone* (**36**)[67] (156 mg, 90%) as orange crystals, m.p. 102-104°C (from light petroleum).

(±)-(1R,3R,4R)-3,4-*Dihydro*-1,3-*dimethyl*-4-*hydroxy*-1H-*benzo*[*c*]*pyran*-5,8-*dione* (**37**) *and* (±)-(4S)-*diastereoisomer* (**38**)

To a solution made by dissolving the alcohol (**47**) (105 mg, 0.47 mmol) in acetonitrile (10 cm^3) and then adding water (5 cm^3) was added a solution of cerium(IV) ammonium nitrate [1.04 g, 1.9 mmol in water (10 cm^3)] over 5 min. Stirring was continued for an additional 20 min. and then the reaction mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to yield *pyran* (**38**) (15 mg, 15%) as a thick yellow oil; ν_{max} 3500 and 1650 cm^{-1}; δ_H (200 MHz) 1.36 (3H, d, *J* 6.1, 3-CH_3), 1.51 (3H, d, *J* 6.8, 1-CH_3), 3.52 (1H, d, *J* 2.5, D_2O exchangeable, *pseudo*-equatorial 4-OH), 3.85 (1H, dq, *J* 7.9 and 6.1, 3-H), 4.35 (1H, ddd, *J* 7.9, 2.5 and 0.9, *pseudo*-axial 4-H), 4.74 (1H, dq, *J* 6.8 and 0.9, 1-H) and 6.73 (2H, s, 6- and 7-H) (Found: M^+, 208.0742. Calc. for $C_{11}H_{12}O_4$: *M*, 208.0736). Further elution with ethyl acetate-light petroleum (3:7) yielded *pyran* (**37**) (65 mg, 66%) as a yellow solid, m.p. 98.5-99.5°C (from light petroleum); ν_{max} 3480 (sharp) and 1650 cm^{-1}; δ_H (200 MHz) 1.37 (3H, d, *J* 6.4, 3-CH_3), 1.45

(3H, d, *J* 6.8, 1-CH_3), 2.24 (1H, d, *J* 7.3, D_2O exchangeable, *pseudo*-axial 4-OH), 3.95 (1H, dq, *J* 6.4 and 2.2, 3-H), 4.37 (1H, dd, *J* 7.3 and 2.2, *pseudo*-equatorial 4-H), 4.85 (1H, q, *J* 6.8, 1-H), 6.74 and 6.82 (each 1H, d, *J* 10.2, 6- and 7-H) (Found: C, 63.65; H, 6.05%; M^+, 208. Calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8%; *M*, 208).

trans-(1R,3R)-5,8-*Dihydroxy*-1,3-*dimethyl*-4-*oxo*-1H-*benzo*[*c*]*pyran* (**39**)

To a stirred mixture of pyran (**50**) (120 mg, 0.51 mmol) in dioxane (5 cm^3) containing silver(II) oxide (253 mg, 2.04 mmol) was added nitric acid (2.5 cm^3 of a 6 $mol.dm^{-3}$ solution) dropwise until all the silver(II) oxide had dissolved. The reaction mixture was stirred for an additional 10 min, after which water (60 cm^3) was added and the solution extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:3) as eluent to afford the *product* (**39**) (66 mg, 62%) as white crystals, m.p. 94-95°C (from light petroleum); ν_{max} 3370, 1700 and 1650 cm^{-1}; δ_H (200 MHz) 1.43 (3H, d, *J* 6.6, 3-CH_3), 1.51 (3H, d, *J* 6.7, 1-CH_3), 4.57 (1H, q, *J* 6.6, 3-H), 4.90 (1H, br s, D_2O exchangeable, 8-OH), 5.23 (1H, q, *J* 6.7, 1-H), 6.67 (1H, d, *J* 8.8, 6-H), 6.87 (1H. d, *J* 8.8, 7-H) and 11.32 (1H, s, D_2O exchangeable, 5-OH) (Found: C, 63.3; H, 5.8%; M^+, 208.0742. Calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8%; *M*, 208.0736).

2-*Acetyl*-1-*hydroxy*-4-*prop*-2'-enylbenzene (**41**)

2,5-Dihydroxyacetophenone (**40**) (3.074 g, 0.02 mol) was mixed with allyl bromide (2.34 g, 0,02 mol) and potassium carbonate (2.2 g, 0.016 mol) in acetone (50 cm^3). The mixture was stirred under reflux for six hours after which it was filtered and the residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) to afford the *product* (**41**) (3.6 g, 93%), m.p. 57-58°C (Lit.[23], 59 - 60°C).

2-*Acetyl*-5-*prop*-2'-*enyl*-1,4-*hydroquinone* (**42a**) *and* 2-*acetyl*-3-*prop*-2'-*enyl*-1,4-*hydroquinone* (**42**)

The allyl-oxyacetophenone (**41**) (7.33 g, 38.3 mmol) was pyrolysed under nitrogen at 215°C (oil bath) for 1.5 h. The hard, tarry product was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to give the *minor product* (**42a**) (620 mg, 8%) as olive-green plates, m.p. 100-102°C (from ethanol); ν_{max} 3285 and 1620 cm^{-1}; δ_H 2.53 (3H, s, $COCH_3$), 3.30 (2H, dt, *J* 6 and 2, $CH_2CH{=}CH_2$), 5.00-5.10 (2H, m, CH_2-CH=CH_2), 5.25 (1H, s, D_2O exchangeable, 3-OH), 5.72-6.22 (1H, m, $CH_2CH{=}CH_2$), 6.80 (1H, s, 5-H), 7.17 (1H, s, 2-H), 11.87 (1H, s, D_2O exchangeable, 6-OH) (Found: C, 68.6; H, 6.4%; M^+, 192. Calc. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25%; *M*, 192). Later fractions yielded the *major product* (**42**) (6.16 g, 84%) as tan crystals, m.p. 104-105°C;

ν_{max} 3420, 3270, 1668 and 1610 cm^{-1}; δ_H 2.60 (3H, s, $COCH_3$) 3.56 (2H, dt *J* 6 and 2, $CH_2CH{=}CH_2$), 4.70 (1H, s, D_2O exchangeable, 3-OH), 5.07 (1H, dm, *J* 17, *trans*-$CH_2CH{=}CH_2$), 5.23 (1H, dm, *J* 9, *cis*-$CH_2CH{=}CH_2$), 5.80-6.30 (1H, m, $CH_2CH{=}CH_2$), 6.78 (1H, d, *J* 9, 5-H), 6.98 (1H, d, *J* 9, 4-H) and 10.30 (1H, s, D_2O exchangeable, 6-OH) (Found: C, 68.7; H, 6.1%; M^+, 192. Calc. for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25%; *M*, 192).

2-Acetyl-3-prop-2'-enyl-1,4-dimethoxybenzene (**43**)

Quinol (**42**) (6.00 g, 31.3 mmol) was dissolved in dry acetone (150 cm^3) containing iodomethane (17.75 g, 125 mmol) and potassium carbonate (17.75 g, 129 mmol) and the resulting mixture was stirred under reflux in a nitrogen atmosphere for 18 h. The cooled reaction mixture was filtered and the filtrate was evaporated to an oil which was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *product* (**43**) (6.89 g, 100%) as an oil; ν_{max} (film) 1690 cm^{-1}; δ_H 2.43 (3H, s, $COCH_3$), 3.30 (2H, dt *J* 6 and 2, $CH_2CH{=}CH_2$, 3.77 (6H, s, 2 x OCH_3), 4.90 (1H, dm, *J* 16, *trans*-$CH_2CH{=}CH_2$), 4.95 (1H, dm, *J* 9, *cis*-$CH_2CH{=}CH_2$), 5.65-6.15 (1H, m, $CH_2CH{=}CH_2$), 6.70 (1H, d, *J* 9, 5-H) and 6.83 (1H, d, *J* 9, 4-H) (Found: C, 71.1; H, 7.3%; M^+, 220. Calc. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3%; *M*, 220).

1,4-Dimethoxy-2-(1'-hydroxyethyl)-3-prop-2'-enylbenzene (**44**)

The ketone (**43**) (2.23 g, 10.1 mmol) in dry ether (50 cm^3) was added dropwise to a stirred slurry of lithium aluminium hydride (760 mg, 20 mmol) in dry ether (60 cm^3) over a period of 5 min. After all the starting material had been consumed (5 h), saturated aqueous ammonium chloride (1 cm^3) was added to quench the reaction. Dichloromethane (100 cm^3) was added and the residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to afford the *product* (**44**) (2.15 g, 96%) as an oil; ν_{max} (film) 3550 cm^{-1}; δ_H 1.50[3H, d, *J* 6, CH(OH)C*H*$_3$], 3.45 (2H, dt, *J* 6 and 2, C*H*$_2$CH=CH$_2$), 3.76 and 3.86 (each 3H, each s, 2 x OCH$_3$), 4.90 (1H, dm *J* 18, *trans*-CH$_2$CH=C*H*$_2$), 4.96 (1H, dm *J* 9, *cis*-CH$_2$-CH=C*H*$_2$), 5.68-6.20 (1H, m, CH$_2$C*H*=CH$_2$) and 6.77 (2H, s, 5- and 6-H) (Found: C, 70.5; H, 8.3%; M^+, 222. Calc. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1%; *M*, 222).

trans-3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-1H-benzo-[c]pyran (**45**)

Potassium *tert*-butoxide (950 mg, 8.5 mmol) was added at once to a stirred solution of the alcohol (**44**) (500 mg, 2.25 mmol) in dry dimethylformamide (10 cm^3) under a nitrogen atmosphere. The reaction mixture was heated to 60°C (oil bath) for 2 h, after which it was cooled and diluted with water (100 cm^3) and extracted with ether (5

x 40 cm^3). The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to afford the *pyran* (**45**) (455 m, 91%) as an oil; ν_{max} (film) 1590 cm^{-1}; δ_H 1.33 (3H, d, *J* 6, 3-CH_3), 1.50 (3H, d, *J* 7, 1-CH_3), 2.27 (1H, dd, *J* 18 and 10, *pseudo*-axial 4-H), 2.78 (1H, dd *J* 18 and 3.5, *pseudo*-equatorial 4-H), 3.73 (6H, s, 2 x OCH_3), 3.80-4.25 (1H, m, 3-H), 5.10 (1H, q, *J* 7, 1-H) and 6.59 (2H, s, 6- and 7-H) (Found: C, 70.5; H, 8.0%; M^+, 222. Calc. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1%, *M*, 222).

(E)-2-*Acetyl*-1,4-*dimethoxy*-3-*prop*-1′-*enylbenzene* (**46**)

Ketone (**43**) (600 mg, 2.73 mmol) was dissolved in freshly distilled tetrahydrofuran (20 cm^3) and the system was flushed with nitrogen for 5 min. Potassium *tert*-butoxide (1.28 g, 9.2 mmol) was added at once to the flask and stirring was continued for 2 h at 60°C (oil bath). Aqueous ammonium chloride (5 cm^3) was added to quench the reaction, followed by water (100 cm^3). The aqueous phase was extracted with dichloromethane and the residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (15:85) as eluent to yield the *product* (**46**) (590 mg, 98%) as a light yellow oil; ν_{max} (film) 1698 cm^{-1}; δ_H 1.85 (3H, d, *J* 6, 3′-CH_3), 2.4[illegible] (3H, s, $COCH_3$). 3.77 and 3.80 (each 3H, each s, 2 x OCH_3), 6.00 (1H, dd, *J* 16 and 6, 2′-CH), 6.45 (1H, d, *J* 16, 1′-CH) and 6.80 (2H, s, 4- and 5-H) (Found:

C, 71.15; H, 7.2%; M^+, 220. Calc. For $C_{13}H_{16}O_3$: C, 70.9; H, 7.3%; *M*, 220).

(E)-1,4-*Dimethoxy*-2-(1-*hydroxyethyl*)-3-*prop*-1′-*enylbenzene* (**47**)

To a slurry of lithium aluminium hydride (490 mg, 12.9 mmol) in dry ether (10 cm^3) was added a solution of ketone (**46**) (570 mg, 2.59 mmol) in dry ether (20 cm^3) over 3 min, followed by stirring of the reaction mixture for an additional 20 min. The reaction was quenched by the addition of saturated ammonium chloride and then diluted by the addition of dichloromethane (80 cm^3). The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) to afford the *product* (**47**) (560 mg, 97%) as a white crystalline solid, m.p. 83.5-84.5°C (from light petroleum); ν_{max} 3520 cm^{-1}; δ_H 1.55[3H, d, *J* 6.5, CH(OH)CH_3], 1.80 (3H, dd, *J* 6.5 and 2, 3′-CH_3), 3.80 and 3.90 (each 3H, each s, 2 x OCH_3), 4.05 (1H, s, D_2O exchangeable, OH), 5.28[1H, q, *J* 6.5, (C*H*(OH)CH_3], 5.80 (1H, dt, *J* 16 and 6.5, 2′-CH), 6.46 (1H, dd, *J* 16 and 2, 1′-CH) and 6.77 (2H, s, 5- and 6-H) (Found: C, 70.4; H, 8.35%; M^+, 222. Calc. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1%; *M*, 222).

(±)-(1R, 3R, 4R)-3,4-*Dihydro*-5,8-*dimethoxy*-1,3-*dimethyl*-4-*hydroxy*-1H-*benzo*[*c*]*pyran* (**48**) *and the* ±-(4S)-*diastereoisomer* (**49**)

To a solution of alcohol (**47**) (105 mg, 0.47 mmol) in acetonitrile (10 cm^3) and water (5 cm^3) was added a solution of cerium(IV) ammonium nitrate (515 mg, 0.94 mmol) in water (10 cm^3) over 5 min. Stirring was continued for a further 20 min, after which the reaction mixture was extracted with dichloromethane. The residue obtained on work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford a mixture of starting material (**47**) and *pyran* (**49**) (30 mg). Purification was achieved by preparative layer chromatography using ethyl acetate-light petroleum (15:85) as eluent finally to yield *pyran* (**49**) (24 mg, 21%) as an oil; ν_{max} (film) 3480-3100 cm^{-1} (br); δ_H (200 MHz) 1.38 (3H, d, *J* 6.1, 3-CH_3), 1.55 (3H, d, *J* 6.7, 1-CH_3), 3.74 and 3.84 (each 3H, s, OCH_3), 3.96 (2H, m, 3-H and *pseudo*-equatorial 4-OH; the signal becomes and ill-defined quartet *J* 7 upon D_2O exchange), 4.54 (1H, d, *J* 7, *pseudo*-axial 4-H), 5.00 (1H, q, *J* 6.7, 1-H), 6.68 and 6.76 (each 1H, d, *J* 8.8, 6- and 7-H) (Found: M^+, 238.1180. Calc. for $C_{13}H_{18}O_4$: *M*, 238.1205). Further elution with ethyl acetate-light petroleum (3:7) yielded *pyran* (**48**) (78 mg, 70%) as white crystals, m.p. 113-115°C (from light petroleum); ν_{max} 3480 cm^{-1} (sharp); δ_H (200 MHz) 1.40 (3H, d, *J* 6.5, 3-CH_3), 1.49 (3H, d, *J* 6.7, 1-CH_3), 2.05 (1H, d, *J* 7.4, D_2O exchangeable, *pseudo*-axial 4-OH), 3.78 and 3.85

(each 3H, s, OCH_3), 4.08(1H, dq, *J* 2 and 6.5, 3-H), 4.54(1H, dd, *J* 7.4 and 2, *pseudo*-equatorial 4-H), 5.10 (1H, q, *J* 6.7, 1-H) and 6.74 (2H, s, 6- and 7-H) (Found: C, 65.3; H, 7.4%; M^+, 238.1184. Calc. for $C_{13}H_{18}O_4$: C, 65.55; H, 7.6%; *M*, 238.1205).

trans-5,8-*Dimethoxy*-1,3-*dimethyl*-4-*oxo*-1H-*benzo*[*c*]*pyran* (**50**)

To a solution of pyran (**48**) (426 mg, 1.79 mmol) in dry dichloromethane (20 cm^3) under an atmosphere of nitrogen was added pyridinium dichromate (10.1 g, 26.9 mmol) and the reaction mixture was stirred for 12 h. After filtration the solvent was removed from the filtrate to leave a residue that was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *ketone* (**50**) (126 mg, 30%) as a white solid, m.p. 82-84°C (from light petroleum); ν_{max} 1690 cm^{-1}; δ_H (200 MHz) 1.39 (3H, d, *J* 6.6, 3-CH_3), 1.48 (3H, d, *J* 6.7, 1-CH_3), 3.75 and 3.81 (each 3H, s, OCH_3), 4.46 (1H, q, *J* 6.6, 3-H), 5.24 (1H, q, *J* 6.7, 1-H), 6.78 (1H, d, *J* 9.1, 6-H) and 6.97 (1H, d, *J* 9.1, 7-H) (Found: C, 66.0; H, 6.5%; M^+, 236.1015. Calc. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8%; *M*, 236.1048). Further elution afforded the starting material (**48**) (250 mg, 59%).

3-Acetyl-1,4,5-trimethoxy-2-(prop-2'-enyl)naphthalene (**61**)[5]

Allyl ether (**85**) (0.52 g; 1.8 mmol) was immersed in an oil bath at 220°C under a nitrogen atmosphere for 35 min., cooled and the residue dissolved in dry acetone (50 cm^3) and then treated with potassium carbonate (2.01 g; 14.6 mmol) and iodomethane (2.10 g; 14.5 mmol). The resulting mixture was stirred under vigorous reflux under a nitrogen atmosphere for 1.5 hr and then cooled and filtered. The residue remaining after the solvent was evaporated was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *allylnaphthalene* (**61**) (0.51 g; 94%) as yellow crystals m.p. 54-55°C (from light petroleum). ν_{max} 1690 and 1620 cm^{-1}; δ_H 2.60 (3H, s, $COCH_3$, 3.56 (2H, dd, *J* 6 and 1, $CH_2CH{=}CH_2$), 3.78, 3.87 and 4.00 (each 3H, s, OCH_3), 4.75-5.20 (2H, m, $CH_2CH{=}CH_2$), 5.60-6.26 (1H, m, $CH_2CH{=}CH_2$), 6.89 (1H, dd, *J* 8 and 2, 6-H), 7.44 (1H, t, *J* 8, 7-H), and 7.70 (1H, dd, *J* 8 and 2, 8-H) (Found: C, 72.0; H, 6.6%, M^+ 300. Calc. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7%, M, 300).

3-(1′-*Hydroxyethyl*)-1,4,5-*trimethoxy*-2-(*prop*-2′-*enyl*)*naphthalene* (**62**)[5]

To a slurry of lithium aluminium hydride (1.27 g; 33.4 mmol) in dry ether (80 cm^3) was added dropwise a solution of ketone (**61**) (1 g; 33 mmol) dissolved in dry ether (10 cm^3). The resulting mixture was stirred an additional 30 min and quenched by the addition of saturated aqueous ammonium chloride. After drying the resulting mixture by adding magnesium sulphate, the residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to obtain the *alcohol* (**62**) (950 mg; 95%) as white crystals m.p. 81-82°C (from light petroleum); ν_{max} 3470 and 1620 cm^{-1}; δ_H 1.62 [3H, d, *J* 6, CH(OH)C*H*$_3$], 3.50-3.80 (2H, m, C*H*$_2$CH=CH$_2$), 3.84, 3.90 and 3.99 (each 3H, s, OC*H*$_3$), 4.15 [1H, s, CH(O*H*)CH, D_2O exchangeable], 4.78 [1H, q, *J* 6, C*H*(OH)CH$_3$], 4.95-5.25 (2H, m, CH$_2$-CH=C*H*$_2$), 5.74-6.40 (1H, m, CH$_2$C*H*=CH$_2$), 6.88 (1H, d, *J* 8, 6-H), 7.38 (1H, t, *J* 8, 7-H), and 7.70 (1H, d, *J* 8, 8-H) (Found: C, 71.75; H, 7.4%, M^+, 302. Calc. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3%, M, 302).

trans 3-(1′-*Hydroxyethyl*)-1,4,5-*trimethoxy*-2-(*prop*-1′-*enyl*)*naphthalene* (**62a**)

Alcohol (**62**) (760 mg; 2.52 mmol) was dissolved in dicholoromethane (40 cm^3) and then treated with palladium dichloride bisacetonitrile (30 mg; 0.11 mmol) and the resulting mixture was stirred at 25°C for 18 h. The residue obtained after filtration was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to give the conjugated *olefin* (**62a**) (760 mg; 100%) as an oil, Lit. [5], an oil; ν_{max} 3450, 1608 and 1568 cm^{-1}; δ_H 1.65 [3H, d, *J* 7, CH(OH)C*H*$_3$], 1.98 (3H, dd, *J* 7 and 2, CH=CH-C*H*$_3$), 3.60 (1H, br, s, D_2O exchangeable, OH), 3.76, 3.90 and 4.00 (each 3H, s, OC*H*$_3$), 5.25 [1H, m, C*H*(OH)CH$_3$], 6.05 (1H, dq, *J* 16 and 7, CH=C*H*CH$_3$) 6.56 (1H, dq, *J* 16 and 2, C*H*=CHCH$_3$), 6.85 (1H, d, *J* 8, 6-H), 7.38 (1H, t, *J* 8 7-H), and 7.75 (1H, d, *J* 8, 8-H).

(±)-*trans*-3,4-*Dihydro*-5,9,10-*trimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (**63**)[5]

Alcohol (**62**) (490 mg; 1.62 mmol) was dissolved in dry dimethylformamide (10 cm^3) and dry nitrogen was passed through the solution for 5 min. Resublimed potassium *tert*-butoxide (730 mg; 6.52 mmol) was added in one batch and the orange solution was stirred at 60°C (oil bath) for 10 min. and then quenched by the addition of dilute

hydrochloric acid. To the cooled solution water (100 cm^3) was added and the resulting mixture was exhaustively extracted with ether. The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to yield the *pyran* (**63**) (431 mg; 88%) as yellow crystals, m.p. 91-92°C (from light petroleum). δ_H 1.38 (3H, d, *J* 6, 3-CH_3), 1.62 (3H, d, *J* 6.5, 1-CH_3), 2.55 (1H, dd, *J* 17 and 11, 4-H *pseudo*-axial), 3.06 (1H, dd, *J* 17 and 3.5, 4-H *pseudo*-equatorial), 3.76, 3.80, and 3.94 (each 3H, s, OCH_3), 4.23 (1H, m, 3-H), 5.32 (1H, q, *J* 6.5, 1-H), 6.82 (1H, d, *J* 8 H, 8-H), 7.30 (1H, t, *J* 8, 7-H), and 7.70 (1H, d, *J* 8, 6-H).

1,4-*Ethano*-1,4-*dihydro*-8-*hydroxy*-1,5-*dimethoxynaphthalene* (**68**)

A solution of the diene (**64**) (1.42 g; 13 mmol) and 1,4-benzoquinone (**65**) (0.982 g, 9 mmol) in dry benzene (20 cm^3) was heated under reflux in a nitrogen atmosphere until t.l.c. showed no more traces of 1,4-benzoquinone (*circa* 2 h). The solvent was evaporated under reduced pressure to give a residue to which was added dry acetone (20 cm^3), potassium carbonate (10,0 g) and iodomethane (2.84 g; 20 mmol). The mixture was vigorously stirred under reflux in a nitrogen atmosphere for 20 h, cooled and filtered. The residue obtained by evaporation of the solvent was chromatographed using ethyl acetate-light petroleum (1:9) as eluent to afford *compound* (**68**) (1.44 g, 68%) m.p. 90-91°C

(dichloromethane - light petroleum); ν_{max} 3300 cm^{-1}, δ_H 1.4-1.9 (4H, m, 2 x $-CH_3$), 3.7 and 3.8 (3H each, s, 2 x $-OCH_3$), 4.2-4.5 (1H, m, 4-H), 6.4-6.8 (4H, m, 2-, 3-, 6- and 7-H), 8.7 (1H, s, 8-OH, D_2O exchangeable) (Found: C, 72.6; H, 6.9%; $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%).

5-Allyloxy-1,4-ethano-1,4-dihydro-8-hydroxy-1-methoxynaphthalene (**69**)

Treatment of the residue obtained using similar quantities as for (**68**) above in dry acetone (20 cm^3) with potassium carbonate (10.0 g) and allyl bromide (1.32 g; 11 mmol) under reflux in a nitrogen atmosphere for 7 h afforded, after chromatographic purification using ethyl acetate-light petroleum (1:9) as eluent, *product* (**69**) (1.97 g, 84%), m.p. 80-81°C (dichloromethane-light petroleum); ν_{max} 3300 cm^{-1}; δ_H 1.4-1.9 (4H, m, 2 x $-CH_2$), 3.7 (3H, s, OCH_3), 4.2-4.6 (3H, m, 4-H and allyl-CH_2), 5.1-5.6 (2H, m, $=CH_2$), 5.6-6.2 (1H, m, allyl-CH), 6.3-6.8 (4H, m, 2-, 3-, 6- and 7-H), 8.7 (1H, s, 8-OH, D_2O exchangeable) (Found: C, 74.3; H, 6.9%; $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%).

5,8-Diacetoxy-1,4-ethano-1,4-dihydro-1-methoxynaphthalene (**71**)

A solution of 1-methoxycyclohexa-1,3-diene (**64**) (7.69 g; 45 mmol) and 1,4-benzoquinone (4.42 g; 40 mmol) in dry benzene (50 cm^3) was

heated under reflux in a nitrogen atmosphere (4 h). The solvent was evaporated to give an oily residue to which was added dry acetone (100 cm^3) and potassium carbonate (12 g). The mixture was vigorously stirred under reflux in a nitrogen atmosphere for 2 h, cooled, filtered and the solvent evaporated under reduced pressure. Acetic anhydride (18 g) and pyridine (14 g) were added and the solution was refluxed (3 h) in a nitrogen atmosphere after which it was poured into water. The solid was filtered off and chromatographed using ethyl acetate-light petroleum (3:7) as eluent to afford *compound* (**71**) (8.5 g, 70%) m.p. 147-148°C (light petroleum) ν_{max} 1750 cm^{-1}; δ_H 1.4-1.8 (4H, m, 2 x CH_2), 2.24 and 2.33 (3H, each s, 2 x CH_3), 3.55 (3H, s, OCH_3), 3.75-3.95 (1H, m , 4-H), 6.25-6.56 (2H, m, 2- and 3-H), 6.65 and 6.85 (1H each, 2 x d, *J* 8 each, 6- and 7-H) (Found: C, 67.5; H, 6.1%; $C_{17}H_{18}O_5$ requires C, 67.55; H, 5.96%)

1,4-*Diacetoxy*-5-*methoxynaphthalene* (**72**)

Compound (**71**) (1.76 g) was heated in a nitrogen atmosphere (oil bath 210°C) for 40 min. Chromatographic purification of the residue using ethyl acetate-light petroleum (3:7) as eluent afforded *compound* (**72**) (1.44 g, 90%) m.p. 122-123°C (light petroleum) ν_{max} 1760 cm^{-1}; δ_H 2.33 and 2.41 (3H each, s, 2 x CH_3), 3.83 (3H, s, OCH_3), 6.8-7.5 (5H,

m, 2-, 3-, 6-, 7- and 8-H (Found: C, 65.9; H, 5.3%; $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%).

1-*Acetoxy*-3-*acetyl*-5-*methoxy*-4-*napththol* (**73**)

Compound (**72**) (5.21 g) and boron trifluoride (20 cm^3) were stirred together for 45 min at 60°C (oil bath temperature) in a nitrogen atmosphere. The reaction mixture was thrown onto ice (50 cm^3) and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the solvent evaporated. Acetic anhydride (2.0 g), pyridine (1,6 g), dry chloroform (50 cm^3) and zinc dust (4 g) were added. The solution was gently boiled under nitrogen for 1 h, cooled, poured into water (50 cm^3) and extracted with dichloromethane. The organic phase was briefly shaken with water (40 cm^3) containing concentrated hydrochloric acid (3 cm^3), separated, washed with water (2 x 30 cm^3) and dried ($MgSO_4$). Evaporation of the solvent and chromatography using ethyl acetate-light petroleum (3:7) afforded *naphthol* (**73**) (69%), identical to the material obtained *via* and alternative route[4(b)].

4-Acetoxy-1-allyloxy-5,8-ethano-5,8-dihydro-5-methoxynaphthalene (**75**)

Naphthol (**69**) (3 g; 11.6 mmol) was dissolved in a mixture of acetic anhydride (60 cm^3) and pyridine (30 cm^3) and the resulting solution was stirred for 12 h after which it was poured onto ice/water to precipitate the *acetate* (**75**) (3.4 g; 97%) as white needles m.p. 96-96.5°C (from light petroleum); ν_{max} 1769 cm^{-1}; δ_H 1.60 (4H, m, 5-8-CH_2CH_2), 2.30 (3H, s, $COCH_3$), 3.58 (3H, s, OCH_3), 4.43 (1H, m, 8-H), 4.50 (2H, dt, *J* 6 and 2, CH_2CH=CH_2), 5.20 (1H, dt, *J* 9 and 2, *cis*-CH_2CH=CH_2), 5.37 (1H, dt, *J* 17 and 2, *trans*-CH_2CH=CH_2), 5.80-6.35 (1H, m, -CH_2C*H*=CH_2), 6.40 (1H, d, *J* 8, 2-H), 6.60 (1H, d, *J* 8, 3-H obscured by 6- and 7-H peaks), and 6.62 (2H, s, 6- and 7-H). (Found: C, 72.2; H, 6.7%; M^+, 300. Calc. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7%; M, 300).

4-Acetoxy-1-allyloxy-5-methoxynaphthalene (**77**) *and 4-acetoxy-2-allyl-1-hydroxy-5-methoxynaphthalene* (**78**)

Acetate (**75**) (3 g; 10 mmol) was pyrolysed in a nitrogen atmosphere at 220°C (oil bath) for 50 min. after which the dark tarry material was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *acetate* (**77**) (136 mg; 5%) as small light yellow needles m.p.

133-134°C (from ethyl acetate-light petroleum); ν_{max} 1753 cm^{-1}; δ_H (200 MHz) 2.25 (3H, s, $COCH_3$), 3.80 (3H,s, OCH_3), 4.58 (2H, dt, *J* 5.1 and 1.5, -CH_2CH=CH_2), 5.22 (1H, ddd, *J* 10.5, 2.9 and 1.5, *cis*-CH_2CH-CH_2), 5.40 (1H, ddd, *J* 17.3, 3.2 and 1.5, *trans*-CH_2CH=CH_2), 6.05 (1H, ddt, *J* 17.3, 10.5 and 5.1, -CH_2CH-CH_2), 6.66 (1H, d, *J* 8.3, 3-H), 6.79 (1H, d, *J* 7.8, 6-H), 6.86 (1H, d, *J* 8.3, 2-H), 7.28 (1H, t, *J* 7.8, 7-H), and 7.85 (1H, d, *J* 7.8, 8-H) (Found: C, 70.8; H, 6.0%; M^+, 272. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%; M, 272). Further elution afforded the *naphthol* (**78**) (2.45 g; 90%) as green plates m.p. 133-134°C (from ethyl acetate-light petroleum); ν_{max} 3380 and 1710 cm^{-1}; δ_H (200 MHz) 2.26 (3H, s, $COCH_3$), 3.20 (2H, dt, *J* 6.3 and 1.5, -CH_2CH=CH_2), 3.79 (3H, s, OCH_3), 5.03 (2H, dm, *J* 14 and 2, -CH_2CH=CH_2), 5.70 (1H, s, D_2O exchangeable, 1-OH), 5.84 (1H, ddt, *J* 17.5, 9.6 and 6.4, -CH_2CH=CH_2), 6.68 (1H, s, 3-H), 6.69 (1H, d, *J* 7.3, 6-H), 7.19 (1H, t *J* 7.3, 7-H), and 7.58 (1H, d, *J* 7.3, 8-H) (Found: C; 70.9; H, 6.1%; M^+, 272. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%; M, 272).

2-Allyl-4-hydroxy-1,5-dimethoxynaphthalene (**79**)

Naphthol (**69**) (1.09 g; 4.2 mmol) was pyrolysed in a nitrogen atmosphere at 200°C (oil bath) for 1 h. Acetone (30 cm^3) was added to dissolve the tarry product and potassium carbonate (4 g; 29 mmol) and

iodomethane (1.5 g; 10.6 mmol) were added and the mixture was then vigorously stirred and heated under reflux in a nitrogen atmosphere for 20 h. The cooled mixture was filtered and removal of solvent from the filtrate under reduced pressure, gave a residue which was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to yield the *product* (**79**) (710 mg; 69%) as a red oil; ν_{max} 3300 cm^{-1}; δ_H 3.50 (2H, dt, *J* 6 and 2, -C*H*$_2$CH=CH$_2$), 3.80 and 4.00 (each 3H, s, OCH_3), 4.90-5.20 (2H, m, -CH_2CH=C*H*$_2$), 5.70-6.20 (1H, m, -CH_2CH=CH_2), 6.67 (1H, s, 3-H), 6.70 (1H, d, *J* 8, 6-H), 7.27 (1H, t, *J* 8, 7-H), 7.61(1H, d, *J* 8, 8-H), and 9.00 (1H, s, D_2O exchangeable, 4-OH) (Found: C, 73.4; H, 6.8%; M^+, 244. Calc. for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6%; M, 244).

4-Acetoxy-2-allyl-1,5-dimethoxynaphthalene (**80**)

Method A

Naphthol (**79**) (1.26 g; 5.2 mmol) was dissolved in acetic anhydride (22 cm^3) containing anhydrous pyridine (1 cm^3) and stirred for 12 h. The resulting reaction mixture was thrown onto ice (150 g) and the aqueous mixture was extracted with dichloromethane (4 x 50 cm^3) and the organic phase was washed with 0.5 M hydrochloric acid (2 x 60 cm^3), saturated sodium hydrogen carbonate (2 x 60 cm^3), and water (100

cm^3). The residue obtained upon work-up was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *acetate* (**80**) (0.86 g; 58%) as white needles m.p. 71-72°C (from light petroleum); ν_{max} 1750 cm^{-1}; δ_H (200 MHz) 2.33 (3H, s, $COCH_3$), 3.55 (2H, dt, *J* 6.4 and 1.4, -CH_2CH=CH_2), 3.86 and 3.89 (each 3H, s, OCH_3), 5.10 (1H, dt, *J* 11.7 and 1.4, *cis*-$CH_2CH{=}CH_2$), 5.12 (1H, dt, *J* 15.4 and 1.4, *trans*-$CH_2CH{=}CH_2$, 5.95 (1H, ddt, *J* 15.4, 11.7 and 6.4, $CH_2CH{=}CH_2$), 6.80 (1H, d, *J* 7.6, 6-H), 6.90 (1H, s, 3-H), 7.39 (1H, t, *J* 7.6, 7-H), and 7.69 (1H, d, *J* 7.6, 8-H) (Found: C, 71.5; H, 6.5%; M^+, 286. Calc. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3%; M, 286).

Method B

A mixture of the naphthol (**78**) (1.66 g; 6.1 mmol) in dry acetone (50 cm^3) containing potassium carbonate (8 g; 58 mmol) and iodomethane (2.5 g; 17.6 mmol) was vigorously stirred and heated under reflux for 20 h. The cooled mixture was filtered and the filtrate was stripped of solvent under reduced pressure to leave a residue which was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford *acetate* (**80**) (1.45 g; 83%) as white rods m.p. 71-72°C (from light petroleum), identical in all respects to material synthesised *via* an alternative route (see Method A).

3-*Acetyl*-2′,3′-*dihydro*-4-*hydroxy*-5-*methoxy*-2′-*methylnaphtho* [1,2-*b*] *furan* (**82**)

Acetate (**80**) (670 mg, 2.34 mmol) was added to freshly distilled boron trifluoride etherate and the resulting solution was stirred and heated under a nitrogen atmosphere at 60°C (oil bath) for 30 min. during which time the solution changed colour from clear to dark brown. The cooled solution was poured onto crushed ice (100 g) and the resulting mixture was extracted with dichloromethane (4 x 40 cm^3). The residue obtained on work-up was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to yield the *furan* (**82**) (150 mg; 22%) as an unstable reddish oil; ν_{max} (film) 3500 and 1695 cm^{-1}; δ_H 1.23 (3H, d, *J* 6, 2′-CH_3), 1.96 (3H, s, $COCH_3$), 2.60-3.0 (2H, m, 3′-H), 3.95 (3H, s, OCH_3), 5.20 (1H, m, 2′-H), 6.70 (1H, d, *J* 8, 6-H), 7.27 (1H, t, *J* 8, 7-H), 7.60 (1H, d, *J* 8, 8-H), and 9.00 (1H, s, D_2O exchangeable, 4-OH) (Found: M^+, 272.10496. Calc. for $C_{16}H_{16}O_4$: M, 272.10485).

1-Acetoxy-3-acetyl-4,5-dimethoxynaphthalene (**83**)

Naphthol (**73**) (0.77 g; 2.8 mmol) in dry acetone (50 cm^3) was treated with potassium carbonate (2.0 g; 14.5 mmol) and iodomethane (3.9 g; 26.9 mmol) and the mixture was vigorously stirred under reflux for 5 h. The cooled reaction mixture was filtered and the solvent removed under reduced pressure to leave a residue that was chromatographed using ethyl acetate-light petroleum (1:4) as eluent to afford the *acetate* (**83**) (0.78 g; 97%) as white crystals, m..p. 105-106°C (from light petroleum); ν_{max} 1765 and 1670 cm^{-1}; δ_H 2.40 (3H, s, OCOCH_3), 2.77 (3H, s, COCH_3), 3.90 and 4.03 (each 3H, s, OCH_3), 6.95 (1H, dd, *J* 6 and 2, 6-H), and 7.35-7.60 (3H, m , 2-, 7- and 8-H) (Found: C, 66.5; H, 5.45%, M^+ 288. Calc. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.55%, M, 288).

3-Acetyl-1-allyloxy-4,5-dimethoxynaphthalene (**85**)

Acetate (**83**) (1 g; 3.5 mmol) was dissolved in methanolic potassium hydroxide (0.25% m/v, 30 cm^3) and stirred for 10 min at 25°C. The reaction mixture was quenched with water (200 cm^3), acidified to pH 6 with dilute hydrochloric acid and extracted with dichloromethane. The residue obtained upon work-up [comprising the phenol (**84**)] was dissolved in dry acetone (50 cm^3) and treated with allyl bromide (1.27

g; 10.6 mmol) and potassium carbonate (1.44 g; 10.4 mmol) and then vigorously stirred and heated under reflux under nitrogen for 3 h. The cooled solution was evaporated and stripped of solvent and the residue was chromatographed using ethyl acetate-light petroleum (15:85) as eluent to afford the *ether* (**85**) (0.91 g; 91%) as yellow crystals, m.p. 69-70°C (from light petroleum); ν_{max} 1670 cm^{-1}; δ_H 2.80 (3H, s, ArCOCH_3), 3.87 and 4.07 (each 3H, s, OCH_3), 4.72 (2H, dt, *J* 6 and 2, CH_2CH=CH_2), 5.18-5.76 (2H, m, CH_2CH=CH_2), 5.82-6.55 (1H, m, CH_2C*H*=CH_2), 6.90 (1H, dd, *J* 7 and 2, 6-H), 7.10 (1H, s, 2-H), 7.50 (1H, t, *J* 7, 7-H), and 7.97 (1H, dd, *J* 7 and 2, 8-H) (Found: C, 71.2; H, 6.1%, M^+ 286. Calc. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3%, M, 286).

(±)(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-5,9,10-*trimethoxy*-1,3-*dimethyl*-1H-*naphtho* [2,3-*c*]*pyran* (**86**) and the 4R-epimer (**86a**)

Method A

Pyran (**63**) (990 mg; 3.28 mmol) was dissolved in dry dimethylformamide (50 cm^3) and a slow stream of dry oxygen was bubbled through the solution. Resublimed potassium *tert*-butoxide (1.84 g; 16.4 mmol) was added all at once and stirring under oxygen was continued for 15 min. after which a further amount of potassium

tert-butoxide (740 mg; 6.61 mmol) was added and stirring under oxygen was continued for a further 45 min. after which the reaction was quenched by the addition of water (20 cm^3). The resulting solution was extracted with ether and chromatographed using ethyl acetate-light petroleum (3:7) as eluent to give *hydroxypyran* (**86**) (863 mg; 80%) as an oil. Lit.[5], oil; ν_{max} 3410 cm^{-1}; δ_H 1.43 (3H, d, *J* 6.5, 3-CH_3), 1.70 (3H, d, *J* 7, 1-CH_3), 2.20 (1H, d, *J* 7, D_2O exchangeable, 4-OH), 3.80, 3.94 and 3.97 (each 3H, s, OCH_3), 3.97 (1H, dq, *J* 8.5 and 7, 3-H), 4.76 (1H, d, 8.5, 4-H), 5.26 (1H, q, *J* 7, 1-H), 6.88 (1H, d, *J* 8, 8-H), 7.40 (1H, t, *J* 8, 7-H), and 7.64 (1H, d, *J* 8, 6-H). Further elution afforded the epimeric alcohol (**86a**) (215 mg; 20%) as yellow crystals, m.p. 170-172°C, Lit.[5] m.p. 170-173°C.

Method B

Alcohol (**62a**) (302 mg; 1 mmol) was dissolved in acetonitrile (30 cm^3 and water (15 cm^3) was added and the resulting mixture was treated dropwise with an aqueous solution of cerium(IV) ammonium nitrate (1.1 g; 2 mmol) in water (20 cm^3) over 5 min. After stirring for a further 20 min., the reaction was quenched by the addition of water (80 cm^3) and the products were extracted with dichloromethane. The residue obtained upon work-up was chromatographed and eluted with ethyl acetate-light petroleum) (3:7) to afford the 4-hydroxypyran (**86**)

(105 mg; 35%) followed by the epimeric alcohol (**86a**) (175 mg; 58%) identical to the compounds prepared *via* the previous route.

(±)(1R,3R)-5,9,10-*Trimethoxy*-1,3-*dimethyl*-4-*oxo*-(1H,3H)*naphtho*[2,3-*c*]*pyran* (**87**)

A mixture of epimers (**86**) and (**86a**) (640 mg; 2 mmol) dissolved in dichloromethane (50 cm^3) was added to pyridinium dichromate (3.0 g; 8 mmol) dispersed on alumina (12 g) and the resulting slurry was stirred at 25°C for 4 h after which it was filtered and the residue obtained was chromatographed using ethyl acetate-light petroleum (3:7) as eluent to yield the ketone (**87**) (570 mg; 90%) as bright yellow crystals, m.p. 80-81°C (from light petroleum); ν_{max} 1695 cm^{-1}, δ_H 1.52 (3H, d, *J* 7, 3-CH_3), 1.69 (3H, d, *J* 7, 1-CH_3), 3.84, 3.92 and 3.98 (each 3H, s, OCH_3), 4.61 (1H, q, *J* 7, 3-H), 5.51 (1H, q, *J* 7, 1-H), 6.95 (1H, d, *J* 7, 8-H), 7.39 (1H, t, *J* 7, 7-H) and 7.93 (1H, d, *J* 7, 6-H) (Found: C, 68.2; H, 6.9%, M^+, 316.1303. Calc. for $C_{18}H_{20}O_5$: C, 68.3; H, 7.0%, M, 316.1311).

(±)-*trans*-3,4-*Dihydro*-9-*hydroxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (**90**) *and* (±)-*cis*-3,4-*dihydro*-9-*hydroxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran*-5,10-*quinone* (**91**)

From compound 4:

To isoeleutherin (**4**) (50 mg, 0.18 mmol) in dichloromethane (10 cm^3) was added aluminium chloride (0.59 g, 4.5 mmol) and the mixture was stirred for 60 min at room temperature. Water (20 cm^3) was added and the mixture extracted with chloroform. The organic phase was washed with water and dried ($MgSO_4$). The residue obtained upon work-up was subjected to p.l.c. [mobile phase, ethyl acetate-light petroleum (3:7)] to afford the *products* (**90**) and (**91**) with identical R_f, (46 mg, 100%) in a ratio of 3:2 (established by ^1H nmr integration) The ^1H nmr spectrum of this *mixture* showed the following signals: δ_H 1.2-1.85 (overlapping doublets due to the four C-1 and C-3 methyls), 2.14-2.36 (overlapping ddd, 2 x *pseudo*-axial 4-H), 2.69-2.85 (overlapping dt and dd, 2 x *pseudo*-equatorial 4H), 3.5-3.7 [m, 3-H of (**91**)], 3.9-4.1 [m, 3-H of (**90**)], 4.75-4.90 [m, 1-H of (**91**)], 4.92-5.1 (dq, *J* 1.5 and 6.8, 1-H of (**90**)], 7.15-7.3 and 7.55-7.65 [6-,7- and 8-H of (**90**) and (**91**)], 12.0 and 12.02 [s, 9-OH of (**90**) and (**91**), D_2O-exchangeable].

Isoeleutherin (**4**) (40 mg, 0.15 mmol) in dichloromethane (10 cm^3) was treated with aluminium chloride (99 mg, 0.75 mmol) at 0°C for 60 min.

Work-up and p.l.c. as above afforded *compound* (**90**) (38 mg, 100%), m.p. 159-161°C (from light petroleum); ν_{max} 1640 an 1620 cm^{-1}; δ_H (200 MHz) 1.25 (3H, d, *J* 6.1, 3-Me), 1.47 (3H, d, *J* 6.6, 1-Me), 2.22 (1H, ddd, *J* 19.5, 10.2 and 1.9, *pseudo*-axial 4-H), 2.75 (1H, dd, *J* 19.3 and 3.2, *pseudo*-equatorial 4-H), 3.9-4.1 (1H, m, 3-H), 5.1 (1H, dq, *J* 6.8 and 1.5, 1-H) 7.15-7.3 and 7.55-7.65 (3H, m, 6-, 7- and 8-H) and 12.02 (s, OH, D_2O-exchangeable 9-OH) (Found: C, 69.6; H, 5.3%. Calc. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.4%).

From compound (**63**)

Pyran (**63**) (200 mg, 0.66 mmol) in dichloromethane (10 cm^3) was treated with aluminium chloride (2.18 g, 16.5 mmol) at room temperature for 20 hours. Work-up and p.l.c. as above afforded a mixture of the *products* (**90**) and (**91**) (36 mg, 21%) in a ratio of 1:1 (established by ^1H nmr integration).

(±)-*Isoeleutherin* (**4**), (±)-*trans*-3,4-*dihydro*-10-*hydroxy*-5,9-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-*c*]*pyran* (**92**) *and its* (±)-*cis-isomer* (**93**)

Treatment of pyran (**63**) (150 mg, 0.497 mmol) with aluminium chloride (328 mg, 2.5 mmol) in dichloromethane (10 cm^3) afforded after work-up and p.l.c. [mobile phase, ethyl acetate-light petroleum (1:9)] *compounds* (in decreasing order of R_f values) (**92**) (40 mg, 28%),

(**93**) (20 mg, 14%) as brown oils, and (**4**) (19 mg, 14%), m.p. 152-153°C (from methanol) (Lit.[8], 154-155°C).

For (**92**):

ν_{max} 3300-3400 cm^{-1}; δ_H (200 MHz) 1.37 (3H, d, *J* 6.1, 3-Me), 1.59 (3H, d, *J* 6.6, 1-Me), 2.55 (1H, dd, *J* 19 and 11, *pseudo*-axial 4-H), 3.05 (1H, dd, *J* 19 and 3, *pseudo*-equatorial 4-H), 3.78 and 4.03 (3H each, 2 x s, 5- and 9-OCH_3) 4.05-4.2 (1H, m, 3-H), 5.3 (1H, q, *J* 6.5, 1-H) 6.72 (1H, d, *J* 7.8, 8-H), 7.28 (1H, t, *J* 7.8, 7-H), 7.65 (1H, d, *J* 7.8, 6-H) and 9.38 (1H, s, OH, D_2O-exchangeable) (Found: C, 70.65; H, 6.7%. Calc, for $C_{17}H_{20}O_4$: C, 70.83; H, 6.9%).

For (**93**):

ν_{max} 3300-3400 cm^{-1}; δ_H (200 MHz) 1.49 (3H, d, *J* 6.15, 3-Me), 1.65 (3H, d, *J* 6.13, 1-Me), 2.55 (1H, dd, *J* 16.4 and 11, *pseudo*-axial 4-H), 3.04 (1H, dd, *J* 16.4 and 2, *pseudo*-equatorial 4-H), 3.6-3.73 (1H, m, 3-H), 3.82 and 4.04 (3H each, 2 x s, 5- and 9-OCH_3), 5.18 (1H, q, *J* 6.35, 1-H), 6.72 (1H, d, *J* 8, 8-H), 7.28 (1H, t, *J* 7.8, 7-H), 7.65 (1H, d, *J* 8, 6-H) and 9.45 (1H, s, OH, D_2O-exchangeable) (Found: C, 70.7; H, 6.65%. Calc. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.9%).

(±)-*Eleutherin* (**94**) *and* (±)-*Isoeleutherin* (**4**)

The *cis*-pyran (**93**) (32 mg, 0.11 mmol) was oxidised with CAN (2.1 molar equivalents) in the usual manner to afford *compound* (**94**) (22 mg, 73%) m.p. 155°C (from ethanol) (Lit.[8] 155-156°C). The ^{1}H nmr spectrum of (**94**) agreed entirely with that reported.[8]

Similarly, the *trans*-pyran (**92**) (25 mg, 0.09 mmol) afforded *compound* (**4**) (17 mg, 70%) upon oxidation with 2.2 molar equivalents of CAN. Its ^{1}H nmr spectrum and m.p. corresponded entirely with that reported earlier.[8.,57b]

(±)-*cis*-3,4-*Dihydro*-5,8-*dimethoxy*-1,3-*dimethyl*-1H-*benzo*[*c*]*pyran* (**95**)

The *trans*-pyran (**45**) (80 mg, 0.36 mmol) in dichloromethane (10 cm^3) was treated with aluminium chloride (238 mg, 1.8 mmol) for 60 min at room temperature. Work-up as for (**90**) and p.l.c. [mobile phase ethyl acetate-light petroleum (1:9)] afforded the *cis*-pyran (**95**)[67] (32 mg, 40%) and starting material (**45**) (32 mg).

Similarly compound (**95**) (42 mg, 0.19 mmol) afforded the *trans*-pyran (**45**)[67] (18 mg, 43%) on treatment with 5 molar equivalents of the Lewis acid as above. [18 mg of (**95**) was recovered]. The ^{1}H nmr spectral data for compounds (**45**) and (**95**) agreed entirely with that reported earlier[67]:

(see T. Kometani and E Yoshii, *J. Chem. Soc.*, Perkin Trans. 1, 1981, 1191.)

3-*Trifluoroacetyl*-1,5-*dimethoxy*-4-*naphthol* (**125**)

1,5-Dimethoxy-4-naphthol (**1**) (1.09 g, 5.3 mmol) was dissolved in dry dichloromethane (25 cm^3) and trifluoroacetic anhydride (T.F.A.A.) (10 cm^3) was slowly added. The solution was stirred at room temperature for 40 h. Evaporation of volatiles and chromatography of the residue (eluent 10% ethyl acetate in light petroleum) gave the *product* (**125**)[66] (1.41 g, 88%) m.p. 126-127°C (ethanol) ν_{max} 1632 cm^{-1}; δ_H 3.94, and 4.05 (3H each, s, OCH_3), 6.91 (1H, q, *J* 2, 2-H), 6.97 (1H, d, *J* 9, 6-H), 7.58 (1H, t, *J* 9, 7-H), 7.82 (1H, d, *J* 9, 8-H) and 12.85 (1H, s, OH, D_2O exchangeable). (Found C, 55.8; H, 3.5; $C_{14}H_{11}F_3O_4$ requires C, 56.0, H, 3.65%);

3-(1,1-*Dihydroxy*-2,2,2-*trifluoroethyl*)-5-*methoxy*-1,4-*naphthoquinone* (**126**)

To a stirred solution of naphthol (**125**) (98 mg) in acetonitrile (20 cm^3) and water (15 cm^3), was added CAN (358 mg, 2 mol equivalents) in water (5 cm^3) over 5 min. at room temperature. The solution was stirred for a further 5 min., then poured into water, and the mixture was extracted with dichloromethane. The residue obtained upon work-up

afforded the *product* (**126**)[66] (85 mg, 86%), m.p. 142-143°C (chloroform-light petroleum) which resolidified m.p. 156-157°C. ν_{max} 3250 br and 1645 cm^{-1}; δ_H (acetone-d_6) 4.04 (3H, s, OCH_3), 7.27 (3H, s, two of which exchanged with D_2O leaving 2-H), and 7.5-8.0 (3H, m, Ar-H). (Found: C, 51.6; H, 2.9. $C_{13}H_9F_3O_5$ requires C, 51.7; H, 3.0%)

1-*Acetoxy*-5-*methoxy*-3-*trifluoroacetyl*-4-*naphthol* (**127**)

To a solution of quinone (**126**) (342 mg, 1.13 mmol) in chloroform (50 cm^3), was added zinc dust (4 g), pyridine (179 mg, 2.3 mmol) and acetic anhydride (230 mg, 2.3 mmol). The mixture was refluxed in an inert atmosphere (nitrogen) for 20 minutes and poured into water. This was extracted with dichloromethane and the organic layer was briefly shaken with diluted hydrochloric acid and washed with water. The residue obtained upon work-up was chromatographed [eluent, ethyl acetate-light petroleum (1:5)] to afford the *product* (**127**) (330 mg, 89%) m.p. 112-113°C (from light petroleum) ν_{max} 1760 and 1620 cm^{-1}; δ_H 2.43 (3H, s, CH_3CO), 4.03 (3H, b r s, OCH_3), 6.68-7.05 (1H, d, *J* 8, 6-H) 7.15-7.75 (3H, m, 2-, 7- and 8-H), and 12.53 (1H, s, OH, D_2O exchangeable) (Found: C, 54.85; H, 3.1%; Calc. for $C_{15}H_{11}F_3O_5$: C, 54.9; H, 3.35%).

1-*Acetoxy*-3-*trifluoroacetyl*-4,5-*dimethoxynaphthalene* (**128**)

To naphthol (**127**) (233 mg, 0.71 mmol) in dry acetone (50 cm^3) was added an excess of iodomethane (6 cm^3) and potassium carbonate (500 mg) and the mixture was refluxed with stirring for 5 hours afer which it was cooled and filtered. The residue obtained upon work-up was chromatographed [eluent: ethyl acetate-light petroleum (3:7)] to afford *product* (**128**) (182 mg, 75%) as an oil. ν_{max} 1760 and 1700 cm^{-1}; δ_H 2.45 (3H, s, CH_3CO), 3.90 (3H, s, OCH_3), 4.08 (6H, br s, 2 x OCH_3), 6.78-7.80 (4H, m, 2-, 6-, 7- and 8-H) (Found: M^+, 342.0698; Calc. for $C_{16}H_{13}F_3O_5$: M^+ 342.0715).

3-*trifluoroacetyl*-4,5-*Dimethoxy*-1-(*prop-2'-enyloxy*)*naphthalene* (**130**)

Acetate (**128**) (206 mg, 0.6 mmol) was stirred in a methanolic potassium hydroxide solution [30 cm^3 of a 0.25% (m/v) solution] for 10 min and poured into water. The organic material was extracted with dichloromethane. This was washed with water and dried ($MgSO_4$). The residue obtained upon work-up was dissolved in dry acetone (50 cm^3). To this was added an excess of allyl bromide (436 mg) and potassium carbonate (300 mg). The reaction mixture was then refluxed with stirring under nitrogen for 1.25 h. The residue obtained upon work-up was chromatographed (eluent: ethyl acetate-light petroleum (3:7)] to afford the *product* (**130**) (147 mg, 72%) as yellow crystals,

m.p. 54-55°C (from light petroleum) ν_{max} 1680 cm^{-1}; δ_H 3.83 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.70 (2H, d, *J* 4, CH_2), 5.25-5.60 (2H, m, vinyl CH_2), 5.75-6.85 (1H, m, vinyl CH), 6.82-7.12 (2H, m, 2- and 6-H), 7.40-7.8 (1H, t, *J* 8, 7-H), and 7.8-8.1 (1H, d, *J* 8, 8-H) (Found: C, 59.8; H, 4.2%; Calc. for $C_{17}H_{15}F_3O_4$: C, 60.0; H, 4.4%).

4,5-*Dimethoxy*-1-(*prop*-2'-*enyloxy*)-3-*naphthoic acid* (**131**)

Compound (**130**) (135 mg, 0.4 mmol) in dimethyl sulphoxide (DMSO) (3 cm^3) was added dropwise over a period of 5 min. to a hot (oil bath temperature 60°C) potassium hydroxide-DMSO solution (30 cm^3 of a 5% m/v solution). The solution was stirred for a further 15 min and poured into water (400 cm^3). The mixture was extracted with dichloromethane. The aqueous phase was then acidified and re-extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and the residue obtained upon work-up afforded the *acid* (**131**) (75 mg, 68%) as light-brown crystals m.p. 122-124°C (from light petroleum) ν_{max} 3650-2500 br, 1690 and 1605 cm^{-1}; δ_H (200 MHz) 3.97 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.74 (2H, dt, *J* 5.1 and 1.5, OCH_2), 5.34 (1H, dq, *J* 10.5 and 1.4, 1H of vinyl CH_2), 5.56 (1H, dq, *J* 17.3 and 1.4, 1H of vinyl CH_2), 6.05-6.25 (1H, m, vinyl CH), 7.01 (1H, d, *J* 7.8, 6-H), 7.42 (1H, s, 2-H), 7.55 (1H, dd, *J* 7.8 and 8.4, 7-H), 7.97 (1H, d, *J*

8.4, 8-H) and 12.0 (1H, s, CO_2H, D_2O exchangeable) (Found: C, 66.5; H, 5.35%. Calc. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.56%).

Methyl 4,5-*dimethoxy*-1-(*prop*-2′-*enyloxy*)-3-*naphthoate* (**132**)

To the acid (**131**) (194 mg, 0.68 mmol) in dry acetone (30 cm^3) was added an excess of iodomethane (3 cm^3) and potassium carbonate (400 mg). The stirred mixture was refluxed for 1 hour. The residue obtained upon work-up was chromatographed [eluent: ethyl acetate-light petroleum (1:5)] to afford the *product* (**132**) (195 mg, 96%) m.p. 78-79°C (from light petroleum). ν_{max} 1730 cm^{-1}; δ_H (200 MHz) 3.88 (3H, s, CO_2Me), 3.95 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.7 (2H, dt, *J* 5.1 and 1.5, OCH_2), 5.35 (1H, dq, *J* 10.5 and 1.4, 1H of vinyl CH_2), 5.5 (1H, dq, *J* 17.2 and 1.4, 1H of vinyl CH_2), 6.05-6.25 (1H, m, vinyl CH), 6.95 (1H, d, *J* 7.8, 6-H), 7.47 (1H, dd, *J* 7.8 and 8.4, 7-H) and 7.94 (1H, d, *J* 8.4, 8-H) (Found: M^+, 302.1164. Calc. for $C_{17}H_{18}O_5$: M, 302.1154).

Methyl 1,4,5-*trimethoxy*-2-(*prop*-2′-*enyl*)-3-*naphthoate* (**134**)

The ester (**132**) (86 mg, 0.29 mmol) was pyrolysed (oil bath temperature: 190°C) for 45 min under nitrogen after which time it was

dissolved in acetone (50 cm^3) and treated with an excess of iodomethane (3 cm^3) and potassium carbonate (160 mg). The mixture was stirred under reflux for 2 hours. The residue obtained upon work-up was chromatographed [eluent: ethyl acetate-light petroleum (1:5)] to afford *compound* (**134**) as an oil. ν_{max} 1730 cm^{-1}; δ_H (200 MHz) 3.57 (2H, dt, *J* 6.25 and 1.6, $-CH_2$), 5.0-5.15 (2H, m, vinyl CH_2), 5.85-6.05 (1H, m, vinyl CH), 6.88 (1H, br d, *J* 7.8, 6-H), 7.45 (1H, dd, *J* 7.8 and 8.4, 7-H) and 7.69 (1H, br, d, *J* 8.4, 8-H) (Found: M^+, 316.1317. Calc. for $C_{18}H_{20}O_5$: M, 316.1311).

3,4-*Dihydro*-5,9,10-*trimethoxy*-3-*methyl*-*naphtho*[2,3-*c*]*pyran*-1H-1-*one* (**135**)

Ester (**134**) (64 mg, 0.2 mmol) in trifluoroacetic acid (3 cm^3) was heated in an oil bath at 70°C under nitrogen for 5 hours. The mixture was poured into a sodium bicarbonate solution (50 cm^3 of a 10% solution) and extracted with dichloromethane. The residue obtained upon work-up was chromatographed [eluent: ethyl acetate-light petroleum (3:7)] to afford the *product* (**135**) [21 mg, 34% or 63% based on unrecovered ester (**134**)] as an oil. ν_{max} 1740-1710 br cm^{-1}; δ_H (200 MHz) 1.51 (3H, d, *J* 6.2, $3-CH_3$), 2.79 (1H, dd, *J* 15.7 and 10.9, *pseudo*-axial 4-H), 3.29 (1H, dd, *J* 15.7 and 2.2, *pseudo*-equatorial 4-H), 3.85

(3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.0 (3H, s, OCH_3), 4.4-4.6 (1H, m, 3-H), 6.92 (1H br d, *J* 7.5, 8-H), 7.54 (1H, dd, *J* 7.5 and 8.3, 7-H), and 7.68 (1H, br d, *J* 8.3, 6-H) (Found: M^+, 302.1158. Calc. for $C_{17}H_{18}O_5$: M, 302.1154).

4.2 *IN VITRO* ANTIMICROBIAL ACTIVITY SCREENING OF SYNTHETIC COMPOUNDS

4.2.1 OBJECTIVES

The objectives were to:

(i) screen the synthetic compounds for antimicrobial activity and specificity against a few selected Gram positive and Gram negative organisms employing the Bauer-Kirby method[68]; and

(ii) establish a possible molecular structure - specificity relationship.

4.2.2 GENERAL METHODOLOGY

Filter paper discs[68] with a diameter of 10 mm were impregnated with the compounds dissolved in triple distilled dichloromethane. The discs were dried under reduced pressure and placed onto the surface of nutrient agar plates inoculated with the test organisms. The plates were incubated at 37°C for 24 hours and the diameter of the zones of inhibition (including that of the impregnated discs) was measured. Inhibition of microbial growth was indicated by a clear zone around the

disc. All determinations were done in duplicate. Except in cases where only a limited amount of the test-compound was available, the discs were impregnated to contain 2.81, 1.40 and 0.70 μmol of compound.

It is important for the reader who is less familiar with the subject to note that antibiotics diffuse through agar gels at different rates so that zone sizes produced are not directly comparable and can thus not be related to relative activities of the compounds under investigation.

The following test organisms were obtained from the South African Bureau of Standards (SABS) in Pretoria for experimental work.

Staphylococcus aureus	SATCC Sta 53
Escherichia coli	SATCC Esc 25
Pseudomonas aeruginosa	SATCC Pse 2
Proteus mirabilis	SATCC Pre 1
Bacillus subtilus	SATCC Bac 96
Candida albicans	Fungus

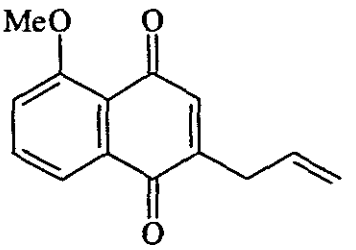
4.2.3 RESULTS

The following Tables (4-1 to 4-39) show the inhibitory activity of some selected synthetic compounds (in numerical order) against the organisms supplied by the SABS.

The author is indebted to Ms Joanne Ireland for collaborating in providing compounds **(136)** - **(139)** and **(143)**, Professor Ivan Green for providing compounds **(140)** - **(142)** and Dr Margaret Brimble for providing compounds **(144)** - **(155)** for evaluation.

TABLE 4-1

Inhibitory Activity of Compound against SABS Organisms

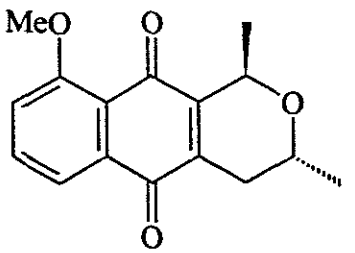


2

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	19
	1.40	16
	0.70	0
Bacillus subtilus SATCC Bac 96	2.81	28
	1.40	22
	0.70	16
Candida albicans fungus	2.81	30
	1.40	22
	0.70	18
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 2.811	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-2

Inhibitory Activity of Compound against SABS Organisms

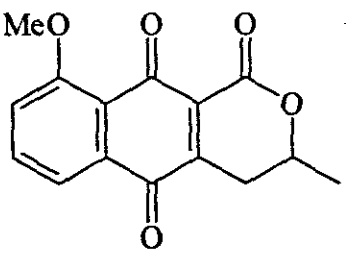


4

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	19
	1.40	15
	0.70	15
Bacillus subtilus SATCC Bac 96	2.81	30
	1.40	25
	0.70	22
Candida albicans fungus	2.81	22
	1.40	20
	0.70	20
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-3

Inhibitory Activity of Compound against SABS Organisms

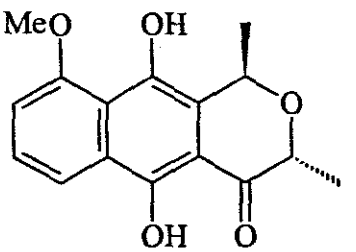


10

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	12
Bacillus subtilus SATCC Bac 96	2.81	14
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-4

Inhibitory Activity of Compound against SABS Organisms

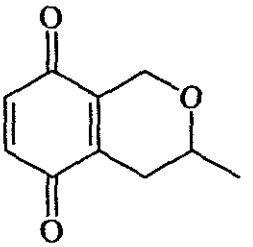


13

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-5

Inhibitory Activity of Compound against SABS Organisms

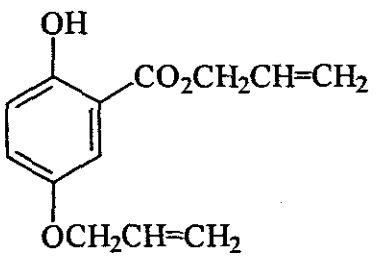


18

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	31
	1.40	25
	0.70	22
Bacillus subtilus SATCC Bac 96	2.81	30
	1.40	26
	0.70	20
Candida albicans fungus	2.81	22
	1.40	18
	0.70	15
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	16
	1.40	12
	0.70	12
Proteus mirabilis SATCC Pre 1	2.81	30
	1.40	18
	0.70	17
Eschericia coli SATCC Esc 25	2.81	16
	1.40	14
	0.70	12

TABLE 4-6

Inhibitory Activity of Compound against SABS Organisms

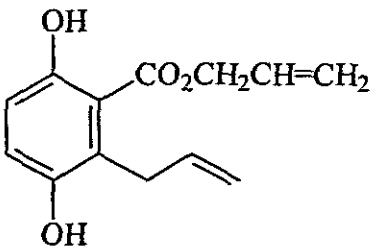


22

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-7

Inhibitory Activity of Compound against SABS Organisms

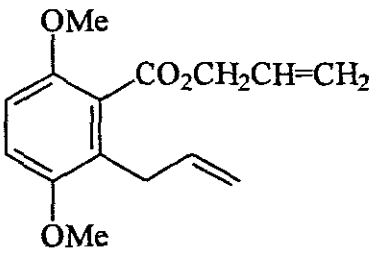


23

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	18
	1.40	16
	0.70	12
Bacillus subtilus SATCC Bac 96	2.81	30
	1.40	25
	0.70	16
Candida albicans fungus	2.81	28
	1.40	22
	0.70	16
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	16
	1.40	15
	0.70	14
Eschericia coli SATCC Esc 25	2.81	18
	1.40	15
	0.70	14

TABLE 4-8

Inhibitory Activity of Compound against SABS Organisms

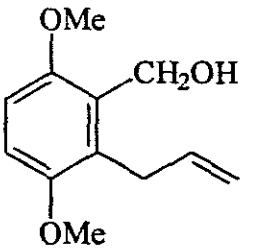


24

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-9

Inhibitory Activity of Compound against SABS Organisms

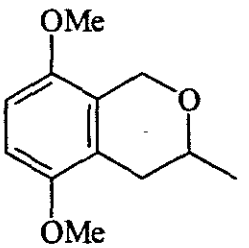


25

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	14
	1.40	14
	0.70	0
Bacillus subtilus SATCC Bac 96	2.81	16
	1.40	14
	0.70	0
Candida albicans fungus	2.81	14
	1.40	0
	0.70	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-10

Inhibitory Activity of Compound against SABS Organisms

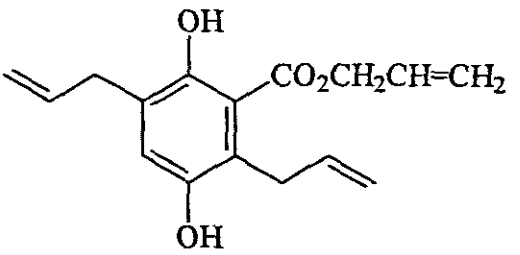


26

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-11

Inhibitory Activity of Compound against SABS Organisms

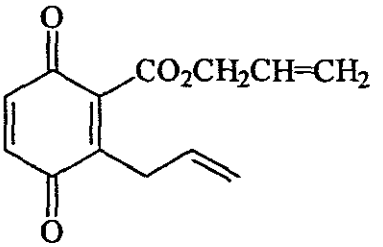


28

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-12

Inhibitory Activity of Compound against SABS Organisms

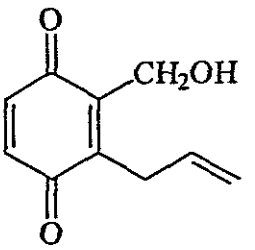


34

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	28
	1.40	24
	0.70	20
Bacillus subtilus SATCC Bac 96	2.81	30
	1.40	24
	0.70	18
Candida albicans fungus	2.81	26
	1.40	20
	0.70	16
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-13

Inhibitory Activity of Compound against SABS Organisms

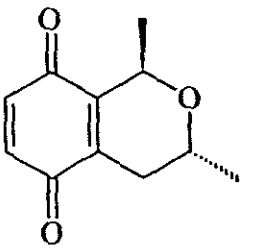


35

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	28
	1.40	20
	0.70	16
Bacillus subtilus SATCC Bac 96	2.81	28
	1.40	22
	0.70	18
Candida albicans fungus	2.81	26
	1.40	22
	0.70	18
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	14
	1.40	0
	0.70	0
Proteus mirabilis SATCC Pre 1	2.81	20
	1.40	14
	0.70	0
Eschericia coli SATCC Esc 25	2.81	22
	1.40	16
	0.70	14

TABLE 4-14

Inhibitory Activity of Compound against SABS Organisms

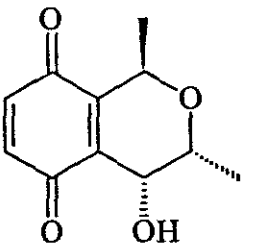


36

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	25
	1.40	24
	0.70	16
Bacillus subtilus SATCC Bac 96	2.81	35
	1.40	30
	0.70	24
Candida albicans fungus	2.81	28
	1.40	20
	0.70	18
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	20
	1.40	16
	0.70	14
Eschericia coli SATCC Esc 25	2.81	20
	1.40	14
	0.70	14

TABLE 4-15

Inhibitory Activity of Compound against SABS Organisms

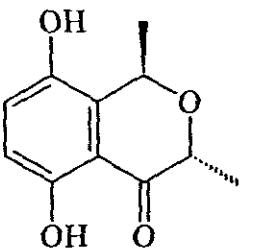


37

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	20
	1.40	20
	0.70	20
Bacillus subtilus SATCC Bac 96	2.81	29
	1.40	26
	0.70	19
Candida albicans fungus	2.81	17
	1.40	17
	0.70	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	15
	1.40	0
Proteus mirabilis SATCC Pre 1	2.81	15
	1.40	13
	0.70	13
Eschericia coli SATCC Esc 25	2.81	15
	1.40	12
	0.70	0

TABLE 4-16

Inhibitory Activity of Compound against SABS Organisms

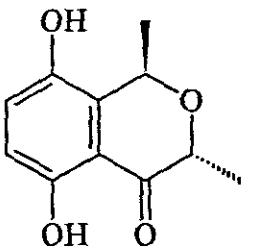


39

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	19
	1.40	17
	0.70	12
Bacillus subtilus SATCC Bac 96	2.81	20
	1.40	17
	0.70	14
Candida albicans fungus	2.81	20
	1.40	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	14
	1.40	0
Eschericia coli SATCC Esc 25	2.81	12
	1.40	0

TABLE 4-16

Inhibitory Activity of Compound against SABS Organisms

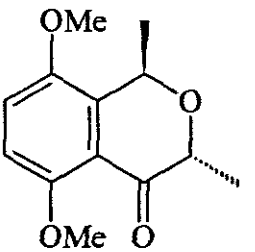


39

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	19
	1.40	17
	0.70	12
Bacillus subtilus SATCC Bac 96	2.81	20
	1.40	17
	0.70	14
Candida albicans fungus	2.81	20
	1.40	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	14
	1.40	0
Eschericia coli SATCC Esc 25	2.81	12
	1.40	0

TABLE 4-17

Inhibitory Activity of Compound against SABS Organisms

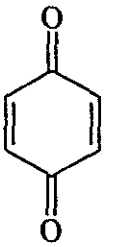


50

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-18

Inhibitory Activity of Compound against SABS Organisms

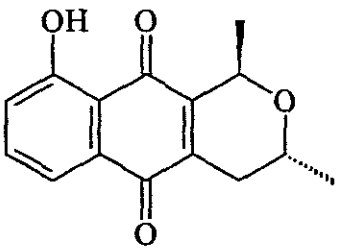


65

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	0
Bacillus subtilus SATCC Bac 96	2.81	0
Candida albicans fungus	2.81	14
	1.40	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	15
	1.40	0
Eschericia coli SATCC Esc 25	2.81	17
	1.40	14
	0.70	0

TABLE 4-19

Inhibitory Activity of Compound against SABS Organisms

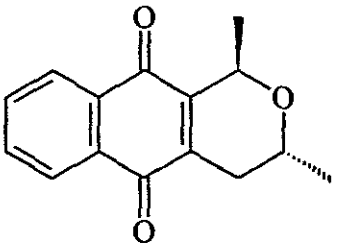


90

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	17
	1.40	14
	0.70	14
Bacillus subtilus SATCC Bac 96	2.81	12
	1.40	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-20

Inhibitory Activity of Compound against SABS Organisms

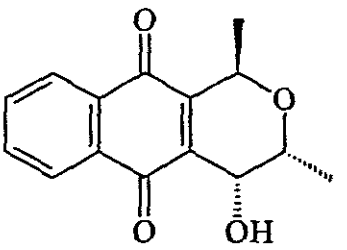


136

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	13
	1.40	12
	0.70	12
Bacillus subtilus SATCC Bac 96	2.81	25
	1.40	21
	0.70	20
Candida albicans fungus	2.81	20
	1.40	20
	0.70	20
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-21

Inhibitory Activity of Compound against SABS Organisms

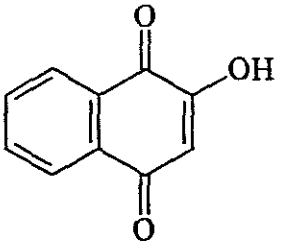


137

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81 0.70	29 23
Bacillus subtilus SATCC Bac 96	2.81 0.70	32 26
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-22

Inhibitory Activity of Compound against SABS Organisms

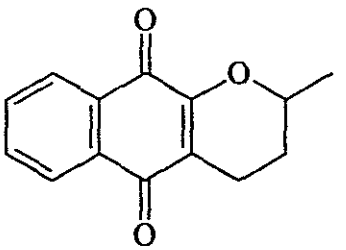


138

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	17
	1.40	12
	0.70	0
Bacillus subtilus SATCC Bac 96	2.81	34
	1.40	30
	0.70	27
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-23

Inhibitory Activity of Compound against SABS Organisms

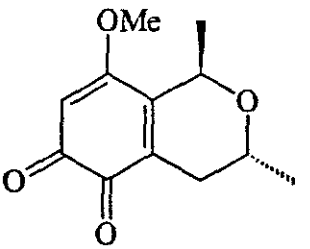


139

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	20
	1.40	20
	0.70	20
Bacillus subtilus SATCC Bac 96	2.81	20
	1.40	19
	0.70	18
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-24

Inhibitory Activity of Compound against SABS Organisms

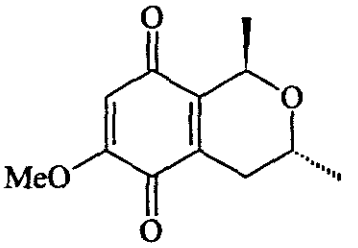


140

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.40	21
	0.70	21
Bacillus subtilus SATCC Bac 96	1.40	17
	0.70	17
Candida albicans fungus	1.40	17
	0.70	15
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.40	0
Proteus mirabilis SATCC Pre 1	1.40	0
Eschericia coli SATCC Esc 25	1.40	15
	0.70	15

TABLE 4-25

Inhibitory Activity of Compound against SABS Organisms

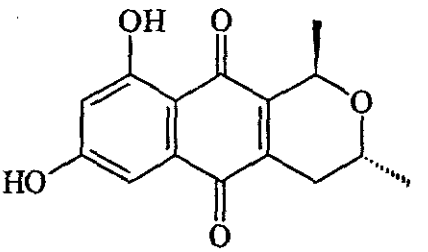


141

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	29
	1.40	28
	0.70	26
Bacillus subtilus SATCC Bac 96	2.81	22
	1.40	21
	0.70	19
Candida albicans fungus	2.81	32
	1.40	31
	0.70	29
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-26

Inhibitory Activity of Compound against SABS Organisms

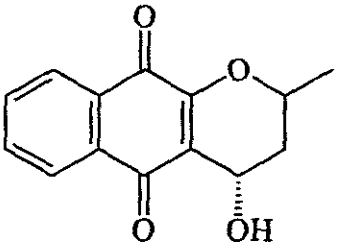


142

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	14
	1.40	0
Bacillus subtilus SATCC Bac 96	2.81	14
	1.40	0
Candida albicans fungus	2.81	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	0
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-27

Inhibitory Activity of Compound against SABS Organisms

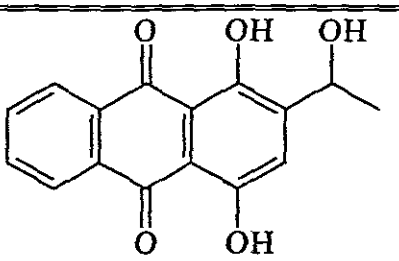


143

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.81	35
	1.40	32
	0.70	28
Bacillus subtilus SATCC Bac 96	2.81	32
	1.40	31
	0.70	25
Candida albicans fungus	2.81	30
	1.40	30
	0.70	28
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.81	0
Proteus mirabilis SATCC Pre 1	2.81	25
	1.40	25
	0.70	23
Eschericia coli SATCC Esc 25	2.81	0

TABLE 4-28

Inhibitory Activity of Compound against SABS Organisms

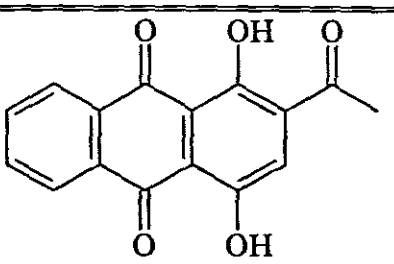


144

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.76	0
Bacillus subtilus SATCC Bac 96	1.76	0
Candida albicans fungus	1.76	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.76	0
Proteus mirabilis SATCC Pre 1	1.76	0
Eschericia coli SATCC Esc 25	1.76	0

TABLE 4-29

Inhibitory Activity of Compound against SABS Organisms

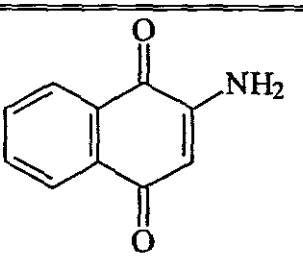


145

Gram positive organism and SABS culture number	**Dose in *μmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.76	0
Bacillus subtilus SATCC Bac 96	1.76	0
Candida albicans fungus	1.76	0
Gram negative organism and SABS culture number	**Dose in *μmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.76	0
Proteus mirabilis SATCC Pre 1	1.76	0
Eschericia coli SATCC Esc 25	1.76	0

TABLE 4-30

Inhibitory Activity of Compound against SABS Organisms

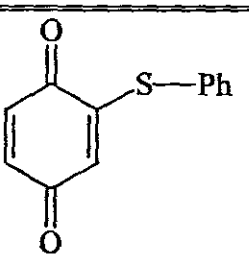


146

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.89	20
Bacillus subtilus SATCC Bac 96	2.89	22
Candida albicans fungus	2.89	13
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.89	0
Proteus mirabilis SATCC Pre 1	2.89	0
Eschericia coli SATCC Esc 25	2.89	13

TABLE 4-31

Inhibitory Activity of Compound against SABS Organisms

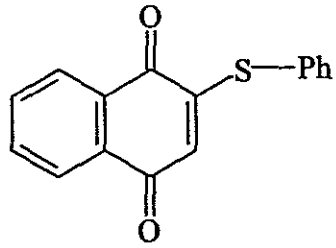


147

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.31	18
Bacillus subtilus SATCC Bac 96	2.31	16
Candida albicans fungus	2.31	12
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.31	0
Proteus mirabilis SATCC Pre 1	2.31	0
Eschericia coli SATCC Esc 25	2.31	0

TABLE 4-32

Inhibitory Activity of Compound against SABS Organisms

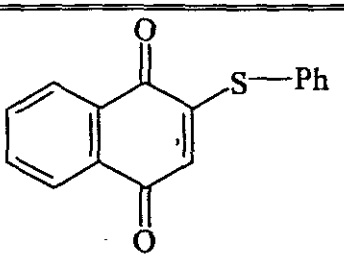


148

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.88	0
Bacillus subtilus SATCC Bac 96	1.88	0
Candida albicans fungus	1.88	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.88	0
Proteus mirabilis SATCC Pre 1	1.88	0
Eschericia coli SATCC Esc 25	1.88	0

TABLE 4-33

Inhibitory Activity of Compound against SABS Organisms

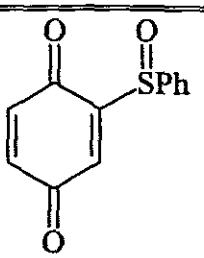


149

Gram positive organism and SABS culture number	**Dose in *μmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.69	0
Bacillus subtilus SATCC Bac 96	1.69	0
Candida albicans fungus	1.69	0
Gram negative organism and SABS culture number	**Dose in *μmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.69	0
Proteus mirabilis SATCC Pre 1	1.69	0
Eschericia coli SATCC Esc 25	1.69	0

TABLE 4-34

Inhibitory Activity of Compound against SABS Organisms

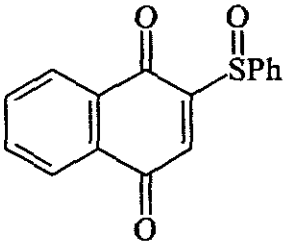


150

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	2.10	14
Bacillus subtilus SATCC Bac 96	2.10	22
Candida albicans fungus	2.10	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	2.10	0
Proteus mirabilis SATCC Pre 1	2.10	0
Eschericia coli SATCC Esc 25	2.10	0

TABLE 4-35

Inhibitory Activity of Compound against SABS Organisms

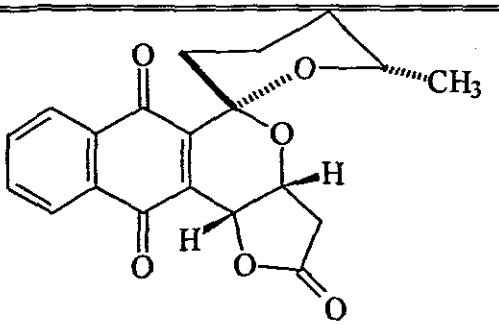


151

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.77	13
Bacillus subtilus SATCC Bac 96	1.77	22
Candida albicans fungus	1.77	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.77	0
Proteus mirabilis SATCC Pre 1	1.77	0
Eschericia coli SATCC Esc 25	1.77	0

TABLE 4-36

Inhibitory Activity of Compound against SABS Organisms

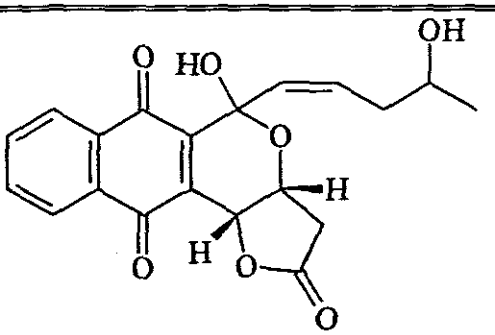


152

Gram positive organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.41	20
Bacillus subtilus SATCC Bac 96	1.41	25
Candida albicans fungus	1.41	0
Gram negative organism and SABS culture number	**Dose in μmol**	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.41	0
Proteus mirabilis SATCC Pre 1	1.41	0
Eschericia coli SATCC Esc 25	1.41	0

TABLE 4-37

Inhibitory Activity of Compound against SABS Organisms

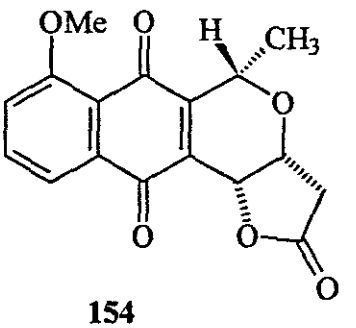


153

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.35	24
Bacillus subtilus SATCC Bac 96	1.35	24
Candida albicans fungus	1.35	14
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.35	0
Proteus mirabilis SATCC Pre 1	1.35	0
Eschericia coli SATCC Esc 25	1.35	0

TABLE 4-38

Inhibitory Activity of Compound against SABS Organisms

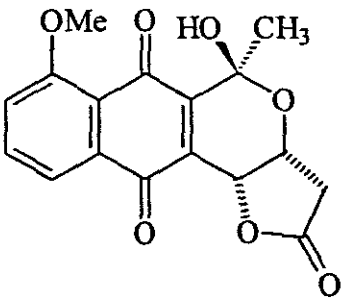


154

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.59	30
Bacillus subtilus SATCC Bac 96	1.59	25
Candida albicans fungus	1.59	20
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.59	0
Proteus mirabilis SATCC Pre 1	1.59	0
Eschericia coli SATCC Esc 25	1.59	0

TABLE 4-39

Inhibitory Activity of Compound against SABS Organisms



155

Gram positive organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Staphylococcus aureus SATCC Sta 53	1.51	14
Bacillus subtilus SATCC Bac 96	1.51	16
Candida albicans fungus	1.51	0
Gram negative organism and SABS culture number	**Dose in *µmol***	**Zone of inhibition in mm**
Pseudomonas aeruginosa SATCC Pse 2	1.51	0
Proteus mirabilis SATCC Pre 1	1.51	0
Eschericia coli SATCC Esc 25	1.51	0

4.2.4 DISCUSSION OF RESULTS

From the results thus far obtained in our synthetic antibiotics evaluation programme, the following may be concluded with respect to a structure-activity-specificity relationship.

(i) the benzo[*c*]pyranquinones and their benzoquinone derivatives have a broader specificity spectrum than their naphtho[2,3-*c*] or [2,3-*b*] analogues.

(ii) the [2,3-*b*]- and [2,3-*c*]naphthopyranquinones are (in general) more active against Gram positive organisms than against Gram negative organisms.

(iii) those benzo[*c*]pyrans and their precursor containing methoxy groups are inactive against all of the test organisms employed. An exception is compound (**25**) which is active only against the Gram positive organisms.

(iv) the anthra-9,10-quinone derivatives (**144**) and (**145**) are both inactive against all of the Gram positive and Gram negative organisms used for evaluation.

(v) introduction of hydroxyl at C-4 of the naphtho[2,3-*b*]pyranquinone (**139**) to afford (**143**), broadens the specificity spectrum. In the case of the naphtho[2,3-*c*]pyranquinone (**136**), introduction of hydroxyl at C-4 to give (**137**) had no effect on the specificity spectrum.

(vi) introduction of a methoxy group at C-9 of (**136**) to afford isoeleutherin (**4**), also has no effect on the specificity spectrum.

(vii) introduction of hydroxy groups at C-7 and C-9 of quinone (**136**) to afford compounds (**90**) and (**142**), leads to a decrease in activity against the Gram positive organisms.

Other noteworthy observations are — within the naphtho[2,3-*c*]pyran class of compounds, (±)isoeleutherin (**4**) is more active against the Gram positive organisms than the (±)pyranone (**10**), whereas (±)hongconin (**13**) is totally inactive as an antimicrobial agent; compound (**23**) which is a broad spectrum antimicrobial agent, is totally inactivated by introducing an allyl group at C-5 as in (**28**); introduction of a hydroxy group at C-4 of pyranquinone (**36**) to give (**37**), increases the activity against *Pseudomonas aeruginosa*; benzoquinone (**65**) is less

active against Gram positive organisms than its benzo[*c*]pyranquinone derivatives; except for pyranquinone (**153**), the fungus, *Candida albicans*, is resistant to those naphthoquinones or naphtho[2,3-*c*]pyranquinones which contain hydroxy groups [e.g. compounds (**90**), (**137**), (**138**) and (**155**)].

Although the *in vivo* evaluations[69] of our synthetic compounds fall outside the scope of this study, the author wishes, for the sake of interest, to report briefly that the pyranquinone (**136**)[67] prepared in our laboratories, was evaluated amongst others, in a rat model for antimicrobial activity and stability, as well as for toxicological and biochemical effects.

HPLC results[70] demonstrated that this quinone is relatively stable *in vivo*. However it causes some haematological changes after repeated administration. For example, a significant increase in the eosinophil count of the test rats between day 0 and day 3 and day 0 and day 6 was observed. This may indicate an allergic reaction to the quinone with subsequent release of the eosinophils.

Micrographs were also prepared from histological slides of the kidneys, liver, spleen, stomach and small intestines of the test rats. These

showed no abnormalities, indicating that the quinone does not cause tissue damage. (See **Figures 4-3** to **4-6**)

Finally, quinone (**136**) was shown to eliminate *Staphylococcus aureus* effectively in rats inoculated with the organism. (See **Figures 4-1** and **4-2**)

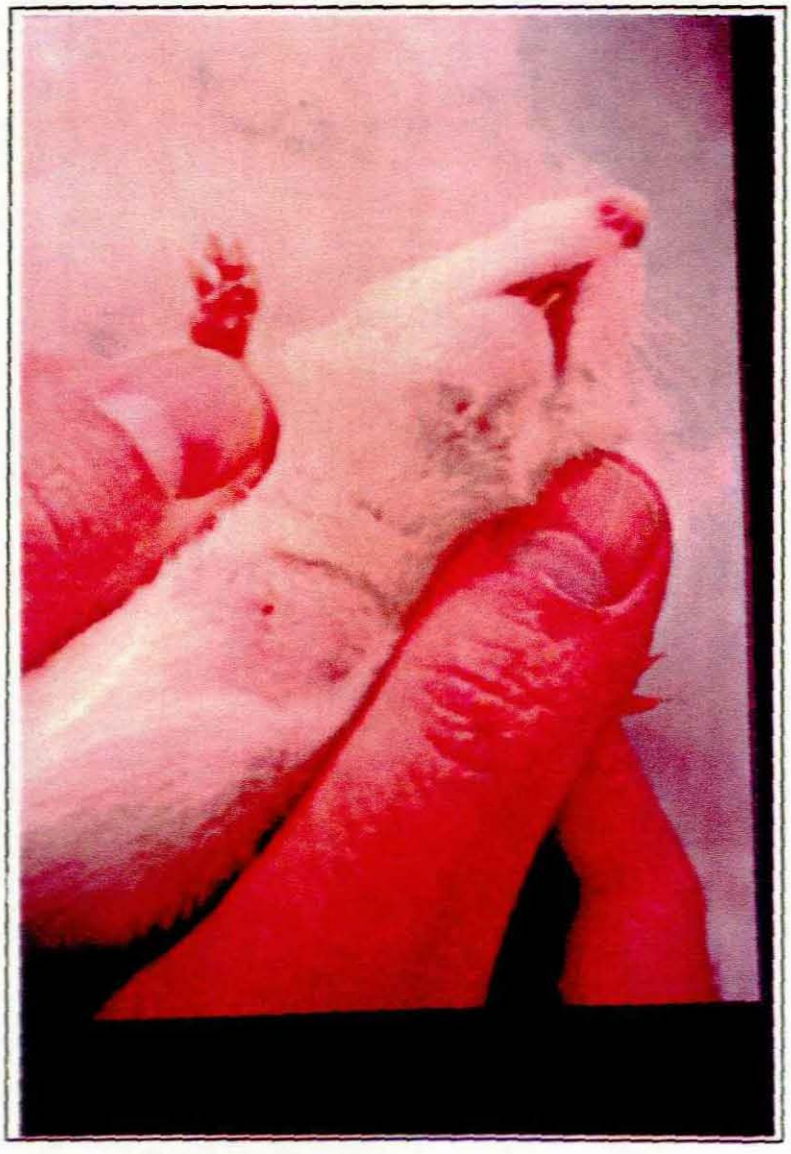


Figure 4-1: Rat showing the wound infected with *Staphylococcus aureus*.

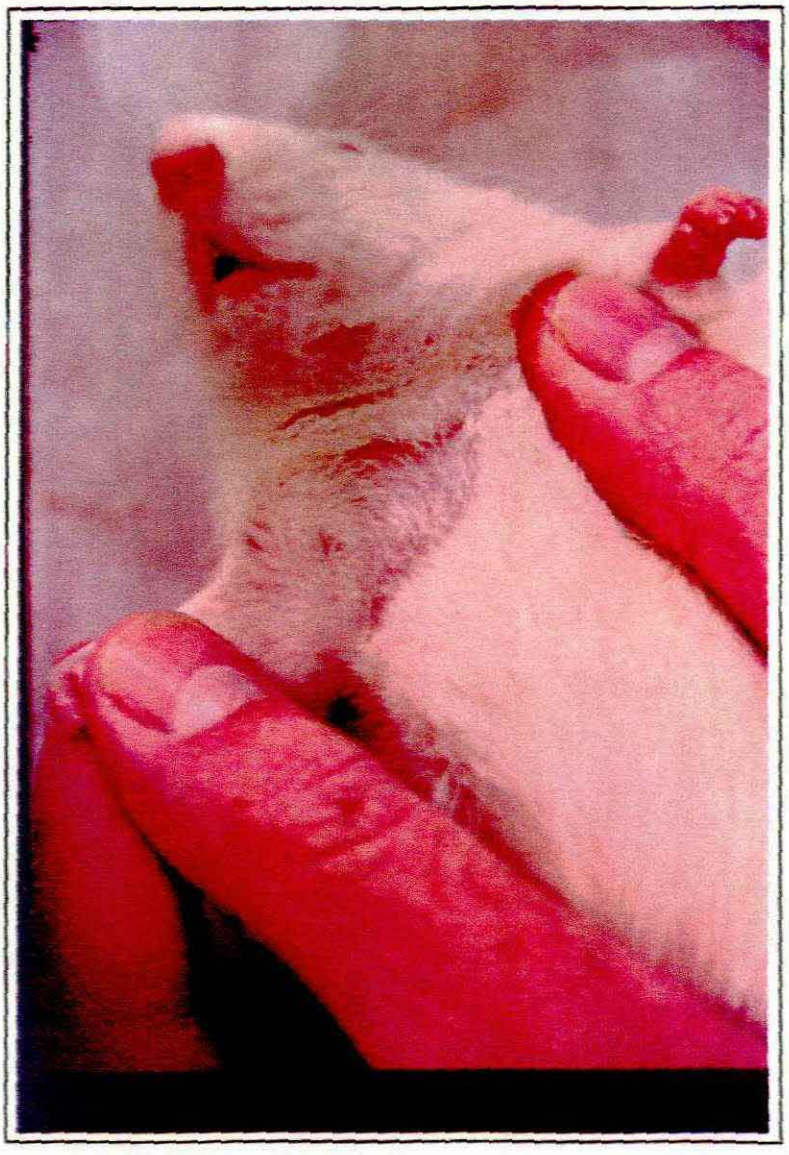


Figure 4-2: Rat showing no infection after treatment with quinone (**136**).

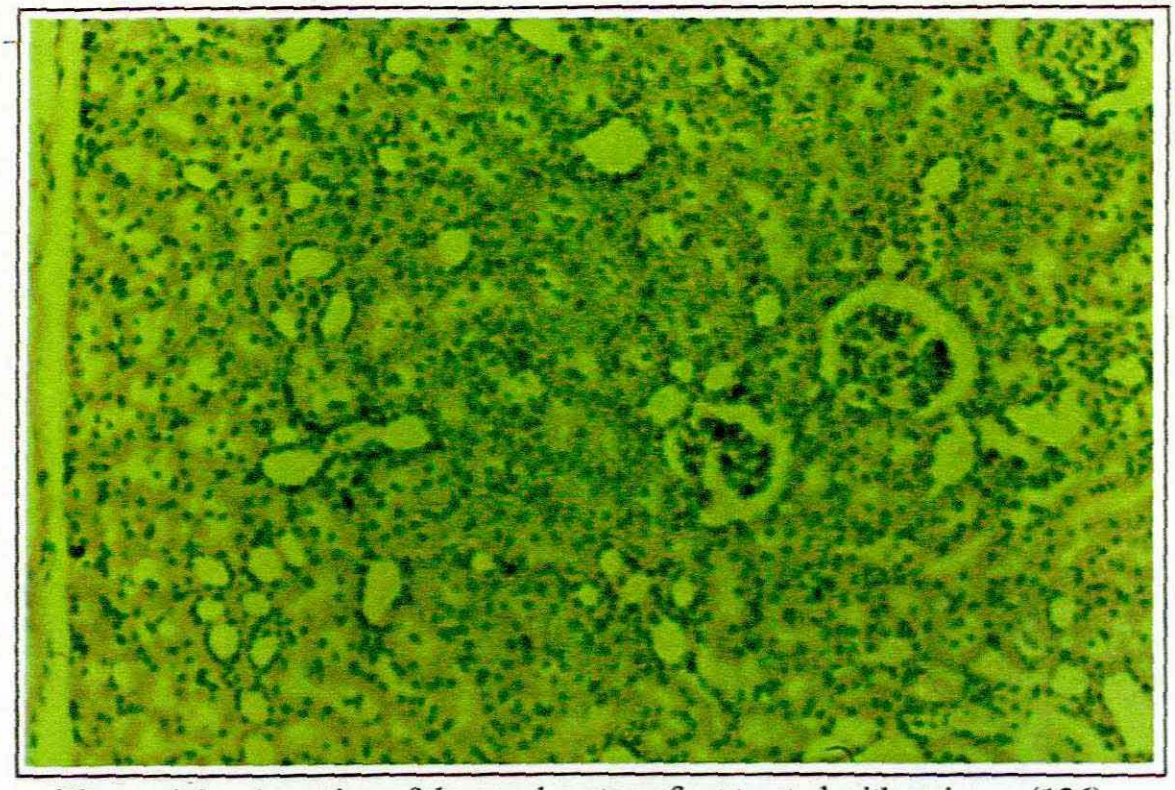


Figure 4-3: A section of the renal cortex of rat treated with quinone (**136**).

No abnormalities can be observed.

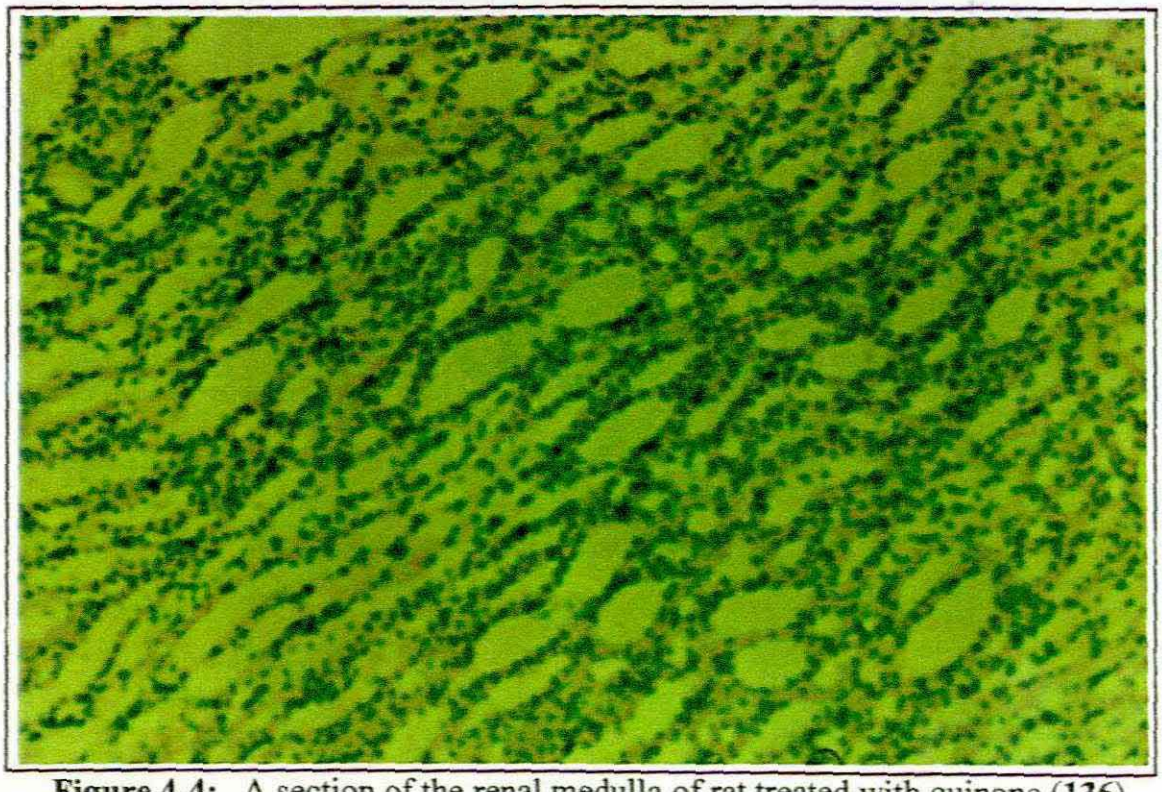


Figure 4-4: A section of the renal medulla of rat treated with quinone (**136**).

No abnormalities can be observed.

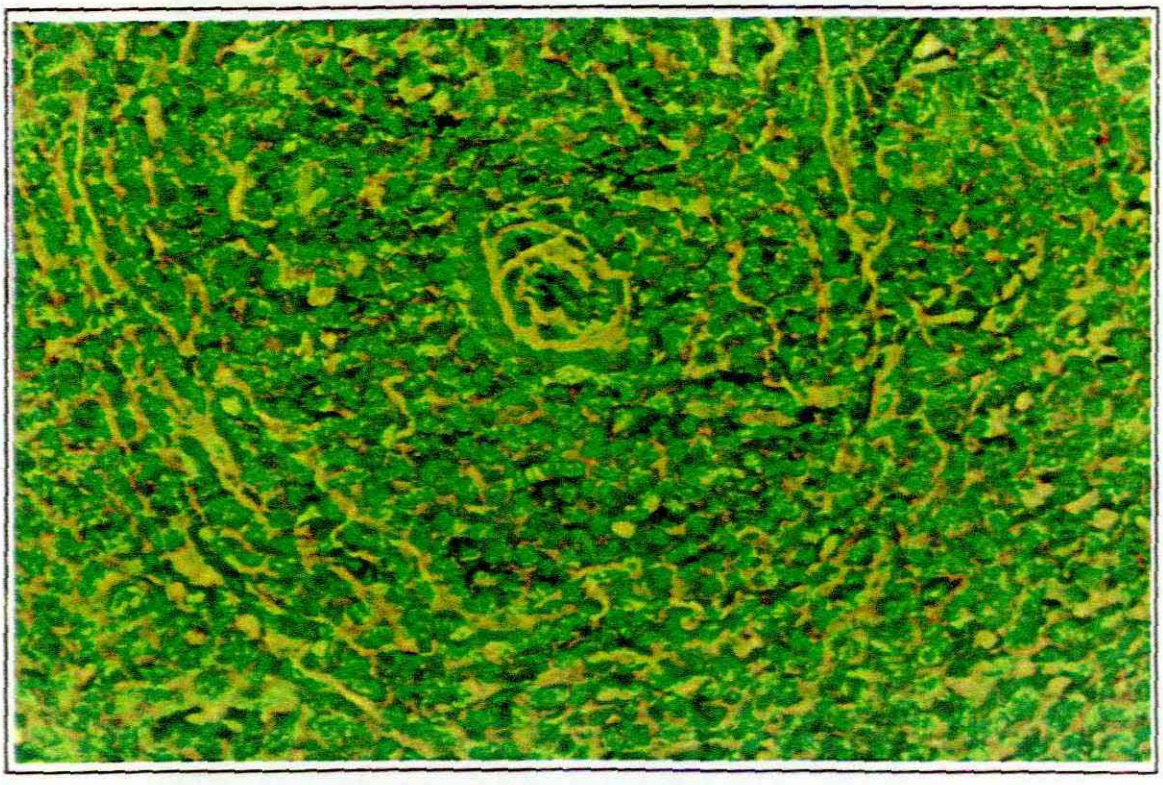
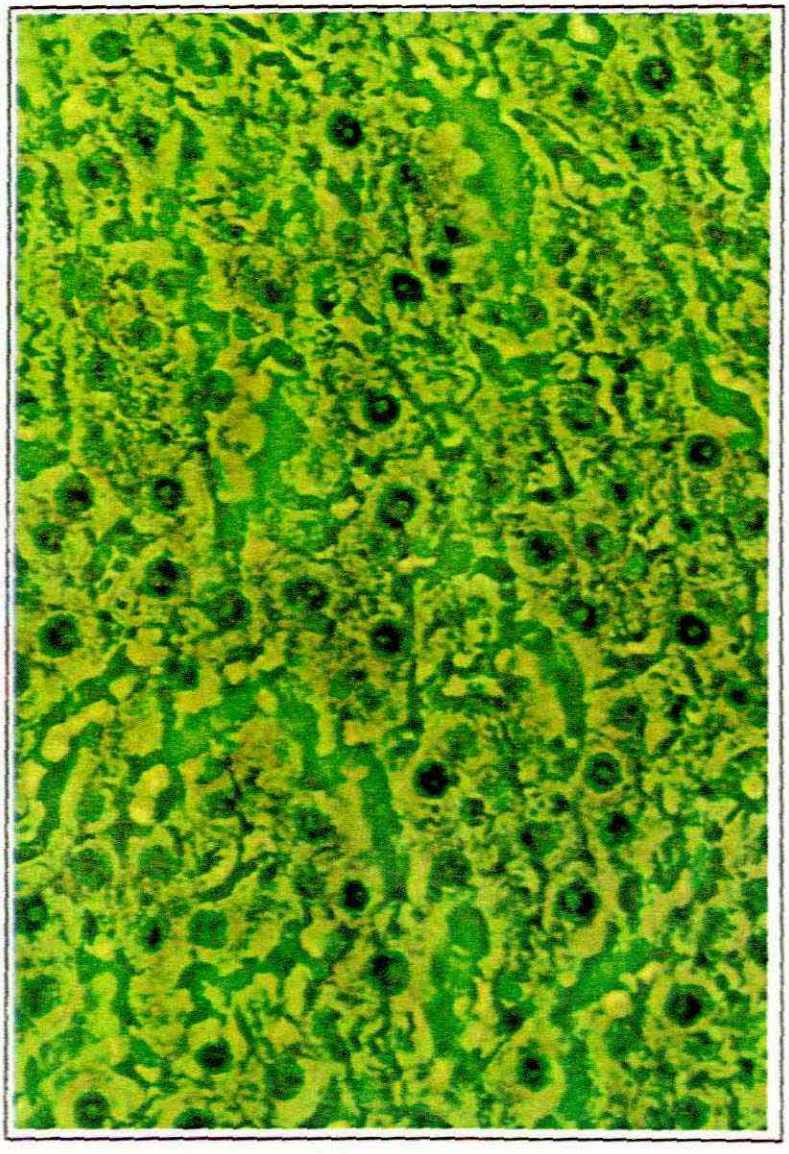


Figure 4-5: A section of the spleen of rat treated with quinone (**136**). No abnormalities can be observed.



Figures 4-6: A section of a liver lobule of rat treated with quinone (**136**). No abnormalities can be observed.

CONCLUSION

The author wishes to conclude by reporting that the objectives of the study have been fully realised. The strategy for the synthesis of benzo[*c*]pyrans is successfully applied to the synthesis of naphtho[2,3-*c*]pyrans - the key-step being C-allylation *via* a Claisen rearrangement reaction.

The new routes to the intermediates (**1**) - (**3**), and, in particular, to ketone (**61**) are overall high-yielding and this constitutes a significant improvement in the total synthesis of isoeleutherin (**4**) and hongconin (**13**). Furthermore the route to the naptho[2,3-*c*]pyranone (**10**) should be applicable for the synthesis of higher oxygenated naphtho[2,3-*c*]pyranones by virtue of the nature of the reagents used in this synthetic approach.

Finally, antimicrobial evaluation of the target compounds showed that the benzo[*c*]pyranquinones have a broader specificity spectrum than their naphtho[2,3-*c*] or naphtho[2,3-*b*] analogues.

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69. This work forms part of a thesis currently being prepared by A J Esterhuyse for the MSc degree in Physiology at the University of Stellenbosch, South Africa. (Supervisors: Prof V I Hugo and Dr D du Plessis)

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