THE SYNTHESIS OF VENTILOQUINONES J AND F

a thesis submitted to the

UNIVERSITY OF THE WESTERN CAPE

in fulfilment of the requirements for

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DOCTOR OF PHILOSOPHY

by

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DECLARATION

I declare that *Synthesis of Ventilquinones J and F* is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

NESTOR VAN EEDEN **MAY 2002**

ABSTRACT

In chapter 2 the synthesis of ventiloquinone J is described, starting from vanillin, the key intermediate *cis*-3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2.3-*c*]pyran-6,9-dione was prepared in 19 steps by using *inter alia* Diels-Alder adduct formation, mild acetylation, oxymercuration and finally converted to ventiloquinone J in an overall yield of 0.5%.

Protection of the C-10 position of the ventiloquinone J precursor was eventually effectively provided by the methoxymethyleneoxy (MOM) group which upon removal with acid treatment provided the hydroxy group in this position unambiguously in the final product. Attempts to effect this same protection using a benzyl group proved ineffective due to the extreme difficulty in separation of the cyclised stereoisomers; *cis* and *trans* 10-benzyloxy-3,4-dihydro-5,6,7,9-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-*c*]pyrans. In addition decomposition of the molecule occurred during the subsequent oxidation step affording low yields of the quinones and finally the unwanted isomer viz., the *trans* 1,3-dimethylpyran was the major product of the cyclisation. Protection of C-10 of the precursor to ventiloquinone J using the 2'-methoxyethoxymethyleneoxy (MEM) group proved problematic in that it was sensitive to the acidity of the silica gel stationary phase used for column chromatography, and that cyclisation of the intermediate alcohol, 2-(1'-hydroxyethyl)-4,5,6,8-tetramethoxy-1-(2'-methoxyethoxymethyleneoxy)-3-prop-2'-enylnaphthalene, led to a mixture of the corresponding *cis* and *trans*

1,3-dimethyl pyrans in which the MEM protecting group had been lost in a combined crude yield of only 25%. In addition all the MEM compounds showed considerable decomposition on standing.

The synthesis of one of the initial target molecules, 6-hydroxy-7-methoxyeleutherin was not completed due to premature displacement of the required C-5 protecting groups employed in the naphthalene precursors upon acylations under Lewis acid conditons.

Ventiloquinone F was successfully synthesised from 3,4,6-trimethoxybenzaldehyde in 12 steps making use of a Stobbe Condensation with methyl succinate to construct the desired oxygenated naphthalene nucleus. An overall yield of 9.5% was obtained and its stereoisomer, isoventiloquinone F was also obtained in an overall yield of 10%.

In the penultimate step, oxidation of the stereoisomeric mixture of *cis*- and *trans*- 5-benzyloxy-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran led to the formation of four pyranquinones which were successfully separated and purified. These were *cis*- and *trans*-5-benzyloxy-3,4-dihydro-7-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-6,9-diones as well as the corresponding *cis* and *trans ortho* quinone isomers.

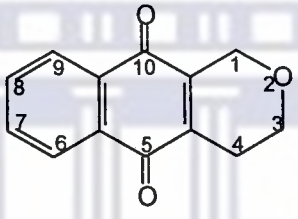
Catalytic hydrogenolysis of the former 6,9-diones afforded ventiloquinone F and its diastereoisomer, isoventiloquinone F. Similar catalytic hydrogenolysis of the ortho quinones, lead suprisingly to the loss of the 7-methoxy group and retention of the 5-benzyloxy group.

LIST OF ABBREVIATIONS

CAN	= Cerium(IV) ammonium nitrate
MOM	= Methoxymethyleneoxy
MEM	= 2'-Methoxyethoxymethyleneoxy
HRMS	= High resolution mass spectrum
DCM	= Dichloromethane
UV	= Ultraviolet
IR	= Infrared
DMF	= *N,N*-dimethylformamide
nmr	= Nuclear magnetic resonance
THF	= Tetrahydrofuran
EtOH	= Ethanol
EtOAc	= Ethyl acetate
HCl	= Hydrochloric acid
MS	= Mass spectrum
M^+	= Molecular ion
AcOH	= Acetic acid
Pyr	= Pyridine
X% eluent	= % ethyl acetate in hexane v/v

INTRODUCTION

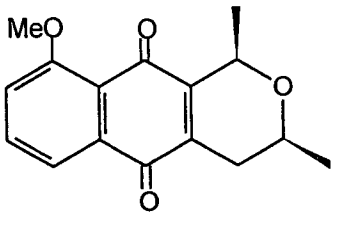
Several naturally occurring naphthopyranquinones containing the [2,3-*c*] pyran ring system **1** have been shown to possess antimicrobial and antineoplastic activity. Additionally, this family of compounds has been shown to exhibit significant activity against Gram-positive bacteria, pathogenic fungi and yeasts, as well as possessing antiviral activity. [1] Thus laboratory syntheses of these antibiotic compounds has become increasingly important.



1

Many of these compounds are isolated from various strains of bacteria and fungi, the majority being microbial in origin.[2]

Eleutherin **2** and isoeleutherin **3**, powerful antibacterial agents, were first isolated from the tubers of *Eleutherine bulbosa* by Schmid and co-workers.[3-5]



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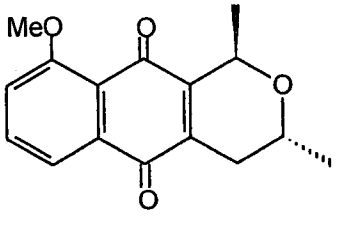

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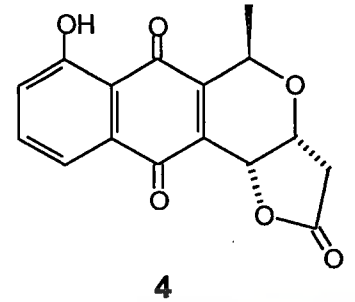
Other naturally occurring naphthopyranquinones include kalafungin [6] **4**, the nanaomycins [7,8] A **5**, B **6**, C **7**, D **8** and naphthocyclinone **9**. [9]



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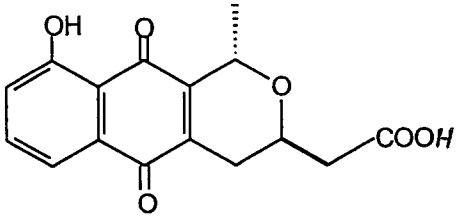

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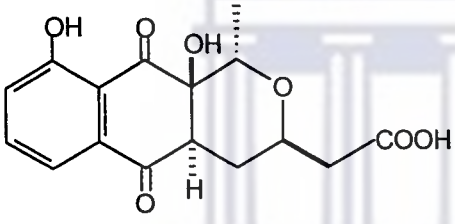

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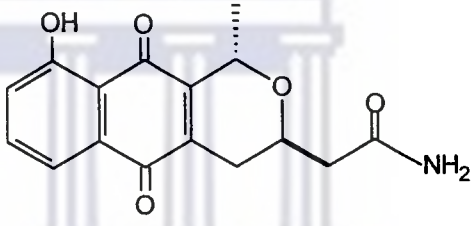

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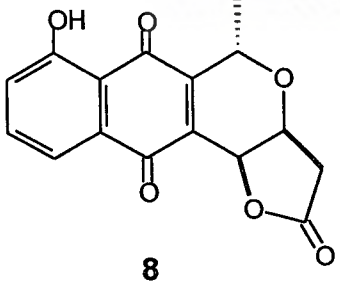

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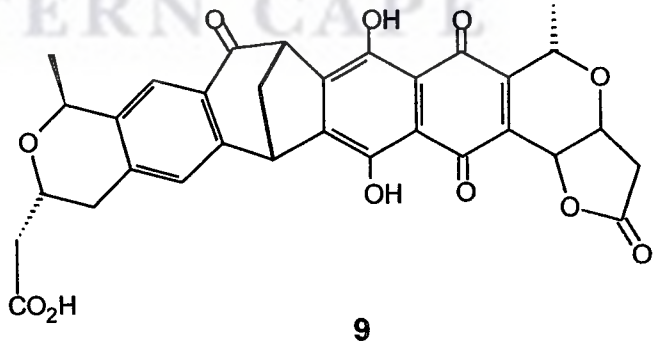

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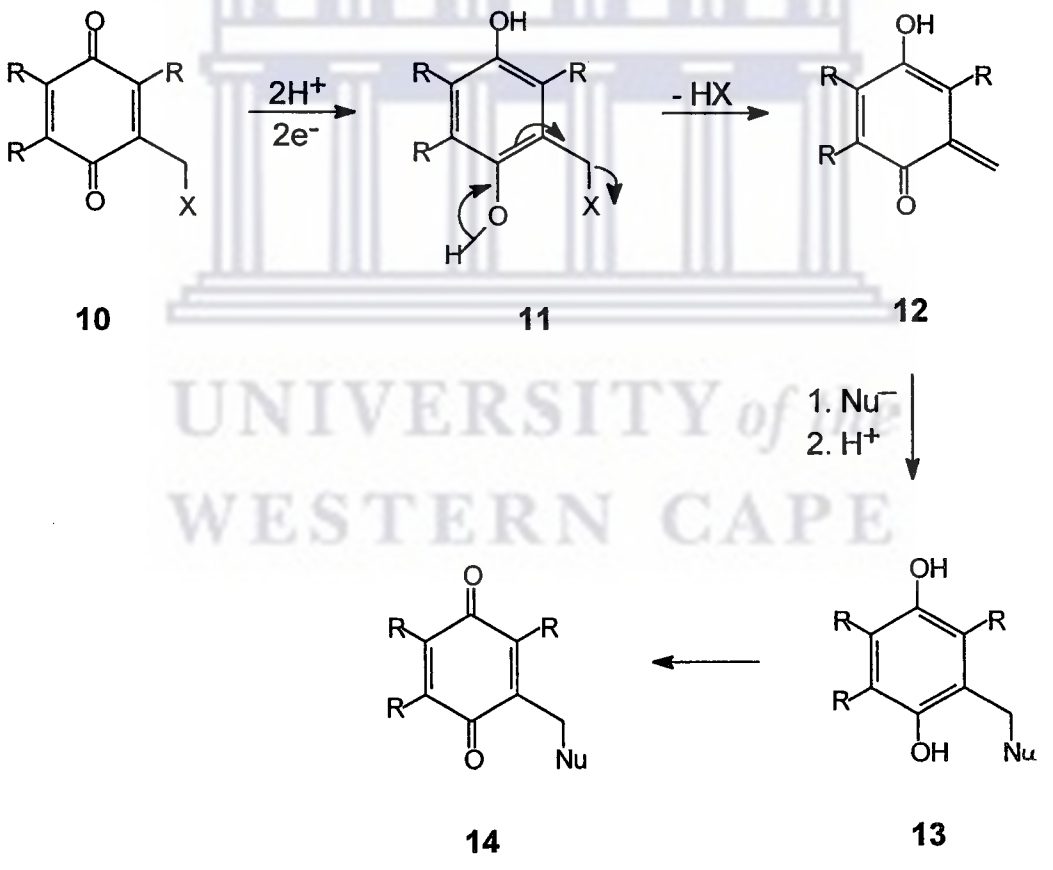
The term "bioreductive alkylation" was first introduced by Lin to explain a proposed mechanism of drug action.[10] Later Moore reviewed several compounds which by virtue of their structures would be expected (and several have been shown) to possess significant antineoplastic activity by acting as bioreductive alkylating agents. [1,11] The idea behind bioactivation lies in introducing a drug in a biologically inactive form after which an *in vivo* transformation results in its activation, thus enabling the active drug to function. The cytotoxic effect of these quinones is evident in the sequence of reactions depicted in **Scheme 1**.



Scheme 1

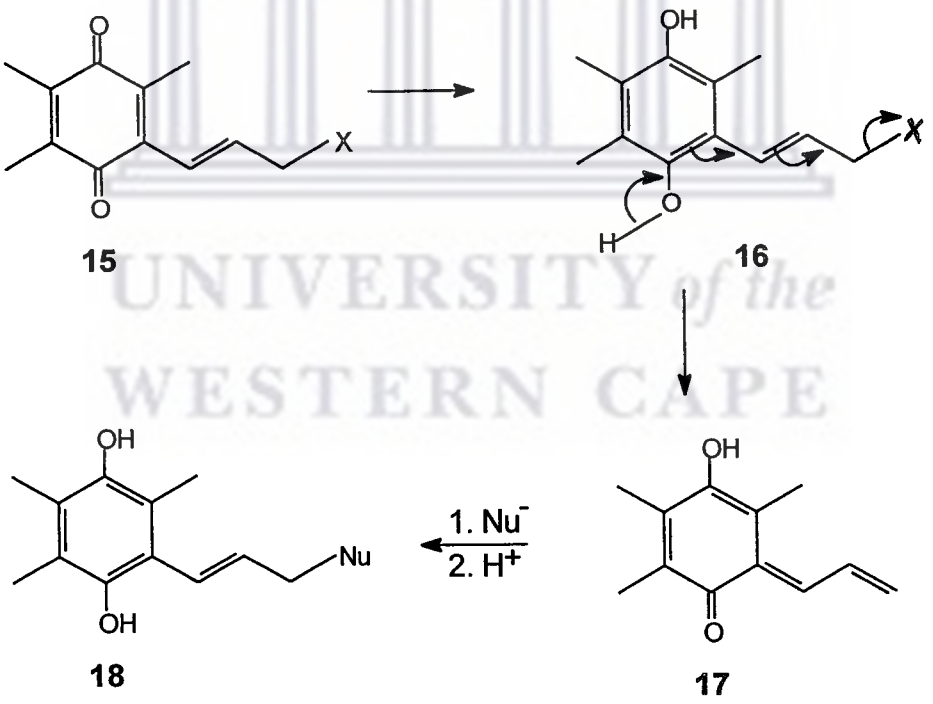
Firstly, the quinone **10** undergoes *in vivo* bioreduction to the hydroquinone **11** and subsequent loss of HX results in the formation of the quinone methide **12**. Michael addition of biological nucleophiles such as DNA, proteins or carbohydrates to the reactive enone system of the quinone methide results in the formation of the covalent adduct **13**, and finally oxidation of **13** results in the biologically inactive quinone **14** which is now covalently bonded to the biological target. This cell will no longer be able to carry out its normal function or to replicate and this will result in cell death.

It has been shown that reduction of a quinone to a hydroquinone system is an essential step for biological activity [12] and thus several mechanistic studies have been employed to determine the importance of hydroquinone formation, which include chemical, electrochemical and enzymatic methods to induce reductive activation *in vitro*. [13,14,15]

In the next step, the hydroquinone is transformed to its quinone methide. The simplest model is the formation of quinone methides *via* bioreduction followed by an elimination as proposed by Lin *et al.* [10] to explain antineoplastic activity of simple quinones with one or more $-CH_2-X$ (X = leaving group) substituents as shown in **Scheme 1**. An important observation is that the R-substituents have a significant effect on the activity of the quinone. Quinones having electron-releasing R groups show greater activity by virtue of the fact that HX elimination to form the quinone methide **12** is enhanced. On the other hand reduction of the quinone **10** to

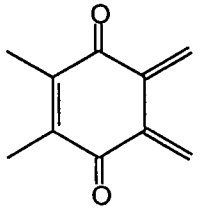
the hydroquinone **11** is more sluggish compared to systems in which the R groups are electron-withdrawing. [10]

Moore [1] suggested a small variation in the mechanism described above for cases in which the quinone is substituted with an alkenyl group as in **15**. A vinylogous quinone methide **17** is formed by the bioreduction of quinone **15** to the corresponding hydroquinone **16** followed by subsequent loss of HX. This could also function as a potent alkylating agent, again by Michael addition of a nucleophile to form **18** as in **Scheme 2**.



Scheme 2

Several quinones are capable of functioning as bis-akylating agents. The two alkylating sites tend to be arranged in a 1,4-cisoid dienyl arrangement, analogous to the general structure **19**.

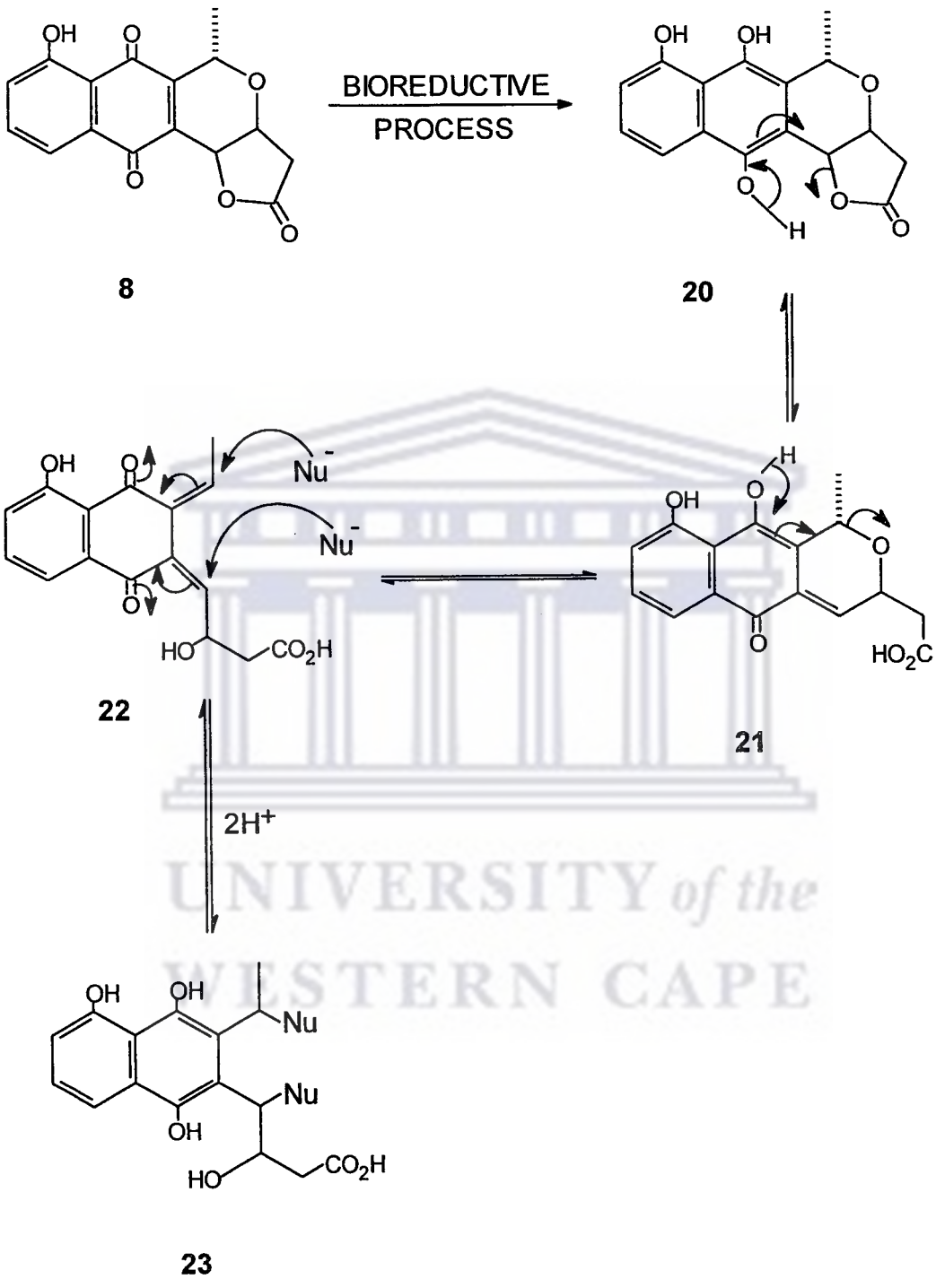


19

A compound such as nanaomycin D **8** which contains the fused pyrano-δ-lactone moiety is biologically inactive but can be transformed by *in vivo* reduction to an active hydroquinone which functions as a bis-alkylating agent. Thus quinone **8** is reduced *in vivo* to the corresponding hydroquinone **20** which undergoes two separate ring-opening steps as depicted in **Scheme 3**. It is the quinone methide **22** that results from the ring opening events that could act as a Michael-type acceptor towards nucleophiles (Nu^-) which may be certain nucleophilic centres in the D.N.A. molecule thereby binding the nucleic acid illustrated by **23**, and thus being insrumental in preventing replication and as a consequence, cell growth.

The biological properties described above have made compounds containing the naphtho[2,3-*c*]pyranquinone ring system **1** a challenging and worthwhile synthetic target, and since some of the more recently discovered natural compounds are structurally quite complex, the former compounds have provided significant synthetic challenges thereby elevating the status of this family of compounds and has resulted in several syntheses. [16, 17, 18]

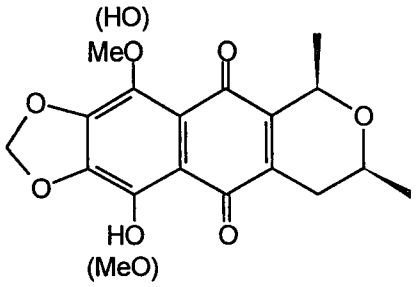
BIOREDUCTIVE PROCESS



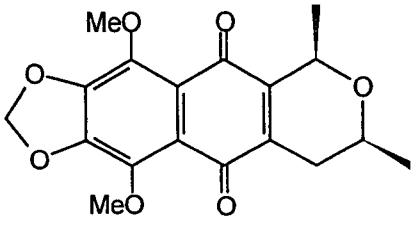
Scheme 3

The ventiloquinones are an important group of phytochemicals distributed in a fairly wide range of plants, but more specifically in *Ventilago maderaspatana* and *Ventilago calyculata*, both members of the Rhamnaceae family found primarily in India. [2] Currently, nearly fourty different quinones have been isolated from the extracts of the root bark of these two plant species. The majority of these quinones are naphthopyranquinones containing the naphthoisochroman skeleton **1** and exhibit antimicrobial activity.

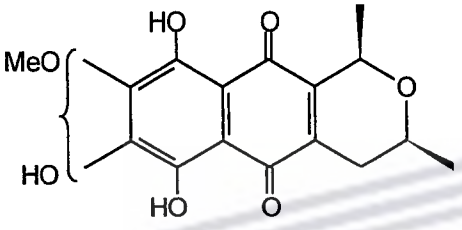
Thomson and co-workers [19] have isolated and characterised eight naphthoisochomans using mainly UV and nmr spectroscopy. Ventiloquinones A **24**, B **25**, C, **26**, D **27**, E **28** F **29**, G **30** and H **31** were identified to be present in the acetone extract of the root bark of *V. maderaspatana* while a further three naphthoisochromans, ventiloquinones I **32**, J **33**, and K **34** were identified in the acetone extract of the root bark of *V. calyculata*. The majority of ventiloquinones are *cis*-3,4,5,10-tetrahydro-1,3-dimethyl-1H-naphtho[2,3-*c*]pyran-5,10-quinones related to eleutherin **2**, but ventiloquinones F **29**, H **31**, I **32**, J **33** and K **34** are 6,9-quinones related to ventilagone **35**. All of the latter quinones are tricyclic systems, the left hand ring being quinonoid and the extreme right hand ring being a pyran having *cis* relative stereochemistry at C-1 and C-3.



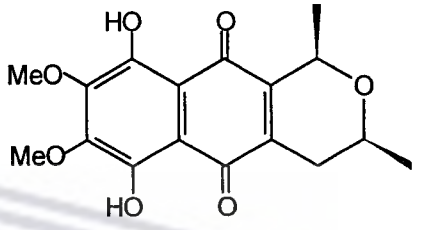
24 = A



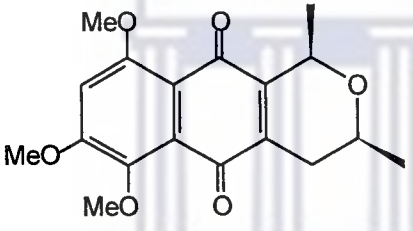
25 = B



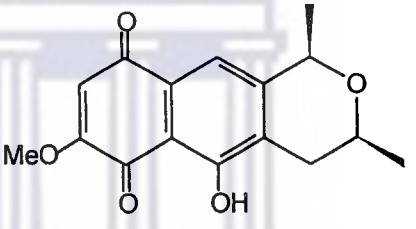
26 = C



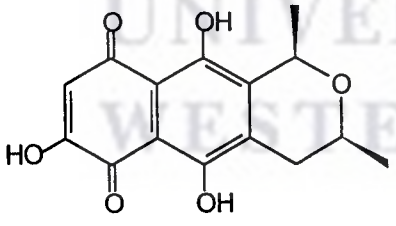
27 = D



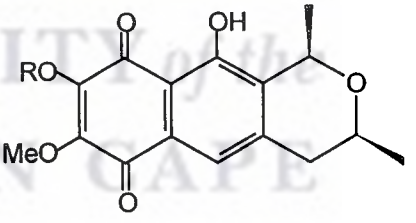
28 = E



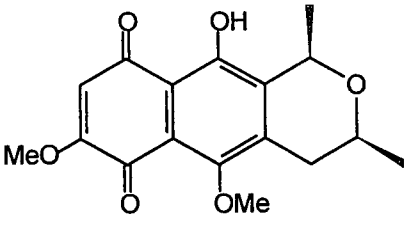
29 = F



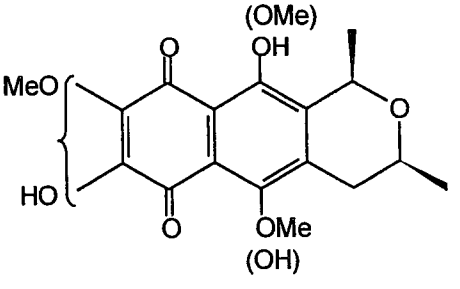
30 = G



31 R = Me = H
32 R = H = I

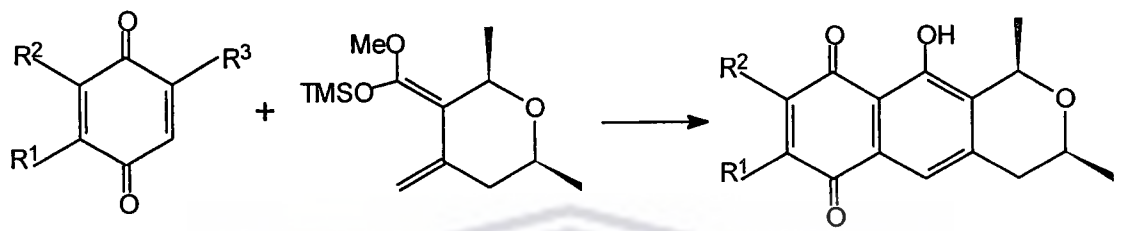


33 = J



34 = K

Brassard *et al.* [20] devised syntheses for the 6,9-isomers, ventilagone **35** and ventiloquinones H **31** and I **32** by the Diels-Alder methodology involving halogenated quinones and electron-rich heterocyclic dienes (**Scheme 4**).



36. $R^1 = R^2 = OMe$, $R^3 = Cl$ ⟶ 31. $R^1 = R^2 = OMe$

37. $R^1 = OMe$, $R^2 = Me$, $R^3 = Br$ ⟶ 38. $R^1 = OMe$, $R^2 = Me$

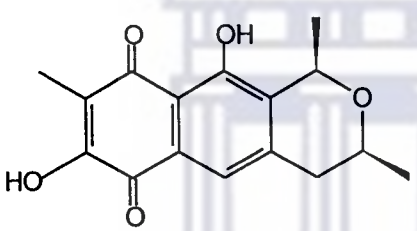
31 —(conc HCl / EtOH)→ 32

38 —(Demethylation)→ 35

Scheme 4

In the synthesis of ventiloquinones E **28** and G **30**, de Koning [21] and co-workers used a similar approach in the ring closure step to that used by Uno *et al.* [22,23] for the synthesis of eleutherin **2**, in order to achieve the *cis* configuration in the pyran ring. This method involved using mecuric acetate and sodium borohydride and yields for the *cis* 1,3-dimethylpyran relative stereochemistry could be maximised by ensuring that the protecting group at O-10 was as small as possible.

When ventiloquinone J was first isolated, Thomson *et al.* [19] proposed two possible structures, **33** and **39** based on the spectral data. In 1991, de Koning [21] *et al.* reported the first total synthesis of compound **39** and found that the physical properties of this compound did not agree with those published for the natural product. Thus it is believed that ventiloquinone J has the structure **33**, and thus its unambiguous synthesis had to be undertaken which is the first main aim of this work and is discussed in chapter 2.



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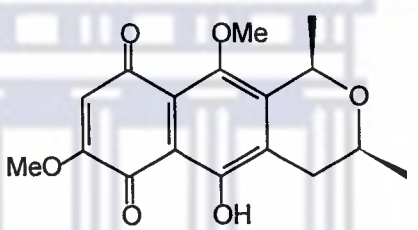


39

The synthesis of ventiloquinone F **29** is the main aim of the work described in chapter 3. Its notable structural features include a naphtho[2,3-*c*]pyran ring with a *cis*-1,3-dimethyl substitution pattern, the left hand ring at the 6,9-quinone oxidation level and an hydroxyl group at C-5. A great deal of regiospecific control had to be effected during the development of the synthetic route to ensure the correct oxygenation pattern in the final molecular structure. To our knowledge the synthesis of ventiloquinone F **29** has not previously been reported.

CHAPTER 1

SYNTHETIC STRATEGIES TOWARDS BENZO-FUSED PYRAN QUINONES

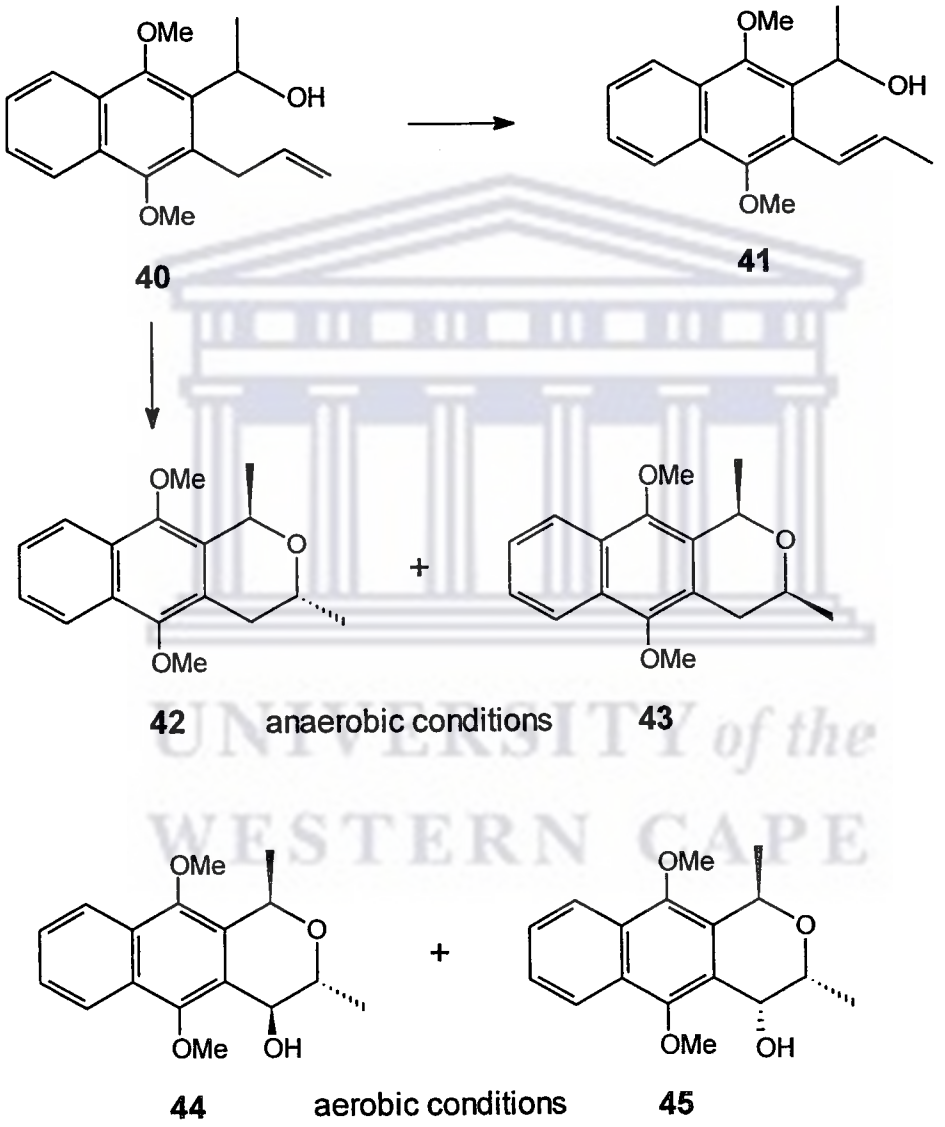
The literature review presented below relates to some of the more commonly used protocols for the preparation of benzo-fused pyran quinones.

1. Base induced cyclisation of naphthalene alcohols

In 1983, Giles *et al.* [24,25] synthesised several members of the aphid pigments and eleutherins both of which contain benzo-fused pyran quinones. The key step in these syntheses was the stereospecific but racemic base-induced cyclisation of precursor naphthalenic alcohols to form the corresponding naphtho[2,3-*c*]pyrans.

Thus treatment of the alcohol **40** with potassium *tert*-butoxide in *N,N*-dimethylformamide (DMF) in the absence of oxygen at 60°C for 5 minutes did not lead to the isolation of the conjugated allylic double bond product alcohol **41** as was desired, but rather led to the formation of the *trans* naphthopyran **42**. Longer reaction times led to the formation of a mixture of the *trans* and *cis* naphthopyrans **42** and **43** (**Scheme 5**).

When this same reaction was attempted in the presence of oxygen with longer reaction times, a 4:1 mixture of the hydroxylated naphthopyrans **44** and **45** was produced (**Scheme 5**).

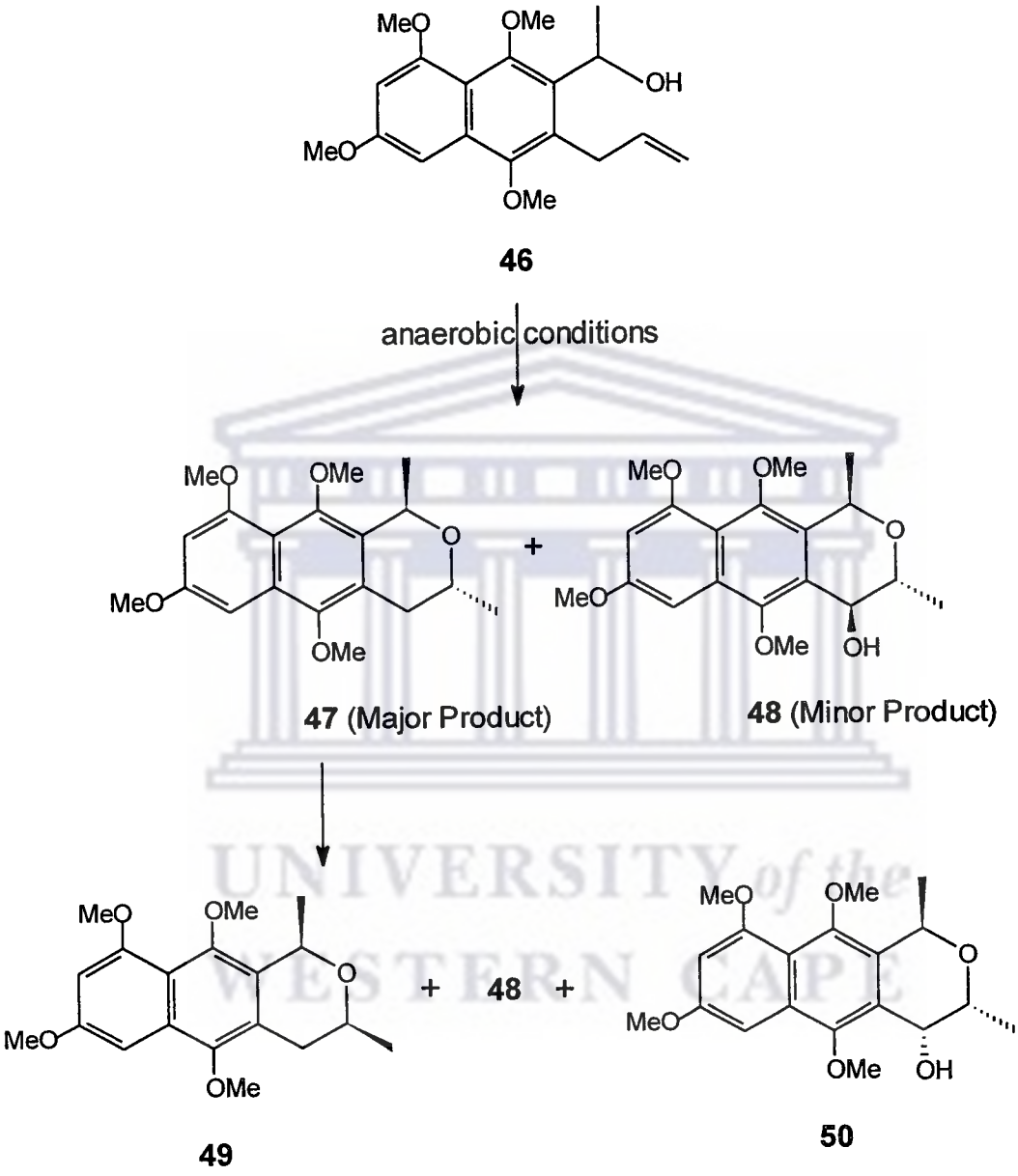


Scheme 5

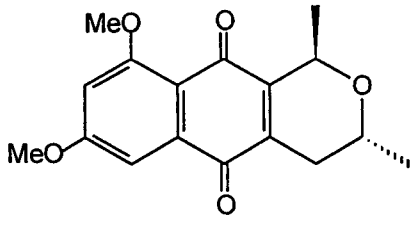
This protocol was used to synthesise naphthopyrans **47, 48, 49** and **50** by cyclisation of the allylic alcohol [24,26] **46** as depicted in **Scheme 6**. Treatment of allylic alcohol **46** with potassium *tert*-butoxide in DMF at 60°C under nitrogen afforded predominantly the *trans* naphthopyran **47** and a minor amount of the C-4 hydroxylated material **48**. Furthermore when the naphthopyran **47** was dissolved in DMF and treated with potassium *tert*-butoxide in air for 2 hours at 60°C, it afforded *cis* naphthopyran **49**, hydroxynaphthopyran **48**, and its C-4 epimer **50** as depicted in **Scheme 6**.

Oxidation of the naphthopyrans **47, 48, 49** and **50** with silver(II) oxide and nitric acid provided quinone **51**, 7-methoxyeleutherin **52** and hydroxynaphthopyranquinones **53** and **54** respectively.

Treatment of trimethoxynaphthalene **55** with potassium *tert*-butoxide in DMF at 60°C in a nitrogen atmosphere afforded solely the *trans* naphthopyran **56** and subsequent oxidation with silver(II) oxide and nitric acid produced isoeleutherin **3** (**Scheme 7**). [26]



Scheme 6



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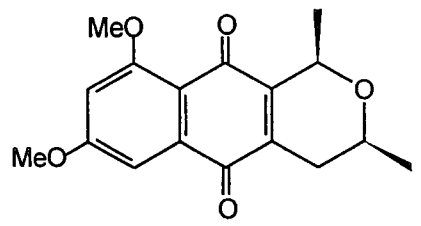
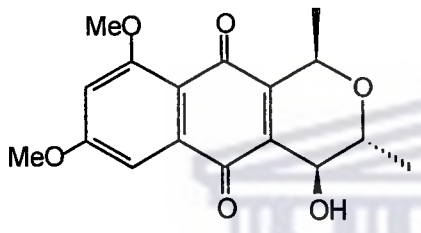
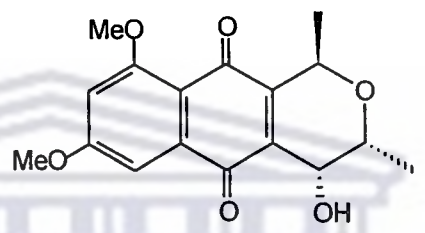


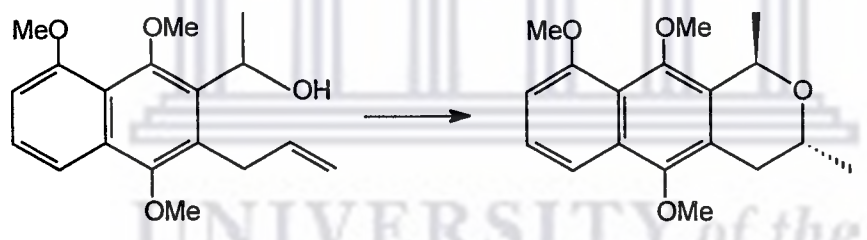
52



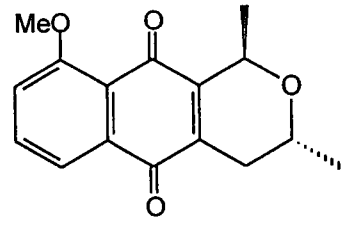
53



54



55 **56**

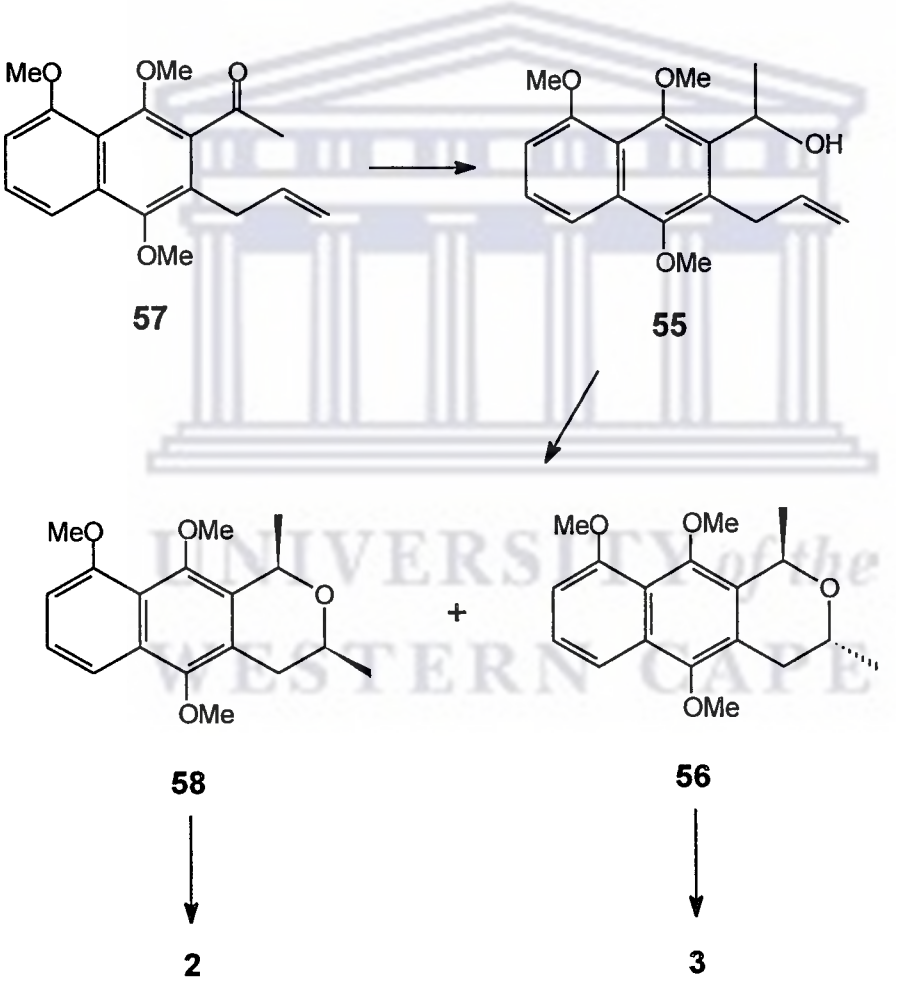


3

Scheme 7

2. Cyclisation of naphthalene alcohols via oxymercuration

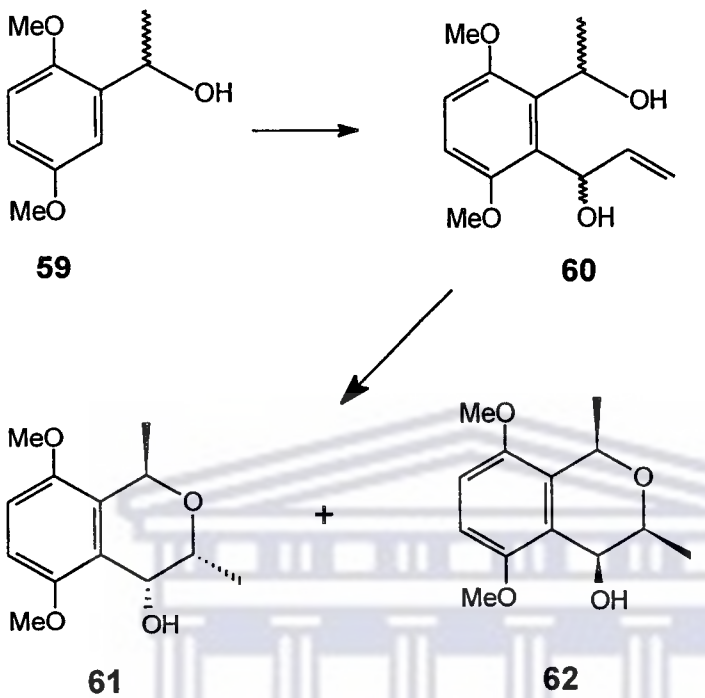
Eleutherin **2** and isoeleutherin **3** were synthesised by Uno *et al.* [22,23] by an intramolecular oxymercuration protocol on the naphthalene alcohol **55** in which case it led to the formation of the naphthopyrans **58** and **56** as shown in **Scheme 8**.



Scheme 8

Thus the naphthalene ketone **57** was reduced by treatment with lithium aluminium hydride at 0°C in dry ether to produce the alcohol **55** which was susequently treated with mercury(II) acetate in a tetrahydrofuran / aqueous sodium hydroxide mixture followed by reduction with sodium borohydride to give a (1:1) mixture of the two diastereomeric naphthopyrans, **58** and **56**. Each of the isomers was separated and each oxidatively demethylated to afford (±) eleutherin **2** and (±) isoeleutherin **3**.

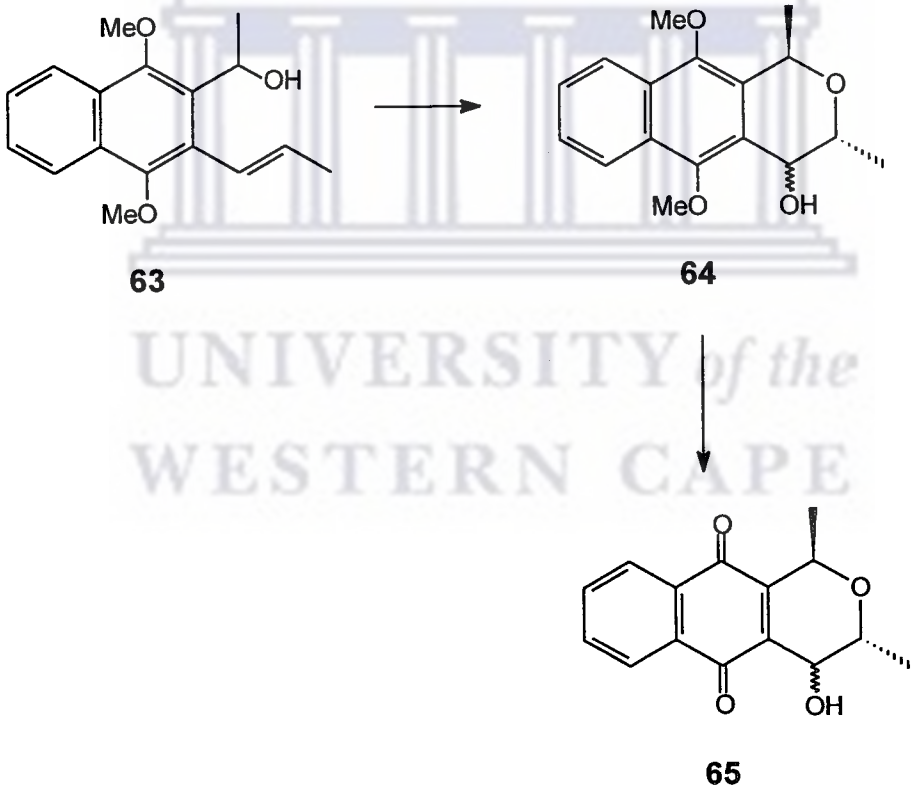
Kraus *et al.* [27] used oxymercuration during the synthesis of racemic hongconin. In this case alcohol **59** was converted into its dianion by treatment with two equivalents of n-butyllithium and this was followed by treatment with acrolein to give diol **60** as a racemic diastereometric mixture. The diol **60** was subsequently treated with mercury(II) acetate and the resulting organomercural complex was reduced with sodium borohydride to afford the two racemic hydroxy pyrans **61** and **62** in a ratio of 5:1 (**Scheme 9**).



Scheme 9

3. Oxidative cyclisation of naphthalene alcohols

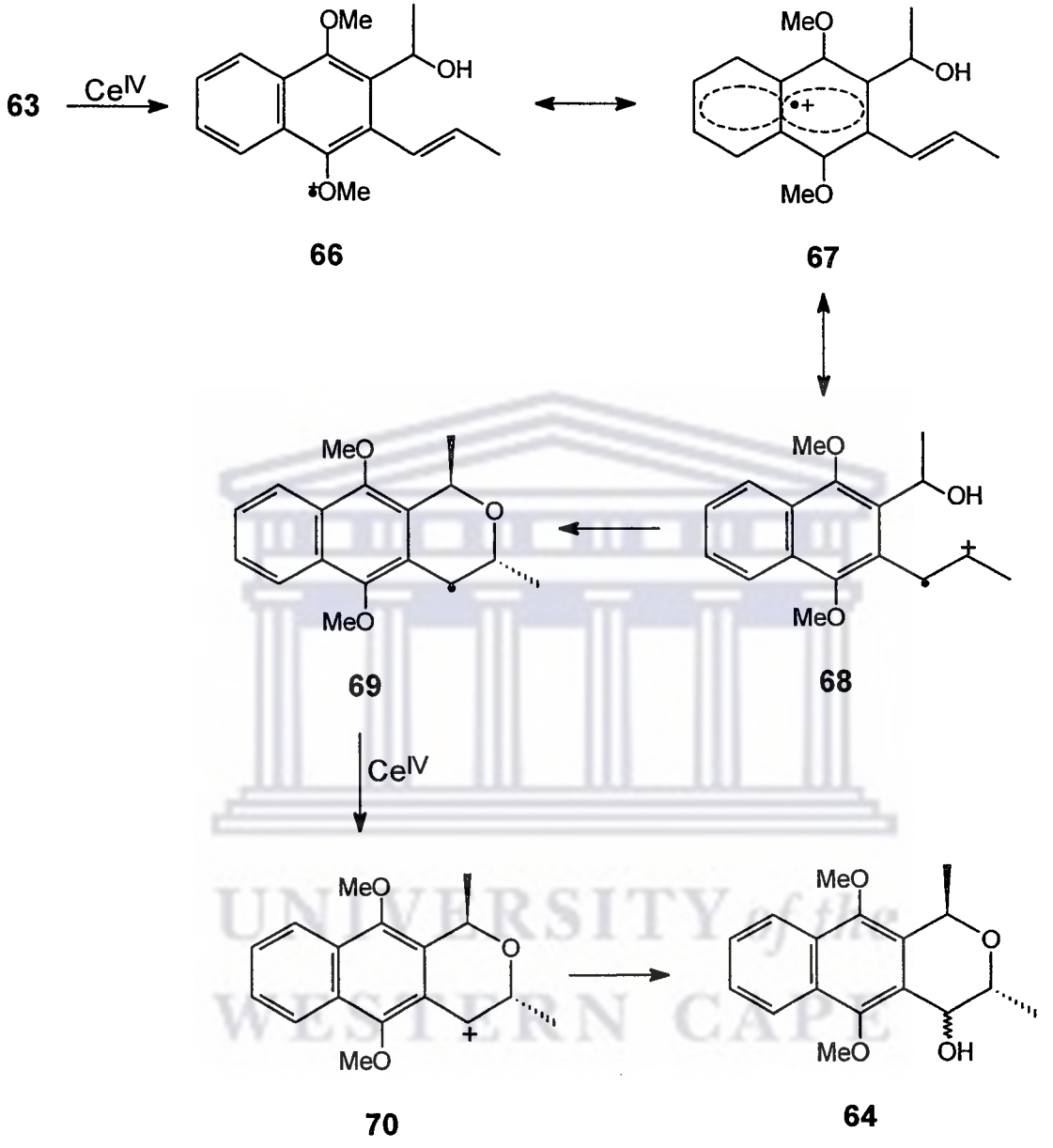
Giles *et al.* [28,29] have reported alternative methodology for the conversion of methoxy 2-alkenyl-(1-hydroxyalkyl)benzenes into the respective benzoisochroman-4-ols in moderate yields. The naphthalene alcohol **63** was treated with four molar equivalents of aqueous cerium(IV) ammonium nitrate (CAN) to afford the naphthopyranquinone **65** in a yield of 79% as depicted in **Scheme 10**.



Scheme 10

Since the intermediate **64** was isolated upon treatment of alcohol **63** with two molar equivalents of cerium(IV) ammonium nitrate (CAN), they proposed that cyclisation precedes oxidation. A mechanism consistent with the results has been proposed and is outlined in **Scheme 11**.[28]

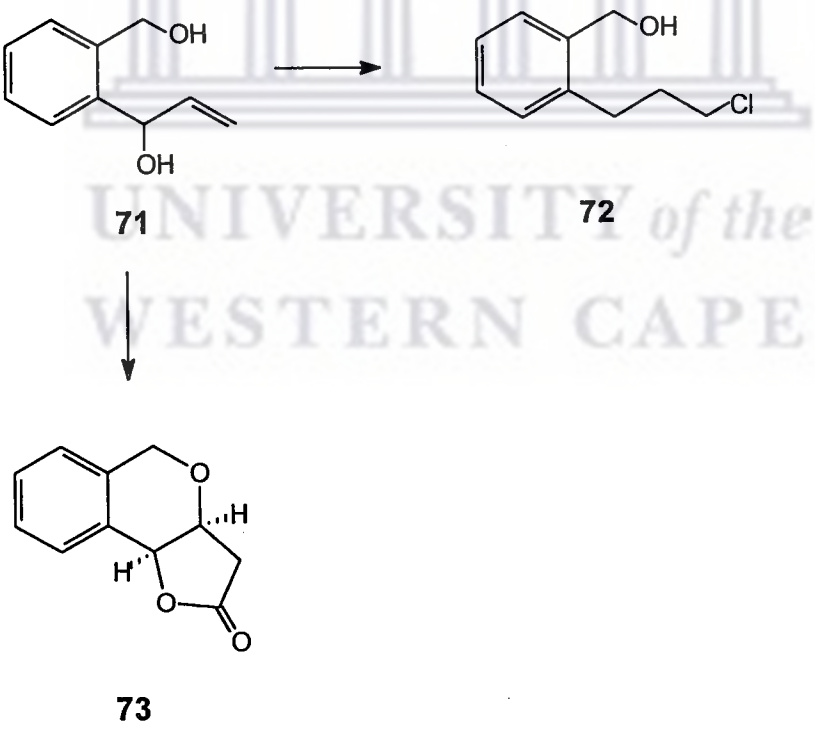
The methoxy group *ortho* to the alkenyl substituent plays an important role in the cerium(IV)-promoted oxidative cyclisation of the alcohol **63**. A resonance stabilised radical cation (**66** ↔ **67** ↔ **68**) is formed by oxidation of **63** at the methyl group *ortho* to the alkenyl substituent with 1 molar equivalent of ceruim(IV). Ring closure and loss of a proton gives rise to a benzilic radical **69** which undergoes oxidation with a second cerium(IV) ion to give the benzilic carbonium ion **70**. Nucleophilic attack by water affords benzoisochroman-4-ol **64**.



Scheme 11

4. Alkoxycarbonylation of hydroxyalkenes

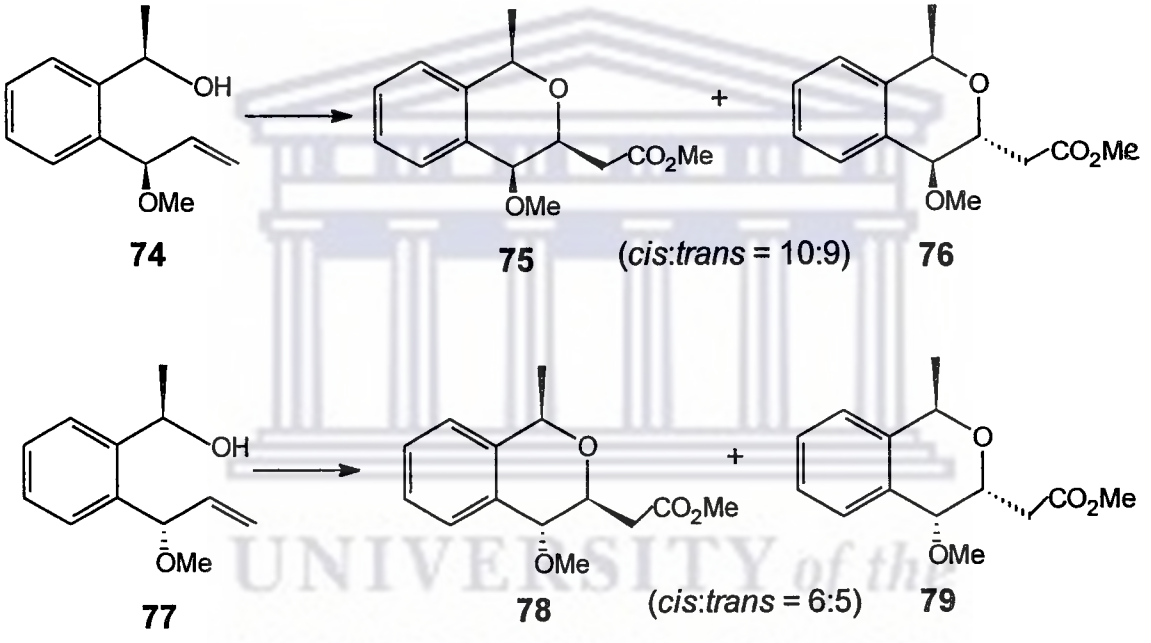
Intramolecular alkoxycarbonylation has been used by Semmelhack [30] to prepare benzopyran lactones. Model reactions investigating the stereoselectivity of the intramolecular alkoxycarbonylation reaction established the requirement regarding the use of a stoichiometric amount of palladium diacetate to afford the desired pyran **73,** with the *cis* 3,4-isomer predominating over the corresponding *trans* isomer in this example, while the standard catalytic conditions of 0.1 molar equivalents of palladium dichloride resulted alternatively in the formation of **72** in which no carbonylation had occurred and is depicted in **Scheme 12.**



71 **72** **73**

Scheme 12

Carbonylation of the monomethyl ethers **74** and **77** gave a nearly equal ratio of their respective 1,3-*cis* and *trans* isomers,**75** and **76** and **78** and **79**, when each were treated with 1 molar equivalent of palladium diacetate under an atmosphere of carbon monoxide in dry tetrahydrofuran as shown in **Scheme 13**.

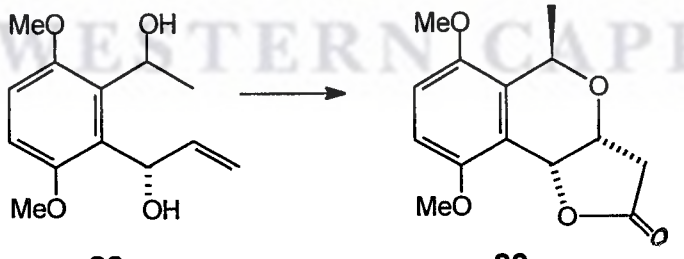


Scheme 13

Semmelhack [31,32] developed a methodology for the synthesis of nanaomycin A **5** by the conjugate addition of an acylate-nickel complex **80** to an appropriate naphthoquinone monoketal **81** followed by treatment with an excess of allyl iodide that led to the adduct **82**. The ketal unit **82** was hydrolysed under argon with a mixture of

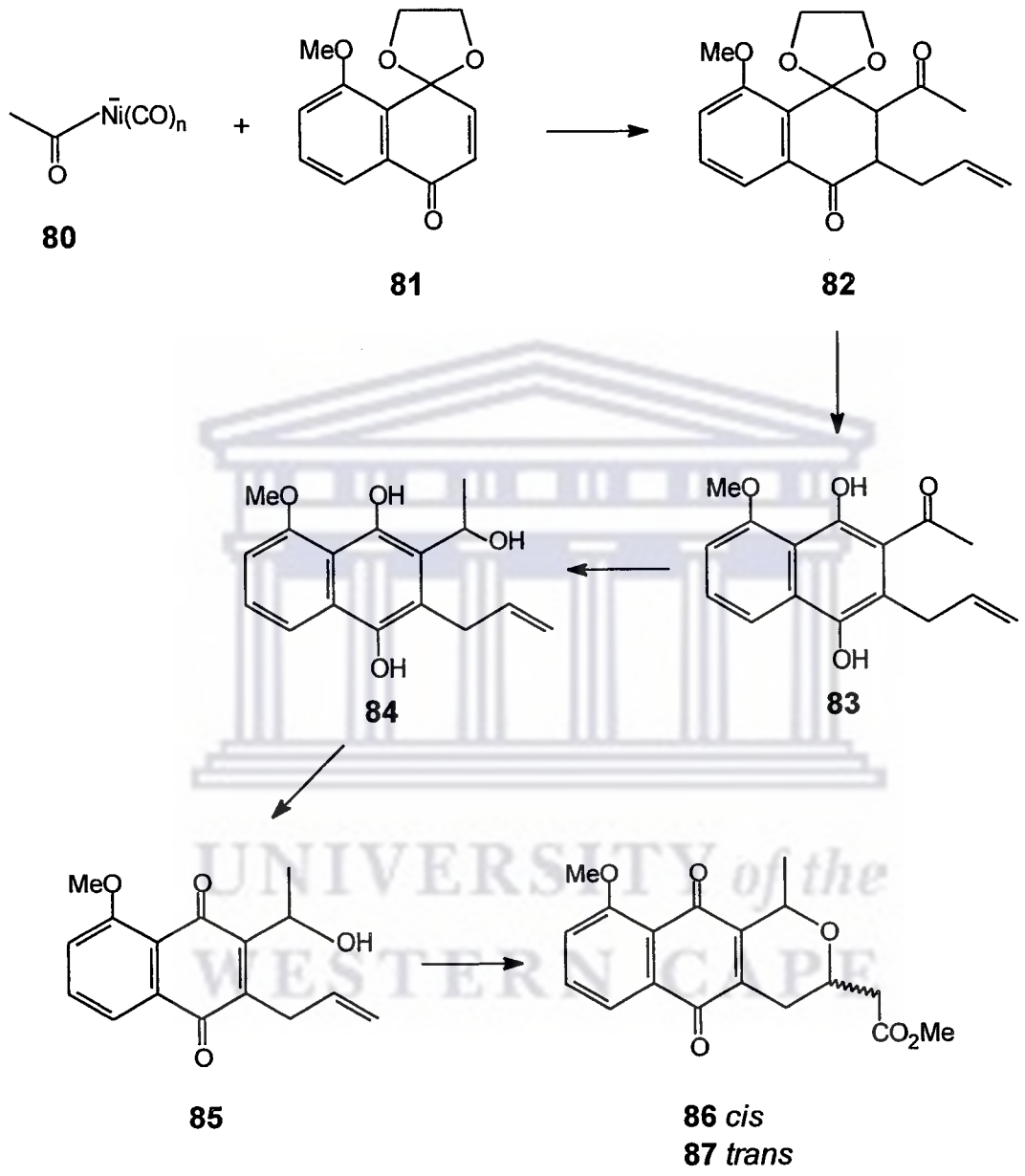
6M hydrochloric acid and dioxane to produce the hydroquinone **83**. Reduction of **83** with sodium borohydride afforded the triol **84** and reoxidation with DDQ furnished the key intermediate quinone **85**. This was followed by treatment of **85** with a catalytic amount of palladium dichloride, excess cupric chloride, and carbon monoxide in methanol to afford the *cis* and *trans* stereoisomeric esters **86** and **87** in the ratio of 3:2 and in a yield of 66% (**Scheme 15**). Previous work [8,33] had also demonstrated the equilibrium between esters **86** and **87**. Finally the deprotection of the methoxy and ester groups produced (+)-nanaomycin A **5** and its isomer.

Kraus and co-workers [34] also used intramolecular alkoxycarbonylation of hydroxyalkenes to obtain the lactone **89**, a key intermediate for the preparation of kalafungin **4**. In this instance the dimethoxybenzene **88** was treated with palladium diacetate and cupric chloride under a carbon monoxide atmosphere to provide a good yield of **89** (**Scheme 14**).



88 **89**

Scheme 14

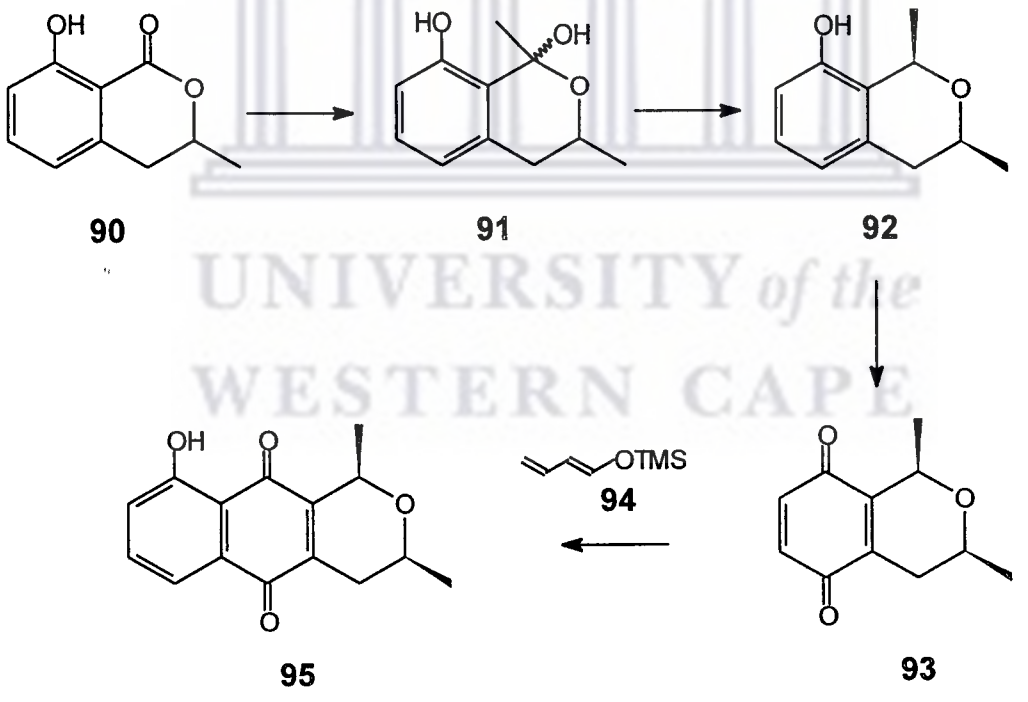


Scheme 15

5. Diels-Alder methodology

Appropriately fuctionalised dienes and dienophiles have been used to construct the required oxygenation pattern of the naphthopyranquinone skeleton by making use of Diels-Alder methodology.

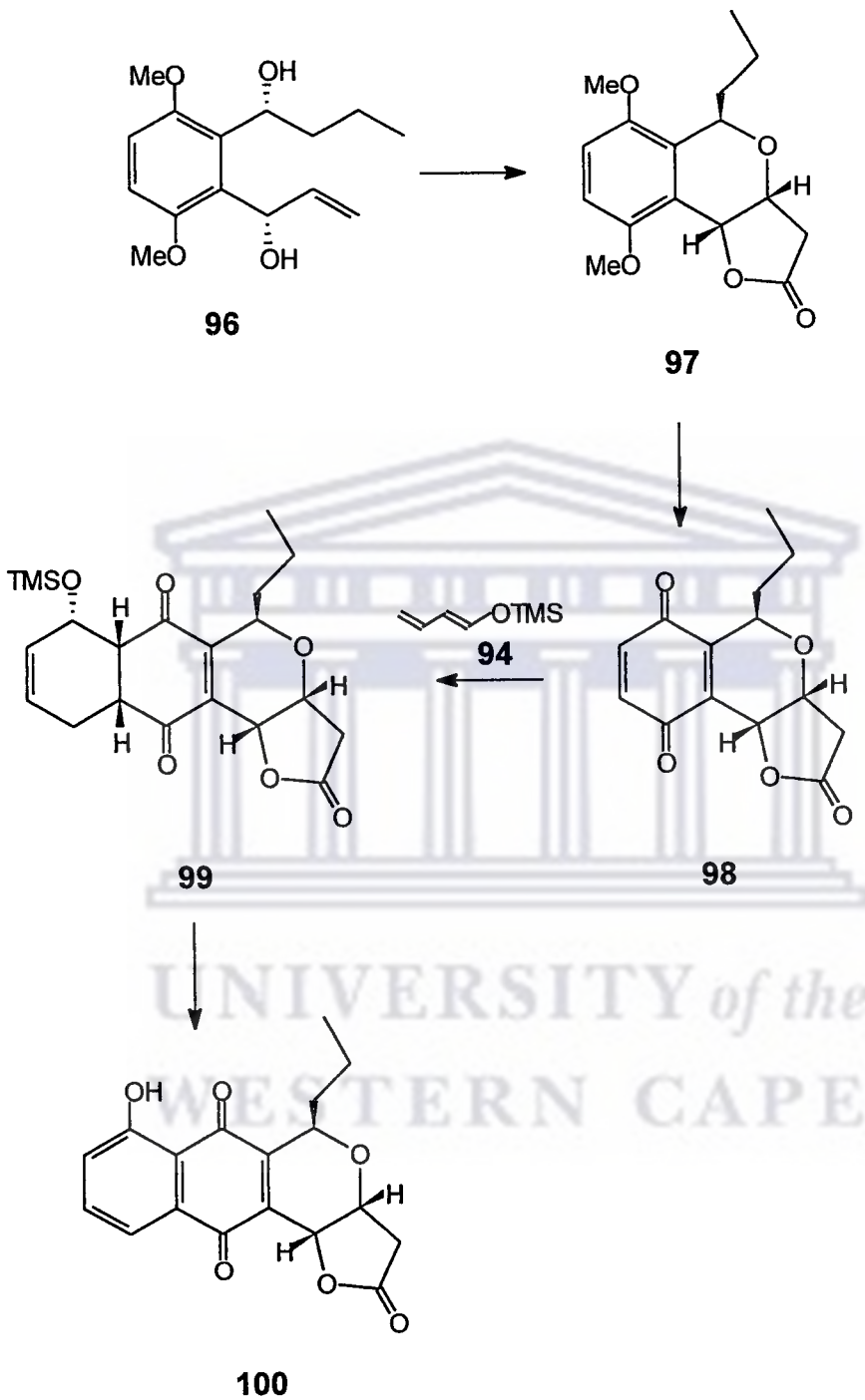
Kraus *et al.*[35] prepared racemic demethyleleutherin **95** in four steps starting from the lactone **90** which was treated with methyllithium at –78°C to afford the lactol **91** as depicted in **Scheme 16**.



Scheme 16

Reduction of **91** with trifluoroacetic acid and Et_3SiH gave the *cis* 1,3-dimethylbenzopyran **92** which was oxidised to the quinone **93** by treatment with Fremy's salt followed by cycloaddition with 1-(trimethylsilyloxy)-butadiene **94** to give after hydrolysis and aromatisation (±)-demethyleleutherin **95**.

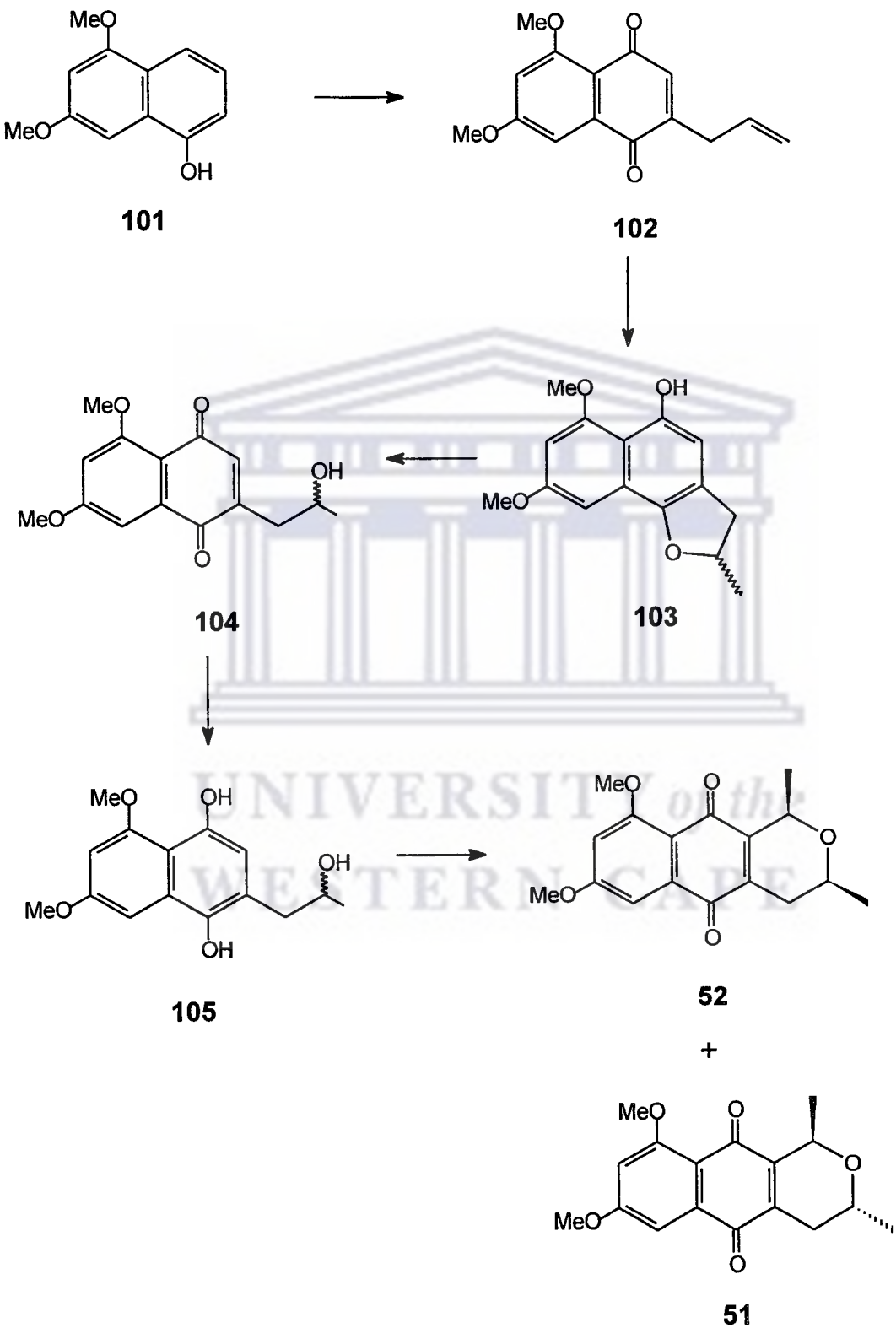
In 1993 Kraus and Li [36] synthesised frenolicin B **100** (**Scheme 17**) by palladium catalysed carbonylation and cyclisation of diol **96** which produced lactone **97**. Oxidation of lactone **97** using silver(II) oxide and nitric acid provided quinone **98** which was treated with **94** to afford the regiospecific Diels-Alder adduct **99**. Treatment of **99** with Jones reagent gave frenolicin B **100**.



Scheme 17

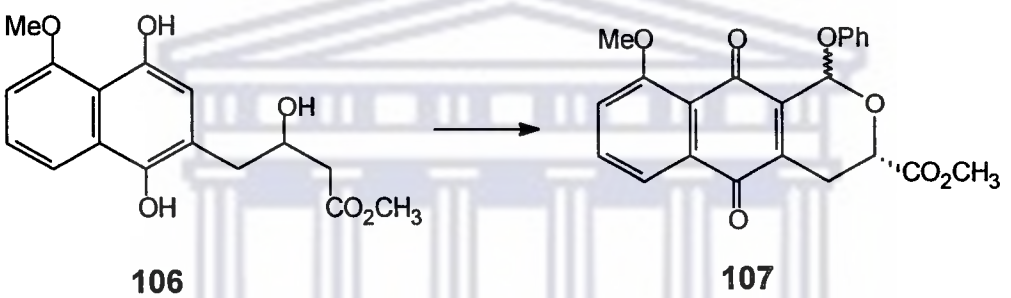
6. Condensation of 3-(2'-hydroxyalkyl)quinones with aldehydes

Eisenhuth and Schmid demonstrated this methodology in the first synthesis of the eleutherins **2** and **3**.[4, 37] An adaptation of this method was later used by Cameron *et al.*[38] for the synthesis of racemic 7-methoxyeleutherin **52** and its *trans* isomer **51** from 5,7-dimethoxy-1-naphthol **101** as depicted in **Scheme 18**. Allylation of **101** and Claisen rearrangement of the product afforded the corresponding *ortho*-allyl naphthol which on oxidation with Fremy salt produced the allyl quinone **102**. Reduction of **102** with tin(II) chloride to the corresponding hydroquinone was followed by refluxing in aqueous hydrobromic acid which effected cyclisation to the dihydrofuran **103** and then reoxidation with iron(III) chloride resulted in the formation of quinone **104**. Finally, hydroxypropylquinone **104** was reduced with zinc and hydrochloric acid to its corresponding quinol **105**, which was followed by condensation with acetaldehyde to afford a 3:1 mixture of the *cis* and *trans* pyranquinones **52** and **51** respectively.[39] The *cis* isomer **52** was then equilibrated to the thermodynamically more stable *trans* isomer **51** by treatment with phosphoric acid.[38]



Scheme 18

Some frenolicin B **100** analogues have been prepared by the condensation of hydroquinone **106** with benzaldehyde in acetone which was followed by oxidation to afford the essential key intermediate quinone **107** (**Scheme 19**).[40]

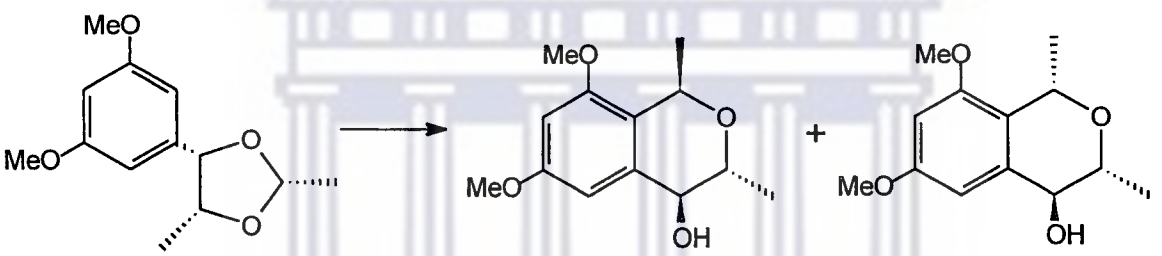


106 **107**

Scheme 19

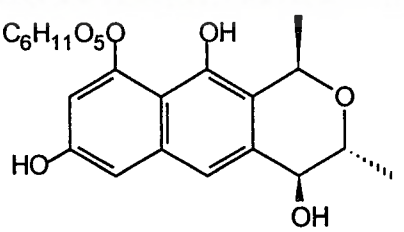
7. Lewis acid promoted cyclisation of naphthyl- and phenyldioxolanes

Giles *et al.* [41] treated phenyldioxolane **108** with two equivalents of titanium tetrachloride in dichloromethane at –78°C and obtained the benzopyrans **109** and **110** in a ratio of 4:1 (**Scheme 20**). These benzopyrans are structurally related to an aphid pigment, namely glucoside B **111**.[42]



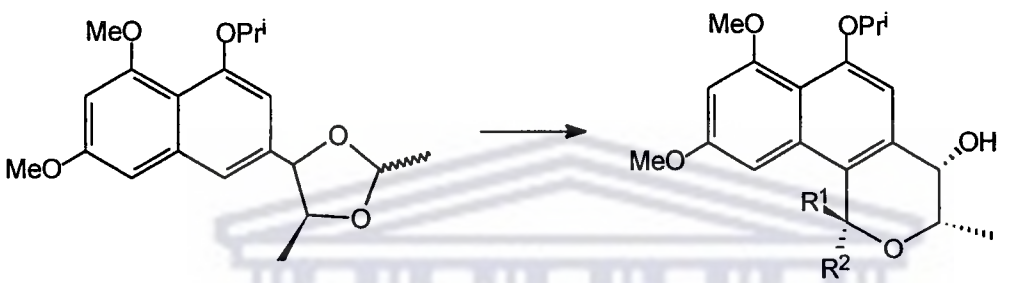
108 **109** **110**

Scheme 20



111

Using the same experimental conditions the 4-naphthyldioxolane **112** afforded the angular racemic naphthopyrans **113** and **114** [43] (**Scheme 21**). A synthesis of linear naphthopyrans has also been reported using this methodology. [44]



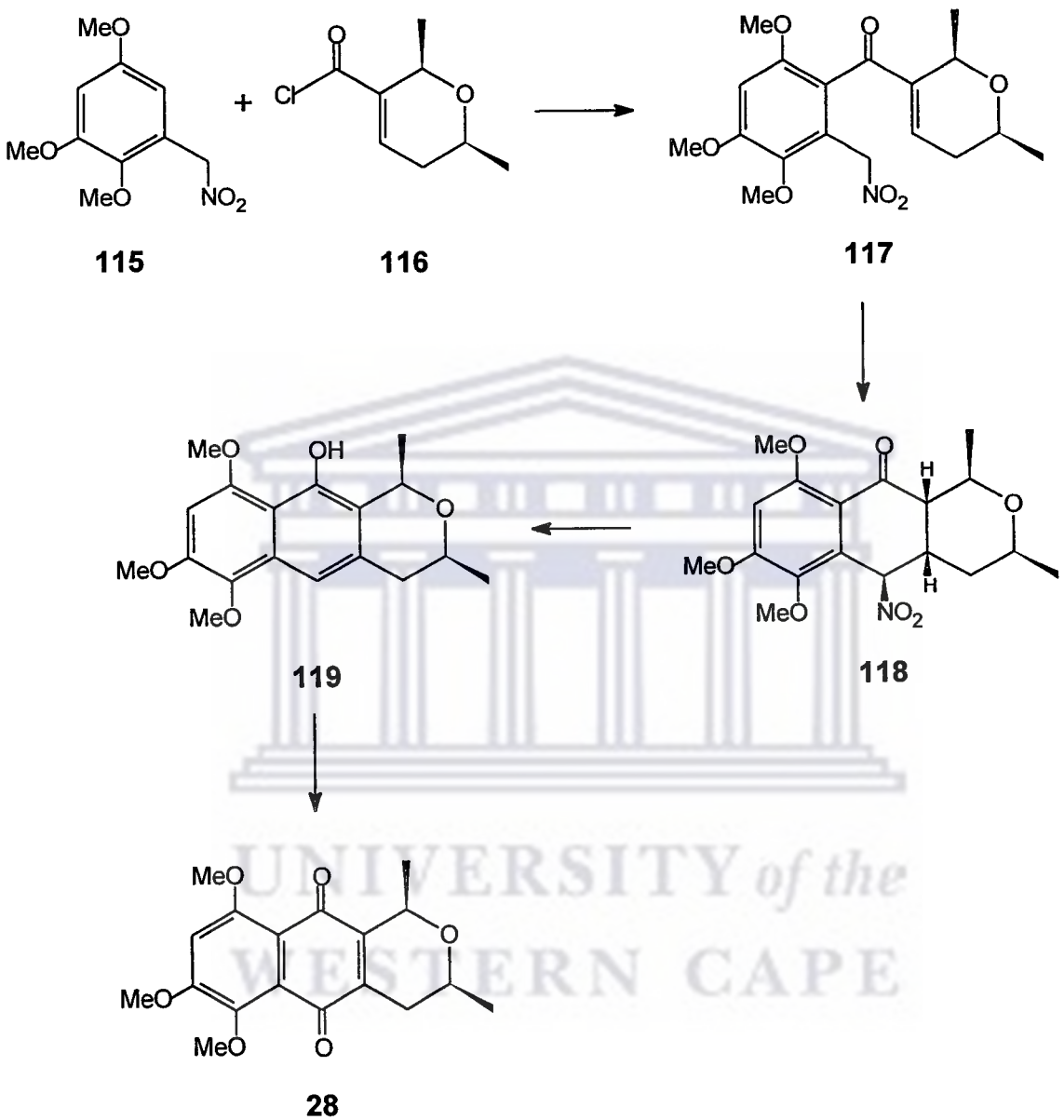
112

113: R^1 = Me, R^2 = H
114: R^1 = H, R^2 = Me

Scheme 21

8. Electrophilic aromatic substitution using acyl halides

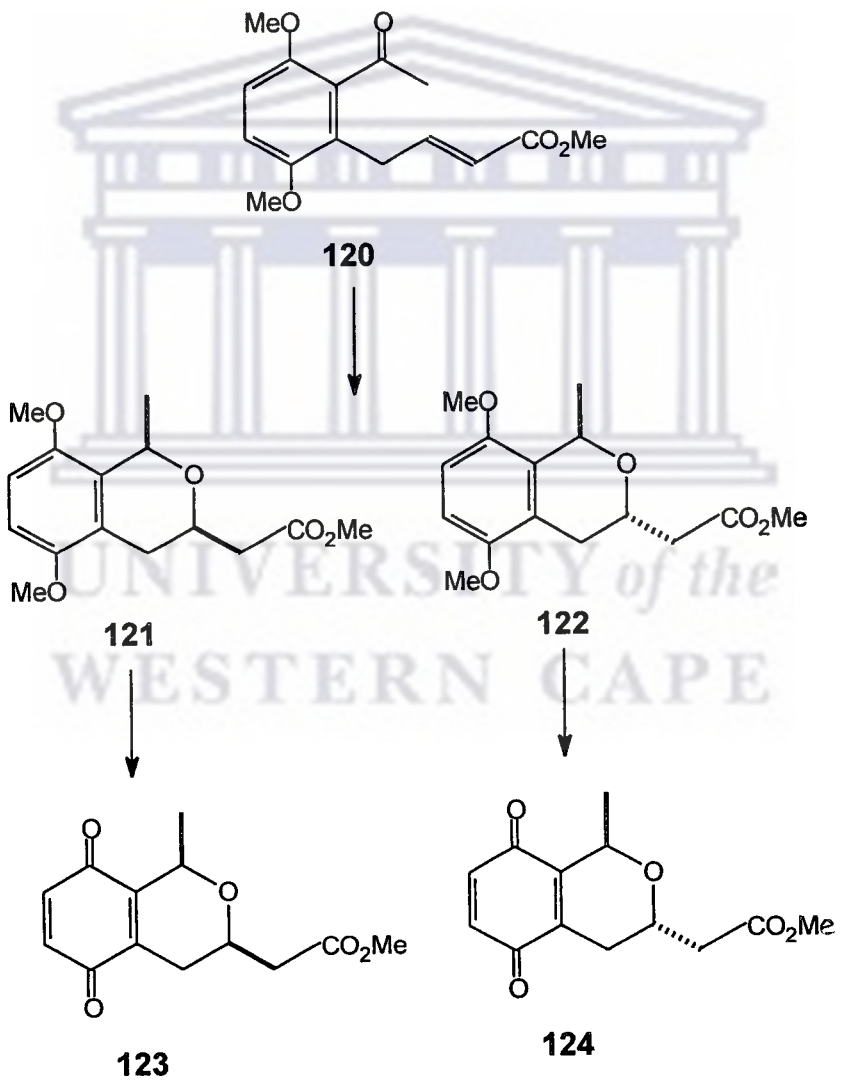
Naphthopyrans have also been generated by treating a suitably substituted nitroalkylbenzene with a suitably activated pyran synthon. [45,46] Thus reaction between the trimethoxyarylnitro alkane **115** and the acid chloride analogue of the pyran **116** with aluminium trichloride in chloroform at 0°C afforded the expected aryl ketone **117**. Subsequent transformation of **117** by treatment with benzyltrimethylammonium hydroxide afforded **118** followed by thermally induced nitrous acid elimination gave the naphthol **119**. Oxidation of **119** with CAN afforded ventiloquinone E **28** (**Scheme 22**).



Scheme 22

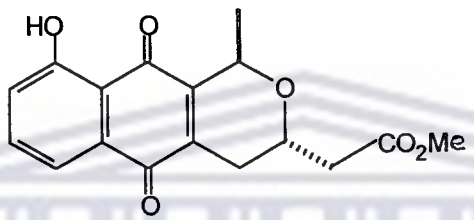
9. Reductive cyclisation with sodium borohydride

An efficient route to the formation of 9-deoxynanaomycin A methyl ester **125** was reported by Yoshii and Kometani in 1981. [47] The conjugated ester **120** was reduced with sodium borohydride in methanol to produce a mixture of *cis*- and *trans*-isochromans, **121** and **122** in a ratio of 1:3.5 as depicted in **Scheme 23**.



Scheme 23

Treatment of **121** and **122** with aqueous CAN resulted in their oxidation to the corresponding quinones **123** and **124**. Quinone **124** was treated with 1- acetoxybuta-1,3-diene in toluene followed by treatment with sodium carbonate in aqueous ethanol to form **125** in a 78% yield.[47]

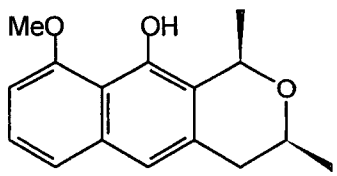


125

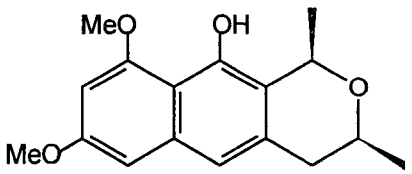
Racemic nanaomycin A **5** was also synthesised via this methodology .[48]

10. Synthesis from other natural compounds

Many pyranquinones have been obtained by transformation of other naturally occurring compounds.[49] For example, eleutherin **2** and 7-methoxyeleutherin **52** have been synthesised from karwinaphthol A **126** and B **127** (from *Karwinskia humboldtiana*)[50] respectively by treatment with Fremy's salt



126



127

Other syntheses of naphthopyrans from naturally occuring compounds include, some ventiloquinones, [20,51] the enantiomer of actinorhodin, [52] and some protoaphins. [53]

11. Other synthetic strategies

Various other synthetic methodologies towards the construction of naphthopyranquinones have been developed. The detail of these procedures have not been discussed in this work but are considered important and relevant and some of these are mentioned briefly below.

The use of Michael acceptor 4-(5-alkoxy-2-furyl)-3-buten-2-ones, [54,55] and the use of a carbohydrate-based Michael acceptor, [56,57] are examples of syntheses making use of phthalide precursors that have been reported.

Conjugate addition to quinones has also been used to construct naphthopyranquinones. Examples include the addition of 2-*tert*-butoxyfuran, [58,59] and the addition of 2-trimethylsilyloxyfuran. [60,61,62]

Liebeskind *et al.* [63,64] established a facile synthesis of racemic nanaomycin A **5**, in which the naphthoquinone nucleus was constructed by intramolecular alkyne insertion into a phthaloylmetal complex. Many other organometallic protocols have also been attempted. [65-68]

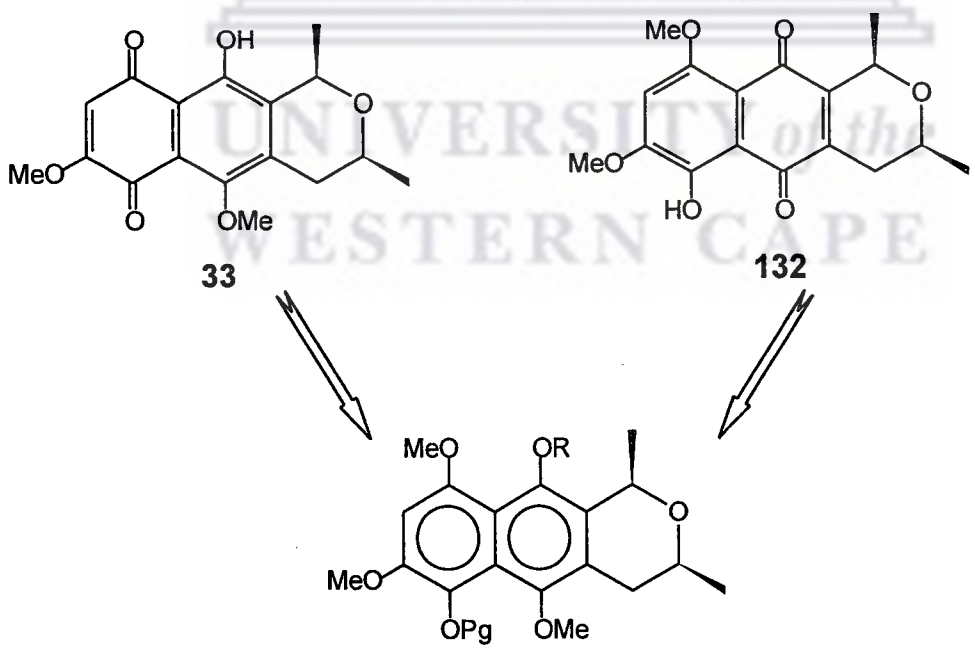
Other methods include electrocyclic ring opening of benzocyclobutanones, [69,70] oxidative cleavage of benzindenes, [47,48] and photoannulation. [71]

CHAPTER 2

SYNTHESIS OF VENTILOQUINONE J

Ventiloquinone J **33** and 6-hydroxy-7-methoxyeleutherin **132**, the initial target compounds of this work both belong to the same family of biologically active natural naphthopyrans that possess the same *cis* stereochemistry at C-1 and C-3 in their pyran rings.

It was proposed that both of these compounds may be derived from the same pre-cursor, the naphthopyran **133** as is represented by the retrosynthesis below.

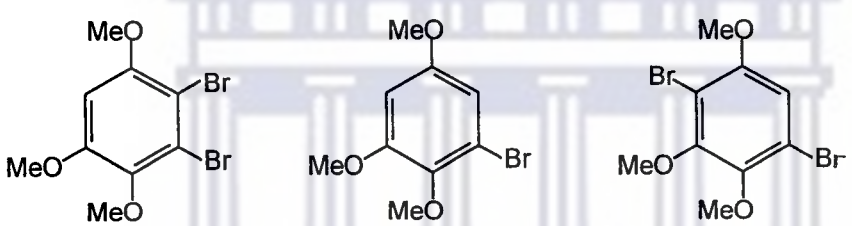


33 **132**

133

Where Pg = Protecting group

The dibromobenzene **134** would represent the left hand ring and it was expected that this compound could be synthesised from vanillin **137** which is commercially available. In 1939 Dorn [72] synthesised 1-bromo-2,3,5-trimethoxybenzene **135** from vanillin, by bromination, followed by replacement of the aldehyde by an hydroxyl group via the Daken reaction and subsequent methylation. Further bromination led to the supposed formation of 1,4-dibromo-2,3,5-trimethoxy benzene **136**. More recent work by McOmie [73] and Crowther [74] has shown however that the alleged 1,4-dibromo-compound was in fact not formed, but rather the 1,2-dibromo-3,4,6-trimethoxybenzene **134** isomer.

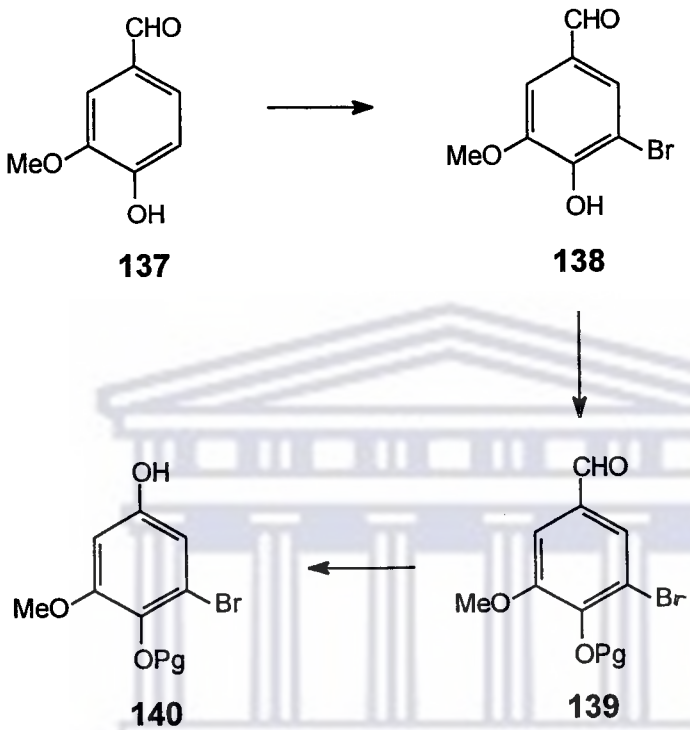


134 **135** **136**

Bromination of vanillin **137** in acetic acid yields 3-bromovanilin [72] **138** in good yield. The phenolic group of **138** would need to be protected viz. **139** in such a manner that it could readily be unmasked at a later stage to afford either the phenol **132** or by suitable transformations be oxidised to ventiloquinone J **33**.

To ensure the correct oxygenation pattern of the left hand ring, the proposed idea was to convert the aldehyde **139** *via* a Baeyer Villiger oxidation [75] into the phenol **140**.

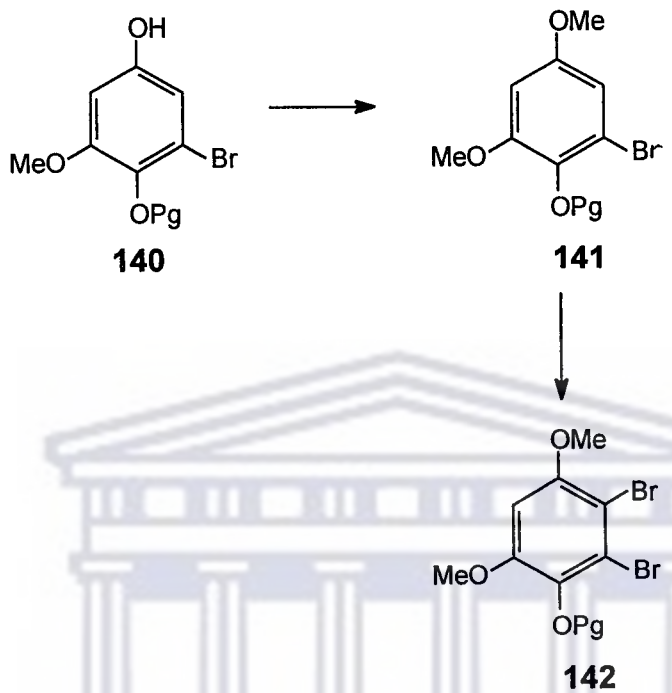
During this latter reaction the more electron rich donating group migrates to the electron deficient oxygen. It is also possible for migration of the hydrogen rather than the aryl group to occur. [76] This is summarised in **Scheme 24** below.



Scheme 24

It has been found in aryl systems that when an electron withdrawing group is *para* to the aldehyde group, hydrogen migration occurs to give the carboxylic acid, rather than the desired formate ester. This places obvious restrictions on the type of protecting group that can be chosen. If the *para* group is electron donating, the formate ester is formed which may be easily hydrolysed to the phenol **140**. Subsequently the phenol **140** may be methylated with dimethyl sulphate and potassium carbonate to afford **141**, followed by bromination with

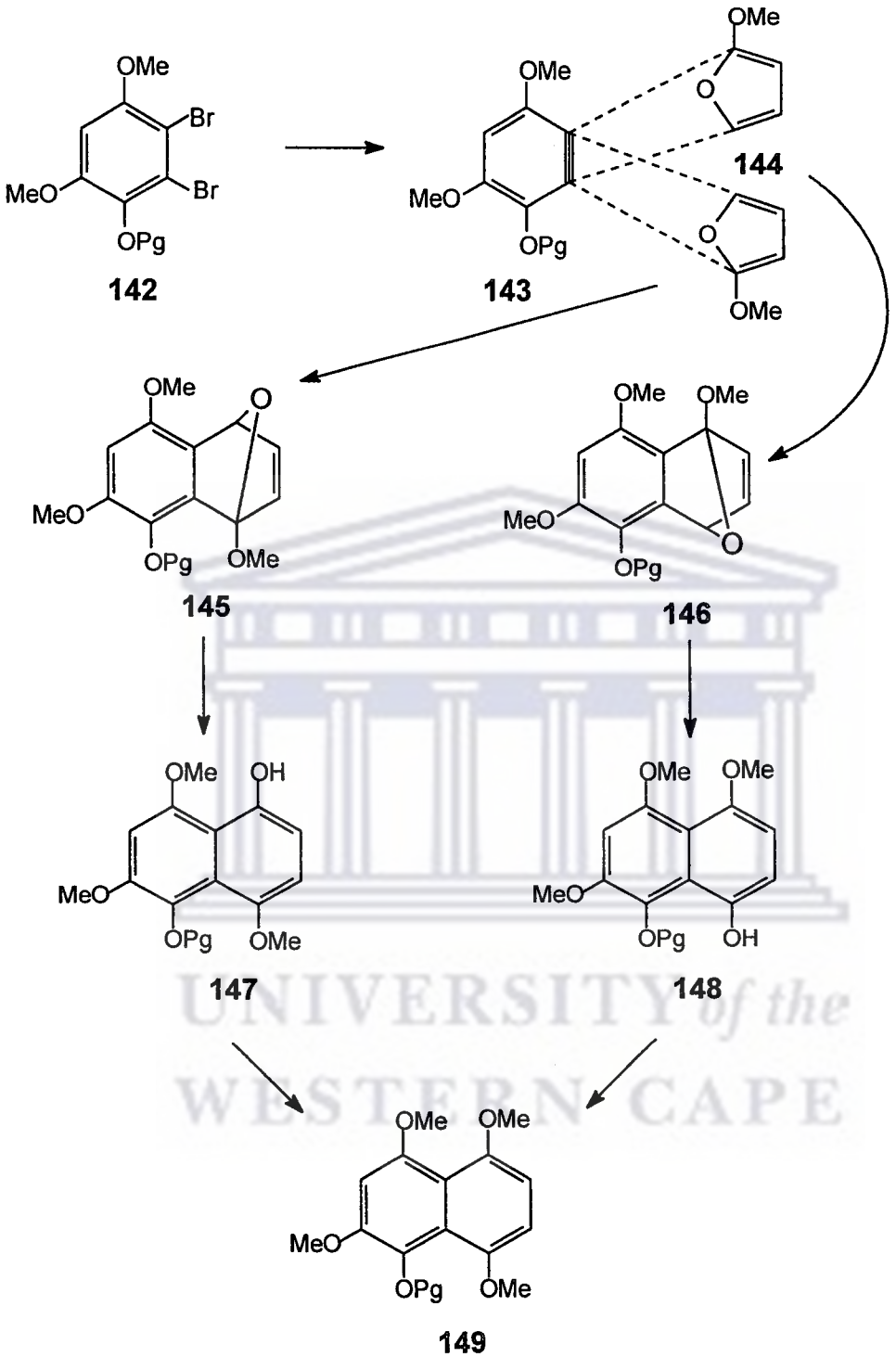
bromine in benzene to form the trialkoxy-dibromo benzene analogue **142**, as depicted in **Scheme 25**.



Scheme 25

It was decided to transform **142** into the naphthalene moiety **149** by way of a Diels-Alder reaction between the benzyne **143** derived from the dehalogenation of **142** and 2-methoxyfuran **144**. This method would provide the required oxygenation substitution pattern for the naphthalene nucleus found in ventiloquinone J **33** and 6-hydroxy-7-methoxyeleutherin **132**.

The desired benzyne intermediate **143** could be generated from compound **142** by removal of bromine by lithium-halogen exchange using *n*-butyllithium in tetrahydrofuran at -78°C.

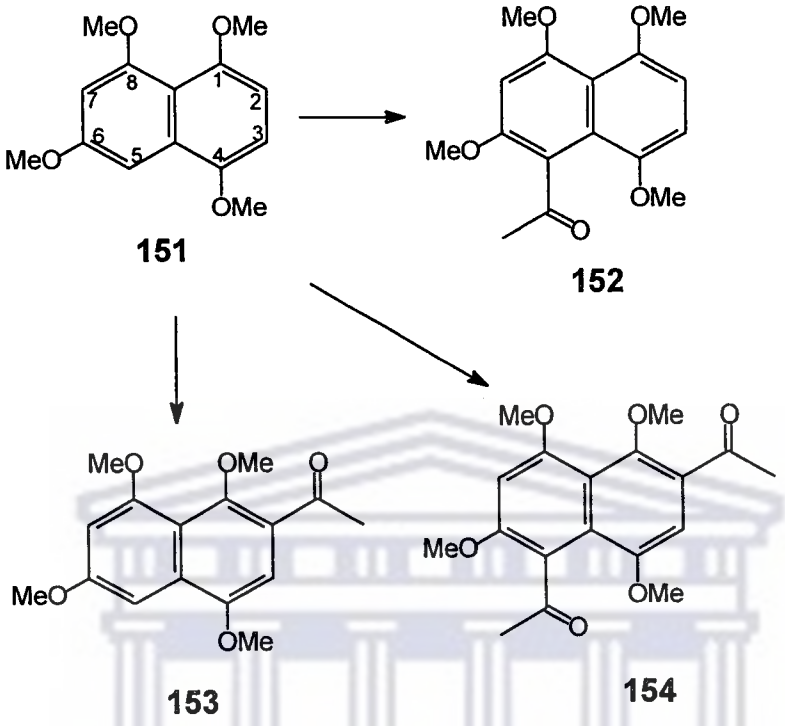


Scheme 26

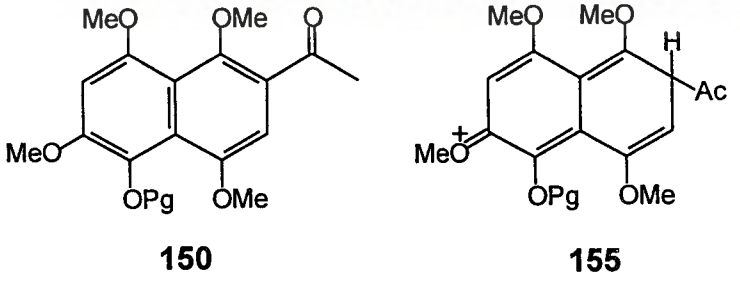
Addition of 2-methoxyfuran **144** to this benzyne **143** can give rise to the two regioisomeric adducts [77] **145** and **146**. The 1,4-oxa heterocyclic ring may be easily opened by acid catalysis to give the two naphthols **147** and **148** which could be used as such. Methylation of this mixture of naphthols should give the same naphthalene **149** as shown in **Scheme 26**. In work by de Koning, [80] it was found that for this Diels-Alder reaction, the optimum yield was obtained when using 0.9 mole equivalents of *n*-butyllithium relative to the dihalogenated aryl system. When an equimolar quantity of base to dihalogenated benzene was used, a butylated by-product was isolated, the presence of which increased with the scale of reaction.

To commence the construction of the pyran ring, compound **149** would need to be selectively acetylated at the C-2 position to afford the acetylnaphthalene **150**. Giles and Green [79] have shown that acetylation of 1,4,6,8-tetramethoxy naphthalene **151** with acetic acid in the presence of trifluoroacetic anhydride leads to the formation of the C-5 acetyl product **152** as the major component and the C-2 acetyl compound **153** as the minor component. When employing an excess of acetic acid and trifluoroacetic anhydride the production of the 2,5-diacetylated product **154** predominates (**Scheme 27**). It was therefore envisaged that if the C-5 position was blocked by a protecting group, the acylation reaction would yield the monoacetylated compound **150** as the sole isomer.

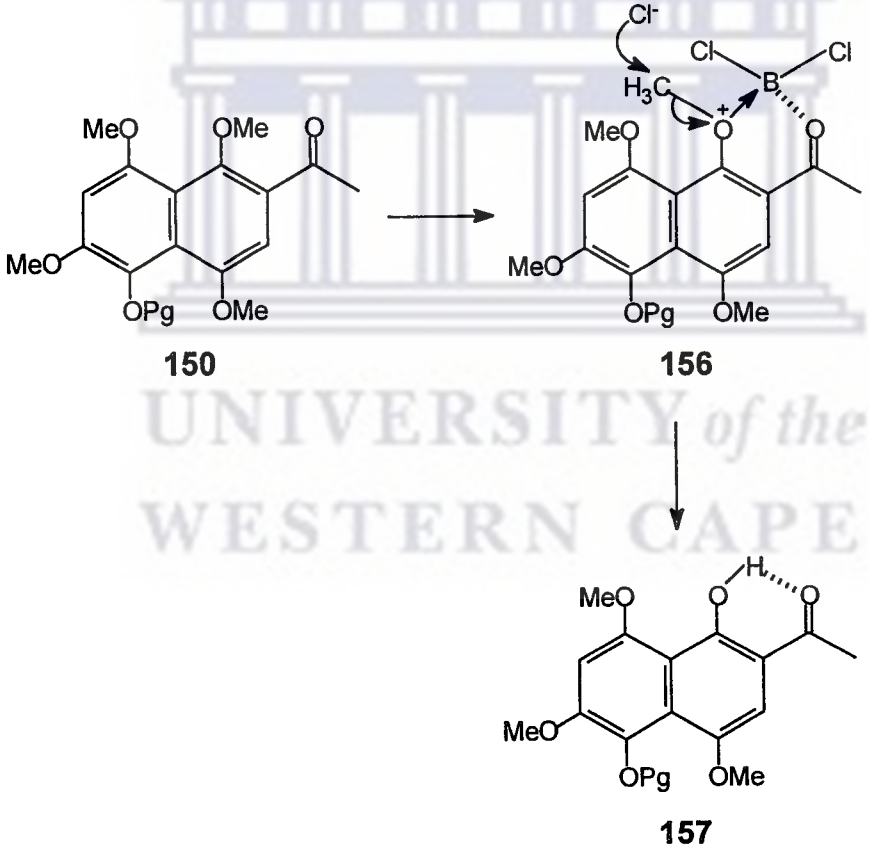
Note that the numbering system of the naphthalene ring will be maintained as indicated for compound 151. Position 1 will always be top-right.



Scheme 27



Further research by Giles and de Koning [80] in 1988 provided evidence to suggest that electrophilic attack should take place solely at C-2 because attack at this position gives a more stable σ-complex **155** intermediate compared to attack at the other two possible positions. An additional advantage of the acetyl group at C-2 of the naphthalene nucleus is that it provides a carbonyl substituent in close proximity to the C-1 methoxy group. This should allow for the selective removal of the methyl group attached to the oxygen at C-1 with boron trichloride, due to the formation of a stable six membered ring in the transition state [21] **156** as illustrated in **Scheme 28**.

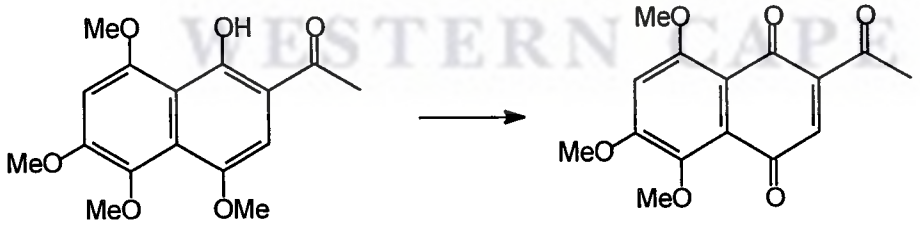


Scheme 28

A sharp lowfield singlet at appoximately δ 13.5 in the ^{1}H-nmr spectrum is an indication of the formation of the naphthol **157**. This phenomenon has been noted before and has been attributed to the phenolic hydrogen being stongly hydrogen-bonded to the acetyl group.[79]

The reason for the formation of the naphthol **157** would be to facilitate preferential oxidation of the phenolic ring to afford the naphthoquinone **158** rather that oxidation of the trioxygenated ring. In **157**, the trioxygenated ring is more electron rich compared to the acetylated ring and thus is more susceptible to oxidation. [81] Preferential oxidation of *para*-dimethoxybenzenes with $CAN^{\cdot}$ as described by Castagnoli *et al.* [81] has been successfully employed.

Consequently by employing similar conditions of aqueous cerium ammonium nitrate, Giles and Green [21] oxidised naphthol **159** into quinone **160** as in **Scheme 29** below.

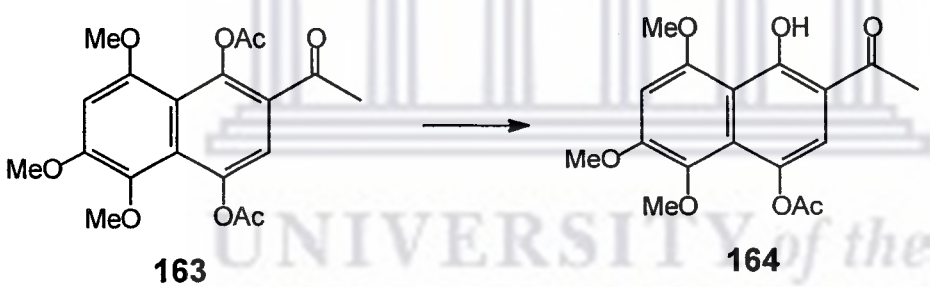


159 **160**

Scheme 29

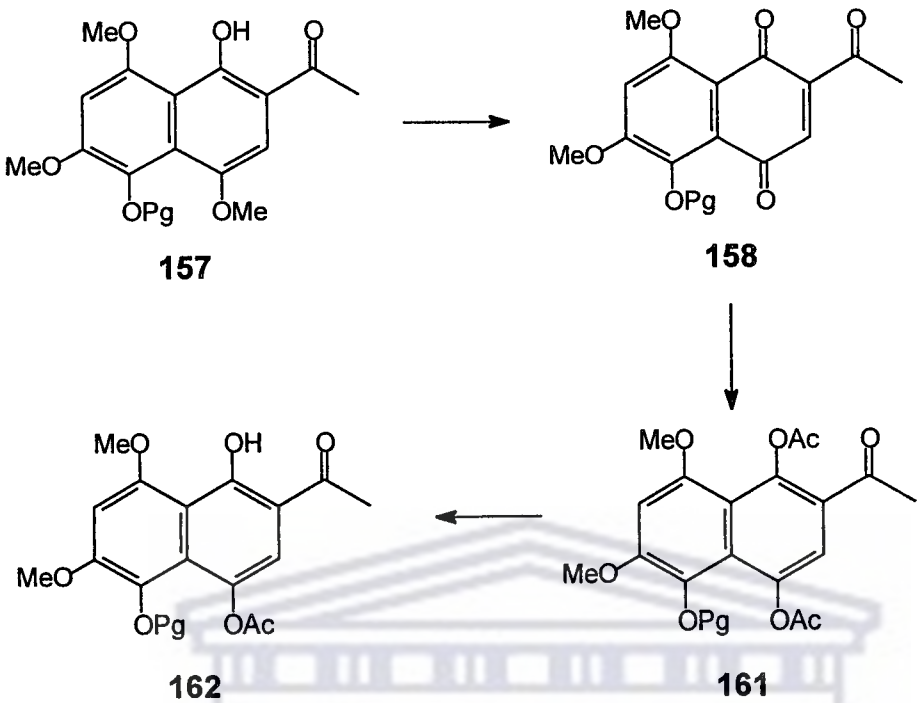
Reductive acetylation of quinone **158** with zinc and acetic acid should lead to the diacetate **161**.

In the work of de Koning, [21] it has been demonstrated that the C-1 acetoxy group of the diacetoxy naphthalene **163** can be selectively hydrolysed to afford **164**. Thus compound **163** similar in structure to our compound **161**, was treated with 1.2 molar equivalents of potassium hydroxide in dilute methanolic solution at room temperature to give the naphthol **164** (**Scheme 30**). Therefore to react **161** in the same way should afford the new naphthol **162** as depicted in **Scheme 31**.



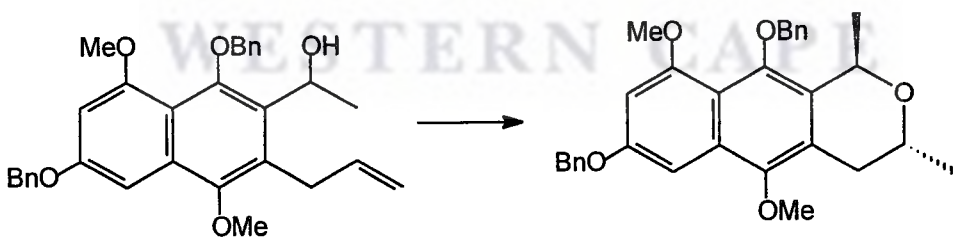
163 **164**

Scheme 30



Scheme 31

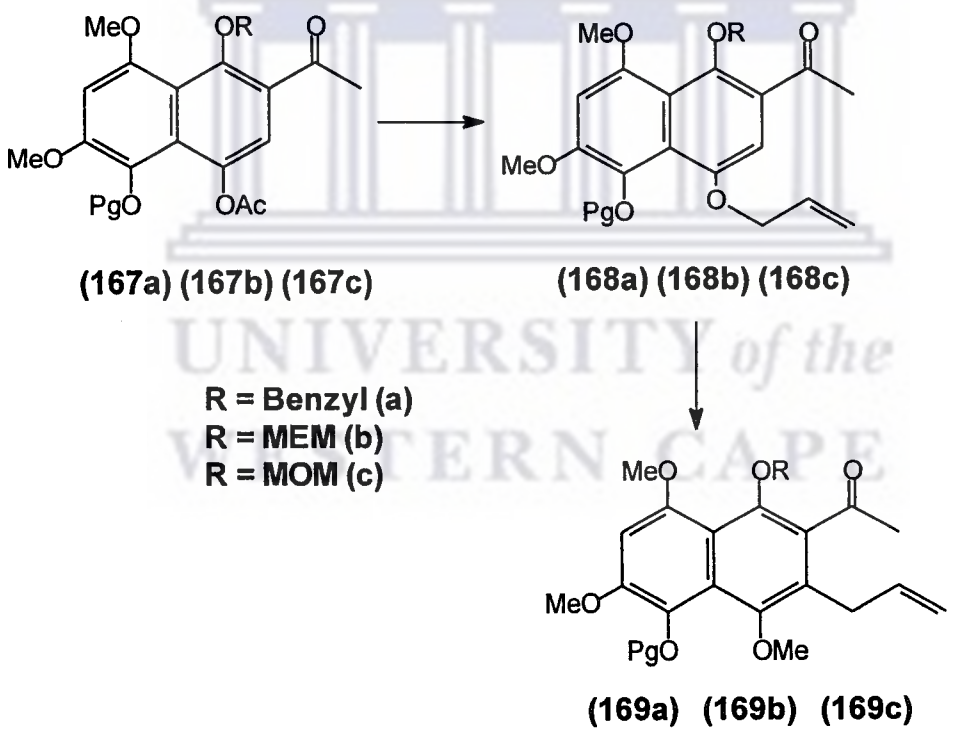
Considering the two target molecules, ventiloquinone J **33** and 6-hydroxy-7-methoxyeleutherin **132**, it becomes evident that the position which this new phenolic group occupies in compound **162** viz., position 1 either has to be retained at position 10 in ventiloquinone J **33** or be selectively oxidised to the quinonoid molecule, the eluetherin **132**, and therefore this phenolic group also needs to be selectively protected. It is important at this stage of the synthesis to give careful consideration to the nature of the protecting group to be employed. The fact that this group will be peri to a pseudoequatorial methyl group of a *cis* 1,3-dimethylpyran ring in the target molecule, ventiloquinone J **33**, suggests that it will have to be as small as possible to maximise the yield of the *cis* compound during cyclisation of its precursor alcohol. [21] Giles and co-workers [21] have protected a similar phenol as a benzyl ether **165**, [82] but this group was evidently too bulky since after ring closure of **165**, only the *trans*-1,3-dimethylpyran **166** was isolated (**Scheme 32**).



165 **166**

Scheme 32

In the current synthetic protocol, the proposal was to reassess the viability of the benzyl group and to compare the results to that of other protecting groups that are to be attempted such as methoxyethoxymethyleneoxy (MEM), and methoxy methyl ether (MOM) [83-86]. It was hoped that in each case the steric bulk of the protecting group will be sufficiently small to promote formation of at least some *cis* 1,3-dimethylpyran. It was also expected that the latter two protecting groups, being acid sensitive ethers, [87-90] would be more readily and selectively removed than the other protecting groups present.



Scheme 33

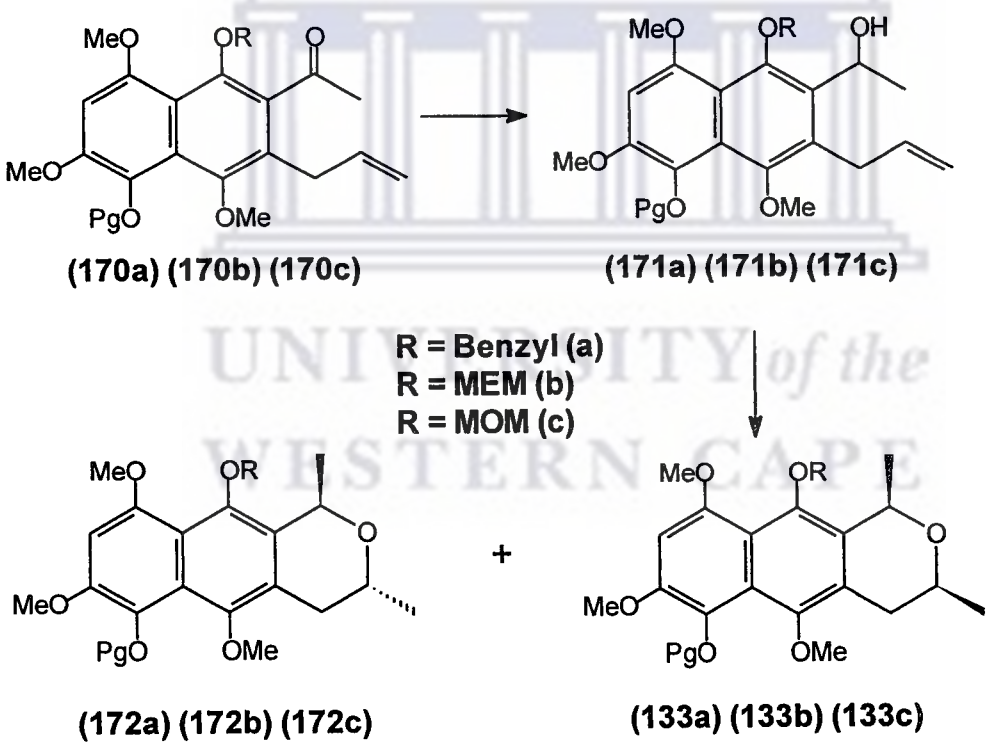
Thus the three monoacetates **167a, 167b** and **167c** derived from treatment of the phenol **162** with benzyl bromide, MEMCl and MOMCl respectively under basic conditions would then be hydrolysed with base resulting in the formation of the corresponding 4-hydroxy analogues which in turn could be allylated with allyl bromide in refluxing acetone in the presence of potassium carbonate to yield the naphthalenes **168a, 168b** and **168c**. These allyl ethers would then be subjected to a Claisen rearrangement, followed by immediate methylation of the resulting phenols to yield naphthalenes **169a, 169b** and **169c** respectively as shown in **Scheme 33.**

The key step in the formation of the intermediate compounds **133a, 133b** and **133c** is the ring closure of alcohols **171a, 171b** and **171c** to form the pyran ring. The alcohols **171a, 171b** and **171c** could be obtained by reduction of the ketones **170a, 170b** and **170c** with lithium aluminium hydride in dry THF. Giles and co-workers [25] secured the thermodynamically preferred *trans* isomer through ring closure with potassium t-butoxide in dimethylformamide. Since in our current work both the target molecules require the *cis* 1,3-dimethylpyran ring, this method was considered inappropriate. A reasonable approach to the formation of the *cis* dimethyl pyran products is an intramolecular acetoxymercuration of **171** and subsequent reduction using sodium borohydride. [22]

Providing that the R protecting group in **171** did not lead to prohibitively large *peri* interactions with the adjacent *pseudo*axial and *pseudo*equatorial methyl

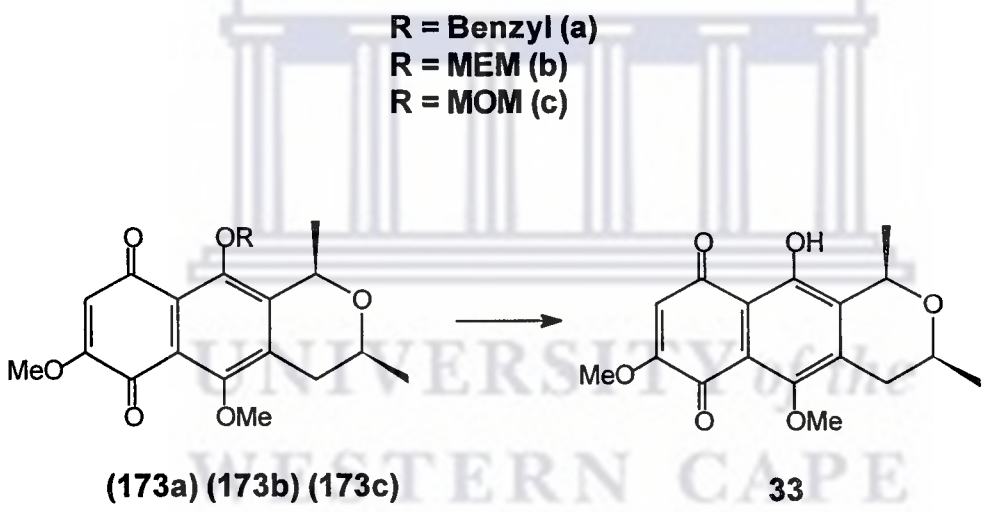
groups, the reaction should hopefully yield both the cis **133** and trans **172** isomers as depicted in **Scheme 34**.

This synthetic protocol would thus yield the naphthopyran skeleton, giving the final intermediates **133a, 133b** and **133c**. One could speculate about the possibility to effect cyclisation of the phenol without the R protecting group, viz. with R = H, to maximise the *cis* product from the acetoxymercuration-demercuration route, in view of the fact that more *cis* product is obtained with smaller groups at C-10.[22]

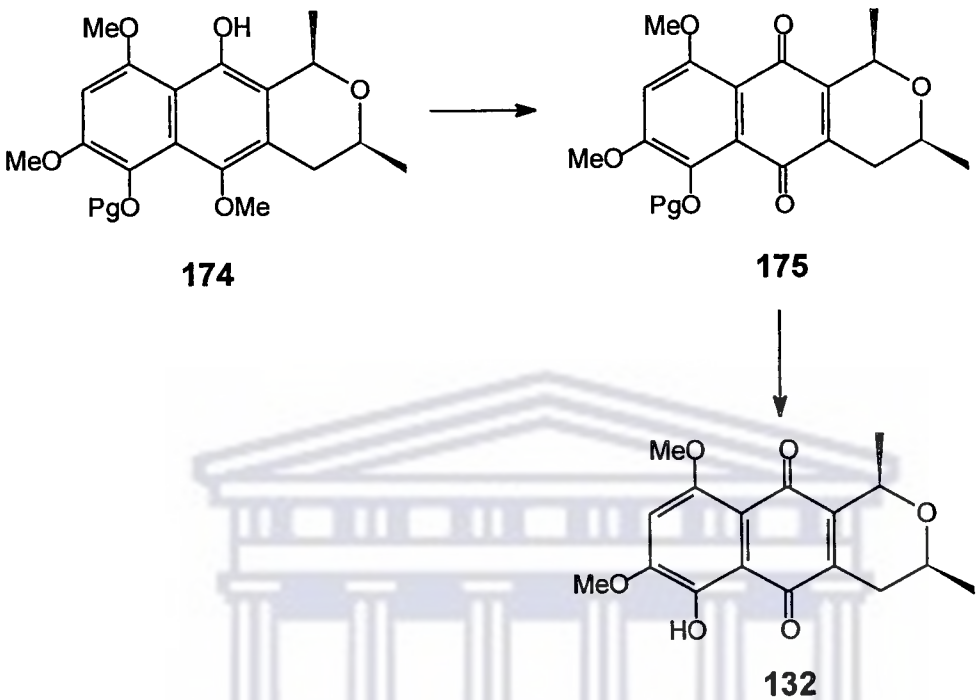


Scheme 34

Subjection of the naphthopyrans **133a**, **133b** and **133c** to oxidative conditions of CAN should generate the 6,9 diones **173a**, **173b** and **173c** in which the more electron rich ring is expected to undergo oxidation. In the final step, selective removal of the R protecting group should finally yield ventiloquinone J **33** (**Scheme 35**). On the other hand, initial removal of the R protecting group to generate the phenol **174** followed by subsequent oxidation of the central phenolic ring should give the 5,10 quinone **175**. After removal of the protecting group at C-6, the 6-hydroxy-7-methoxyeleutherin **132** should be obtained as depicted in **Scheme 36**.



Scheme 35

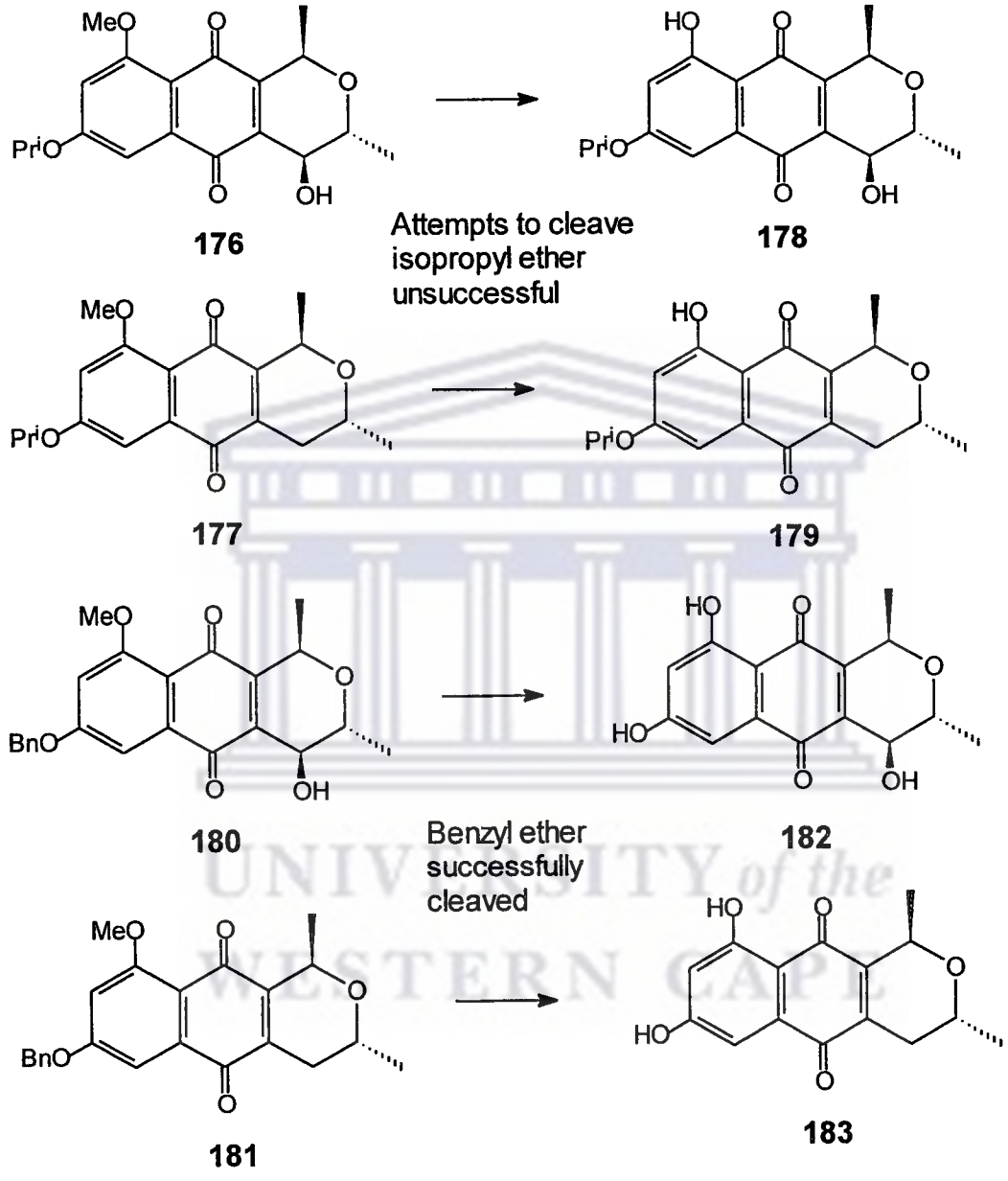


Scheme 36

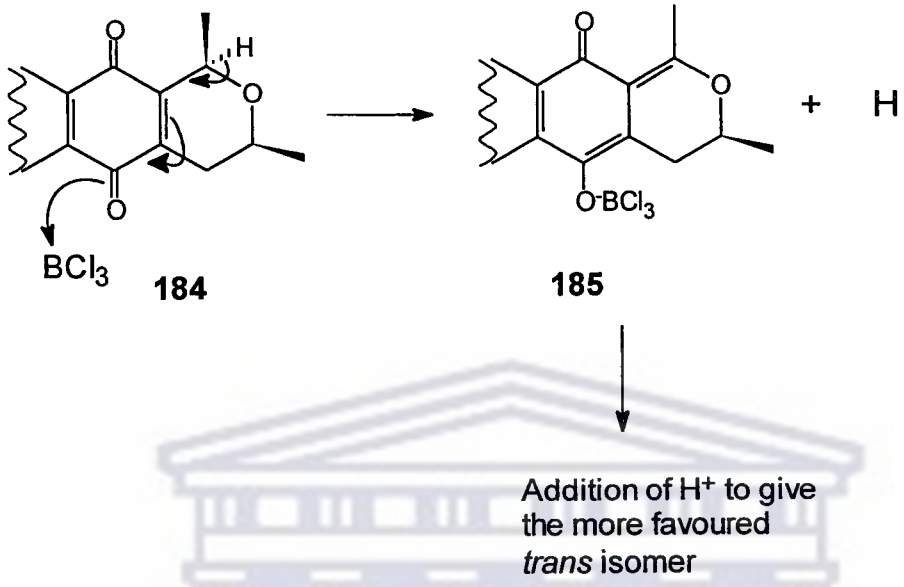
1. RESULTS AND DISCUSSION

The two key requirements for the group chosen to protect the phenolic group of 3-bromovanillin **138** are that it is stable to a Lewis acid, such as boron trichloride, at -78°C, during the removal of the *ortho* methyl group to the acetyl group of compound **150**, and that it should be cleaved in the final step in the synthesis of 6-hydroxy-7-methoxyeleutherin **132** without disruption to the pyran ring system. An isopropyl ether [91] is more stable to Lewis acids than the more commonly used benzyl ether. [92] The isopropyl ether has however been found difficult to remove [92] with a number of reagents, in complex systems such as the aphid pigment derivatives.[82] Thus Giles *et al.* treated **176** and **177** with boron trichloride at -78°C but only isolated products **178** and **179** in which the *peri*-methoxy group had been removed. On the other hand, treating **180** and **181** under similar conditions led to the isolation of the desired deprotected quinones **182** and **183** respectively in which both the benzyl and peri-methoxy groups had been removed. This is summarised in **Scheme 37**.

In addition, boron trichloride, the more usual reagent for the cleavage of an isopropyl ether, has been found to cause isomerization of a *cis* pyran ring into the *trans* pyran ring, which has less unfavourable steric interactions. [92] Mechanistically it was suggested that the H-1 was lost to form an extended conjugated system thereby destroying the tetrahedral nature of the C-1 position of the pyran ring through dienolisation as depicted by the transformation of **184** to **185** in **Scheme 38**.



Scheme 37

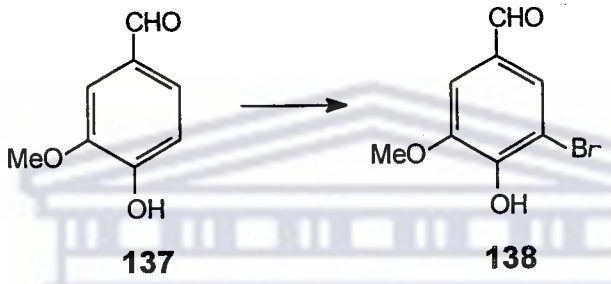


Scheme 38

The benzyl ether, however has been successfully cleaved with boron trichloride in the last step of the synthesis of aphid pigment derivatives.[82]

With the potential advantages and disadvantages of these two protecting groups in mind, it was decided to use both the isopropyl ether and the benzyl ether and to carry the synthesis forward in two parallel streams as far as compound **157**, to determine if selective removal of the methoxy *ortho* to the acetyl group in naphthalene **150** could be achieved without the loss of the protecting group at C-5.

In both sequences, the first step towards ventiloquinone J **33** and 6-hydroxy-7-methoxyeleutherin **132** is the bromination of vanillin **137**.[72] This simple electrophilic substitution gave the 3-bromo isomer **138** which was supported by two sets of *meta*-coupled doublets at δ 7.37 and 7.65 with *J* 1.7 Hz in the ^{1}H-nmr spectrum (**Scheme 39**). The product **138** was obtained in a good yield of 75% after recrystallisation of the crude material from methanol.

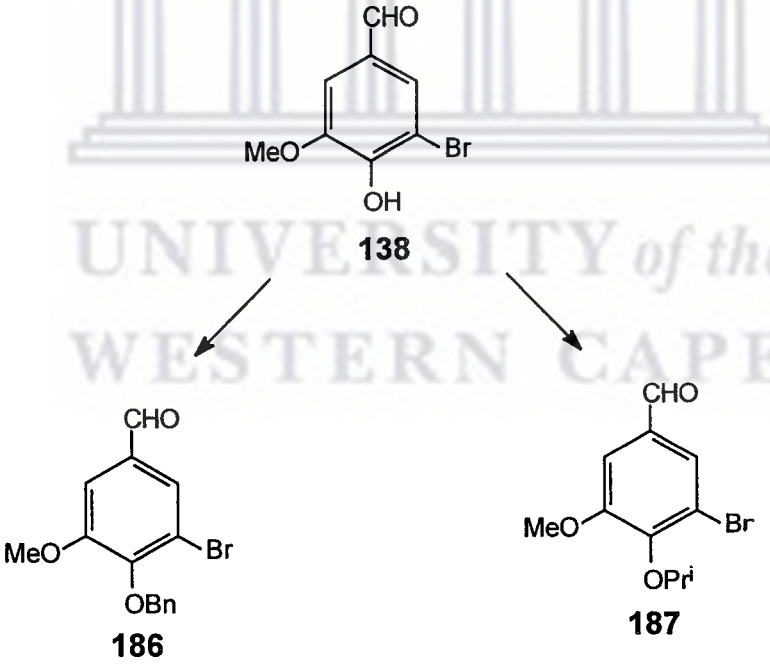


137 **138**

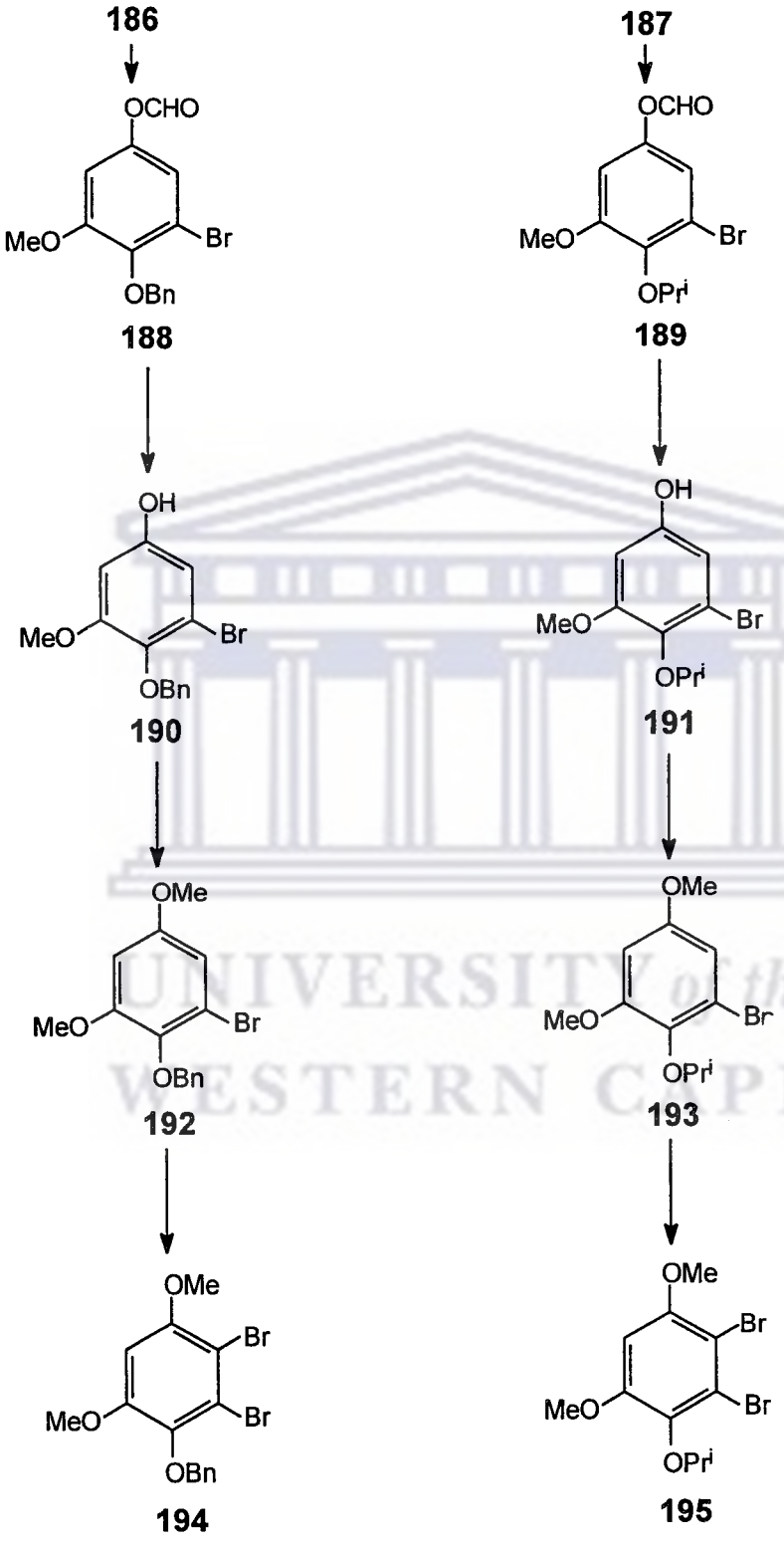
Scheme 39

3-Bromovanillin **138** was treated with benzyl bromide and potassium carbonate in dry DMF at 80°C with vigorous stirring under a nitrogen atmosphere to produce the benzylated compound **186** in a good yield of 85%. In the same way 3-bromovanillin was also reacted with 2-bromopropane and potassium carbonate in DMF to afford a quantitative yield of the isopropoxy analogue **187**. The benzyloxy and isopropoxy analogues **186** and **187** were transformed further as two parallel series of compounds (**Scheme 40**). The next transformation for both compounds was the conversion of the aldehyde group of each into the corresponding formate esters **188** and **189** respectively by treatment with *m*-chloroperbenzoic acid in DCM under reflux according to the Baeyer-Villiger oxidation protocol. [75] Without isolation of the latter formates, they were

hydrolysed to afford the phenols **190** (77%) and **191** (88%) respectively. The absence of the aldehyde peak at approximately δ 9.8 in the ^{1}H-nmr spectra in both of these products confirmed the success of the methodology. The ^{13}C-nmr spectra confirmed that the expected aryl migration had occurred due to the lack of a carboxylic acid carbonyl signal in the region δ 190 - 200. Methylation of each of the phenols **190** and **191** by treatment with dimethyl sulphate and potassium carbonate in acetone under reflux with vigorous stirring afforded the methylated products **192** and **193** in yields of 77% and 88% respectively. Subsequent bromination with bromine in acetic acid afforded the two dibrominated analogues **194** (87%) and **195** (74%) respectively and is summarised in **Scheme 40**.

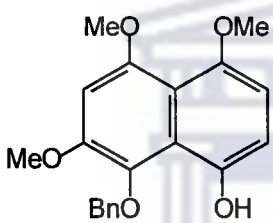


Scheme 40

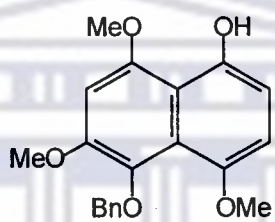


Scheme 40 Continued

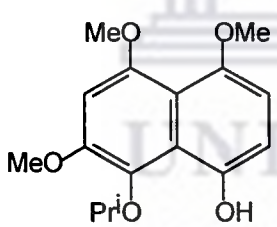
Each of the dibrominated analogues **194** and **195** was treated with 0.9 molar equivalents of *n*-butyllithium as described by de Koning [21] to generate the corresponding benzynes (see **Scheme 26**) and then followed by addition of 2-methoxyfuran **144** to form the isomeric 1,4-oxa analogues which were not isolated but immediately hydrolysed to the isomeric phenols **196** and **197** and **198** and **199** and finally methylated to afford the two C-5 alkoxy analogues **200** and **201** respectively.



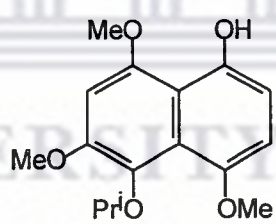
196



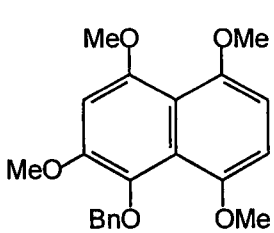
197



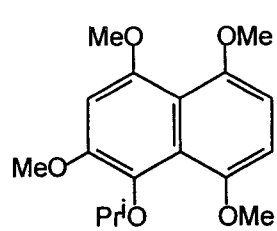
198



199



200



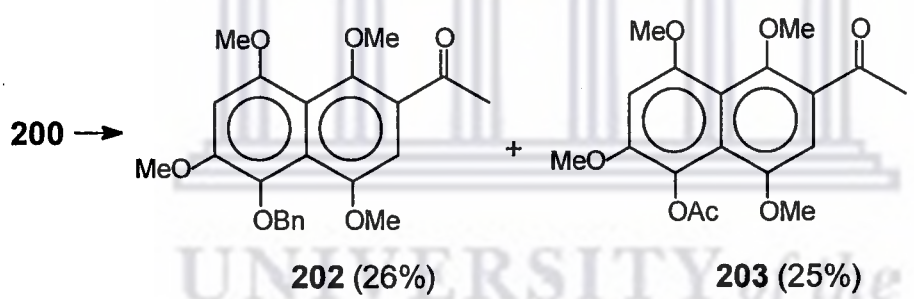
201

The presence of the two regioisomers in the mixture was apparent for both the benzyloxynaphthols **196** and **197** and the isopropoxynaphthols **198** and **199** by two sharp lowfield singlets at approximately δ 9.2 and 9.9 for the naphthol hydrogens in the ^{1}H-nmr spectra of each. These peaks are strongly deshielded due to hydrogen bonding. Both mixtures of naphthols **196** and **197**, and **198** and **199**, were subjected to methylation by treatment with potassium carbonate and dimethyl sulphate in acetone under reflux in an atmosphere of nitrogen. The corresponding tetramethoxy analogues **200** and **201** were obtained in overall yields of 42% and 54% respectively for the two steps. The structures of the analogues **200** and **201** were supported by the presence of four methoxy signals in their ^{1}H-nmr spectra.

Construction of the pyran ring in both the penta-alkoxynaphthalenes **200** and **201** required their treatment with a premixed solution of trifluoroacetic anhydride and acetic acid. It was expected that acylation would take place soley at C-2 due to formation of a more stable σ-complex as described earlier, [80] and subsequently favour the selective removal of the methoxy methyl group at C-1 with a Lewis acid due to the formation of a stable six membered ring in the transition state. [21]

Thus the benzyloxytetramethoxynaphthalene **200** was dissolved in dichloromethane and treated with a premixed solution of trifluoroacetic anhydride and acetic acid at 20°C for 24 hours. Chromatographic purification of the product mixture afforded some starting material **200** (10%) and the desired acetylated benzyloxynaphthalene **202** (26%) which showed the presence of the

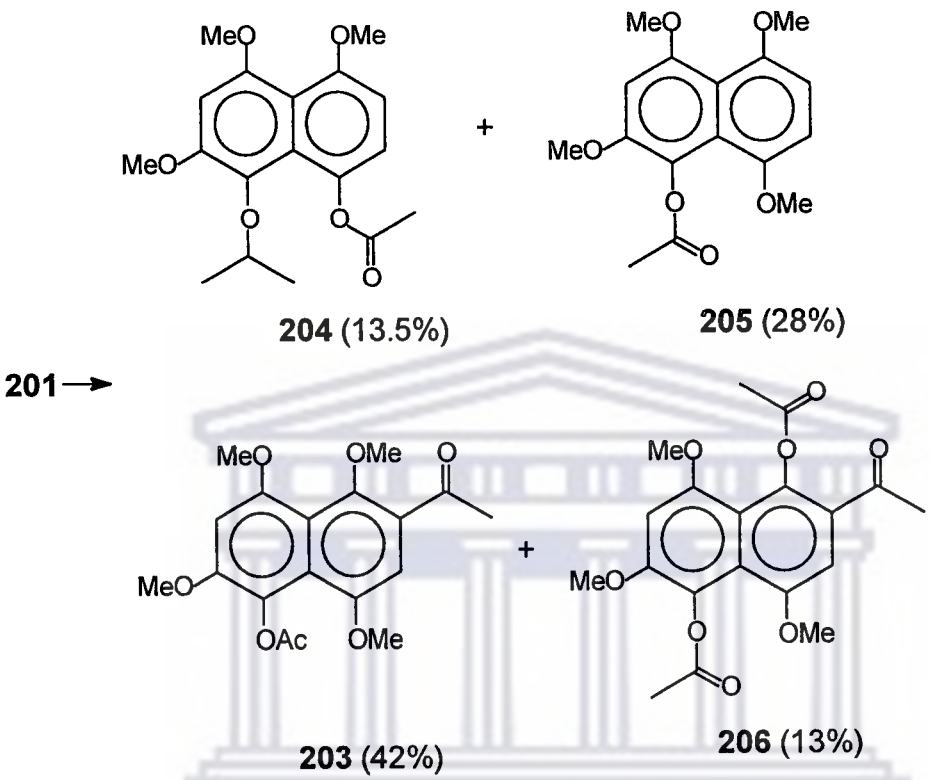
acetyl hydrogens at δ 2.40 in the ^{1}H-nmr spectrum and the appearance of a carbonyl peak at δ 199.8 in the ^{13}C-nmr spectrum. Some of the unwanted diacetylated compound **203** (25%) was also obtained (**Scheme 41**) which was identified by the absence of the benzyl protecting group at C-5 in the ^{1}H-nmr spectrum. Apart from four methoxy signals in the proton spectrum and two aromatic hydrogen signals at δ 6.78 and δ 7.08 for H-7 and H-3, there were two signals at δ 2.74 and δ 2.36 each integrating for three protons assigned to the 2-acetyl and 5-acetoxy groups respectively. The presence of two signals at δ 170.23 and δ 200.00 in the ^{13}C-nmr spectrum confirmed the presence of acetoxy and acetyl functional groups.



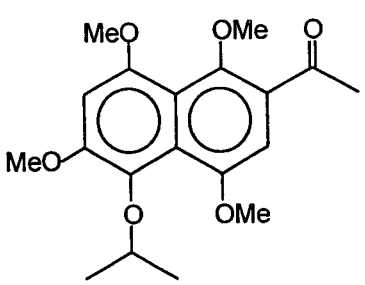
202 (26%) **203** (25%)

Scheme 41

The isopropoxytetramethoxynaphthalene **201** was subjected to the same reaction conditions as described above. Four compounds were isolated by chromatography of the product mixture and were identified as, **204** (13%), **205** (28%), **203** (42%) and **206** (13%). The desired compound **207** was not obtained.



Scheme 42



207

In **204**, the IR spectrum had a strong peak at 1747 cm^{-1} representing the ester carbonyl stretching frequency and the presence of a six proton doublet in the ^{1}H-nmr spectrum at δ 1.25 (*J* 6.20 Hz) indicated that the isopropoxy group at C-5 was still in place and the presence of a nine proton singlet at δ 3.93 indicated the presence of only three methoxy groups and this provided evidence that one methoxy had been removed. It is suspected that the methoxy at C-4 is replaced since the three methoxy signals had the same chemical shift value. Any alternative replacement would result in the methoxy signals appearing at 3 different values. An acetyl three-proton singlet was observed at δ 2.33, while two *ortho* coupled protons signals were evident as doublets at δ 6.64 and 6.94 (each *J* 8.80 Hz) for H-2 and H-3 respectively which showed that acetylation had not occurred at C-2. A singlet at δ 6.71 for H-7 was also observed. The ^{13}C-nmr spectrum displayed two equivalent methyl carbons at δ 22.16 for the isopropyl methyl groups while a signal at δ 75.74 was assigned to the methine carbon of the isopropyl group. Signals at δ 56.72, 56.78 and 57.72 accounted for the three methoxy groups while signals at δ 98.90, 103.47 and 115.01 were assigned to C-7, C-2 and C-3 respectively. A signal at δ 21.46 and a carbonyl carbon signal at δ 170.07 supported the presence of the acetoxy group at C-4 while the signals for the five carbon atoms bonded to oxygen in the naphthalene ring appeared at δ 143.25, 139.39, 150.58, 154.36 and 155.62 for C-5, C-6, C-1, C-8, and C-4. The molecular formula was supported by HRMS molecular ion of 334.3701 ($C_{18}H_{22}O_6$ requires 334.3691) and the micro elemental analysis gave oxygen as 28.18% (by difference) ($C_{18}H_{22}O_6$ requires 28.74%) which further substantiated that the functionality at C-4 was acet**oxy** as opposed to acetyl.

The IR spectrum of **205** showed the expected ester carbonyl peak at 1764 cm^{-1} and the ^{1}H-nmr spectrum showed the expected four methoxy signals at δ 3.84, 3.88, 3.93 and 3.96 but the presence of a pair of *ortho* coupled naphthalene hydrogens at δ 6.65 for H-2 and δ 6.77 for H-3 both as doublets (*J* 9.3) and a singlet at δ 6.74 for H-7 indicated that the desired acetylation at C-2 had not occurred. Absence of the isopropoxy six-proton doublet at δ 1.25 and the presence of a three-proton singlet at δ 2.37 suggested the replacement of the isopropyl group by acetyl at C-5 to produce the monoacetate **205**. The ^{13}C-nmr spectrum showed a methyl carbon signal at δ 20.75 and an ester carbonyl carbon signal at δ 181.80 of the acetoxy group while the four methoxy carbon signals were present at δ 56.86, 57.09, 57.39 and 57.49. Signals at δ 97.12 and 105.55 (× 2) were assigned to C-7, C-2 and C-3 respectively, the latter having similar δ values. The C-O bonded carbons were present further downfield at δ 148.91, 149.24, 151.58, 156.07 and 170.34 for C-1, C-4, C-6, C-8, and C-5. A HRMS molecular ion of 306.3148 ($C_{16}H_{18}O_6$ requires 306.3153) and the micro elemental analysis (C, 62.75%; H, 5.88%, $C_{16}H_{18}O_6$ requires C, 62.75%; H, 6.15%) also supported the molecular formula.

The third fraction to elute was assigned structure **203** which was isolated earlier from the similar reaction with benzyloxynaphthalene **200** as the starting material. The product displayed identical physical and spectral characteristics.

The last fraction to elute from the column was assigned the structure **206** representing a 2-acyl-1,5-diacetoxytrimethoxy naphthalene and is based on the following evidence. The IR spectrum had strong absorption peaks at 1755 and 1690 cm^{-1} for the carbonyl groups and singlets at δ 3.91, 3.95 and 4.00 in the ^{1}H-nmr spectrum indicated only three methoxy groups and thus one was replaced. The absence of a six proton doublet at δ 1.25 and the appearance of two three proton singlets at δ 2.36 and 2.40 suggested displacement of the isopropyl group and one methoxy methyl group followed by acetylation at each to afford the diacetoxy derivative with the groups being at C-5 and C-1. In this case demethylation at C-1 is favoured due to the activation of the adjacent acyl carbonyl groups during the complexation with the trifluoroacetic acid. A three-proton singlet at δ 2.59 indicated the desired acetyl group at C-2 while two singlets for H-7 and H-3 appeared at δ 6.74 and 7.15 respectively. The ^{13}C-nmr showed *inter alia* signals at δ 20.64, δ 21. 30 and 31.07 for the two acetoxy carbons and the acetyl carbon respectively. The three methoxy carbons appeared at δ 56.60, 56.71 and 56.79 and the three carbonyl signals appeared at δ 189.43, 194.36 and 197.43. The mass spectrum gave a HRMS molecular ion of 376.3635 ($C_{19}H_{20}O_8$ requires 376.3630) and the elemental analysis result was (C, 60.31%; H, 5.67 %), ($C_{19}H_{20}O_8$ requires C, 60.64%; H, 5.32%) which supported the assigned molecular formula.

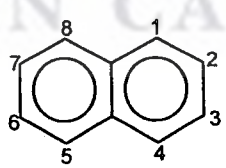
Numerous variations of reaction conditions of both the above-described reactions failed to afford good yields of the desired C-2 monoacetyl products **202** and **207** in which the protecting group at C-5 was retained. Due to the problem that both protecting groups are readily displaced under the acetylation reaction conditions employed, it was decided to abandon the idea of synthesising the eleutherin analogue, 6-hydroxy-7-methoxyeleutherin **132** and concentrate solely on ventiloquinone J **33** as the main target molecule.

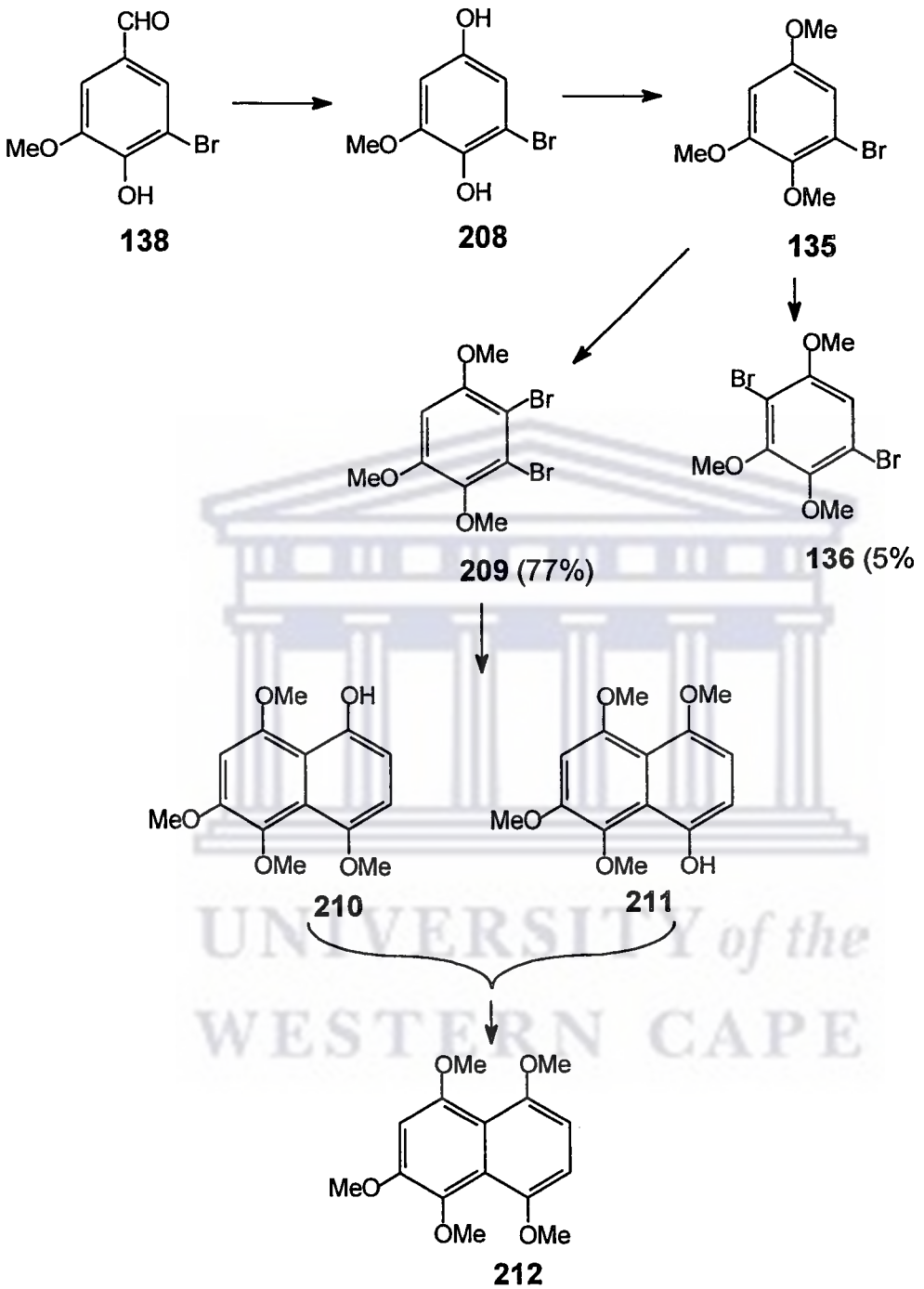
Thus 3-bromovanillin **138** was dissolved in potassium hydroxide solution followed by treatment with 3% hydrogen peroxide solution to afford the formate ester which was hydrolysed to subsequently afford the crude quinol **208** which was immediately subjected to the methylation conditions of potassium carbonate, dimethyl sulphate in acetone under reflux in a nitrogen atmosphere. In this way 2,3,5-trimethoxybromobenzene **135** was isolated in a yield of 77%, confirmed by ^{1}H-nmr spectral analysis which showed three methoxy signals at δ 3.76, 3.77 and 3.83 and the *meta* coupled protons H-4 and H-6 respectively as doublets at δ 6.43 and 6.62, *J* 3.0 Hz. The dibromo compound **136** (5%) was also obtained as a by-product carried through from the dibromination of vanillin **137**. The ^{1}H-nmr spectrum indicated the methoxy signals as three-proton singlets at δ 3.73, 3.84 and 3.94 and only one aryl hydrogen as a singlet at δ 6.57 for H-5 and mp 197 – 198°C. [72]

The bromobenzene **135** was dissolved in benzene and treated with bromine [72] to afford the dibromo product **209** (80%). As expected the ^{1}H-nmr spectrum showed one singlet in the aromatic region at δ 6.54.

Subsequently the dibromobenzene **209** was treated with 2-methoxyfuran **144** and 0.9 molar equivalents of *n*-butyllithium in a similar manner to the previously discussed Diels–Alder reactions, [21] and the resulting two isomeric phenols **210** and **211** were immediately methylated by treatment with dimethyl sulphate and potassium carbonate in dry acetone under reflux to afford the pentamethoxynaphthalene **212** in an overall yield of 67%. The ^{1}H-nmr spectrum clearly showed the five methoxy signals between δ 3.80 and 4.00. Doublets at δ 6.66 and 6.79 with *J* 8.4 Hz are assigned to H-2 and H-3 respectively while H-7 appeared as a singlet at δ 6.74.

In this text numbering of the naphthalene nucleus will be as shown to maintain consistency throughout:





Scheme 43

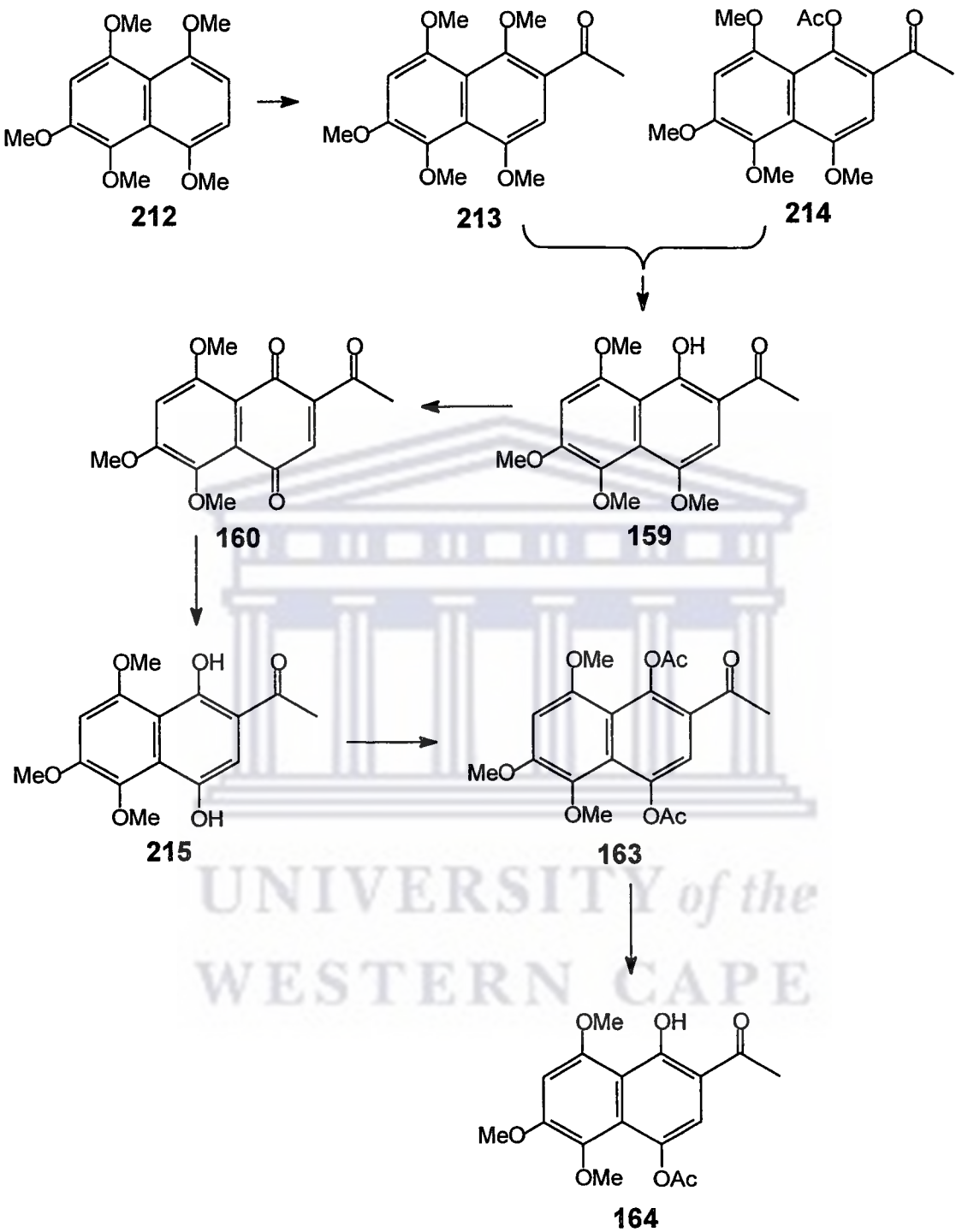
Acetylation at C-2 in the pentamethoxynaphthalene **212** was achieved by dissolving it in dry dichloromethane and treatment with premixed triflouroacetic anhydride and acetic acid. In this case the reaction afforded the C-2 monoacetyl pentamethoxynaphthalene **213** in a high yield (71%) with the ^{1}H-nmr spectrum showing apart from the five methoxy singlets, two aromatic singlets at δ 6.77 and 7.10 for H-7 and H-3 respectively and an acetyl three-proton singlet at δ 2.75. Infrared analysis showed a carbonyl stretching vibration at 1676 cm^{-1} while the ^{13}C-nmr spectrum indicated a carbonyl carbon signal at δ 200.00. It was accepted that the acetyl group would be at C-2 due to the arguments given earlier. This is also confirmed by the subsequent reactions since if the acetyl group were not at C-2 the correct regiochemistry of the pyran ring would not have been achieved. A small amount of the acetylacetoxy compound **214** was also isolated (9%). The ^{1}H-nmr spectrum shows two three-proton singlets at δ 2.39 and 2.60 the former for the acetoxy and the latter for the acetyl methyl groups and four three-proton singlets at δ 3.80, 3.93, 3.98 and 3.99 as well as singlets for both H-7 and H-3 at δ 6.73 and 7.16 respectively. Basic hydrolysis of this compound **214** afforded the same product **159** derived by the boron trichloride demethylation reaction depicted in **Scheme 44** on the pentamethoxyacetynaphthalene **213**.

Thus the product mixture **213** and **214** was dissolved in dry dichloromethane and treated with 1.5 molar equivalents of boron trichloride at –78°C followed by hydrolysis with water. In this way the naphthol **159** was obtained in a good yield of 80% yield. The ^{1}H-nmr spectrum showed a downfield hydroxyl proton singlet

at δ 14.08 while in the IR spectrum a broad peak at 3215 cm^{-1} was observed for the hydroxyl group.

Oxidation of the naphthol **159** with CAN afforded the quinone **160** which was immediately reduced to the quinol **215** by shaking up with aqueous sodium dithionate. The crude hydroquinol was immediately dissolved in dry pyridine and acetic anhydride was added and the mixture was heated and stirred under nitrogen at 80°C (oil bath) for 2 hours. Addition of water and careful acidification with dilute hydrochloric acid afforded the diacetate **163** (70%) as shown in **Scheme 44**. The presence of three, three proton singlets at δ 2.34, 2.39 and 2.57 in the ^{1}H-nmr spectrum supported the 2-acetyl-1,4-diacetoxynaphthalene structure **163** and in addition, two acetoxy ester carbonyl stretching bands were observed in the IR spectrum at 1764 cm^{-1} and 1755 cm^{-1}, while the acetyl carbonyl band appeared at 1680 cm^{-1}. The ^{13}C-nmr spectrum also showed the three methyl carbons attached to the carbonyl carbons at δ 20.60, 21.38 and 30.74 respectively as well as the two ester carbons at δ 169.38 and the ketone carbon at δ 195.55.

It was now necessary to chemoselectively differentiate between the two acetate groups in compound **163** as has been demonstrated previously [80] in order to protect the oxygen at C-1 to later ensure that the target molecule **33** will have the phenolic group at C-1 as discussed earlier (see **Scheme 30**).



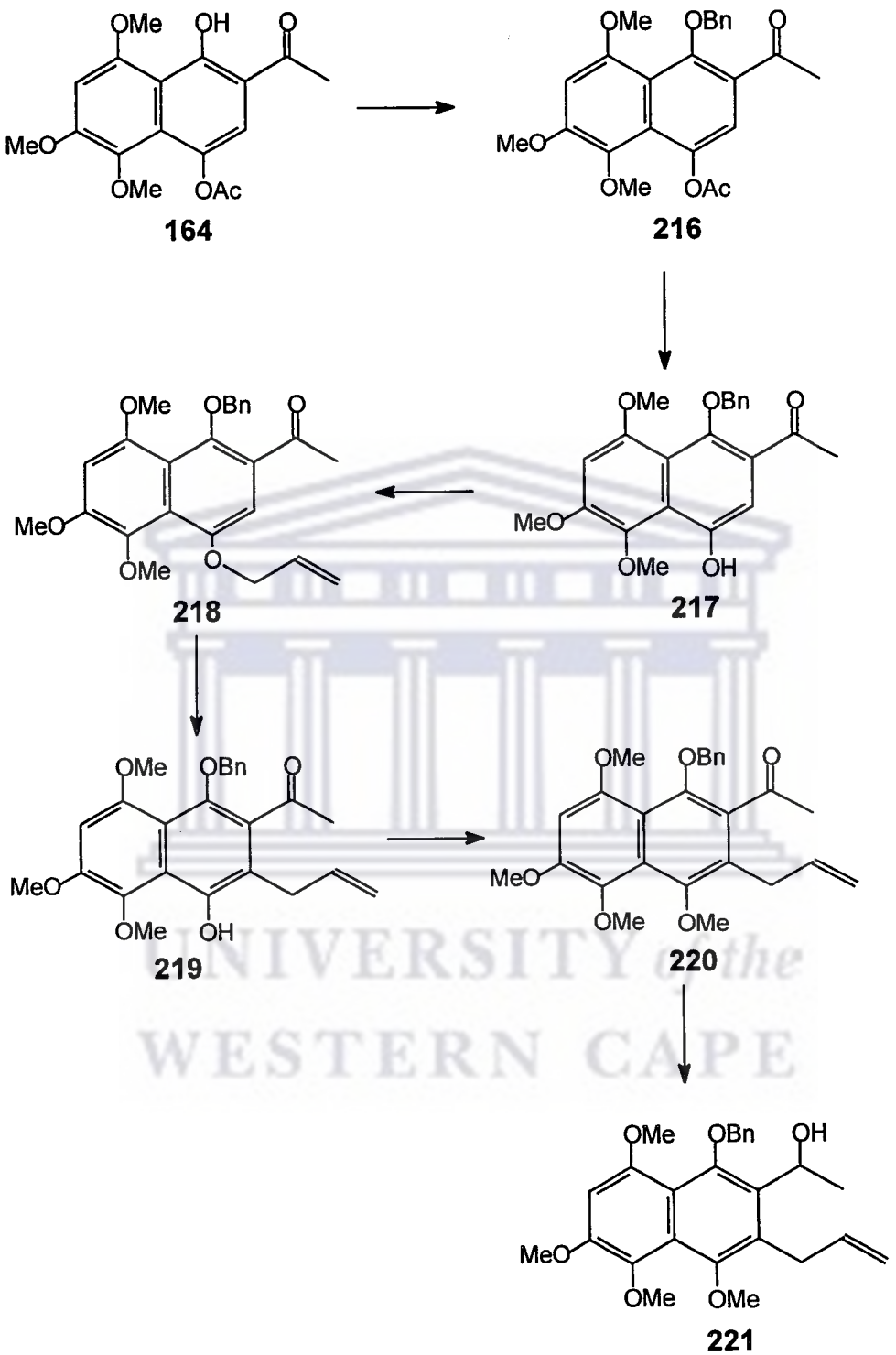
Scheme 44

Treatment of the diacetate **163** with 1.2 molar equivalents of potassium hydroxide in a dilute methanolic solution at room temperature furnished the naphthol **164** as depicted in **Scheme 44**. Removal of the acetate at C-1 is favoured due to the greater stability of the derived anion being in conjugation with the adjacent acetyl group at C-2 in **164**. To introduce the benzyl protecting group the naphthol **164** was immediately reacted with benzyl bromide in the presence of potassium carbonate in boiling acetone to afford the monoacetate **216**. The ^{1}H-nmr spectrum showed *inter alia*, the acetate group as a singlet at δ 2.35, the acetyl group as a singlet at δ 2.62 and the three methoxy groups at δ 3.81, 3.86 and 4.00 each as singlets. The characteristic aromatic signals appeared as a multiplet at δ 7.34 – 7.47 confirming the presence of the benzyl group at C-1.

Naphthalene **216** was next hydrolysed in dilute methanolic potassium hydroxide which was later acidified to afford the phenol **217** and this was immediately taken up in dry acetone and treated with 5 molar equivalents of allyl bromide and potassium carbonate with stirring under reflux for 20 hours to give the allylated naphthalene **218**. Comparison of the ^{1}H-nmr spectrum with that of the preceding compound **216** showed the disappearance of the acetate group at δ 2.35 and new signals representing the coupled protons of the allyl group. The following signals are *inter alia* typical of such ethers. A doublet of triplets at δ 4.65 (*J* 5.2 and 1.4 Hz) integrating for the 2 protons for H-1', two doublets of quartets **(The signals actually appear as doublets of quartets and will be referred to as such throughout the thesis although it is realised that the signals are in fact**

doublets of doublets of doublets, the latter two being so close together to give the appearance of a disfigured quartet.), one at δ 5.32 (*J* 10.4 and 1.4 Hz) for *cis* H-3' and the other at δ 5.56 (*J* 17.4 and 1.4 Hz) for *trans* H-3' and also a multiplet at δ 6.19 for H-2'. This was supported by also comparing their ^{13}C-nmr spectra that showed the disappearance of the methyl C signal of the acetate group at δ 20.69 and the ester carbonyl carbon signal at δ 170.04.

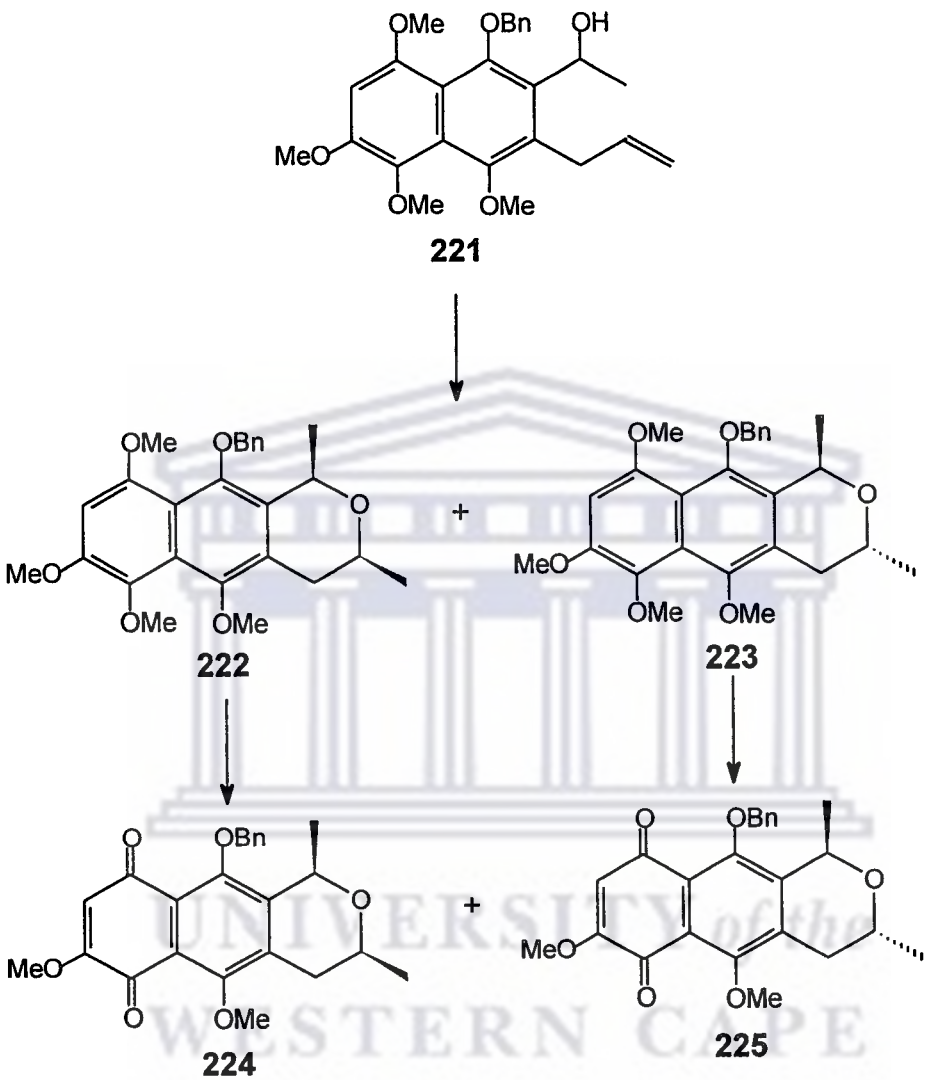
Naphthalene **218** was subsequently pyrolysed at 160°C under a nitrogen atmosphere to be transformed to the naphthol **219** by a Claisen rearrangement and was immediately taken up in acetone and treated with 5 molar equivalents of potassium carbonate and iodomethane and stirred under reflux for 12 hours. Work-up of the reaction mixture gave 2-acetyl-1-benzyloxy-4,5,6,8-tetramethoxy-3-prop-2'-enylnaphthalene **220** (76%) that clearly showed the four methoxy signals at δ 3.79, 3.80, 3.89 and 4.02 in the ^{1}H-nmr spectrum. Ketone **220** was then reduced by dissolving it in dry ether and allowing it to drip into a stirring slurry of 5 molar equivalents of lithium aluminium hydride in ether at 20°C to form the crude alcohol **221** (83%) which was not further purified (**Scheme 45**). The ^{1}H-nmr spectrum of the crude alcohol showed all the expected signals including the disappearance of the acetyl methyl signal at δ 2.56 and the appearance of a broad D_2O exchangeable singlet at δ 1.90 for the proton of the hydroxyl group and a doublet at δ 1.60 (*J* 6.8 Hz) for the methyl group of the hydroxyethyl side chain at C-2.



Scheme 45

At this point in the synthesis it was necessary to form the pyran ring with specifically the *cis* 1,3-dimethyl relative stereochemistry. There has to date and to our knowledge been no reported synthetic methodology whereby only the *cis* 1,3-dimethyl pyrans have been obtained. The reductive mercury(II) cyclisation has been found to consistently yield approximately equal amounts of *cis* and *trans* isomers. [22,23] The alcohol **221** was taken up in THF and water and treated with mercuric acetate and stirred for an hour after which sodium hydroxide solution was added and stirring continued for another hour. A mixed solution of sodium borohydride and sodium hydroxide was added to the mixture to afford the cyclised material as an inseparable mixture of both *cis* **222** and *trans* **223** isomers after chromatography (75%) in a ratio of 1:2 as derived from the relative intergrations of the H-3 signals at δ 3.63 and 4.14 for **222** and **223** respectively.

After several unsuccessful attempts to separate the two isomers, it was decided to oxidise the mixture to the corresponding quinones **224** and **225** by dissolving the mixture in acetonitrile and water and treating the solution with 2.2 molar equivalents of CAN solution. Chromatography on a long column afforded the pure *cis* pyranquinone **224** (12%) and further elution gave a mixture of the isomers **224** and **225** (5%) followed by pure the *trans* pyranquinone **25** (24%) **(Scheme 46)**.



Scheme 46

The ^{1}H-nmr spectrum for the *trans* pyranquinone **225** showed *inter alia* two methoxy signals at δ 3.83 and 3.86 and the CH_2 of the benzyl group appeared as two pairs of doublets at δ 4.78 and 4.93 with *J* 11.0 Hz, and a multiplet at δ 4.05 was assigned to H-3. In the case of the *cis* isomer **224** similar signals were observed but in this case H-3 appeared as a multiplet at δ 3.49.

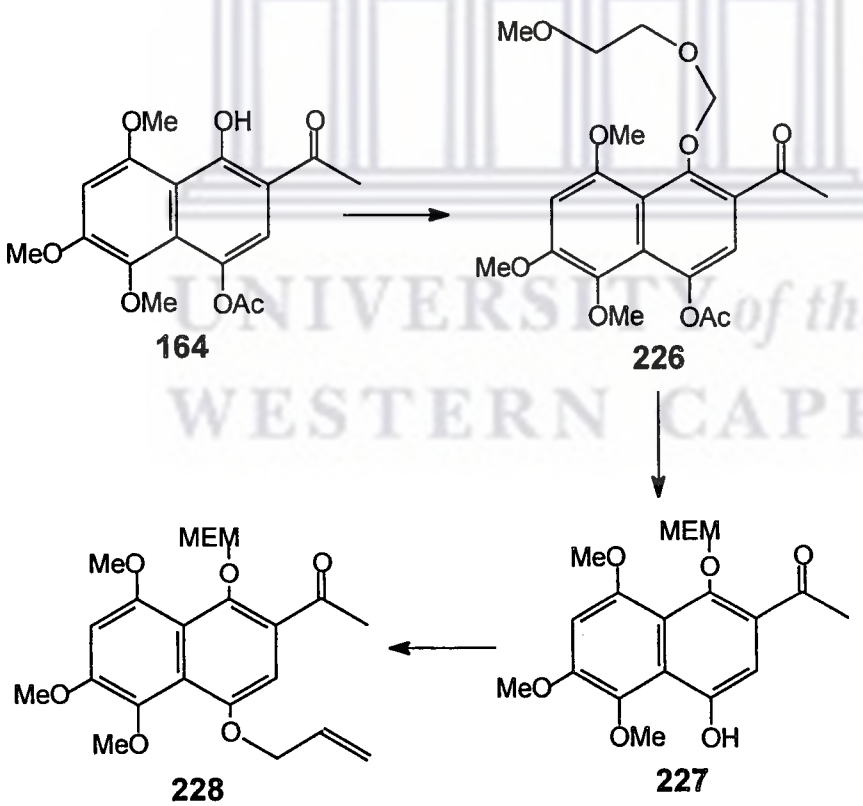
Use of the benzyl group for protecting the C-1-O of alcohol **221** was reconsidered in the light of the extreme difficulty in separating the *cis* and *trans* pyrans **222** and **223** and that during oxidation a fair deal of decomposition occurred with the remaining quinones **224** and **225** being very difficult to obtain in a reasonable yield. In addition the ratio of *cis* to *trans* isomers was 1:2 making the route non-viable. It was evident that the large aryl ring at C-1 in the precursor **221** was not conducive for the formation of *cis* 1,3-dimethylnaphthopyran ring systems.

Due to the limited success of the above methodology, it was decided to attempt to use a different protecting group viz., the methoxyethoxymethyleneoxy (MEM) group. A similar synthetic approach was used as previously described whereby the naphthol **164** was treated with three molar equivalents of 1-chloromethoxy-2-methoxyethane in the presence of potassium carbonate vigorously stirred in dry acetone under reflux in an nitrogen atmosphere. Observation of tlc plates of the crude reaction product indicated that reaction had taken place and that all the starting material had been consumed. On analysis of the product purified by column chromatography using ethyl acetate / hexane (60:40) as eluent, it

appeared that in addition to the product **226,** considerable amounts of starting material **164** were obtained. At this stage we could only assume that the slight acidity of the stationary phase and the necessity of the lengthy exposure time of the material **226** to it during the chromatographic purification was effecting the removal of the MEM protecting group. This was confirmed by introducing 1% by volume of triethylamine to the eluent mixture to make the mobile phase slightly basic and in this way a quantitative yield of the desired product **226** was obtained. Comparison of both the ^{1}H-nmr and ^{13}C-nmr spectra with that of the diacetoxy precursor **163** showed the disappearance of the acetoxy group at C-1. The ^{1}H-nmr spectrum showed *inter alia* two singlets at δ 2.33 and 2.73 for the acetate and acetyl methyl hydrogens respectively and also a three proton singlet at δ 3.33 for the methoxy group of the MEM side chain. The other protons of the MEM group were multiplets at δ 3.46 and 3.49, each 2H for $CH_3OCH_2CH_2O$- respectively and a two proton singlet δ 5.15 for the two methylene protons of the methylene dioxy segment of the MEM group. In the ^{13}C-nmr spectrum the MEM group could be identified by signals at δ 61.99 for the methyl carbon, δ 70.44 and 71.12 for -OCH_2CH_2O- and δ 101.12 for the (-OCH_2O-).

The new MEM compound **226** was hydrolysed with methanolic potassium hydroxide followed by careful acidification to afford the phenol **227** which was not purified but the crude material was immediately dissolved in dry acetone and treated with allyl bromide and potassium carbonate and heated with stirring under reflux in a nitrogen atmosphere for 48 hours. Purification of the material employing similar chromatographic precautions described earlier which was now

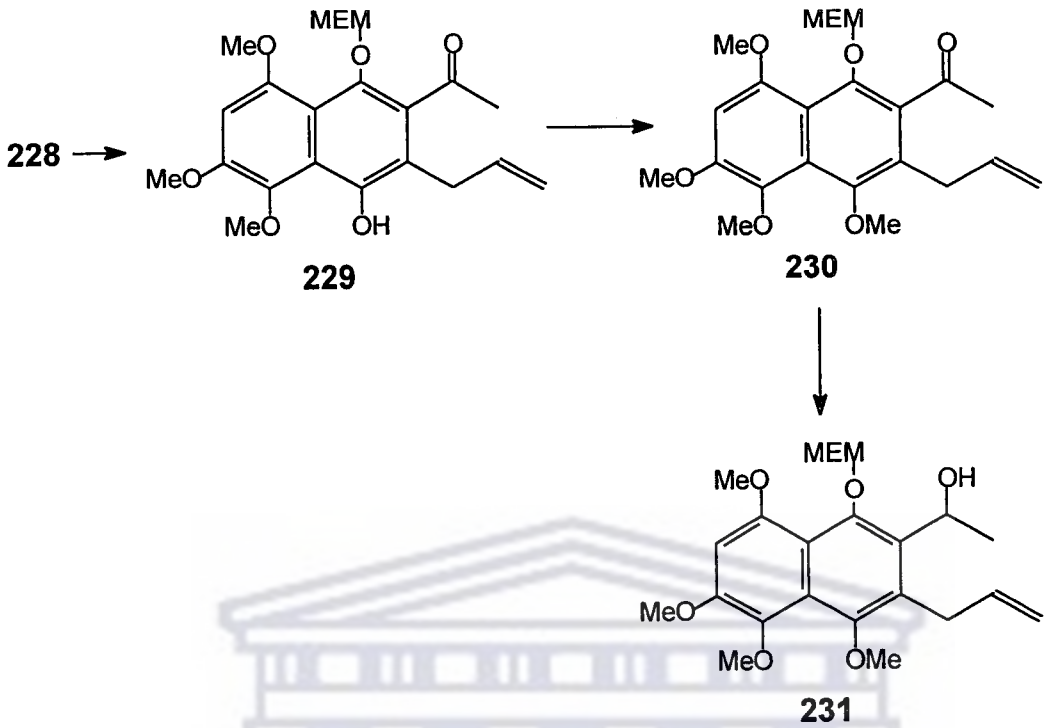
to be used throughout the MEM series of compounds to prevent the hydrolysis of the MEM group, afforded the allyloxy ketone **228** (46%) (**Scheme 47**). The ^{1}H-nmr spectrum showed *inter alia* that the MEM group had been retained by the singlet for the MEM methoxy at δ 3.32, the muliplets for the -OCH_2CH_2O- hydrogens at δ 3.46 and 3.64 and the -OCH_2O- methylene hydrogens at δ 5.10. The allyloxy group at C-4 was evident from the doublet of triplets at δ 4.62 (*J* 5.2 and 1.4 Hz) for the two C-1' hydrogens, two sets of doublets of quartets at δ 5.30 (*J* 10.4 and 1.4 Hz) and δ 5.54 (*J* 17.0 and 1.4 Hz), showing clearly the *cis* and *trans* coupled hydrogens at C-3' respectively. A multiplet for the one hydrogen at C-2' appeared at δ 6.16.



Scheme 47

Allyloxynaphthalene **228** was now heated to 135°C in an oil bath under a nitrogen atmosphere and the Claisen rearranged product, viz. phenol **229** obtained after 4 hours was immediately taken up in dry acetone and treated with five molar equivalents of potassium carbonate and 5 molar equivalents of iodomethane and the mixture stirred under reflux in a nitrogen atmosphere for 12 hours. The usual chromatography procedure afforded the pure tetramethoxy MEM ketone **230** (89%). The ^{1}H-nmr spectrum showed *inter alia* five methoxy singlets at δ 3.37, 3.75 3.78, 3.96 and 4.01, and the disappearance of the singlet for the phenolic proton on the C-4 OH at δ 7.01 for **229**. The methylenedioxy protons for the MEM group appeared as a singlet at δ 5.05.

Reduction of the ketone **230** was effected efficiently by lithium aluminium hydride in dry ether and afforded the expected alcohol **231** in an crude yield of 80% as depicted in **Scheme 48**.

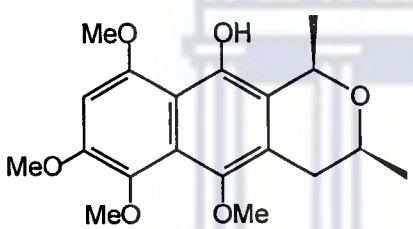


Scheme 48

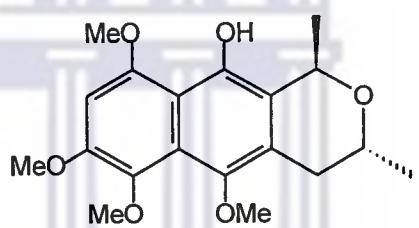
The crude alcohol **231** was dissolved in THF and water and treated with 1.4 equivalents of mercuric acetate and aqueous sodium hydroxide solution after which an excess of sodium borohydride was added to furnish a mixture of *cis* **232** and *trans* **233** pyrans in a combined yield of 25%. It would appear that the MEM group is sensitive to the cyclisation protocol of mercuric acetate and the crude product mixture indicates that although pyran formation indeed occurred by *inter alia* signals at δ 2.44 and δ 2.90 for the H-4 pyran protons, the array of the other signals at δ 1.50 and δ 4.90 gave indications that apart from the low recovery of the products **232** and **233**, that there was considerable decomposition of the MEM group since the MEM group had been completely lost viz. no signal at δ 3.37 - δ 3.40.

Attempts to improve the yields of pyrans **232** and **233** with the view of protecting the C-10 OH were not successful and it was also found that on standing, the crude reaction mixture decomposed.

In view of the above, it was decided to abandon the MEM group as protecting group for the oxygen at the C-10 position and to construct ventiloquinone J **33** using the MOM group to protect the oxygen at C-10.



232



233

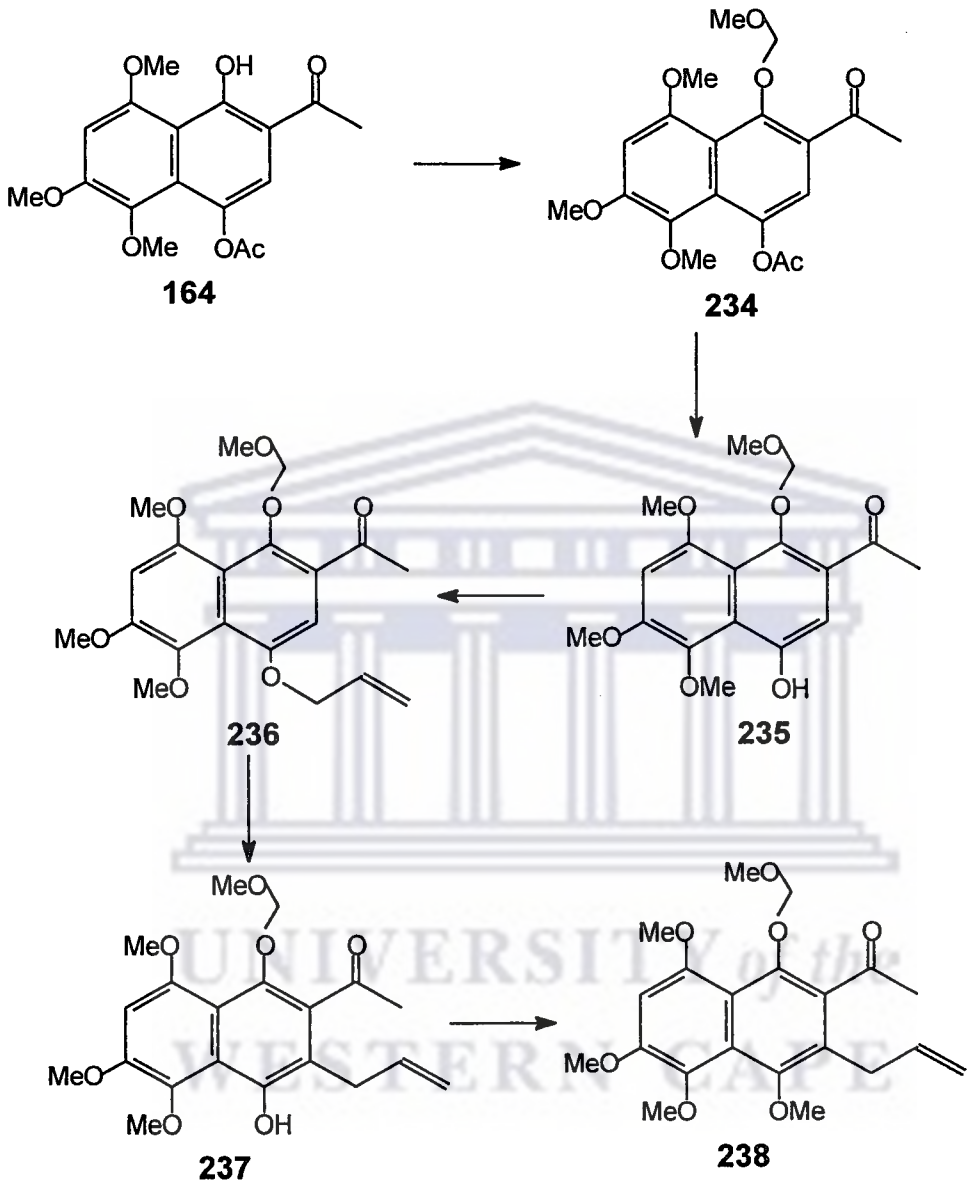
The MOM group was introduced onto the naphthalene nucleus by dissolving the naphthol **164** in acetone and treating the solution with 5 equivalents of potassium carbonate and chloromethyl methyl ether and stirring the mixture vigorously under reflux in an atmosphere of nitrogen for 12 hours. Work-up of the reaction mixture was followed by chromatographic purification on an 800 cm long and 15 mm wide column using a 49:1:50 ethyl acetate / triethylamine / hexane solvent system. Triethylamine was added as a precaution as it was feared that the slight acidity of the column would effect the removal of the MOM group in a similar manner as was experienced earlier with the MEM group.

Later it was found that omitting triethylamine from the eluent mixture had a negligible effect on the purified yield and that the MOM group was not removed from any of the subsequent compounds synthesised. In **234** obtained in a 60% yield from phenol **194**, the MOM group was observed in the ^{1}H-nmr spectrum as a three-proton singlet at δ 3.45 for the MOM methoxy group and a two-proton singlet at δ 5.04 for the methylenedioxy group. The ^{13}C-nmr spectrum had *inter alia* signals at δ 56.66, 56.85, 58.58 and 62.00 for the three naphthalene methoxy groups and the MOM methoxy group as well as a signal at δ 102.25 for the methylenedioxy carbon.

The following series of reactions depicted in **Scheme 49** are similar to those described earlier for the benzyloxy and MEM analogues in which the groups were used to protect the C-1-O in the synthesis of ventiloquinone J **33**.

The MOM protected naphthalene acetate **234** was dissolved by stirring in warm methanol and a 5% methanolic potassium hydroxide solution was added to the cooled solution and stirring continued for 10 minutes after which water and dichloromethane were added and the mixture was acidified with hydrochloric acid. Work-up of the reaction mixture gave the crude phenol **235** which was immediately dissolved in acetone and treated with 5 equivalents of potassium carbonate and allyl bromide and stirred under reflux in a nitrogen atmosphere for 48 hours and then allowed to cool to room temperature. The residue obtained upon work-up was purified by chromatography to afford the naphthoketone **236** in a yield of 99%.

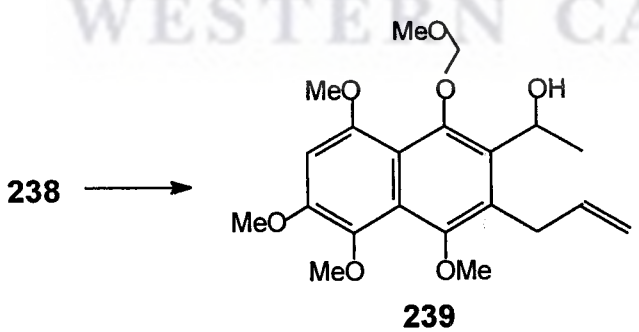
The addition of the allyl group at the C-4 oxygen was evident by the disappearance of the acetoxy three-proton singlet at δ 2.34 in the ^{1}H-nmr spectrum that was present in the precursor **234** and also the appearance of a doublet of triplets integrating for the two protons for H-1', two doublets of doublets, one at δ 5.30 (*J* 10.6 and 1.6 Hz) for the *cis* H-3' and another at δ 5.54 (*J* 17.4 and 1.6 Hz) for the *trans* H-3' as well as a multiplet at δ 6.16 for H-2'. This was supported in the ^{13}C-nmr spectrum by the disappearance of the acetoxy methyl carbon signal at δ 20.67 and its carbonyl carbon at δ 170.01 and the appearance of signals at δ 71.01, δ 117.69 and δ 133.42 for C-1', C-3' and C-2' respectively. The naphthoketone **236** was pyrolysed at 160°C in an oil bath in a nitrogen atmosphere for 2 hours to afford the crude phenol **237** which showed a doublet of triplets at δ 3.44 (*J* 5.4 and 1.4 Hz) for the two C-1' protons, two doublets of quartets, one at δ 4.95 (*J* 10.4 and 1.4 Hz) for *cis* H-3' and the other at δ 5.00 (*J* 17.5 and 1.4 Hz) for *trans* H-3' and a multiplet δ 5.98 for H-2' in the ^{1}H-nmr spectrum. A D_2O exchangeable proton signal at δ 10.24 was assigned to the hydroxyl group at C-4 and the usual naphthalene methoxy signals and MOM signals were also observed. Disappearance of the singlet at δ 7.00 for the proton at C-3 gave evidence that the Claisen Rearrangement had been effected. The phenol was dissolved in acetone and treated with five equivalents of potassium carbonate and iodomethane and then vigorously stirred under reflux in a nitrogen atmosphere for 12 hours.



Scheme 49

The product **238** (79%) was isolated by the usual work-up and purification procedures and gave similar ^{1}H-nmr signals and integration as described for the phenol **237**. An additional three-proton singlet at δ 3.75 and the disappearance of the D_2O exchangeable hydroxyl proton at δ 10.24 indicated methoxy functionality at C-4. Five methoxy carbons were also evident in the ^{13}C-nmr spectrum at δ 56.60, 56.83, 58.06, 62.13 and 62.79 for the four naphthalene methoxy groups and one for the MOM group. The C atoms of the prop-2-enyl side chain appeared at δ 33.69, 116.14 and 137.26 for C-1', C-3' and C-2' respectively in the spectrum.

Consequently naphthoketone **238** was dissolved in dry ether and dripped into a stirring slurry of two equivalents of lithium aluminium hydride in dry ether under nitrogen and stirring was continued for a further 10 minutes after which the reaction mixture was quenched by the addition of saturated ammonium chloride solution followed by the usual work-up and chromatographic purification to afford the alcohol **239** in a quantitative yield shown in **Scheme 50.**



Scheme 50

The appearance of a broad D_2O exchangeable singlet at δ 4.35 in the ^{1}H-nmr spectrum is ascribed to the hydroxyl group and the disappearance of the carbonyl carbon signal in the ^{13}C-nmr spectrum at δ 205.48 support the fact that the ketone group was indeed reduced. The IR spectrum showed a broad absorption peak at 3430 cm^{-1} for the hydroxyl group.

To effect cyclisation, the alcohol **239** was dissolved in THF and water and one equivalent of mercuric acetate was added to the stirring solution followed by addition of aqueous sodium hydroxide solution and finally an excess of sodium borohydride. The organic material was extracted into ethyl acetate and the residue obtained upon work-up was chromatographed on a PLC plate to afford the *cis* pyran **240** as a front band. The ^{1}H-nmr spectrum showed doublets for the pyran methyl groups at δ 1.40 (*J* 5.8 Hz) for 3-CH_3 and δ 1.68 (*J* 6.2) for 1-CH_3. The C-4 hydrogens appeared as a doublet of doublets at δ 2.55 (*J* 15.6 and 10.6 Hz) for the pseudoaxial proton for which no long range coupling was observed and a doublet of doublet of doublets at δ 3.11 (*J* 15.6, 3.4 and 1.0 Hz) for the pseudoequatorial proton. A three-proton singlet at δ 3.59 is assigned the MOM methoxy hydrogens and four three-proton singlets for the naphthalenemethoxy hydrogens were observed at δ 3.79, 3.81, 3.94, and 4.00. A multiplet at δ 3.70 is assigned to the H-3 suggesting the *cis* 1,3-dimethylpyran stereochemistry while a doublet of quartets at δ 5.29 (*J* 6.2 and 1.0 Hz) is assigned to H-1 in which long range coupling is observed between the H-1a and the H-4e. It was interesting to note that the two methylenedioxy protons appeared as two one-proton doublets at δ 4.83 and 5.09 (*J* 6.6 Hz) indicating that they exist in different magnetic

environments due to them being diastereoisotopic as a result of the asymmetric centre at C-1 of the pyran ring. A singlet at δ 6.67 is assigned to the single aromatic proton H-8. The ^{13}C-nmr spectrum showed *inter alia* signals for the pyran methyl carbons at δ 21.91 (3-CH_3) and 22.78 (1-CH_3) and the three pyran-ring carbons at δ 31.66 (C-4), 69.48 (C-3) and 71.69 (C-1). The five methoxy carbon signals appeared at δ 56.87, 56.99, 57.80, 61.67 and 62.07. The slower moving fraction isolated from the plate was assigned the *trans* stereochemical structure **241**, again demonstrating the typical ^{1}H-nmr spectrum variation for the H-4 pyran ring protons which appeared as doublets of doublets at δ 2.58 (*J* 17.2 and 11.0 Hz) for the pseudoaxial H-4 and at δ 3.10 (*J* 17.2 and 3.4 Hz) for the pseudoequatorial H-4. In this case H-3 appeared as a multiplet at δ 4.05 demonstrating the *trans* 1,3-dimethyl relative stereochemistry of the pyran ring while H-1 appeared as a quartet at δ 5.46 (*J* 6.6 Hz).

The successfully separated pyrans **240** and **241**, were each oxidised by dissolving in acetonitrile and water and treating with 2.2 molar equivalents of aqueous CAN solution. The residue obtained upon work-up in each case was chromatographed on a PLC plate (*trans* = plate T, *cis* = plate C) and each gave two distinct bands after eluting both plates twice in ethyl acetate-hexane (1:4) as eluent.

The front band from the oxidation of the *trans* material **241** (plate T) was assigned the structure **244** (isoventiloquinone E) (56%). The ^{1}H-nmr spectrum had two three proton doublets at δ 1.33 (*J* 6.2 Hz) and δ 1.51 (*J* 6.6 Hz) for the

pyran methyl groups at C-3 and C-1 respectively and two single proton doublet of doublet of doublets at δ 2.21 (*J* 18.6, 9.8 and 1.8 Hz) and δ 2.65 (*J* 18.6, 3.6 and 1.0Hz) for the C-4 axial and equatorial hydrogens respectively and in which long range coupling was clearly evident. Three methoxy three proton singlets at δ 3.87, 3.98 and 3.99 were observed. The disappearance of the two doublets (each *J* 6.2) at δ 4.86 and δ 5.11 for the methylenedioxy group indicated that the MOM group had been completely removed and confirmed that oxidation had occurred at C-5 and C-10 and not at C-6 and C-9 as had been expected. The hydrogen at C-3 appeared as a multiplet at δ 3.97 and the hydrogen at C-1 appeared as doublet of quartets at δ 4.98 (*J* 6.6 and 1.8) confirming the *trans* pyran configuration. A singlet at δ 6.74 for the naphthalene ring hydrogen at C-8 was observed. The ^{13}C-nmr spectrum had *inter alia* signals at δ 19.76 and δ 21.60 for the pyran methyl carbons at C-3 and C-1 respectively and a signal at δ 29.65 for C-4. Three methoxy carbon signals occurred at δ 56.31, δ 56.79 and δ 61.38 and signals at δ 62.66 and 67.30 were assigned to C-3 and C-1 respectively. A signal at δ 101.35 represented C-8 and the appearance of two carbonyl carbon signals at δ 181.68 and δ 184.22 confirmed the quinone structure. This was supported by the IR spectrum which displayed strong absorption at 1660 cm^{-1} and the HRMS having the correct molecular ion M^+ = 332.12587 ($C_{18}H_{20}O_6$ requires 332.12599). The second band removed from plate T was the required product **243** (43%). The ^{1}H-nmr had a singlet for the three methoxy hydrogens of the MOM group at δ 3.57 and also two other three proton singlets at δ 3.83 and δ 3.97 for the methoxy hydrogens at C-5 and C-7. Two

doublets (*J* 6.4 Hz) for the methylenedioxy hydrogens appeared at δ 4.81 and 5.07. The hydrogens at C-4 appeared as doublets of doublets at δ 2.42 (*J* 17.6 and 10.6 Hz) for H-4a and at δ 2.92 (*J* 17.6 and 3.4 Hz) for the H-4e while a single proton multiplet at δ 4.02 confirmed the *trans* stereochemistry of the pyran ring. A quartet at δ 5.28 for H-1 (*J* 6.6 Hz) and a singlet at δ 5.94 for the hydrogen at C-8 were also observed. Signals at δ 19.81 and 21.83 in the ^{13}C-nmr spectrum represented the pyran methyl carbons attached at C-3 and C-1 respectively and a signal at δ 30.44 for C-4 was present. The three methoxy carbons, one from the MOM group and the other two attached to the naphthalene ring at C-5 and C-7, gave signals at δ 57.11, δ 57.90 and δ 61.46. Carbon signals at δ 62.19, δ 69.04, δ 102.60, and δ 102.89 were assigned C-3, C-1, the methylene dioxy, and C-8 respectively. Two carbonyl carbon atoms gave signals at δ 170.08 and δ 179.49 for the quinone functionality. The IR spectrum had a strong absorption band at 1652 cm^{-1} for the carbonyl group while the HRMS gave a molecular ion of M^+ = 362.13592 ($C_{19}H_{22}O_7$ requires 362.13655) which also supported the molecular formula.

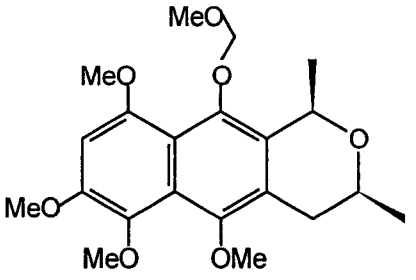
Similarly, the front band removed from plate C was identified as the ventiloquinone E **28** (59%) which differed significantly from its *trans* stereoisomer **244** in the ^{1}H-nmr spectrum with respect to the protons at C-3 and C-4. The two protons at C-4 were displayed as a doublet of doublet of doublets at δ 2.11 (*J* 18.2, 10.2 and 3.6 Hz) for H-4a and a doublet of triplets at δ 2.80 (*J* 18.2 and 2.6 Hz) for H-4e while a multiplet at δ 3.54 represented H-3. All the analytical data were consistent with that published by Bergeron and Brassard. [51]

The back band on plate C was *cis* 3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-*c*]pyran-6,9-dione **242** which also displayed similar spectral features to its isomer **243** except for the typical differences in the ^{1}H-nmr spectrum with respect to the pyran protons at C-3 and C-4. In this instance H-4a appeared as doublet of doublet of doublets (*J* 17.2, 10.2 and 1.8 Hz) at δ 2.42 and H-4e was a doublet of triplets (*J* 17.2 and 2.2 Hz) at δ 2.92 while H-3 appeared as a multiplet at δ 3.58.

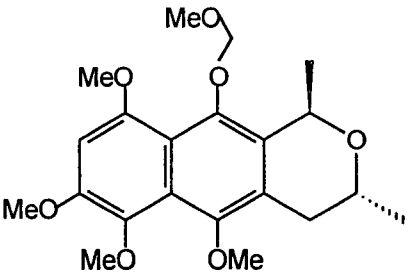
Ventiloquinone J **33** was finally prepared by dissolving the quinone **242** in dioxane and water and stirring with tosic acid for 18 hours at 55°C after which the reaction mixture was poured into water and extracted with dichloromethane and the residue obtained upon work-up was purified by PLC. The spectral and physical properties (see experimental) were consistent with those of the natural product.[19] Isoventiloquinone J **245** was similarly obtained from **243** by selective removal of the MOM group. The ^{1}H-nmr spectrum displayed two three-proton doublets at δ 1.40 for the 3-CH_3 (*J* 6.2 Hz) and δ 1.61 (*J* 6.6 Hz) for the 1-CH_3. A doublet doublets at δ 2.44 (*J* 17.6 and 10.6 Hz) was assigned H-4a, while a doublet of doublets at δ 2.93 (*J* 17.6 and 3.5 Hz) was assigned to H-4e. A one-proton multiplet at δ 4.03 was assigned to H-3. Both the methoxy groups appeared as 3-proton singlets at δ 3.84 and δ 3.99 and a quartet at δ 5.09 (*J* 6.6 Hz) was assigned to H-1. A singlet at δ 6.10 was assigned to H-8 while a D_2O exchangeable signal at δ 13.40 was assigned to the OH at C-10. The IR spectrum had absorption peaks at 1660 cm^{-1} for the quinone carbonyl double bonds and at

3368 cm^{-1} for the hydroxyl group. The HRMS supported the molecular formula, $M^+ = 318.11150$ ($C_{19}H_{18}O_6$ requires 318.11030).

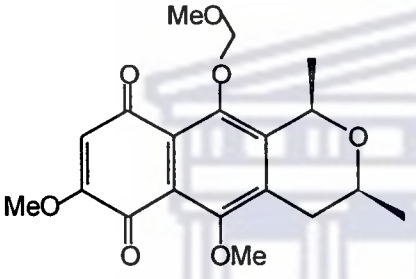
In an alternative strategy, to improve the yield of the 6,9 quinone **242**, the pyran **240** was treated with 2 molar equivalents of silver(II) oxide and nitric acid. In this instance both quinone **242** and **28** were obtained but the yields in this instance were less than that obtained by the CAN methodology.



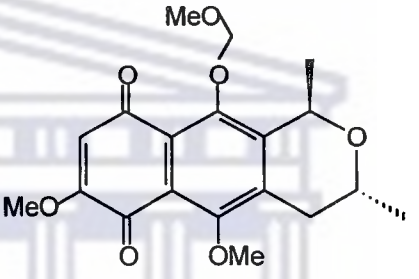
240



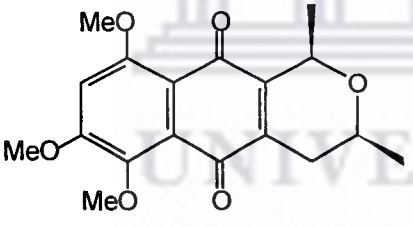
241



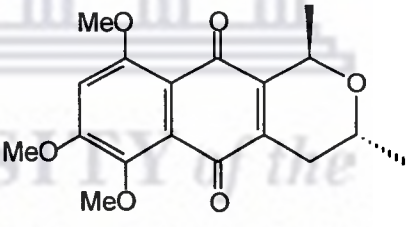
242



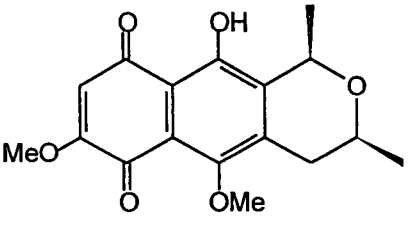
243



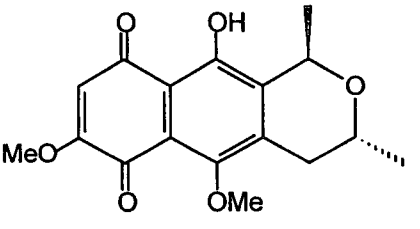
28



244



33



245

CONCLUSION

The synthesis of one of the target molecules, 6-hydroxy-7-methoxyeleutherin **132**, was abandoned due to premature displacement of the C-5 protecting group. Both benzyl and isopropoxyl groups were employed to afford protection of the C-5 oxygen in the naphthalene **149**. In attempts to selectively acetylate the benzyloxytetramethoxynaphthalene **200** at C-2, which was required to commence construction of the pyran ring, only 26% of the desired product **202** was isolated, while the same reaction conditions applied to the isopropoxytetramethoxynaphthalene **201** did not produce any of the desired product **207**.

In the construction of ventiloquinone J **33**, it was found that protection of the C-1 position using the benzyl group was not effective for the formation of *cis* 1,3-dimethylnaphthopyran ring systems. After the formation of the pyran ring, separation of the *cis* **222** and *trans* **223** pyrans proved to be extremely difficult. During oxidation of the mixed pyrans a fair deal of decomposition occurred resulting in very low yields of the quinones **224** and **225** and in addition the *trans* isomer was the major product (*cis*:*trans* = 1:2).

Protection of C-1 using the MEM group also presented several problems. Firstly purification of the MEM-substituted compounds by column chromatography resulted in the complete loss of the MEM group. This difficulty was overcome by adding 1% triethylamine to the eluent to compensate for the slight acidity of the

silica gel stationary phase. Cyclisation of the MEM-alcohol **231** furnished a mixture of the *cis* **232** and *trans* **233** pyrans in which the MEM group had been lost in a combined crude yield of only 25%. The ^{1}H-nmr spectrum showed that considerable decomposition of the MEM group had occurred and that after allowing the crude material to stand further decomposition occurred. Attempts to improve the yields of the pyrans **232** and **233** were not successful and thus this methodology was not considered viable and was not investigated further.

Using the MOM group to protect C-1, cyclisation of the alcohol **239** afforded a mixture of both *cis* **240** and *trans* **241** pyrans that were separated by PLC in yields of 39% and 40% respectively. Oxidation of these naphthopyrans with CAN led to the formation of four naphthopyranquinones, viz., *cis*-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-dione (ventiloquinone E) **28** (59%), *cis*-3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione **242** (39%), *trans*-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-dione (isoventiloquinone E) **244** (56%) and *trans*-3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione **243** (43%). Using silver(II) oxide and nitric acid as oxidant also gave the 6,9 and the 5,10 quinones and thus exclusive oxidation of the left-hand ring was not possible. Quinone **242** was acidified with tosic acid to remove the MOM protecting group which afforded ventiloquinone J **33** in a yield of 56%. Isoventiloquinone J **245** (67%) was obtained similarly from **243**.

constants are given in Hertz. Splitting patterns are designated as "s", "d", "t", "q", "m", "bs", and "sept", these symbols indicate "singlet", "doublet", "triplet", "quartet", multiplet", broad singlet" and "septet".

^{13}C-nmr (nuclear magnetic resonance) spectra were recorded on a Varian 200 MHz spectrometer and are reported to 2 decimal places while it is realised that 1 decimal place is required. Spectra were recorded in deuterated chloroform ($CDCl_3$) and chemical shifts are reported as parts per million (ppm) relative to the central signal of deuterated chloroform, taken as 77.109 ppm.

Infrared spectra were recorded on a Perkin Elmer Fourier Transform Spectrometer, Paragon 2000. Oil samples were recorded as thin films between sodium chloride plates, while solids were recorded as sodium bromide pellets.

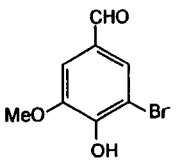
Mass Spectra were recorded on a Finnigan-MAT GCQ, gas chromatograph / mass spectrometer. Mass spectrometry data are reported as *m/z* (% relative abundance).

Elemental analyses were performed on both oil and solid samples on a Carlo Erba 1500 NA analyser and are recorded as percentage to two decimal places although only one decimal place is required.

Other General Procedures

The term "residue obtained upon work-up" refers to the drying of the extract over magnesium sulphate followed by filtration and the removal of the solvent by rotary evaporation.

3-Bromo-4-hydroxy-5-methoxybenzaldehyde (138)



138

Vanillin **137** (45.1 g, 0.30 mol) was dissolved in glacial acetic acid (140 ml) at room temperature. A solution of bromine (16 ml, 0.62 mol) in glacial acetic acid (60 ml) was added dropwise with stirring. After stirring for an additional 1h, the reaction mixture was quenched with water (800 ml) and the precipitate was collected by filtration. Recrystallisation provided the product **138** (52 g, 75%) as colourless prisms mp163 – 164°C (from methanol) (lit.[72], mp 164 – 165°C); δ_H (90 MHz) 3.99 (3H, s, OCH_3), 6.54-6.65 (1H, bs, OH, D_2O exchangeable), 7.37 (1H, d, *J* 1.7, 6-H), 7.65 (1H, d, *J* 1.7, 2-H) and 9.79 (1H, s, CHO); δ_C 56.6 (OCH_3), 107.98 (C-6), 108.16 (C-5)[a], 129.99 (C-4)[a], 130.09 (C-2) 147.66 (C-3)[a], 148.86 (C-1)[a], 189.69 (CHO), (assignments with the same superscript may be interchanged).

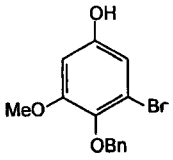
4-Benzyloxy-3-bromo-5-methoxybenzaldehyde (186)

186

3-Bromovanillin **138** (52 g, 0.23 mol) and benzyl bromide (191 g, 1.12 mol) were dissolved in dry dimethylformamide (DMF) (400 ml) and potassium carbonate (155 g, 1.12 mol) was added. The mixture was stirred vigorously on a hot plate / stirrer in a conical flask at 65°C with a calcium chloride drying tube attached. After 6h the mixture was filtered and poured into water (1000 ml). The organic portion was extracted into ether (3 × 200 ml). The reside obtained upon work-up was chromatographed in a fume cupboard (20% eluent) to give the product **186** (63 g, 85%) as white needles, mp 44°C (from hexane / ethyl acetate) (lit.[78], mp 46°C); δ_H (90 MHz)

3.90 (3H, s, OCH_3), 5.19 (2H, s, OCH_2Ph), 7.20-7.74 (7H, m, Ar-H, $PhCH_2$) and 9.85 (1H, s, CHO).

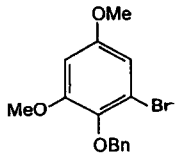
***4-Benzyloxy-3-bromo-5-methoxyphenol* (190)**



190

A solution of **186** (16.8 g 0.052 mol) and m-chloroperbenzoic acid (19.8g, 0.11 mol) in dichloromethane (200 ml) was heated under reflux for 4h. The cooled solution was washed with saturated sodium bicarbonate (3 × 200 ml) followed by water (100 ml). The organic portion was then evaporated to an oil without drying and treated with potassium hydroxide solution (8 g in 280 ml water) and stirred for 8h at 25°C. The reaction mixture was then acidified with aqueous hydrochloric acid (1M) and extracted into ethyl acetate. The residue obtained upon work-up was chromatographed (40% eluent) to afford the phenol **190** (11.3 g, 70%) as colourless needles; mp 100 - 101°C (from ethyl acetate / hexane); (Found: C, 54.89; H, 4.32. $C_{14}H_{13}O_3Br$ requires C, 54.37; H, 4.21%); $\nu_{max.}$ 3360 cm^{-1} (OH), 1610 and 1582 cm^{-1} (C=C); δ_H (90 MHz) 3.85 (3H, s, OCH_3), 5.20 (2H, s, OCH_2Ph), 5.89 (1H, bs, OH), 6.44 (1H, d, *J* 3.0, 6-H), 6.66 (1H, d, *J* 3.0, 2-H), 7.35-7.71 (5H, m, CH_2Ph); δ_C 55.87 (OCH_3), 75.30 (CH_2Ph), 100.18 (C-6), 110.77 (C-2), 117.70 (C-1'), 128.23 (C-4'), 128.29 (C-3'/5')[a], 128.74 (C-2'/6')[a], 135.56 (C-5)[b], 139.43 (C-4)[b], 152.92 (C-3)[b] and 154.07 (C-1)[b] (assignments with the same superscript may be interchanged).

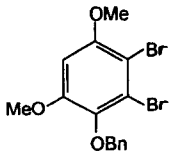
***2-Benzyloxy-3,5-dimetyloxybromobenzene* (192)**



192

The phenol **190** (19.0 g 61.5 mmol) in dry acetone (500ml) containing potassium carbonate (33.9 g, 246 mmol) and dimethyl sulphate (31 g, 246 mmol) under nitrogen was heated and vigorously stirred under reflux for 18 hours. The mixture was cooled, filtered and the solvent removed under reduced pressure and the residue dissolved in ether (300 ml) which was then washed with 25% ammonia solution (100 ml), followed by water (100 ml), 10% hydrochloric acid solution (100 ml), and then water (100 ml). The resulting residue obtained upon work-up was chromatographed (20% eluent) to afford the methylated product **192** (15.2 g, 77%) as a yellow oil; (Found: C, 56.00; H, 4.78. $C_{15}H_{15}O_3Br$ requires C, 55.73; H, 4.64%); $\nu_{max.}$ 1250 cm^{-1} (C-O); δ_H (90 MHz) 3.32 and 3.38 (each 3H, s, OCH_3), 4.52 (2H, s, OCH_2Ph), 6.02 (1H, d, *J* 3.0, H-4), 6.22 (1H, d, *J* 3.0, H-6), 6.89-7.13 (5H, m, CH_2Ph); δ_C 55.65 and 55.95 (OCH_3), 74.80 (OCH_2Ph), 99.93 (C-4), 107.87 (C-6), 117.84 (C-1')[a], 127.93 (C-4')[a], 128.21 (C-3' and C-5')[b], 128.42 (C-2' and C-6')[b], 137.22 (C-5)[c], 139.49 (C-3)[c], 154.24 (C-2)[c] and 156.46 (C-1)[c] (assignments with the same superscript may be interchanged); *m/z* 324/322 (M^+, 31%/31%), 243 (22), 233/231 (59/54) and 91 (100).

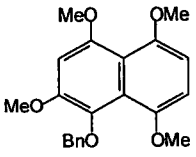
1,2 Dibromo-3-benzyoxy-4,6-dimethoxybenzene (194)



194

The triether **192** (4.9 g 15.2 mmol) and sodium acetate (1.9 g, 22.8 mmol) in acetic acid (100 ml) was stirred at 25°C and treated with bromine (2.43g, 15.2 mmol) in acetic acid (70 ml) dropwise. The solution was stirred for an additional 15 minutes and then poured into water (600 ml) and stirred for 15 minutes. The precipitate was filtered and washed with water to remove all traces of acetic acid then oven dried. Recrystallisation afforded the dibromo product **194** (5.28g, 87%) as off white plates, mp 106°C (from methanol); (Found: C, 44.97; H, 3.88. $C_{15}H_{14}O_3Br_2$ requires C, 44.78; H, 3.48%); $\nu_{max.}$ 1583 and 1563 cm^{-1} (C=C); δ_H (90 MHz) 3.85 and 3.86 (3H, s, OCH_3), 4.85 (2H, s, OCH_2Ph), 6.50 (1H, s, H-5), 7.28-7.60 (5H, m, OCH_2Ph); δ_C 56.38 and 56.90 (OCH_3), 74.84 (OCH_2Ph), 97.20 (C-5), 105.44 (C-1)[a], 122.53 (C-2)[a], 128.08 (C-4')[b], 128.28(C-3' and C-5')[c], 128.42 (C-2' and C-6')[c], 136.93 (C-1')[b], 140.41 (C-3)[d], 153.14 (C-4)[d] and 153.71 (C-6)[d] (assignments with the same superscript may be interchanged); *m/z* 404/402/400 (M^+ 0.6%/1%/0.6%), 313/311/309 (9/18/9) and 91 (100).

***5-Benzyloxy-1,4,6,8-tetramethoxynaphthalene* (200)**



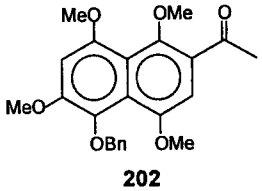
200

The dibrominated compound **194** (6.5 g, 16.2 mmol) and 2-methoxyfuran **144** (1.8 g, 18.6 mmol) were stirred in dry tetrahydrofuran (THF) (55 ml) at -78°C under nitrogen. *n*-Butyllithium [10 ml (1.45M), 14.55 mmol] was added dropwise over 15 minutes and the reaction mixture was stirred for a further 10 minutes after which time it was allowed to warm to room temperature. The mixture was then poured into water (250 ml) and the organic material extracted into ether (4 × 100 ml). The residue obtained upon work-up was flash chromatographed (40% eluent) to give a yellow oil. This was immediately dissolved in dry acetone (170 ml) and dimethyl sulphate (10.2 g, 80.9 mmol) and potassium carbonate (11.2 g, 80.9 mmol) were added. The mixture was vigorously stirred and heated under reflux for 48h after which it was cooled and filtered, the cake being washed with acetone. After removing the solvent under reduced pressure, the brown oily residue was taken up in ether (400 ml) and washed with 25% aqueous ammonia solution (100 ml), water (100 ml), 0.5M hydrochloric acid (100 ml) and then water (200 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford the product **200** (2.36g, 42%) as brown needles; mp 106 – 107°C (from dichloromethane / hexane); (Found: C, 71.59; H, 6.56. $C_{21}H_{22}O_5$ requires C, 71.19; H, 6.21%); δ_H (90 MHz) 3.81 and 3.91 (each 3H, s, 2 × OCH_3), 3.96 (6H, s, 2 × OCH_3), 4.95 (2H, s, OCH_2Ph), 6.66 (1H, d, *J* 8.8, H-2), 6.76 (1H, s, H-7), 6.80 (1H, d, *J* 8.8, H-3), 7.30-7.46 (3H, m, OCH_2Ph) and 7.54-7.62 (2H, m, OCH_2Ph); δ_C 57.39 (OCH_3), 57.46 and 57.59 (3 × OCH_3), 76.19

(OCH_2Ph), 99.23 (C-7), 105.34 (C-2), 108.83 (C-3), 115.75 (C-4a)[a], 124.56 (C-8a)[a], 127.64 (C-4'), 128.34 (C-3' and C-5')[b], 128.41 (C-2' and C-6')[b], 137.05 (C-1'), 138.78 (C-5), 150.29 (C-1)[c], 150.69 (C-4)[c], 151.67 (C-6)[c] and 151.29 (C-8)[c] (assignments with the same superscript may be interchanged); *m/z* 354 (M^+ 7%), 263 (100), 235 (14), 231 (46), 203, (12) and 91 (34).

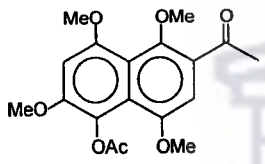
***2-Acetyl-5-benzyloxy-1,4,6,8-tetramethoxynaphthalene* (202) and *5-acetyloxy-2-acetyl-1,4,6,8-teramethoxynaphthalene* (203)**

The penta-alkoxynaphthalene **200** (1.44 g, 4.07 mmol) was dissolved in dry dichloromethane (50 ml) and treated with premixed triflouroacetic anhydride (TFAA) (2.42 g, 2.3 ml, 16.3 mmol) and acetic acid (1.0 g, 1 ml, 16.3 mmol) at 20°C under nitrogen. The solution turned purple and was left stirring for 24h after which the reaction mixture was quenched by successive additions of methanol (10 ml) and saturated sodium bicarbonate slowly until the effervescence stopped and the acids were neutralised. The mixture was thrown into water (350 ml) and extracted with dichloromethane (3 × 100 ml). The residue obtained upon work-up was chromatographed (30% eluent) to give three fractions. The first fraction was identified as starting material (0.15 g, 10%) by TLC. Further elution afforded the desired product **202** (0.38 g, 26%) as light brown plates; mp 167.5 – 169.0°C (from ethanol); (Found: C, 69.71; H, 6.40. $C_{23}H_{24}O_6$ requires C 69.70, H 6.06%); (Found: HRMS, 396.4397. $C_{23}H_{24}O_6$ requires 396.4400); $\nu_{max.}$ 1660 cm^{-1} (C=O); δ_H 2.38 (3H, s, CH_3CO), 3.67 and 3.78 (each 3H, s,



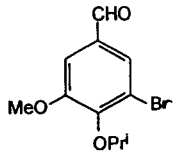
202

OCH_3), 3.95 (6H, s, 2 × OCH_3), 4.13 (2H, s, CH_2Ph), 6.41 (1H, s, H-7), 6.70 (1H, s, H-3) and 7.19-7.30 (5H, m, CH_2Ph); δ_C 20.63 ($COCH_3$), 56.73, 56.87, 57.34 and 62.38 (4 × OCH_3), 76.50 (CH_2Ph), 96.12 (C-7), 107.64 (C-3), 116.50 (C-4a)[a], 124.97 (C-8a)[a], 126.15 (C-4')[b], 128.55 (C-3' and 5')[b], 129.11 (C-2' and 6')[b], 132.07 (C-1'), 139.90 (C-2), 140.87 (C-6)[c], 145.78 (C-5)[c], 149.29 (C-4)[c], 153.73 (C-1)[c], 156.62 (C-8)[c], and 199.8 ($COCH_3$) (assignments with the same superscript may be interchanged); *m/z* 396 (M^+, 50%), 354 (75), 339 (100), 324 (12), 311 (4), 277 (3), 262 (5), 248 (2), 165 (3), 91 (16), 43 (34). Further elution afforded the acetate **203** (0.32g, 25%) as off-white needles, mp 157 –160°C (from ethanol); (Found: C, 62.19; H, 5.99. $C_{18}H_{20}O_7$ requires C 62.07, H 5.75%); (Found: HRMS, 348.3520. $C_{18}H_{20}O_7$ requires 348.3526); $\nu_{max.}$ 1758 and 1658 cm^{-1} (C=O); δ_H 2.36 and 2.74 (each 3H, s, CH_3CO), 3.78, 3.88, 3.96 and 4.05 (each 3H, s, OCH_3), 6.78 (1H, s, H-7), 7.08 (1H, s, H-3); δ_C 20.67 ($COCH_3$), 31.42 ($OCOCH_3$), 56.53, 56.70, 56.78, 63.90, (4 × OCH_3), 96.39 (C-7), 106.08 (C-3), 116.39 (C-4a)[a], 125.16 (C-8a)[a], 127.10 (C-2)[a], 127.45 (C-5)[a], 150.94 (C-1)[b], 151.03 (C-4)[b], 152.98 (C-6)[b], 156.34 (C-8)[b], 170.23 ($OCOCH_3$) and 200.33 ($COCH_3$) (assignments with the same superscript may be interchanged); *m/z* 348 (M^+, 35%), 306 (100), 291 (58), 276 (10), 262 (7), 254 (4), 231 (2), 217 (2), 91 (3), 43 (39).



203

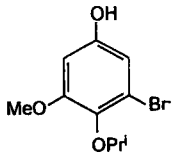
3-Bromo-4-isopropoxy-5-methoxybenzaldehyde (187)



187

3-Bromovanillin **138** (21.15 g, 0.066 mol) and 2-bromopropane (40.55 g, 31 ml, 0.329 mol) were dissolved in dry dimethylformamide (DMF) (550 ml) and potassium carbonate (45.5 g, 0.329 mol) was added. The mixture was vigorously stirred and heated to 80°C under nitrogen for 6h after which the mixture was allowed to cool to room temperature before pouring it into water (600 ml) and extracting the resultant solution with ether (3 × 200 ml). The residue obtained upon work-up was chromatographed (20% eluent) to afford the product **187** (23.85 g; 99.7%) as white needles; mp 41 - 42°C (from hexane); (Found: C, 48.15; H, 4.65. $C_{11}H_{13}O_3Br$ requires C, 48.35; H, 4.80%); $\nu_{max.}$ 1698 cm^{-1} (C=O), 1575 and 1459 cm^{-1} (C=C); δ_H (90 MHz) 1.36 (6H, d, *J* 6.2, $C(CH_3)_2$), 3.92 (3H, s, OCH_3) 4.75 (1H septet, *J* 6.2, $OCH(CH_3)_2$), 7.38 (1H, d, *J* 1.8, H-6), 7.55 (1H, d, *J* 1.8, H-2), and 9.84 (1H, s, CHO); δ_C 22.59 ($C(CH_3)_2$), 56.08 (OCH_3), 77.43 ($OCH(CH_3)_2$), 109.72 (C-6)[a], 116.61 (C-2)[a], 128.99 (C-1), 132.46 (C-3), 150.21 (C-5)[b], 154.26 (C-4)[b], 190.17 (CHO) (assignments with the same superscript may be interchanged); *m/z* 274/272 (M^+,5%/5%), 232/230 (100/91), 79 (14) and 43 (34).

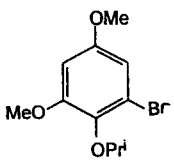
***3-bromo-4-isopropoxy-5-methoxyphenol* (191)**



191

A solution of **187** (23.85 g, 0.087 mol) and *m*-chloroperbenzoic acid (22.7g; 0.13 mol) in dry dichloromethane (300 ml) was stirred and heated under reflux for 4h, after which time the solvent was removed under reduced pressure and the resulting oil taken up in ether (250 ml) and washed with saturated sodium bicarbonate (3 × 200 ml). The ether layer was recovered and the residue obtained upon solvent evaporation was treated with potassium hydroxide solution (10 g in 300 ml) and methanol (10 ml) was added. The mixture was stirred at 20°C for 72 hours after which it was acidified with hydrochloric acid (conc.) and then extracted with ethyl acetate (4 × 100 ml). The residue obtained upon work-up was chromatographed (30% eluent) to give the phenol **191** (18.2 g, 80%) as colourless needles, mp 119 – 120°C (from hexane); (Found: C, 46.40; H, 5.11. $C_{10}H_{13}O_3Br$ requires C, 45.98; H, 4.98%); $\nu_{max.}$ 3623 cm^{-1} (OH); 1581 and 1605 cm^{-1} (C=C); δ_H (90 MHz) 1.32 (6H, d, *J* 6.2, $C(CH_3)_2$), 3.71 (3H, s, OCH_3), 4.44 (1H, septet, *J* 6.2, $OCH(CH_3)_2$), 6.35 (1H, d, *J* 2.8, H-6), 6.49-6.55 (1H, OH, D_2O exchangeable), and 6.63 (1H, d, *J* 2.8, H-2); δ_C 22.25 ($C(CH_3)_2$), 55.80 (OCH_3), 76.58 ($OCH(CH_3)_2$), 100.14 (C-2)[a], 111.03 (C-6)[a], 116.35 (C-3), 137.51 (C-1), 152.66(C-5)[b] and 154.25 (C-4)[b] (assignments with the same superscript may be interchanged); *m/z* 263/261 ($(M+1)^+$, 1.0%/1.4%), 220/218 (93/100), 205/203 (38/36), 177/175 (11/12), 69 (16) and 43 (22).

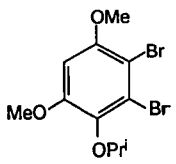
2-Isopropoxy-3,5-dimethoxybromobenzene (193)



193

The phenol **191** (3.14 g 12 mmol) in dry acetone (100ml) containing potassium carbonate (8.3 g, 60.2 mmol) and dimethyl sulphate (7.58 g, 60.2 mmol) was heated and stirred under reflux for 12 hours under nitrogen. The mixture was cooled, filtered and the solvent removed under reduced pressure and the residue dissolved in ether (100 ml) which was then washed with 25% aqueous ammonia solution (50 ml), followed by water (50 ml), 10% hydrochloric acid solution (50 ml), and then water (50 ml). The resulting residue obtained upon work-up was chromatographed (20% eluent) to afford the methylated product **193** (2.89 g, 88%) as a yellow oil; (Found: C, 48.15; H, 5.40. $C_{11}H_{15}O_3Br$ requires C 48.00, H 5.50%); $\nu_{max.}$ 1600 and 1570 cm^{-1} (C=C); δ_H (90 MHz) 1.31 (6H, d, *J* 6.2, $OCH(CH_3)_2$), 3.75 and 3.80 (each 3H, s, OCH_3), 4.43 (1H, septet, *J* 6.2 , $OCH(CH_3)_2$), 6.43 (1H, d, *J* 2.8, H-4) and 6.64 (1H, d, *J* 2.8, H-6); δ_C 22.33 ($OCH(CH_3)_2$), 55.57, 55.81 (each OCH_3), 75.67 ($OCH(CH_3)_2$), 99.61 (C-4)[a], 108.00 (C-6)[a], 116.30 (C-1), 138.73 (C-3)[b], 154.23 (C-2)[b], and 155.61 (C-5)[b] (assignments with the same superscript may be interchanged); *m/z* 276/274 (M^+, 8%/9%), 234/232 (87/100), 219/217 (53/55), 191/189 (16/19), 124 (13), 95 (14), 69 (14), and 43 (18).

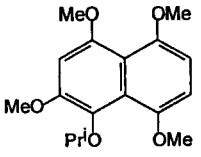
1,2-Dibromo-3-isopropoxy-4,6-dimethoxybenzene (195)



195

The triether **193** (2.89 g 10.5 mmol) and sodium acetate (1.29 g, 15.8 mmol) in acetic acid (60 ml) was stirred and treated with bromine (1.68g, 10.5 mmol) in acetic acid (40 ml) dropwise. The solution was stirred for an additional 15 minutes and then poured into water (400 ml) and stirred for 15 minutes. The precipitate was filtered and washed with water to remove all traces of acetic acid and then oven dried. Recrystallisation from methanol afforded the dibromo product **195** (2.74g, 74%) as very fine white needles; mp 76 – 77°C; (Found: C, 37.45; H, 4.05. $C_{11}H_{14}O_3Br_2$ requires C, 37.29; H 3.95%); $\nu_{max.}$ 1589 and 1560 cm^{-1} (C=C); δ_H 1.31 (6H, d, *J* 6.2, $OCH(CH_3)_2$), 3.86 and 3.88 (each 3H, s OCH_3), 4.47 (1H, septet, *J* 6.2, $OCH(CH_3)_2$), and 6.53 (1H, s, H-5); δ_C 22.32 ($OCH(CH_3)_2$), 56.28 and 56.66 (2 × OCH_3), 76.58 ($OCH(CH_3)_2$), 97.34 (C-5), 105.63 (C-1)[a], 123.00 (C-2)[a], 139.76 (C-3)[b], 153.04 (C-4)[b], 153.12 (C-6)[b] (assignments with the same superscript may be interchanged); *m/z* 356/354/352 (M^+, 4%/8%/4%), 314/312/310 (50/100/51), 299/297/295 (22/47/25), 271/269/267 (7/16/9), 69 (12) and 43 (22).

***5-Isopropoxy-1,4,6,8-tetramethoxynaphthalene* (201)**



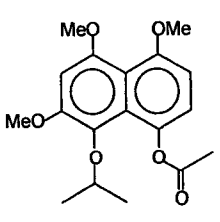
201

The dibrominated compound **195** (6.61 g, 18.6 mmol) and 2-methoxyfuran (2.1 ml ≈ 2.25 g, 23.0 mmol) were stirred in dry tetrahydrofuran (THF) (70 ml) at -78°C under nitrogen. *n*-Butyllithium (8.6 ml, 17.0 mmol) was added dropwise over 15 minutes and the reaction mixture was stirred for a further 30 minutes after which time it was allowed to warm to room temperature. The reaction mixture was then poured into water (100 ml) and the organic material extracted with ether (4 × 100 ml). The residue obtained upon work-up was flash chromatographed (40% eluent) to give a brown oil. This was immediately dissolved in dry acetone (100 ml) and dimethyl sulphate (12.22 g, 9.4 ml, 96.9 mmol) and potassium carbonate (13.37 g, 96.9 mmol) were added. The resulting reaction mixture was vigorously stirred under reflux for 48h after which time it was cooled and filtered, the cake being washed with acetone. After removing the solvent under reduced pressure, the brown oily residue was taken up in ether (400 ml) and washed with 25% aqueous ammonia solution (100 ml), water (100 ml), 0.5M hydrochloric acid (100 ml) and then water (200 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford the product **201** (3.07g, 54%) as a brown oil; (Found: C, 66.75; H, 7.48. $C_{17}H_{22}O_5$ requires C, 66.67; H, 7.19%); δ_H 1.26 (6H, d, *J* 6.2, OCH(CH_3)$_2$), 3.86, 3.89, 3.94 and 3.95 (each 3H, s, 4 × OCH_3), 4.29 (1H, septet, *J* 6.2, OC*H*(CH_3)$_2$), 6.65 (1H, d, *J* 8.5, H-2), 6.74 (1H, s, H-7) and 6.78 (1H, d, *J* 8.5, H-3); δ_C 21.89 (OCH(CH_3)$_2$), 57.28 (2 × OCH_3), 57.45 (2 × OCH_3), 75.89 (O*C*H(CH_3)$_2$), 99.48 (C-7), 105.17 (C-2)[a], 108.98 (C-

3)[a], 115.68 (C-4a)[b], 124.76 (C-8a)[b], 135.42 (C-1)[c], 150.09 (C-4)[c], 159.6 (C-5)[c], 151.60 (C-6)[c], and 153.52 (C-8)[c] (assignments with the same superscript may be interchanged); *m/z* 306 (M^+, 68%), 268 (100), 249 (82), 231 (55), 203 (22), 175 (11), 132 (14), and 43 (11).

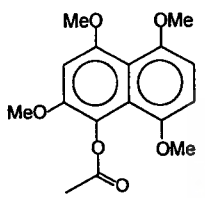
***4-Acetoxy-5-isopropoxy-1,6,8-trimethoxynaphthalene* (204); *5-Acetoxy-1,4,6,8-tetra-methoxynaphthalene* (205); *5-Acetoxy-1,4,6,8-tetramethoxy-2-acetylnaphthalene* (203) *and 1,5-diacetoxy-4,6,8-trimethoxy-2-acetylnaphthalene* (206)**

The penta-alkoxynaphthalene **201** (3.07 g, 10.0 mmol) was dissolved in dry dichloromethane (60 ml) and treated with premixed trifluoroacetic anhydride (TFAA) (10.5 g, 7.05 ml, 50.0 mmol) and acetic acid (3g, 3ml, 50.0 mmol) under nitrogen at 20°C. The solution turned light green and was left stirring for 24h after which the reaction was quenched by successive additions of methanol (10 ml) and saturated sodium bicarbonate slowly until the effervescence stopped and the acids became neutralised. The mixture was thrown into water (500 ml) and the organic portion extracted with dichloromethane (3 × 150 ml) and the residue obtained upon work-up was chromatographed (20% eluent) to give four fractions. The first fraction was identified as **204** (450 mg, 13.5%) as white flakes; mp 128 – 130°C (from hexane / ethyl acetate); (Found: C, 64.90; H, 6.92. $C_{18}H_{22}O_6$ requires C, 64.67; H 6.59%); (Found: HRMS, 334.3701. $C_{18}H_{22}O_6$ requires 334.3691); $\nu_{max.}$ 1747 cm^{-1} (C=O); δ_H 1.25 (6H, d, *J* 6.2, $CH(CH_3)_2$), 2.33 (3H, s, CH_3CO), 3.93 (9H, s, 3 × OCH_3), 4.30 (1H, septet, *J*

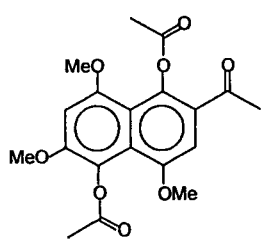


204

6.2, C*H*$(CH_3)_2$), 6.64 (1H, d, *J* 8.8, H-2), 6.71 (1H, s, H-7) and 6.94 (1H, d, *J* 8.8, H-3); δ_C 21.46 (*C*H_3CO), 22.16 (CH(*C*$H_3)_2$) 56.72, 56.78 and 57.72 (3 × OCH_3), 75.74 (*C*H$(CH_3)_2$), 98.90, (C-7), 103.47 (C-2)[a], 115.01 (C-3)[a], 120.39 (C-4a)[b], 126.45 (C-8a)[b], 134.25 (C-5)[c], 139.39 (C-6)[c], 150.58 (C-1)[c], 154.36 (C-8)[c], 155.62 (C-4)[c] and 170.07 (CH_3*C*O_2) (assignments with the same superscript may be interchanged); *m/z* 333 (M^+-1, 21%), 290 (25), 249 (100), 234 (14), 220 (13), 205 (3), 190 (3), 175 (4) and 43 (12). Further elution afforded compound **205** (850 mg, 28%) as off-white fine flakes; mp 161 – 162°C (from hexane / ethyl acetate); (Found: C, 62.74; H, 6.15. $C_{16}H_{18}O_6$ requires C, 62.75; H 5.88%); (Found: HRMS, 306.3148. $C_{16}H_{18}O_6$ requires 306.3153); $\nu_{max.}$ 1764 cm^{-1} (C=O); δ_H 2.37 (3H, s, CH_3CO), 3.84, 3.88, 3.93 and 3.96 (each 3H, s, 4 × OCH_3), 6.65 (1H, d, *J* 9.3, H-2), 6.74 (1H, s, H-7) and 6.77 (1H, d, *J* 9.3, H-3); δ_C 20.75 (CO_2*C*H_3), 56.86, 57.09, 57.39, 57.49 (4 × OCH_3), 97.12 (C-7), 105.55 (C-2 and C-3), 108.31 (C-4a)[a], 122.83 (C-8a)[a], 148.91 (C-1)[b], 149.24 (C-4)[b], 151.58 (C-6)[b], 156.07 (C-8)[b], 170.34 (C-5)[b] and 181.80 (CH_3*C*O_2) (assignments with the same superscript may be interchanged); *m/z* 306 (M^+, 38%), 264 (100), 249 (84), 235 (9), 221 (14), 217 (4), 203 (8), 189 (4), 175 (3), 161 (2), 147 (2) 131 (3), 103 (2), 77 (3), 69 (6), 57 (5) and 43 (26). Further elution afforded compound **203** (1450 mg, 42 %) which had identical physical and spectroscopic properties to that of a similar compound previously synthesised from the compound **200** . The last fraction isolated was identified as the diacetate **206** (500 mg, 13%) as light off white plates; mp 145 – 146°C (from hexane / ethyl acetate);



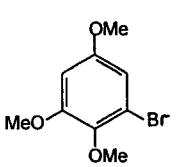
205



206

(Found: C, 60.31; H 5.67. $C_{19}H_{20}O_8$ requires C, 60.64; H 5.32%); (Found: HRMS, 376.3635. $C_{19}H_{20}O_8$ requires 376.3630); $\nu_{max.}$ 1755 and 1690 cm^{-1} (C=O); δ_H 2.36 and 2.40 (6H, s, 2 × CO_2CH_3), 2.59 (3H, s, CH_3CO), 3.91, 3.95 and 4.00 (9H, s, 3 × OCH_3), 6.74 (1H, s, H-7) and 7.15 (1H, s, H-3); δ_C 20.64 (CO_2CH_3), 21.30 (CO_2CH_3), 31.07 ($COCH_3$), 56.60, 56.71, 56.79, (3 × OCH_3), 96.90 (C-7), 100.82 (C-3), 105.65 (C-2), 132.39 (C-4a)[a], 141.35 (C-8a)[a], 151.09 (C-4)[b], 152.58 (C-6)[b], 155.87 (C-8)[b], 170.07 (C-5)[c], 181.52 (C-1)[c], 189.43 (CO_2CH3) 194.36 (CO_2CH_3) and 197.43 ($COCH_3$) (assignments with the same superscript may be interchanged); *m/z* 375 (M^+-1, 38%), 375 (9), 347 (4), 333 (17), 305 (20), 291 (100), 276 (22), 262 (7), 233 (7), 216 (2), and 43 (40).

***3-Bromo-1,2,5-trimethoxybenzene* (135) and *3,6-dibromo-1,2,4-trimethoxybenzene* (136)**

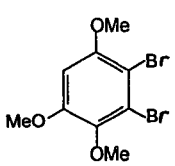


135

3-Bromovanillin **138** (23 g, 0.1 mol) was dissolved with stirring in 1M potassium hydroxide solution (105 ml) to give a yellow solution. 3% Hydrogen peroxide solution (225 ml) was carefully added over 30 minutes during which time the solution turned black. This solution was heated and stirred at 45 – 50°C for 1h and then allowed to cool to 20°C and acidified (Litmus Paper) with 5M hydrochloric acid and the organic material extracted with ether (4 × 250 ml). The crude quinol **208** obtained upon work-up was dissolved in dry acetone (250 ml) and treated with potassium carbonate (68g, 0.5 mol) and dimethyl sulphate (62.74g, 0.5 mol) and vigorously stirred under reflux under nitrogen atmosphere for 24h. The solution was then cooled

and filtered and the solvent evaporated under reduced pressure. The residue was taken up in ether (400 ml), washed with 25% ammonia solution (100 ml), water (100 ml), dilute hydrochloric acid (100 ml) and water (100 ml) and then dried and evaporated to an oil. Chromatography (20% eluent) yielded the trimethoxybromobenzene product **135** as an oil (18,9 g, 77%); δ_H 3.76 (6H, s, 2 × OCH_3), 3.83 (3H, s, OCH_3), 6.43 (1H, d, *J* 3.0, H-6), and 6.62 (1H, d, *J* 3.0, H-4). Further elution yielded compound **136** (as a by-product carried through from the bromination of vanillin **137**) (1.7 g, 5.2%) as white crystals mp 197 – 198°C (from ethyl acetate); δ_H 3.73, 3.84, 3.94 (each 3H, s, OCH_3), and 6.57 (1H, s, H-5).

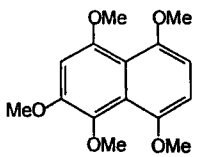
***1,2-Dibromo-3,4,6-trimethoxybenzene* (209)**



209

Compound **135** (15.04 g, 0.061 mol) was dissolved in benzene (45 ml) and bromine (11.6 g, 3.75 ml, 0.15 mol) was added dropwise with stirring at 25°C. After stirring for an additional 1h, the mixture was washed with aqueous sodium carbonate (50 ml of a 20% solution). The benzene layer was removed, dried and evaporated to afford the dibromo product **209** (17.4 g, 80%) as white needles; mp 96 - 98°C (from benzene)(lit.[72] 97°C); δ_H 3.79 (3H, s, OCH_3), 3.88 (6H, s, 2 × OCH_3) and 6.54 (1H, s, H-5).

***1,4,5,6,8-Pentamethoxynaphthalene* (212)**

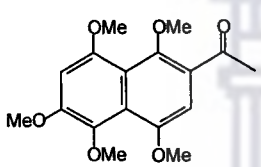


212

The dibromotrimethoxybenzene **209** (6.0 g, 18.4 mmol) and 2-methoxyfuran (2.7 g, 2.7 ml, 27.6 mmol) were stirred in freshly distilled dry THF (65 ml) at -78°C under nitrogen. *n*-Butyllithium [11.9 ml (1.48M), 16.6 mmol] was added dropwise over 15 minutes and the reaction mixture was stirred for a further 10 minutes after which time it was allowed to warm to room temperature. The mixture was then poured into water (200 ml) and the organic material extracted into ether (4 × 100 ml). The residue obtained upon work-up was flash chromatographed (40% eluent) to give starting material **209** (870 mg, 15%) and the mixed tetramethoxynaphthols **210** and **211** (2.79 g, 68%) (based on unrecovered starting material) as a light brown oil. The naphthols were immediately dissolved in dry acetone (100 ml) and dimethyl sulphate (6.7 g, 4.8 ml, 53.0 mmol) and potassium carbonate (7.3 g, 53.0 mmol) were added. The reaction mixture was vigorously stirred and heated under reflux for 48h after which it was cooled and filtered, the cake being washed with acetone. After removing the solvent under reduced pressure, the brown oily residue was taken up in ether (200 ml) and washed with 25% ammonia solution (100 ml), water (100 ml), 0.5M hydrochloric acid (100 ml) and finally water (200 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford the product **212** (2.9 g, 67% based on unrecovered starting material and 99% based on the naphthols) as white needles; mp 104 – 105°C (from hexane) (lit.[21], mp 105 – 106°C); (Found: C, 64.60; H, 6.71. $C_{15}H_{18}O_5$ requires C, 64.75; H, 6.47%); (Found: HRMS, 278.3037,

$C_{15}H_{18}O_5$ requires 278.3049); $\nu_{max.}$ 1600 cm^{-1} (C=C); δ_H 3.81, 3.89, 3.91, 3.94, 3.98 (each 3H, s, OCH_3), 6.66 (1H, d, *J* 8.4, H-2), 6.74 (1H, s, H-7), 6.79 (1H, d, *J* 8.4, H-3); δ_C 57.30, 57.33, 57.61, 57.85, 61.90 (5 × OCH_3), 99.13 (C-7), 105.27 (C-2)[a], 109.06 (C-3)[a], 115.67 (C-8a)[b], 124.34 (C-4a)[b], 138.10 (C-5)[c], 150.18 (C-8)[c], 150.34 (C-1)[c], 151.67 (C-6)[c] and 154.08 (C-4)[c] (assignments with the same superscript may be interchanged); *m/z* 278 (M^+, 100%), 263 (60) and 249 (20).

***2-Acetyl-1,4,5,6,8- pentamethoxynaphthalene* (213)**

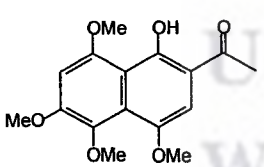


213

The pentamethoxynaphthalene **212** (6.0 g, 21.6 mmol) was dissolved in dry dichloromethane (240 ml) and treated with premixed triflouroacetic anhydride (TFAA) (31.8 g, 21.2 ml, 151.2 mmol) and acetic acid (9.1 g, 9.1 ml, 151.2 mmol) at 20°C under nitrogen. The solution turned dark red and was left stirring for 24h after which the reaction mixture was quenched by slow successive additions of methanol (10 ml) and saturated aqueous sodium bicarbonate until the effervescence stopped and the acids were neutralised. After stirring for an additional 1h the mixture was poured into water (150 ml) and the organic compounds extracted with dichloromethane (3 × 100 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford compound **213** (4.9 g, 71%) as pale yellow flakes, mp 110 – 111°C (from ethyl acetate / hexane) (lit.[21], mp 108 – 109°C); (Found: C, 63.70; H, 6.36. $C_{17}H_{20}O_6$ requires C, 63.75; H, 6.25%); (Found: HRMS, 320.3431. $C_{17}H_{20}O_6$ requires 320.3422); $\nu_{max.}$ 1676 cm^{-1} (C=O) and 1591 cm^{-1} (C=C); δ_H 2.75 (3H, s, $COCH_3$), 3.78, 3.80, 3.96, 4.00

and 4.02 (each 3H, s, OCH_3), 6.77 (1H, s, H-7) and 7.10 (1H, s, H-3); δ_C 31.43 ($COCH_3$), 56.75, 56.83, 57.16, 61.96 and 63.77 (5 × OCH_3) 98.14 (C-7), 105.80 (C-3), 116.65 (C-8a)[a], 126.49 (C-4a)[a], 126.98 (C-2)[a], 138.32 (C-1)[b], 152.07 (C-4)[b], 152.50 (C-6)[b], 152.93 (C-5)[b], 154.37 (C-8)[b] and 200.55 (CO) (assignments with the same superscript may be interchanged); *m/z* 320 (M^+, 100%), 305 (60), 290 (10), 277 (20), 273 (17), 274 (10)and 43 (20). Further elution afforded the acetyl acetate **214** as a white crystalline material, (660 mg, 9%); δ_H 2.39 (3H, s, $OCOCH_3$), 2.60 (3H, s, $COCH_3$), 3.80, 3.93, 3.98 and 3.99, (each 3H, s, OCH_3), 6.73 (1H, s, H-7) and 7.16 (1H, s, H-3). Upon mild base hydrolysis, this material was transformed to the same phenol **159** described below and was thus not investigated further.

***2-Acetyl-4,5,6,8-tetramethoxy-1-naphthol* (159)**

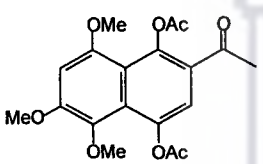


159

The naphthalene **213** (3g, 9.38 mmol) in dry dichloromethane (140 ml) was stirred and treated at –78°C with boron tribromide (10 ml of a 1M solution in CH_2Cl_2, 10 mmol) under nitrogen. After 30 minutes stirring, the reaction mixture was allowed to warm to room temperature (20°C) and then hydrolysed with water (150 ml). The organic material was extracted with dichloromethane (3 × 100 ml) and the residue obtained upon work-up was chromatographed (40% eluent) to afford the naphthol **159** (2.27 g, 79%) as yellow parallelograms; mp 156°C (from 2-propanol) (lit.[21], mp 157 – 158°C); (Found: C, 62.60; H 5.95. $C_{16}H_{18}O_6$ requires C, 62.75; H, 5.88%); $\nu_{max.}$ 3215 cm^{-1} (OH), 1688 cm^{-1} (C=O) and 1615

cm^{-1} (C=C); δ_H 2.65 (3H, s, $COCH_3$), 3.80, 3.91, 4.01, 4.03, (each 3H, s, OCH_3), 6.72 (1H, s, H-7), 7.01 (1H, s, H-3) and 14.08 (1H, s, OH, D_2O exchangeable); δ_C 27.82 ($COCH_3$) 56.67, 57.05, 58.28, and 62.02 (4 × OCH_3), 96.89 (C-7), 108.09 (C-3), 111.82 (C-8a)[a], 112.76 (C-4a)[a], 128.10 (C-2), 137.86 (C-4)[b], 147.21 (C-5)[b], 154.42 (C-6)[b], 157.44 (C-8)[b], 160.01 (C-1)[b], 202.10 (CO) (assignments with the same superscript may be interchanged) ; *m/z* 306 (M^+, 100%), 291 (40), 277 (9), 262 (12 and 43 (25).

***2-Acetyl-1,4-diacetoxy-5,6,8-trimethoxynaphthalene* (163)**

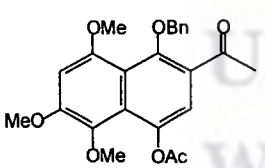


163

The naphthol, compound **159** (1 g, 3.27 mmol) was dissolved in acetonitrile (120 ml) and water (40 ml) was added. The stirred mixture was treated dropwise with a solution of cerium(iv) ammonium nitrate [4.66 g, 8.28 mmol in water (10 ml)] over 10 minutes and stirring was continued for a further 15 minutes. The reaction mixture was poured into water (150 ml) and extracted with dichloromethane (3 × 150 ml). The organic layer was separated and shaken with an aqueous solution of sodium dithionate (10 g in 800 ml) (2 × 400 ml) in a separating funnel. The residue obtained upon work-up of the fluorescent green organic phase was immediately dissolved in dry pyridine (50 ml) and acetic anhydride (10 ml) was added. The mixture was heated to 80 °C with stirring for 2h under nitrogen. The reaction mixture was added to water (200 ml) and the organic material extracted into dichloromethane (3 × 100 ml) keeping the pyridine in the water phase by carefully acidifying with dilute hydrochloric acid. The residue obtained upon

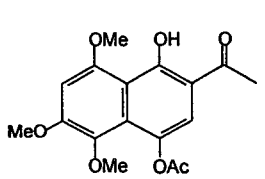
work-up was chromatographed (40% eluent) to afford the diacetate **163** (861 mg, 70%) as pale yellow rectangles; mp 174 – 176°C (from hexane / dichloromethane) (lit.[21], mp 170 – 171°C); (Found: C, 60.57; H, 5.36. $C_{19}H_{20}O_8$ requires C, 60.65; H, 5.32%); $\nu_{max.}$ 1764 and 1755 cm^{-1} (C=O), and 1680 cm^{-1} (C=O); δ_H 2.34 and 2.39 (each 3H, s, $OCOCH_3$), 2.57 (3H, s, $COCH_3$), 3.77, 3.90, and 3.95 (each 3H, s, OCH_3), 6.69 (1H, s, H-7), and 7.43 (1H, s, H-3); δ_C 20.60, 21.38 and 30.74 (3 × CH_3CO), 56.09, 56.48 and 61.55 (3 × OCH_3), 97.32 (C-7), 115.37 (C-8a)[a], 119.85 (C-3)[b], 124.73 (C-2)[b], 126.29 (C-4a)[a], 135.45 (C-1)[c], 142.47 (C-4)[c], 144.81 (C-6)[c], 152.03 (C-5)[c], 154.37 (C-8)[c], 169.38 (2 × CO) and 195.55 (CO) (assignments with the same superscript may be interchanged); *m/z* 376 (M^+, 23%), 334 (35), 292 (80), 277 (100), 43 (40), 32 (79) and 28 (100).

***4-Acetoxy-2-acetyl-1-benzyloxy-5,6,8-trimethoxynaphthalene* (216)**



216

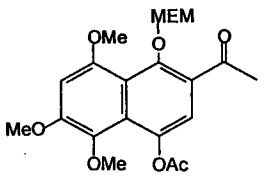
The diacetyl naphthalene **163** (576 mg, 1.53 mmol) was dissolved by warming in methanol (100 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (10.4 ml of a 1% m/v, 1.86 mmol) and the solution stirred at 25°C for 10 minutes. To the reaction mixture was added water (100 ml) and dichloromethane (200 ml) and the mixture carefully acidified with dilute hydrochloric acid and then extracted with dichloromethane. The residue obtained upon work-up was flash chromatographed (50% eluent) to yield the naphthol **164** (511 mg, 100%) as clear needles, mp 174°C (from hexane / ethyl acetate); δ_H



164

2.34 (3H, s, $OCOCH_3$), 2.62 (3H, s, $COCH_3$), 3.78, 4.00 and 4.02 (each 3H, s, OCH_3), 6.69 (1H, s, H-7) and 7.24 (1H, s, H-3). Of this material (290 mg, 0.87 mmol) was dissolved in dry acetone (50 ml). Potassium carbonate (599 mg, 4.34 mmol) and benzyl bromide (742 mg, 4.34 mmol) were added and the mixture vigorously stirred and heated under reflux under nitrogen for 1h. The cooled reaction mixture was filtered and the solvent evaporated and the residue chromatographed (50% eluent) to afford the product **216** (357 mg, 97%) as white grains; mp 147 – 148°C (from isopropanol) (lit.[21], mp 147 – 148°C); Found (C, 68.05; H, 5.80. $C_{24}H_{24}O_7$ requires C, 67.92; H, 5.70%); $\nu_{max.}$ 1753 and 1661 cm^{-1} (C=O); δ_H 2.35 (3H, s, $OCOCH_3$), 2.62 (3H, s, $COCH_3$), 3.81, 3.86 and 4.00 (each 3H, s, OCH_3), 4.94 (2H, s, CH_2Ph), 6.74 (1H, s, H-7), 7.35 (1H, s, H-3) and 7.34-7.47 (5H, m, $PhCH_2$); δ_C 20.69 and 31.50 (2 × CH_3CO), 56.61, 56.74 and 62.00 (3 × OCH_3), 78.97 (CH_2Ph), 97.31 (C-7), 116.85 (C-8a)[a], 120.43 (C-3), 125.00 (C-4a)[a], 127.05-128.66 (C of Ph), 136.17 (C-2)[b], 137.25 (C-1)[b], 141.49 (C-4)[c], 152.30 (C-6)[c], 155.17 (C-5)[c], 155.21 (C-8)[c], 170.04 (C=O of ester) and 199.39 (C=O of ketone) (assignments with the same superscript may be interchanged); *m/z* 424 (M^+, 28%), 382 (17), 340 (23), 325 (12), 291 (100), 234 (18), 233 (12), 91 (69), 43 (61), 32 (46) and 28 (100).

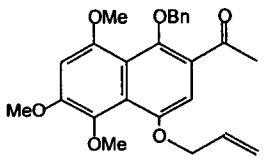
***4-Acetoxy-2-acetyl-5,6,8-trimethoxy-1-(2'-methoxyethoxymethyleneoxy)-naphthalene* (226)**



226

The naphthol **164** (346 mg, 1.04 mmol) was dissolved in dry acetone (100 ml) and potassium carbonate (414 mg, 3.0 mmol) and 1-chloromethoxy-2-methoxyethane (327 mg, 3.0 mmol) were added. The mixture was vigorously stirred and heated under reflux under nitrogen for 48h after which the cooled reaction mixture was filtered and the solvent evaporated. This residue was chromatographed using an ethyl acetate - hexane - triethylamine (60:39:1) as eluent to afford the product **226** (497 mg, 100%) as orange cubes; mp 83 – 85°C (from hexane / ethyl acetate); (Found: C, 59.99; H, 6.51. $C_{21}H_{26}O_9$ requires C, 59.72; H, 6.16%); (Found: HRMS, 422.4319. $C_{21}H_{26}O_9$ requires 422.4310); $\nu_{max.}$ 1690 and 1659 cm^{-1} (C=O), 1225 cm^{-1} (C-O); δ_H 2.33 (3H, s, $OCOCH_3$), 2.73 (3H, s, $COCH_3$), 3.33 (3H, s, $-CH_2OCH_3$), 3.46 (2H, m, $-OCH_2CH_2O-$), 3.69 (2H, m, $-OCH_2CH_2O-$), 3.78, 3.98 and 3.99 (each 3H, s, OCH_3), 5.15 (2H, s, $-OCH_2O-$), 6.74 (1H, s, H-7) and 7.26 (1H, s, H-3); δ_C 20.66 ($OCOCH_3$), 31.59 ($COCH_3$), 56.65, 56.83, 59.11 (each OCH_3), 61.99 ($-OCH_2OCH_2CH_2OCH_3$), 70.44 ($-OCH_2CH_2O-$), 71.82 ($-OCH_2CH_2O-$), 97.58 (C-7), 101.12 ($-OCH_2O-$), 116.39 (C-4a)[a], 120.13 (C-3), 126.81 (C-8a)[a], 129.23 (C-1)[b], 136.27 (C-4)[b], 141.58 (C-2)[c], 152.07 (C-6 and C-8)[c], 154.82 (C-5)[c], 169.98 ($OCOCH_3$) and 200.39 ($COCH_3$) (assignments with the same superscript may be interchanged); *m/z* 422 (M^+, 19%), 380 (10), 334 (16), 304 (24), 292 (46), 277 (100), 262(84), 247 (29), 233 (14), 219 (12), 89 (79), 59 (83) and 43 (69).

***2-Acetyl-1-benzyloxy-5,6,8-trimethoxy-4-prop-2'-enyloxynaphthalene* (218)**

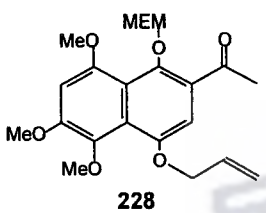


218

Compound **216** (294.8 mg, 0.72 mmol) was dissolved by warming in methanol (65 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (5% m/v, 4 ml, 3.59 mmol) and the solution was stirred at 25°C for 10 minutes. To the reaction mixture was added water (110 ml), and dichloromethane (200 ml). The solution was then carefully acidified with dilute hydrochloric acid and then extracted into the dichloromethane. The phenol residue obtained upon work-up was dissolved in dry acetone (100 ml) and dry potassium carbonate (495 mg, 3.59 mmol) and allyl bromide (462 mg, 3.81 mmol) were added and the mixture was vigorously stirred and heated under reflux under a nitrogen atmosphere for 20h. The reaction mixture was cooled to 25°C, filtered and the cake washed with acetone and the filtrate evaporated to an oily residue which was chromatographed (40% eluent) to give the product **218** (270 mg, 89%) as light yellow plates; mp 105 – 107°C (from isopropanol) (lit.[21], mp 105 – 106°C); (Found: C, 71.15; H, 6.18. $C_{25}H_{26}O_6$ requires C, 71.09; H, 6.16%); $\nu_{max.}$ 1648 cm^{-1} (C=O); δ_H 2.64 (3H, s, $COCH_3$), 3.81, 3.85, and 4.01 (each 3H, s, OCH_3), 4.65 (2H, dt, *J* 5.2 and 1.4, H-1'), 4.89 (2H, s, CH_2Ph), 5.32 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.56 (1H, dq, *J* 17.4 and 1.4, *trans* H-3'), 6.19 (1H, m, H-2'), 6.76 (1H, s, H-7), 7.09 (1H, s, H-3) and 7.26-7.49 (5H, m, CH_2Ph); δ_C 31.62 (CH_3CO), 56.54, 56.80 and 61.96 (3 × OCH_3), 70.83 (OCH_2), 78.57 (CH_2Ph), 97.60 (C-7), 107.72 (=CH), 116.70 (C-8a)[a], 117.48 ($=CH_2$), 126.53 (C-4a)[a], 127.49-128.40 (C of Ph), 133.27 (C-3)[b], 137.30 (C-1)[b], 138.07 (C-2)[b], 150.82 (C-4)[b], 150.94 (C-6)[b], 152.11 (C-5)[b], 154.26 (C-8)[b] and 200.51 (CO) (assignments

with the same superscript may be interchanged); *m/z* 422 (M^+, 20%), 331 (47), 282 (18), 272 (12), 91 (100), 65 (15), 43 (30) and 41 (25).

***2-Acetyl-5,6,8-trimethoxy-1-(2'-methoxyethoxymethyleneoxy)-4-prop-2'-enyloxynaphthalene* (228)**

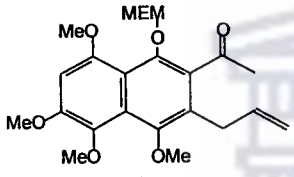


228

Compound **226** (327.0 mg, 0.77 mmol) was dissolved by warming in methanol (70 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (5% m/v, 4.3 ml, 3.85 mmol) and the solution stirred at 25°C for 20 minutes. To the reaction mixture was added water (120 ml) and dichloromethane (200 ml) and the mixture was then carefully acidified with dilute hydrochloric acid (38 ml of a 0.1M solution). The organic component was extracted into the dichloromethane. The phenol residue obtained upon work-up was dissolved in dry acetone (100 ml) and dry potassium carbonate (531 mg, 3.58 mmol) and allyl bromide (433 mg, 3.58 mmol) were added and the mixture was vigorously stirred and heated under reflux for 48h under nitrogen. The reaction mixture was cooled to 25°C, filtered and the cake washed with acetone and the filtrate evaporated to an oily residue which was preabsorbed using ethyl acetate – hexane – triethylamine (60:39:1), then chromatographed using the same eluent to afford the product **228** (150 mg, 46%) as a brown / yellow oil, (Found: C, 62.49; H, 6.95. $C_{22}H_{28}O_8$ requires C, 62.86; H, 6.67%); ν_{max} 1680 cm^{-1} (C=O); δ_H 2.75 (3H, s, $COCH_3$), 3.32 (3H, s, $-OCH_2CH_2OCH_3$) 3.46 (2H, m, $-OCH_2C_2O-$), 3.64 (2H, m, $-OCH_2CH_2O-$) 3.79, 3.97, 4.00 (each 3H, s, OCH_3) 4.62 (2H, dt, *J* 5.2 and 1.4, H-

1'), 5.10 (2H, s, -OCH_2O-) 5.30 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.54 (1H, dq, *J* 17.0 and 1.4, *trans* H-3'), 6.16 (1H, m, H-2'), 6.76 (1H, s, H-7) and 7.01 (1H, s, H-3); *m/z* 420 (M^+, 20%), 380 (19), 338 (8), 277 (70), 89 (60) 59 (100) and 43 (22).

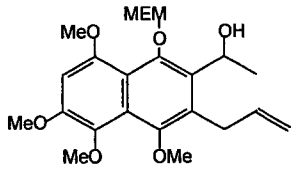
***2-Acetyl-4,5,6,8-tetramethoxy-1-(2'-methoxyethoxymethyleneoxy)-3-prop-2'-enylnaphthalene* (230)**



230

The allyl compound **228** (261 mg, 0.62 mmol) was heated in an oil bath under nitrogen at 130 – 140°C for 4h. The Claisen rearranged product **229** was immediately dissolved in dry acetone (100 ml) and dry potassium carbonate (425 mg, 3.1 mmol) and iodomethane (440 mg, 3.1 mmol) were added and the mixture was vigorously stirred and heated under reflux under nitrogen for 12h. The cooled reaction mixture was filtered and the residue was chromatographed using ethyl acetate – hexane – triethylamine (60:39:1) as eluent to afford **230** (240 mg, 89%) as a clear oil, (Found: C, 63.50; H, 7.00. $C_{23}H_{30}O_8$ requires C, 63.59; H 6.91%), $\nu_{max.}$ 1679 cm^{-1} (C=O); δ_H 2.59 (3H, s, $COCH_3$), 3.37 (3H, s, -$OCH_2CH_2OCH_3$), 3.56 (2H, m, -OCH_2CH_2O-), 3.75 (3H,s, OCH_3), 3.76 (2H, m, -OCH_2CH_2O-), 3.78, 3.96, 4.01 (each 3H, s, OCH_3), 4.94 (1H, dq, *J* 17.0 and 1.4, *trans* H-3'), 5.03 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.05 (2H, s, -OCH_2O-), 5.90 (1H, m, 2-H'), and 6.72 (1H, s, H-7).

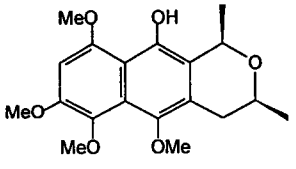
***2-(1'-Hydroxyethyl)-4,5,6,8-tetramethoxy-1-(2'-methoxyethoxyethyleneoxy)-3-prop-2'-enylnaphthalene* (231)**



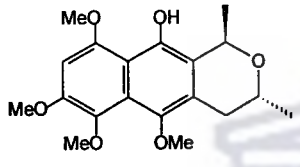
231

The ketone **230** (240 mg, 0.56 mmol) was dissolved in dry ether (15 ml) and dripped into a stirring slurry of lithium aluminium hydride (38 mg, 1.0 mmol) in dry ether (15 ml) and stirring was continued until the reduction was complete (by tlc). The reaction was worked up by the careful addition of a saturated solution of ammonium chloride (about 10 – 12 drops), then water (5ml) and ether (30 ml). The ether layer was separated and the impure residue obtained upon work-up **231** (200 mg, 80%) was used without further purification, δ_H 1.20 (3H, d, *J* 6.4, CH_3CHOH), 3.37 (3H, s, CH_3OCH_2-), 3.58 (2H, dt, *J* 5.2 and 1.4, H-1'), 3.74 and 3.77 (each 3H, s, OCH_3), 3.80 (4H, m $-OCH_2CH_2O-$), 3.94 and 4.00 (each 3H, s, OCH_3), 4.90 (1H, dq, *J* 17.0 and 1.4, *trans* H-3'), 5.05 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.10 (1H, q, *J* 6.4, $CHCH_3$), 5.18 (1H, bs, OH, D_2O exchangeable), 6.12 (1h, m, H-2') and 6.70 (1H, s, H-7).

***Cis* 10-Hydroxy-3,4-dihydro-5,6,7,9-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (232) and *trans* 10-hydroxy -3,4-dihydro-5,6,7,9-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (233)**



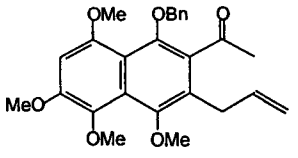
232



233

The crude alcohol **231** (200 mg, 0.46 mmol) was dissolved in THF (5 ml) and water (5 ml) was added after which mercuric acetate (207 mg, 0.65 mmol) was added and then the mixture was stirred for 1h. Sodium hydroxide solution (4.6 ml of 3M) was added and the milky mixture was stirred for another 1h. A mixed solution of sodium borohydride (255 mg, 6.9 mmol) solution and sodium hydroxide (4.6 ml 3M) was added and the mixture stirred for another 1h. The reaction mixture was extracted with ethyl acetate and the residue obtained upon work-up was chromatographed using a 60% ethyl acetate / 1% triethylamine / 39% hexane solvent system as eluent. Chromatography yielded a mixture of both *cis* **232** and *trans* **233** pyrans (50 mg, 25%), δ_H 1.36 (3H, d, *J* 6.0, 3-CH_3), 1.56 (3H, d, *J* 6.8, 1-CH_3), 2.44 (1H, m, H-4a), 2.90 (1H, dm, *J* 16.0, H-4e), 3.82, 3.85, 3.87 and 3.98 (each 3H, s, OCH_3), 3.70 and 4.02 (1H, 2 × m, H-3), 4.85 and 5.05 (1H, 2 × m, H-1) and 6.68 (1H, s, H-7). No MS as the molecule was not pure enough.

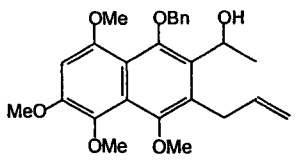
***2-Acetyl-1-benzyloxy-4,5,6,8-tetramethoxy-3-prop-2'-enylnaphthalene* (220)**



220

The ketone **218** (270 mg, 0.64 mmol) was heated to 160°C in an oil bath under nitrogen for 6h. The black residue **219** was immediately dissolved in acetone (50 ml) and treated with potassium carbonate (532 mg, 3.86 mmol) and iodomethame (548 mg, 3.86 mmol) and stirred vigorously under reflux for 12 h. The cooled reaction mixture was filtered and the residue obtained upon removal of solvent was chromatographed (30% eluent) to afford the ketone **220** (213mg, 76%) as a light yellow oil, (Found: C, 72.16; H, 6.59. $C_{26}H_{28}O_6$ requires C, 71.56; H, 6.42%), $\nu_{max.}$ 1695 cm^{-1} (C=O); δ_H 2.56 (3H,s,$COCH_3$), 3.56 (2H,dt, *J* 5.4 and 1.4, H-1'), 3.79, 3.80, 3.89 and 4.02 (each 3H, s, OCH_3), 4.82 (2H, s, CH_2Ph), 4.96 (1H, dq, *J* 17.0 and 1.4, *trans* H-3'), 5.04 (1H, dq, *J* 10.0 and 1.4, *cis* H-3'), 5.97 (1H, m, H-2'), 6.73 (1H, s, H-7) and 7.25-7.49 (5H, m, CH_2Ph); δ_C 30.48 (CH_3CO), 33.46 ($CH_2CH=CH_2$), 56.53, 56.84, 62.16 and 62.87 (each OCH_3), 78.60 (CH_2Ph), 96.75 (C-7), 116.19 ($CH_2CH=CH_2$), 120.06 (C-4a)[a], 126.44 (C-8a)[a], 127.14 (C-1'), 128.05 (C-4'), 128.25 (C-3' and C-5')[b], 128.60 (C-2' and C-6')[b], 133.49 (C-3)[c], 137.19 ($CH_2CH=CH_2$), 137.62 (C-2)[c], 148.05 (C-1)[d], 149.84 (C-5)[d], 150.71 (C-4)[d], 151.00 (C-6)[d], 153.74 (C-8)[d] and 206.30 (C=O) (assignments with the same superscript may be interchanged); *m/z* 436 (M^+, 68%).

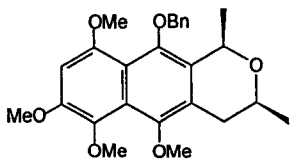
***1-Benzyloxy-2-(1'-hydroxyethyl)-4,5,6,8-tetramethoxy-3-prop-2'-enylynaphthalene* (221)**



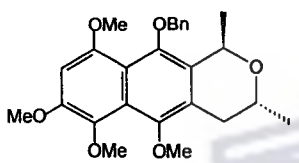
221

The ketone **220** (205 mg, 0.47 mmol) was dissolved in dry ether (15 ml) and dripped into a stirring slurry of lithium aluminium hydride (38 mg, 1 mmol) in dry ether (15 ml) and stirring was continued until the starting material was consumed by monitoring the reaction by tlc. The reaction mixture was quenched by the addition of ammonium chloride (10 – 12 drops carefully), and then water (5ml) and then ether (30 ml). The ether layer was separated and the residue obtained upon work-up afforded the crude alcohol **221** (171 mg, 83%) as a solid which was not further purified. The ^{1}H-nmr spectrum of the crude material supported the correct structure, δ_H 1.60 (3H, d, *J* 6.8, C*H*$_3$CH), 1.90 (1H, bs, CH$_3$CHO*H*, D_2O exchangeable), 3.80 (2H, m, H-1'), 3.77, 3.80, 3.83, 4.00 (each 3H, s, OCH_3), 5.00 (4H, m, H-3' and CH_2Ph), 6.05 (1H, m, H-2'), 6.73 (1H, s, H-7) and 7.42 (5H, m, Ph).

***cis*-10-Benzyloxy-3,4-dihydro-5,6,7,9-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (222) and *trans*-10-benzyloxy-3,4-dihydro-5,6,7,9-tetramethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (223)**



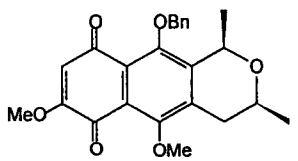
222



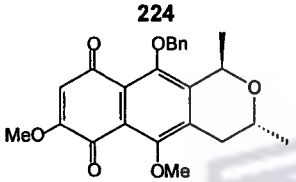
223

The crude alcohol **221** (171 mg, 0.39 mmol) was dissolved in THF (5 ml) and water (5 ml) was added followed by mercuric acetate (175 mg, 0.55 mmol) and the solution was stirred for 1h. Sodium hydroxide solution (4.0 ml of 3M) was added and the milky mixture was stirred for another 1h. A mixed solution of sodium borohydride (216 mg, 5.85 mmol) and sodium hydroxide (4.0 ml 3M) solution was added and the mixture stirred for another 1h. The reaction mixture was extracted with ethyl acetate and the residue obtained upon work-up was chromatographed (30% eluent) to afford a mixture of both *cis* **222** and *trans* **223** pyrans (120 mg, 75%) as an oil, δ_H 1.40 and 1.39 (3H, d, *J* 6.2, 3-CH_3), 1.65 and 1.66 (3H, d, *J* 6.2 1-CH_3), 2.60 (1H, m, 4-Ha), 3.13 (1H, dm, *J* 17.4, 4-He), 3.63 (½H, m, *cis* H-3), 3.80, 3.82, 3.84, 3.85, 3.98, 4.00 (12H, s, OCH_3), 4.14 (½H, m, *trans*, H-3), 4.70 (1H, d, *J* 10.6, CH_2Ph), 4.98 (1H, d, *J* 10.6, CH_2Ph), 5.13 and 5.33 (1H, q, *J* 6.2, H-1), 6.69 (1H, bs, H-7) and 7.36 (5H, m, Ph).

cis ***10-Benzyloxy-3,4-dihydro-5,7-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione*** **(224) and** ***trans*** ***10-benzyloxy-3,4-dihydro-5,7-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione*** **(225)**



224

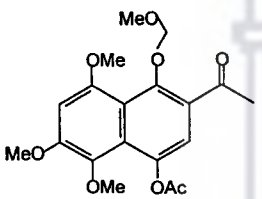


225

The pyrans **222** and **223** (120 mg, 0.27 mmol) were dissolved in acetonitrile (5 ml) and water (1 ml) was added and the resulting solution treated dropwise with cerium(IV) ammonium nitrate (330 mg, 0.60 mmol) in water (1.0 ml). The solution was stirred for 15 min and then water (50 ml) was added and the organic material extracted with dichloromethane (3× 50 ml). The residue obtained upon work-up was chromatographed (40% eluent) to yield the *cis* pyranquinone **224** (14 mg, 12%) as an oil, (Found: C, 70.35; H, 5.60; M^+ 408. $C_{24}H_{24}O_6$ requires C, 70.59; H, 5.88; M^+ 408); $\nu_{max.}$ 1665 (C=O); δ_H 1.36 (3H, d, *J* 6.2, 3-CH_3), 1.59 (3H, d, *J* 6.6, 1-CH_3), 2.44 (1H, dd, *J* 17.9 and 11.0, 4-Ha), 2.95 (1H, dd, *J* 17.9 and 3.5, 4-He), 3.49 (1H, m, H-3), 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.76 (1H, d, *J* 11.2, CH_2Ph), 4.91 (1H, d, *J* 11.2, CH_2Ph), 5.08 (1H, q, *J* 6.6, H-1), 5.93 (1H, s, H-8) and 7.40 (5H, m, *Ph*CH_2); δ_C 20.24 (C-3-CH_3), 21.81 (C-1-CH_3), 30.30 (C-4), 57.00 (CH_3O), 61.50 (CH_3O), 62.25 (C-3), 68.90 (C-1), 77.26 (*C*H_2Ph), 102.91 (C-8), 121.34 (C-5a)[a], 122.48 (C-9a)[a], 127.68 (C-2' and C-6')[b], 128.43 (C-4'), 128.86 (C-3' and C-5')[b], 135.45 (C-1'), 136.93 (C-4a)[a], 145.12 (C-10a)[a], 150.04 (C-7)[c], 150.71 (C-5)[c], 158.22 (C-10)[c], 179.66 (C=O) and 183.14 (C=O) (assignments with the same superscript may be interchanged). Further elution afforded the *trans* pyranquinone compound **225** (28 mg, 24%) as red rosettes, mp

195 – 196°C (from hexane / ethyl acetate); (Found: C, 70.40; H, 5.70; M^+ 408. $C_{24}H_{24}O_6$ requires C, 70.59; H, 5.88; M^+ 408); $\nu_{max.}$ 1666 (C=O); δ_H 1.36 (3H, d, *J* 6.2, 3-CH_3), 1.58 (3H, d, *J* 6.6, 1-CH_3), 2.43 (1H, dd, *J* 18.0 and 11.0, 4-Ha), 2.93 (1H, dd, *J* 18.0 and 3.5, 4-He), 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.05 (1H, m, H-3), 4.78 (1H, d, *J* 11.0, C*H*$_2$Ph), 4.93 (1H, d, *J* 11.0, C*H*$_2$Ph), 5.08 (1H, q, *J* 6.6, H-1), 5.93 (1H, s, H-8) and 7.40 (5H, m, *Ph*CH_2).

***4-Acetoxy-2-acetyl-5,6,8-trimethoxy-1-methoxymethyleneoxynaphthalene* (234)**

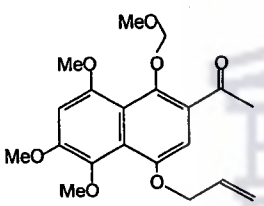


234

The naphthol **164** (580 mg, 1.74 mmol) was dissolved in acetone (80 ml) and potassium carbonate (1198 mg, 8.7 mmol) and chloromethyl methyl ether (695 mg, 8.7 mmol) were added and the mixture was vigorously stirred under reflux under nitrogen for 12 h. The cooled reaction mixture was filtered and the cake washed with acetone and the residue obtained upon solvent evaporation was chromatographed on a long column (50% eluent with 1% triethylamine) to afford the product **234** (397 mg, 60%) as off white needles, mp 132 –134°C (from methanol); (Found: C, 76.31; H, 6.05. $C_{19}H_{22}O_8$ requires C, 76.19; H 5.82%); $\nu_{max.}$ 1755 and 1659 cm^{-1} (C=O); δ_H 2.34 (3H, s, $OCOCH_3$), 2.73 (3H, s, $COCH_3$), 3.45 (3H, s, OCH_2OCH_3), 3.79, 3.99 and 4.00 (each 3H, s, OCH_3), 5.04 (2H, s, OCH_2OCH_3), 6.75 (1H, s, H-7) and 7.26 (1H, s, H-3); δ_C 20.67 (CH_3COO), 31.53 (CH_3CO), 56.66, 56.85, 58.58 and 62.00 (each CH_3O), 97.60 (C-7), 102.25 (OCH_2O), 116.80 (C-4a)[a], 120.10 (C-3), 126.41 (C-8a)[a], 126.77 (C-2)[b], 129.29 (C-4)[b],

141.56 (C-1)[a], 152.02 (C-5)[c], 152.03 (C-6)[c], 154.82 (C-8)[c], 170.01 (CH_3COO) and 200.47 (CH_3CO) (assignments with the same superscript may be interchanged); *m/z* 378 (M^+, 26%), 347 (4), 336 (22), 305 (12), 294 (26), 277 (7), 262 (100), 274 (40), 234 (28), 219 (6) and 43 (1).

***2-Acetyl-5,6,8-trimethoxy-1-methoxymethyleneoxy-4-prop-2'-enyloxynaphthalene* (236)**

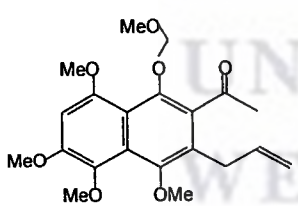


236

The naphthalene acetate **234** (280 mg 0.74 mmol) was dissolved by warming in methanol (70 ml). To the cooled solution was added a methanolic solution of potassium hydroxide (5% m/v, 4.2 ml, 3.7 mmol) and the solution stirred for 10 minutes. To the reaction mixture was added water (100 ml), and dichloromethane (100 ml). The whole was then carefully acidified with dilute hydrochloric acid (39 ml of a 0.1M solution) and extracted with the dichloromethane. The phenolic residue **235** obtained upon work-up was dissolved in dry acetone (100 ml) and dry potassium carbonate (511 mg, 3.7 mmol) and allyl bromide (448 mg, 3.7 mmol) were added and the mixture was vigorously stirred and heated under reflux under nitrogen for 48h. The reaction mixture was cooled to 25°C, filtered and the cake washed with acetone and the filtrate evaporated to an oily residue. The residue was preabsorbed using ethyl acetate - hexane – triethylamine (60:39:1) as the solvent and then chromatographed in the same solvent system to afford the product **236** as light yellow rods (274 mg, 99%), mp 70 – 72°C (from hexane); (Found: C, 63.51; H, 6.30. $C_{20}H_{24}O_7$ requires: C, 63.83; H, 6.43%); $\nu_{max.}$ 1650 cm^{-1} (C=O);

δ_H 2.76 (3H, s, $COCH_3$), 3.42 (3H, s, OCH_2OCH_3), 3.79, 3.98 and 4.00 (each 3H, s, OCH_3), 4.62 (2H, dt, *J* 5.4 and 1.6, $OCH_2CH{=}CH_2$), 5.00 (2H, s, OCH_2OCH_3), 5.30 (1H, dd, *J* 10.6 and 1.6, *cis* H-3'), 5.54 (1H, dd, *J* 17.4 and 1.6, *trans* H-3'), 6.16 (1H, m, H-2'), 6.77 (1H, s, H-7) and 7.00 (1H, s, H-3); δ_C 31.76 ($COCH_3$), 56.76, 56.96, 58.53 and 62.07 (each OCH_3), 71.01 (C-1'), 98.09 (C-7), 101.97 (OCH_2O), 107.75 (C-3), 116.53 (C-4a)[a], 117.69 (C-3'), 126.43 (C-8a)[a], 129.39 (C-2), 133.42 (C-2'), 138.30 (C-4)[b], 147.83 (C-1)[b], 151.21 (C-5)[b], 152.03 (C-6)[b], 154.11 (C-8)[b] and 201.68 ($COCH_3$) (assignments with the same superscript may be interchanged); *m/z* 376 (M^+, 28%), 361 (3), 331 (29), 316 (23), 301 (81), 287 (100), 273 (41), 259 (19), 241 (10), 227 (6), 167 (3), 115 (2), and 45 (1).

***2-Acetyl-4,5,6,8-tetramethoxy-1-methoxymethyleneoxy-3-prop-2'-enylnaphthalene* (238)**

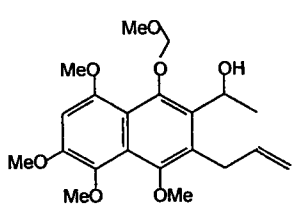


238

The naphthoketone **236** (134 mg 0.36 mmol) was pyrolysed in an oil bath at 160° for 2h under nitrogen. The resulting phenol **237** [δ_H 2.59 (3H, s,CH_3CO), 3.44 (2H, dt, *J* 5.4 and 1.4, H-1') 3.49 (3H, s, CH_3OCH_2-) 3.96, 3.97, and 3.99 (each 3H, s, OCH_3), 4.90 (2H, s, OCH_2O), 4.95 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.00 (1H, dq, *J* 17.5 and 1.4, *trans* H-3'), 5.98 (1H, m, H-2'), 6.64 (1H, s, H-7) and 10.24 (1H, s, C-4-OH, D_2O exchangeable)] was dissolved in acetone (80 ml) and treated with dry potassium carbonate (248 mg, 1.8 mmol) and iodomethane (254 mg, 1.8 mmol) and vigoruosly stirred and heated under reflux under nitrogen for 12h. The residue obtained upon filtration and solvent evaporation

was chromatographed (30% eluent with 1% triethylamine) to afford the product **238** (111 mg, 79%) as light orange cubes, mp 86 – 89°C (from hexane / ethyl acetate); (Found: C, 64.99; H, 6.98. $C_{21}H_{26}O_7$ requires C, 64.62; H, 6.67%); $\nu_{max.}$ 1700 cm^{-1} (C=O); δ_H 2.61 (3H, s, $COCH_3$), 3.50 (3H, s, OCH_2OCH_3), 3.57 (2H, dt, *J* 6.0 and 1.6, $CH_2CH{=}CH_2$), 3.75, 3.78, 3.97, 4.00 (each 3H, s, OCH_3), 4.94 (1H, dq, *J* 17.6 and 1.6, *trans* H-3'), 4.95 (2H, s, OCH_2OCH_3), 5.03 (1H, dq, *J* 10.4 and 1.6, *cis* H-3'), 5.82-6.05 (1H, m, $CH_2CH{=}CH_2$), and 6.72 (1H, s, H-7); δ_C 29.73 (CH_3CO), 33.69 (C-1'), 56.60, 56.83, 58.06, 62.13 and 62.79 (each (OCH_3), 96.89 (C-7), 101.81 (OCH_2O), 115.65 (C-4a)[a], 116.15 (C-3'), 126.33 (C-8a)[a], 127.11 (C-3)[b], 133.39 (C-2)[b], 136.81 (C-1)[c], 137.26 (C-2'), 145.84 (C-4)[c], 149.93 (C-5)[c], 151.00 (C-6)[c], 153.48 (C-8)[c] and 205.48 (C=O) (assignments with the same superscript may be interchanged); *m/z* 390 (M^+, 66%), 375 (4), 362 (12), 345 (32), 330 (20), 315 (71), 301 (100), 288 (43), 273 (85), 257 (22), 241 (16), 227 (11), 213 (6), 185 (5), 115 (3), 91 (1) and 45 (1).

***2-(1'-Hydroxyethyl)-4,5,6,8-tetramethoxy-1-methoxymethyleneoxy-3-prop-2'-enylnaphthalene* (239)**

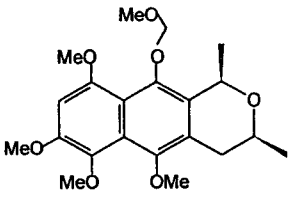


239

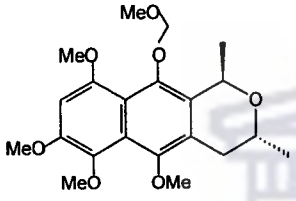
The naphthoketone **238** (189 mg, 0.48 mmol) was dissolved in dry ether (5 ml) and dripped into a stirring slurry of lithium aluminium hydride (36.5 mg, 0.96 mmol) in dry ether (10 ml). The reaction mixture was stirred for a further 10 minutes after which time the reaction mixture was quenched with 10 drops of saturated ammonium chloride, and ether (50 ml) was added. The residue

obtained upon work-up was chromatographed (60% eluent with 1% triethylamine) to afford the product alcohol **239** (190 mg, 100%) as light white flakes, mp 112 - 115°C (from hexane / dichloromethane); (Found: C, 64.51; H, 7.38. $C_{21}H_{28}O_7$ requires: C, 64.29; H 7.14%), $\nu_{max.}$ 3430 cm^{-1} (OH); δ_H 1.68 (3H, d, *J* 7.0, HC(OH)CH_3), 3.57 (3H, s, OCH_2OCH_3), 3.73 (2H, sharp m, H-1'), 3.74, 3.77, 3.94, and 3.99 (each 3H, s, OCH_3), 4.35 (1H, bs, OH, D_2O exchangeable), 4.86 (1H, dq, *J* 17.4 and 1.4, *trans* H-3'), 4.95 (1H, d, *J* 8.0, OCH_2O), 5.05 (1H, dq, *J* 10.4 and 1.4, *cis* H-3'), 5.15 (2H, m, OCH_2O and C*H*OHCH$_3$), 6.10 (1H, m, H-2') and 6.70 (1H, s, H-7); δ_C 23.61 (*C*H$_3$CH), 30.37 (C-1'), 56.87 (×2), 57.83, 62.03, and 62.62 (each OCH_3), 66.08 (*C*H(OH)), 97.25 (C-7), 101.62 (OCH_2O), 115.57 (C-3'), 116.06 (C-4a)[a], 125.27 (C-8a)[a], 129.65 (C-2)[b], 132.62 (C-3)[b], 136.75 (C-1)[c], 137.81 (C-2'), 148.49 (C-4)[c], 149.59 (C-5)[c], 149.94 (C-6)[c] and 152.70 (C-8)[c] (assignments with the same superscript may be interchanged); *m/z* 392 (M^+, 23%), 374 (3), 330 (82), 315 (100), 300 (21), 287 (41), 269 (17), 255 (23), 241 (14), 227 (8), 115 (2), 69 (1) and 45 (1).

***cis*-3,4-Dihydro-5,6,7,9-tetramethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (240) *and* *trans*-3,4-Dihydro-5,6,7,9-tetramethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran (241)**



240

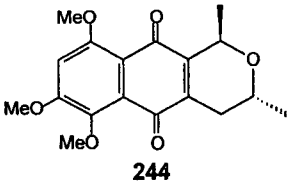


241

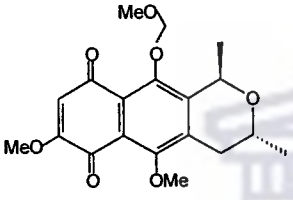
The alcohol **239** (115 mg, 0.29 mmol) was dissolved in THF (5 ml) and water (5 ml) was added after which mercuric acetate (94 mg, 0.30 mmol) was added to the stirring solution. After 1h sodium hydroxide solution (4.5 ml of 3M), was added and the reaction was stirred for another 1h. Sodium hydroxide solution (4.5 ml of 3M) and sodium borohydride (159 mg, 4.2 mmol) were added and the mixture stirred for 1 h. Water (50 ml) was added and the organic material extracted with ethyl acetate (3 × 50 ml) and the residue obtained upon work-up was chromatographed on a PLC plate which was eluted three times (20% eluent). The first product to elute was assigned as the *cis* pyran **240** (45 mg, 39%) as a yellow oil, (Found: C, 64.31; H, 7.24; M^+ 392. $C_{21}H_{28}O_7$ requires C, 64.29; H, 7.14%; M^+ 392); $\nu_{max.}$ 1390 cm^{-1} (C-O); δ_H 1.40 (3H, d, *J* 5.8, 3-CH_3), 1.68 (3H, d, *J* 6.2, 1-CH_3), 2.55 (1H, dd, *J* 15.6 and 10.6, pseudoaxial H-4), 3.11 (1H, ddd, *J* 15.6, 3.4 and 1.0, pseudoequatorial H-4), 3.59 (3H, s, C*H*$_3$OCH$_2$), 3.70 (1H, m, H-3), 3.79, 3.81, 3.94 and 4.00 (each 3H, s, OCH_3), 4.83 (1H, d, *J* 6.6, OCH_2O), 5.09 (1H, d, *J* 6.6, OCH_2O), 5.29 (1H, dq, *J* 6.2 and 1.0, H-1), and 6.67 (1H, s, H-8); δ_C 21.91 (3-CH_3), 22.78 (1-CH_3), 31.66 (C-4), 56.87, 56.99, 57.80, 61.67 and 62.07 (each OCH_3), 69.48 (C-3), 71.69 (C-1), 96.87 (C-8), 101.50 (OCH_2O), 115.95 (C-4a)[a], 124.73 (C-10a)[a], 127.98 (C-5a)[b],

129.63 (C-9a)[b], 136.50 (C-10)[c], 146.50 (C-5)[c], 147.73 (C-6)[c], 149.43 (C-7)[c] and 152.76 (C-9)[c] (assignments with the same superscript may be interchanged). The next product to elute was assigned as the *trans* pyran **241** (46 mg; 40%) as a yellow oil, (Found: C, 64.35; H, 7.30; M^+ 392. $C_{21}H_{28}O_7$ requires C, 64.29; H, 7.14%; M^+ 392); $\nu_{max.}$ 1388 (C-O); δ_H 1.38 (3H, d, *J* 6.2, 3-CH_3), 1.65 (3H, d, *J* 6.6, 1-CH_3), 2.58 (1H, dd, *J* 17.2 and 11.0, pseudoaxial H-4), 3.10 (1H, dd, *J* 17.2 and 3.4, pseudoequatorial H-4), 3.60 (3H, s, C*H*$_3$OCH$_2$), 3.77, 3.80, 3.95 and 3.99 (each 3H, s, OCH_3), 4.05 (1H, m, H-3), 4.86 (1H, d, *J* 6.2, OCH_2O), 5.11 (1H, d, *J* 6.2, OCH_2O), 5.46 (1H, q, *J* 6.6, H-1), and 6.67 (1H, s, H-8); δ_C 20.42 (3-CH_3), 22.18 (1-CH_3), 30.67 (C-4), 56.73, 57.02, 57.61, 61.34 and 62.04 (each OCH_3), 62.56 (C-3), 69.06 (C-1), 96.67 (C-8), 101.52 (OCH_2O), 115.74 (C-4a)[a], 124.71 (C-10a)[a], 126.44 (C-5a)[b], 128.92 (C-9a)[b], 136.80 (C-10)[c], 146.35 (C-5)[c], 148.36 (C-6)[c], 149.35 (C-7)[c] and 152.73 (C-9)[c] (assignments with the same superscript may be interchanged).

***trans*-3,4-Dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-dione (isoventiloquinone E) (244) and *trans*-3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione (243)**



244

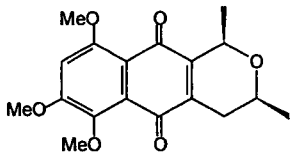


243

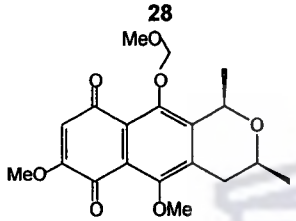
The trans pyran **241** (20 mg, 0.051 mmol) was dissolved in acetonitrile (2ml) and water (0.5 ml). Cerium(IV) ammonium nitrate (60 mg, 0.110 mmol) in water (1 ml) was added dropwise with stirring and the solution stirred for a further 15 min. Water (20 ml) was added and the organic material was extracted with dichloromethane (3 × 30 ml). The residue obtained upon work-up was chromatographed on a PLC plate (20% eluent) which was eluted twice. The front band was identified as the *trans* quinone **244** (9.5 mg, 56%) obtained as light brown / yellow crystals, mp 169 – 171°C (from hexane); (Found: C, 65.18; H, 6.12. $C_{18}H_{20}O_6$ requires C, 65.06; H, 6.02%); (Found: HRMS: 332.12587. $C_{18}H_{20}O_6$ requires 332.12599); $\nu_{max.}$ 1660 cm^{-1} (C=O); δ_H 1.33 (3H, d, *J* 6.2, 3-CH_3), 1.51 (3H, d, *J* 6.6, 1-CH_3), 2.21 (1H, ddd, *J* 18.6, 9.8 and 1.8, H-4a), 2.65 (1H, ddd, *J* 18.6, 3.6 and 1.0, H-4e), 3.87, 3.98 and 3.99 (each 3H, s, OCH_3), 3.97 (1H, m, H-3), 4.98 (1H, dq, *J* 6.6 and 1.8, H-1), 6.74 (1H s, H-8); δ_C 19.76 (3-CH_3), 21.60 (1-CH_3), 29.65 (C-4), 56.31, 56.79 and 61.38 (each OCH_3), 62.66 (C-3), 67.30 (C-1), 101.35 (C-8), 114.00 (C-4a)[a], 126.58 (C-10a)[a], 140.43 (C-5a)[b], 143.61 (C-9a)[b], 146.81 (C-6)[c], 158.17 (C-7)[c], 159.69 (C-9)[c], 181.68 (C=O) and 184.22 (C=O) (assignments with the same superscript may be interchanged); *m/z* 332 (M^+, 100%), 317 (83), 302 (29), 287 (17), 274 (20), 212 (12), 149 (7),

115 (9), 77 (7), 57 (19) and 43 (17). A second band was assigned the structure **243** (8 mg, 43%) as yellow crystals mp 130 - 132°C (from hexane); (Found: C, 63.05; H, 6.13. $C_{19}H_{22}O_7$ requires C, 62.98; H, 6.08%); (Found: HRMS: 362.13592. $C_{19}H_{22}O_7$ requires 362.13655); $\nu_{max.}$ 1652 cm^{-1} (C=O); δ_H 1.37 (3H, d, *J* 5.8, 3-CH_3), 1.60 (3H, d, *J* 6.6 1-CH_3), 2.42 (1H, dd, *J* 17.6 and 10.6 H-4a), 2.92 (1H, dd, *J* 17.6 and 3.4, H-4e), 3.57 (3H, s, C*H*$_3$OCH_2), 3.83 and 3.97 (each 3H, s, OCH_3), 4.02 (1H, m, H-3), 4.81 (1H, d, *J* 6.4, OCH_2O), 5.07 (1H, d, *J* 6.4, OCH_2O), 5.28 (1H, q, *J* 6.6, H-1) and 5.94 (1H, s, H-8); δ_C 19.81 (3-CH_3) 21.83 (1-CH_3), 30.44 (C-4), 57.11, 57.90 and 61.46 (each OCH_3), 62.19 (C-3), 69.04 (C-1), 102.60 (OCH_2O), 102.89 (C-8), 121.13 (C-4a)[a], 125.63 (C-10a)[a], 135.19 (C-5a)[a], 145.07 (C-9a)[a], 149.41 (C-10)[b], 150.64 (C-5)[b], 158.17 (C-7)[b], 170.08 (C=O) and 179.49 (C=O) (assignments with the same superscript may be interchanged); *m/z* 362 (M^+, 2%), 334 (22), 319 (23), 317 (100), 302 (9), 289 (16), 288 (16), 275 (10), 273 (9), 247 (10), 245 (13), 115 (5), 45 (2) and 43 (7).

***cis*-3,4-Dihydro-6,7,9-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-5,10-dione (ventiloquinone E)** (28) **and** ***cis*-3,4-dihydro-5,7-dimethoxy-10-methoxymethyleneoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione** (242)



28

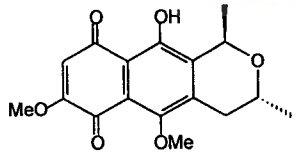


242

The cis pyran **240** (17 mg, 0.043 mmol) was dissolved in acetonitrile (2ml) and water (0.5 ml) was added. Cerium(IV) ammonium nitrate (52 mg, 0.095 mmol) in water (1 ml) was added dropwise and the solution stirred for 15 min. Water (20 ml) was added and the organic material was extracted with dichloromethane (3 × 30 ml). The residue obtained upon work-up was purified by PLC (20% eluent) which was eluted twice. The front band was assigned the *cis* quinone **28** (8.5 mg, 59%) as yellow flakes, mp 130 – 132°C (from hexane) (Lit.[51] 127 –128°C; (Found: C, 65.20; H, 6.13. $C_{18}H_{20}O_6$ requires C, 65.06; H, 6.02%); (Found: HRMS: 332.12759. $C_{18}H_{20}O_6$ requires 332.12599); $\nu_{max.}$ 1660 cm^{-1} (C=O); δ_H 1.34 (3H, d, *J* 6.2, 3-CH_3), 1.50 (3H, d, *J* 6.6, 1-CH_3), 2.11 (1H, ddd, *J* 18.2, 10.2 and 3.6, H-4a), 2.80 (1H, dt, *J* 18.2 and 2.6, H-4e), 3.54 (1H, m, H-3), 3.88 (3H, s, OCH_3), 3.98 (6H, s, 2 × OCH_3), 4.81 (1H, ddq, *J* 6.6, 3.6 and 2.6, H-1), 6.73 (1H s, H-8); δ_C 20.70 (3-CH_3), 21.37 (1-CH_3), 29.70 (C-4), 56.31, 56.86 and 61.43 (each OCH_3), 68.99 (C-3), 70.16 (C-1), 101.41 (C-8), 113.62 (C-4a)[a], 126.63 (C-10a)[a], 140.77 (C-5a)[a], 143.42 (C-9a)[a], 147.70 (C-6)[b], 157.68 (C-7)[b], 159.46 (C-9)[b], 182.70 (C=O) and 183.82 (C=O) (assignments with the same superscript may be interchanged); *m/z* 332 (M^+, 99%), 317 (100), 302 (47), 299 (23), 289 (14), 287 (17), 274 (25)259 (22), 137 (5), 15 (5), 57 (19) and 43 (17).

The second band was assigned the *cis* quinone **242** (6.0 mg, 39%) as yellow crystals mp 134 - 135°C (from hexane); (Found: C, 63.10; H, 6.15. $C_{19}H_{22}O_7$ requires C, 62.98; H, 6.08%); (Found: HRMS: 362.13655. $C_{19}H_{22}O_7$ requires 362.13655); $\nu_{max.}$ 1652 cm^{-1} (C=O); δ_H 1.38 (3H, d, *J* 6.2, 3-CH_3), 1.60 (3H, d, *J* 6.2 1-CH_3), 2.42 (1H, ddd, *J* 17.2, 10.2 and 2.2, H-4a), 2.92 (1H, dt, *J* 17.2 and 1.8, H-4e), 3.56 (3H, s, CH_3OCH_2), 3.58 (1H, m, H-3), 3.85 and 3.97 (each 3H, s, OCH_3), 4.77 (1H, d, *J* 6.2, OCH_2O), 5.04 (1H, d, *J* 6.4, OCH_2O), 5.07 (1H, qt, *J* 6.2 and 2.0, H-1) and 5.94 (1H, s, H-8); δ_C 21.36 (3-CH_3) 21.56 (1-CH_3), 31.14 (C-4), 56.99, 57.91 and 61.52 (each OCH_3), 68.99 (C-3), 71.65 (C-1), 102.40 (OCH_2O), 102.82 (C-8), 121.13 (C-4a)[a], 129.80 (C-10a)[a], 136.41 (C-5a)[a], 141.60 (C-9a)[a], 145.43 (C-10)[b], 150.37 (C-5)[b], 157.43 (C-7)[b], 170.07 (C=O) and 179.54 (C=O) (assignments with the same superscript may be interchanged); *m/z* 362 (M^+, 3%), 334 (13), 319 (17), 317 (100), 302 (19), 289 (19), 288 (23), 273 (12), 247 (10), 245 (14), 219 (6), 115 (5), 45 (2) and 43 (7).

***Racemic <u>trans</u>-3,4-Dihydro-10-hydroxy-5,7-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-<u>c</u>]pyran-6,9-dione (isoventiloquinone J)* (245)**

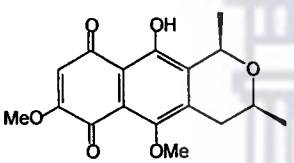


245

The quinone **243** (10 mg, 0,028 mmol) was dissolved in dioxane (10 ml) and water (4ml) was added. The stirring solution was treated with tosic acid (1.5 mg) and stirred for a further 18h at 55°C. The reaction mixture was poured into water (80 ml) and extracted with dichloromethane. The product, compound **245** was purified by PLC, (20 % eluent) and obtained as red crystals (6 mg, 67%), mp 140 – 142°C (from 2-propanol); (Found: C, 64.20; H, 5.67. $C_{17}H_{18}O_6$ requires C,

64.15; H, 5.66%); (Found: HRMS: 318.11039. $C_{19}H_{22}O_7$ requires 318.11030); $\nu_{max.}$ 3368 cm^{-1} (OH) and 1660 cm^{-1} (C=O); δ_H 1.40 (3H, d, *J* 6.2, 3-CH_3), 1.61 (3H, d, *J* 6.6, 1-CH_3), 2.44 (1H, dd, *J* 17.6, 10.6, H-4a), 2.93 (1H, dd, *J* 17.6 and 3.5, H-4e), 3.84 and 3.99 (each 3H, s, OCH_3), 4.03 (1H, m, H-3), 5.09 (1H, q, *J* 6.6, H-1), 6.10 (1H, s, H-8) and 13.40 (1H, s, 10-OH, D_2O exchangeable).

***Racemic cis-3,4-Dihydro-10-hydroxy-5,7-dimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dinone (ventiloquinone J)* (33)**



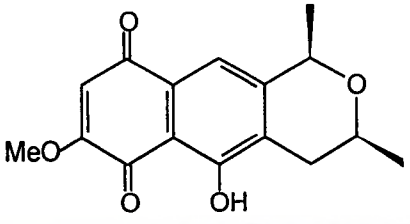
33

The quinone **242** (10 mg, 0,028 mmol) was dissolved in dioxane (10 ml) and water (4 ml) was added. The stirring solution was treated with tosic acid (1.5 mg) and stirred for a further 18 h at 55°C. The reaction mixture was poured into water (80 ml) and extracted with dichloromethane. The product, compound **33** was purified by PLC, (20 % eluent) and obtained as red crystals 5 mg (56%), mp 140 – 142°C (from 2-propanol) lit.[19] 141°C. The spectral data of the compound were identical to the published data; (Found: C, 64.21; H, 5.67. $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.66%); (Found: HRMS: 318.11150. $C_{19}H_{22}O_7$ requires 318.11030); $\nu_{max.}$ 3368 cm^{-1} (OH) and 1660 cm^{-1} (C=O); δ_H 1.48 (3H, d, *J* 6.6, 3-CH_3), 1.72 (3H, d, *J* 6.6, 1-CH_3), 2.50 (1H, ddd, *J* 17.2, 10.2 and 1.8, H-4a), 2.97 (1H, dt, *J* 17.2 and 1.8 H-4e), 3.60 (1H, m, H-3), 3.86 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.06 (1H, dq, *J* 6.6 and 1.8, H-1), 6.06 (1H, s, H-8) and 13.50 (1H, s, 10-OH, D_2O exchangeable). Lit.[19] 1.49 (3H, d, *J* 7.0, 3-CH_3), 1.74 (3H, d, *J* 7.0, 1-CH_3), 2.50 (1H, ddd, *J* 17.2, 10.2 and 1.8, H-4a), 2.97 (1H, dt, *J* 17.2 and 1.8 (H-4e),

3.61 (1H, m, H-3), 3.84 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.04 (1H, dq, *J* 7.0 and 1.0, H-1), 6.04 (1H, s, H-8) and 13,02 (1H, s, 10-OH, D_2O exchangeable).

CHAPTER 3

SYNTHESIS OF VENTILOQUINONE F

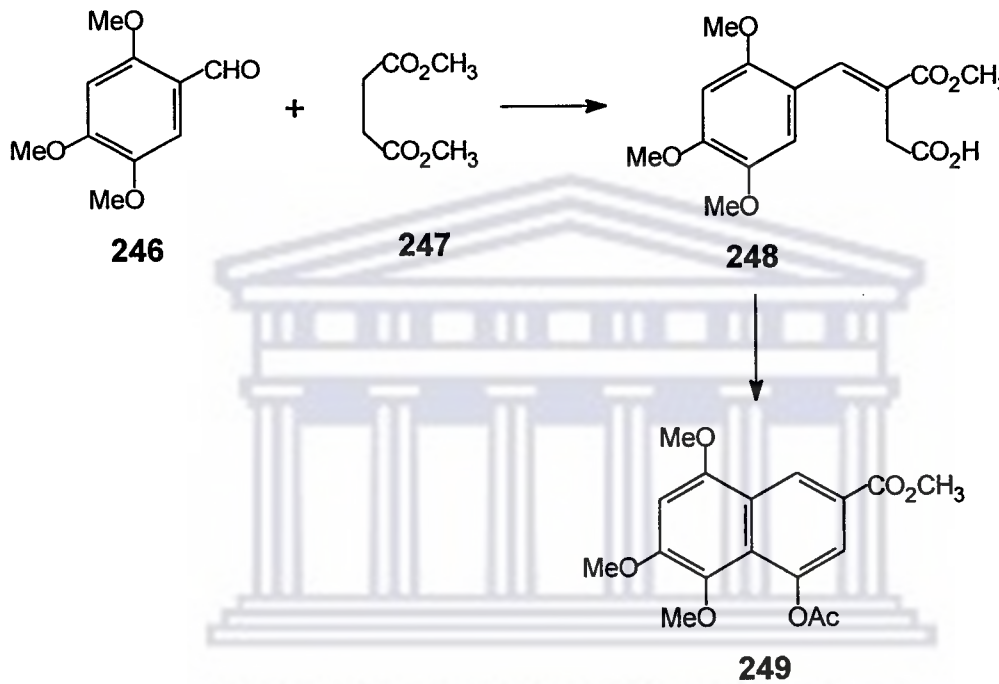


29

1. RESULTS AND DISCUSSION

It was decided to use the Stobbe Condensation [93-95] to construct the naphthalene **249** with the correct oxygenation pattern in the synthetic route towards the target molecule, ventiloquinone F **29**. Thus the trimethoxybenzaldehyde **246** [75] together with dimethyl succinate **247** was dissolved in hot absolutely dry tertiary butyl alcohol and this hot solution was then carefully dripped into a rapidly stirring and refluxing solution of potassium tertiary butoxide in tertiary butyl alcohol under a nitrogen atmosphere. After a 2h boiling period the cooled solution was poured into water and carefully acidified with hydrochloric acid and extracted with ether. The ether layer was in turn again extracted with sodium hydrogen carbonate and the alkaline extracts were carefully acidified with 5M hydrochloric acid to precipitate the resulting crude itaconic acid **248**. The mother liquors were extracted with additional ether that was later removed by rotary evaporation to provide additional acid **248** in a yield of 84%.

The crude itaconic acid **248** and sodium acetate were stirred in acetic anhydride under reflux under nitrogen for 6 hours after which the mixture was allowed to cool and then thrown into ice water which caused the naphthalene **249** to precipitate in an overall yield of 84% as depicted in **Scheme 51**.



Scheme 51

The ^{1}H-nmr spectrum of **249** showed signals for the methyl hydrogens of both the ester groups as singlets, the aryl ester appearing at δ 2.38 and the methyl ester at δ 3.82. Three methoxy singlets appeared at δ 3.95, 4.01 and 4.02, while the singlet for the hydrogen at C-7 appeared at δ 6.70 and two doublets at δ 7.67 and 8.85 *J* 1.8 Hz represented the meta-coupled hydrogens at C-1 and C-3 respectively. The ^{13}C-nmr spectrum showed *inter alia* the methyl carbon atoms

of both ester groups at δ 20.78 and δ 52.28, the three methoxy carbons at δ 56.05, 56.86 and 61.95 and also the carbonyl carbons at δ 166.62 and δ 169.86. The IR spectrum also showed strong carbonyl peaks at $\nu_{max.}$ 1690 and 1705 cm^{-1}.

Having successfully synthesised and characterised the naphthyl trimethoxy diester **249** it was decided to proceed towards the synthesis of ventiloquinone F **29** as proposed in **Scheme 52**.

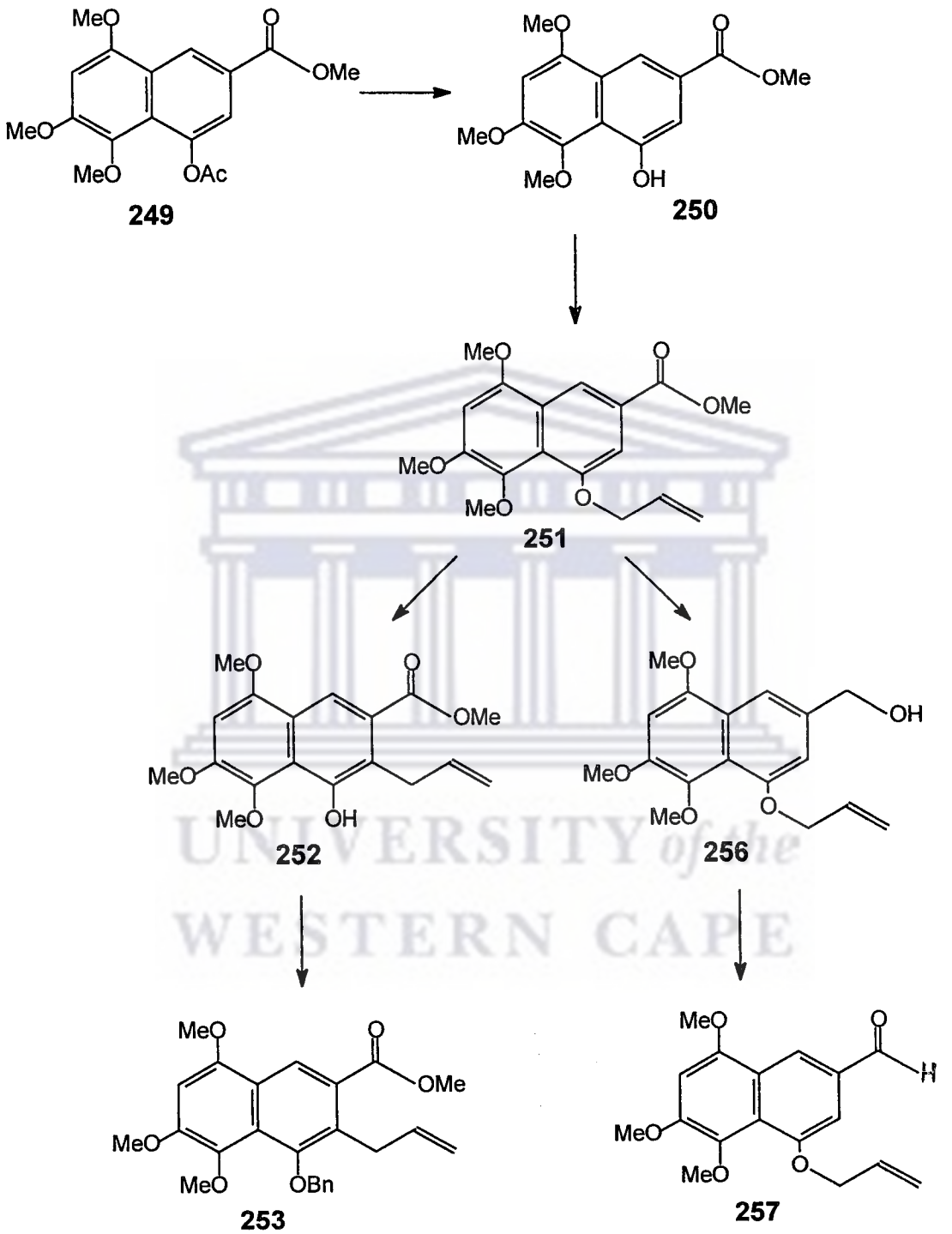
The naphthalene **249** was dissolved in a warm methanolic potassium hydroxide solution and stirred under gentle reflux after which the cooled solution was acidified and extracted with dichloromethane to afford compound **250** in a 94% yield. The ^{1}H-nmr spectrum showed the presence of a D_2O exchangeable hydroxyl hydrogen at δ 9.70 and in the IR spectrum a broad absorption peak at $\nu_{max.}$ 3280 cm^{-1} which indicated that hydrolysis had been successful. Additionally the disappearance of the acetate methyl carbonyl signals in the ^{13}C-nmr spectrum, viz. δ 20.78 for the methyl carbon and δ 169.86 for the carbonyl of gave further evidence that the hydrolysis of the acetate had occurred at C-4 as expected.

The phenol **250** (was only purified for analysis) was immediately dissolved in dry acetone and allylated by treating with 5 equivalents each of dry potassium carbonate and allyl bromide under reflux for 12h. The cooled reaction mixture was filtered and the residue obtained upon work-up was dissolved in a hot ethyl acetate / hexane solvent mixture. On cooling the product **251** precipitated. Both

the IR and ^{1}H-nmr spectra showed the disappearance of the hydroxyl group from the preceding phenol **250**. The ^{1}H-nmr spectrum had *inter alia* the following signals to demonstrate the presence of the allyloxy group at C-4, a doublet of multiplets at δ 4.71 (*J* 5.0 Hz) for the two C-1' protons as, two doublets of quartets at δ 5.33 for the *cis*, *J* 10.6 and 1.4 Hz and δ 5.60 for the *trans*, *J* 17.2 and 1.4 Hz coupled hydrogens at C-3'. The C-2' hydrogen appeared as a multiplet at δ 6.21. The ^{13}C-nmr had three additional carbon signals at δ 70.54 (C-1'), 117.66 (C-3') and 133.29 (C-2') confirming that the allyl group had been added at the C-4-O atom.

At this juncture two routes towards the desired aldehyde **255** were proposed as depicted in **Scheme 52**. Both routes involved the same reactions but in a different sequence Thus the aim of the next protocol development was to assess which of the two parallel routes provided the highest yield of aldehyde **255**. As it happened, better yields were obtained when the allyloxy naphthalene **251** was first heated at 180°C to effect a Claisen Rearrangement to afford the phenol **252** in a 98% yield. The IR spectrum showed a broad hydroxyl peak at 3270 cm^{-1} and a sharp carbonyl peak at 1705 cm^{-1}. The propenyl group was apparent in the ^{1}H-nmr spectrum by a doublet of triplets at δ 3.87 (*J* 5.8 and 1.5 Hz) for the hydrogens at C-1'. Two doublets of quartets at δ 4.97, *J* 11.1 and 1.6 Hz for the *cis* and δ 5.04, *J* 18.0 and 1.6 Hz for the *trans* coupled hydrogens at C-3' and a multiplet at δ 6.11 for the hydrogen at C-2' were also present.

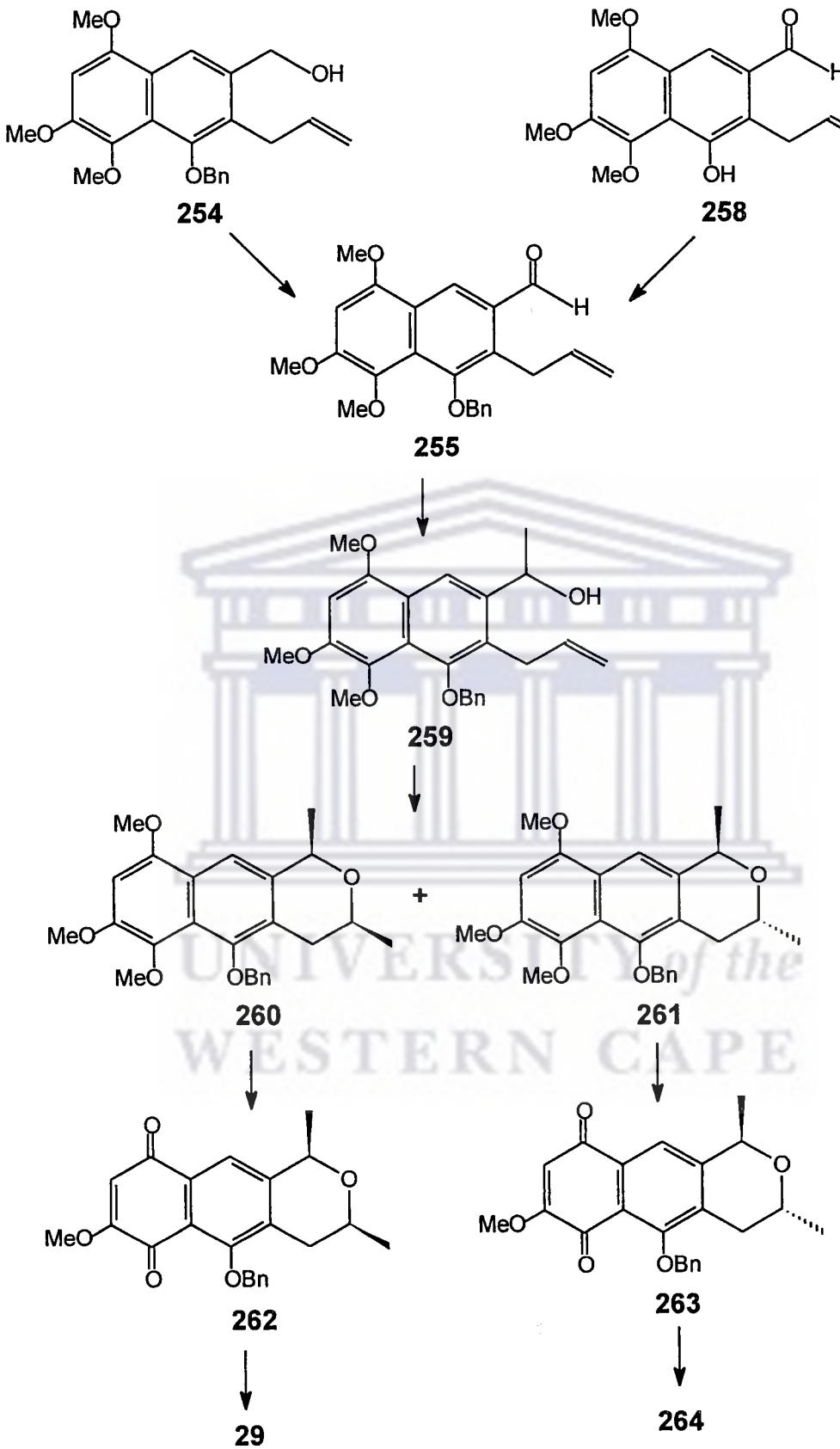
The naphthol **252** was then benzylated by dissolving it in dry acetone and treating with dry potassium carbonate and benzyl bromide and the mixture stirred vigorously under reflux in a nitrogen atmosphere. The residue obtained upon work-up afforded the expected product **253** in a 97% yield. The hydroxyl signals observed in the IR and ^{1}H-nmr spectra of the preceding phenol **252** had disappeared. The ^{1}H-nmr and ^{13}C-nmr spectra both showed the additional signals for the benzyloxy group. The structure was further corroborated by a molecular ion of *m/z* 422 in the mass spectrum and a carbonyl absorption in the IR spectrum at 1705 cm^{-1}. The benzyloxynaphthalene **253** was dissolved in dry THF and dripped into a slurry of 1.5 equivalents of lithium aluminium hydride in dry THF while stirring under nitrogen and heated to 50°C for 30 minutes after which the reaction was quenched by the addition of saturated ammonium chloride solution. Work-up of the reaction mixture and subsequent chromatography afforded the alcohol **254** in a quantitative yield. The broad absorption peak at 3450 cm^{-1} in the IR spectrum indicated the presence of an hydroxyl group. The ^{1}H-nmr spectrum displayed a two proton single peak at δ 4.81 for the hydroxymethyl group. The ^{13}C-nmr spectrum also supported the assigned structure by a signal at δ 25.69 for the hydroxymethyl carbon and the disappearance of the carbonyl signal at δ 168.35.



Scheme 52

The alcohol **254** was dissolved in dry benzene and treated with an excess of manganese dioxide and stirred under reflux with a Dean Stark Trap for 18h in a nitrogen atmosphere. The cooled mixture was filtered and the residue chromatographed to afford the aldehyde **255** in a 69% yield. The disappearance of the hydroxyl peak at 3450 cm^{-1} and the appearance of the carbonyl peak at 1705 cm^{-1} in the IR spectrum indicated that the reaction was successful. This was supported by the disappearance of the 2 proton singlet at δ 4.81 for the hydroxymethyl group. Further evidence of the aldehyde **255** was the appearance of the carbonyl signal in the ^{13}C-nmr spectrum at δ 192.32 and the mass spectrum had a molecular ion *m/z* 392.

An alternative route that was investigated in the conversion of ester **251** into aldehyde **255** as depicted in **Scheme 52.** Naphthoate **251** was first reduced with lithium aluminium hydride in THF to afford the alcohol **256** in a quantitative yield. The IR spectrum showed the disappearance of the peak at 1715 cm^{-1} for the ester carbonyl and the appearance of a broad hydroxyl absorption band at 3453 cm^{-1}. The ^{1}H-nmr spectrum indicated an hydroxyl singlet at δ 7.26 and a loss of one methoxy group. As expected the ^{13}C-nmr spectrum did not show a carbonyl carbon and had an additional signal at δ 65.92 for the hydroxymethyl carbon. Consequently alcohol **256** was oxidised with excess manganese dioxide as described earlier to the aldehyde **257** in a yield of 56%. The IR spectrum had a carbonyl peak at 1625 cm^{-1} and no hydroxyl absorption peak. In the ^{1}H-nmr spectrum a singlet for the aldehyde hydrogen appeared at δ 9.99. The ^{13}C-nmr spectrum also showed the carbonyl carbon at δ 191.95.



Scheme 52

The aldehyde **257** was subsequently rapidly pyrolysed at 180°C and the Claisen rearranged product **258** was immediately dissolved in acetone and treated with 5 equivalents of potassium carbonate and benzyl bromide under reflux for 12h to afford the same benzyloxy aldehyde **255** as described previously in a yield of 57%. The overall yield obtained by conversion sequence of naphthoate **251 - 256 - 257 - 258** to the aldehyde **255** was only 31%, compared to 66% obtained by the former sequential route of naphthoate **251 - 252 - 253 - 254 - 255**. Consequently all the subsequent material was converted via the more favourable sequence of transformations.

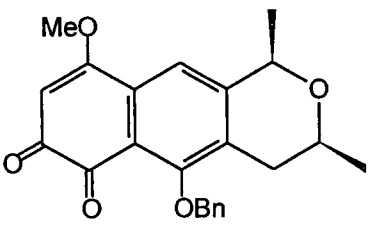
The next step in the synthetic protocol required the use of a methyl Grignard reagent. Thus aldehyde **255** was dissolved in dry ether and dripped into a freshly prepared solution methylmagnesium iodide. The reaction mixture was allowed to stir for 1h after which it was quenched by the addition of saturated ammonium chloride solution followed by water. All organic matter was extracted into ether and the residue obtained upon work-up was purified by column chromatography to afford the alcohol **259** in a quantitative yield as a thick clear oil.

Pyran ring formation was expidited in the following way. The alcohol **259** was dissolved in THF and water and one equivalent of mercuric acetate was added to the stirring solution with stirring being continued at room temperature for 1h after which aqueous sodium hydroxide (5M) was added and stirring was continued for further 1h and then an additional amount of the aqueous sodium hydroxide was added along with an excess of the sodium borohydride and

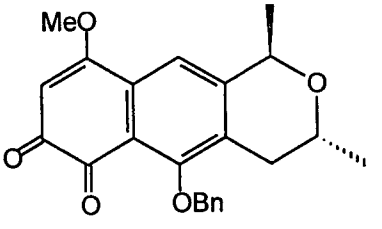
stirring was continued for a further 1h. Water was subsequently added and the mixture was extracted with ethyl acetate to afford an inseparable mixture of pyrans **260** and **261** in a yield of 71% and in a ratio of 1:1 based on the integration of appropriate signals in the ^{1}H-nmr spectrum of the mixture.

The doubling up of signals obtained in the ^{1}H-nmr spectrum showed clear evidence that a mixture of the stereoisomers **260** and **261** was present. It was hoped that oxidation of the pyran mixture **260** and **261** to the expected *para* quinones **262** and **263** would be separable at this higher oxidation level.

Thus the pyran mixture of **260** and **261** was oxidised by dissolving in acetonitrile and water and treatment with 2 equivalents of cerium ammonium nitrate in water at room temperature. The yellow organic material was extracted into dichloromethane and the residue was chromatographed to afford two fractions, the first of which was a mixture of the expected *para*-naphthopyranquinones **262** and **263** in a 46% yield, followed by a mixture of the two *ortho*-naphthopyranquinones **265** and **266** in a 42% yield.



265



266

Each of the two mixtures were now subsequently and separately re-subjected to chromatography using 1m long columns and 20% ethyl acetate in hexane as eluent. In this way the respective *cis* and *trans* stereoisomers were separated in pure form.

Thus the *para*-naphthopyranquinone mixture **262** and **263** afforded the pure *cis* stereoisomer **262** in a yield of 22% as light yellow crystals followed by the *trans* stereoisomer **263** in a yield of 24% also as light yellow crystals. Both the IR spectra showed two carbonyl absorption peaks at 1648 cm^{-1} and 1689 cm^{-1}. The ^{1}H-nmr spectra for the *para* naphthoquinones **262** and **263** differed in those hydrogens attached the pyran ring and were used to make the assignments. In the case of the *cis*-isomer **262**, the H-4a appeared as a doublet of doublet of doublets at δ 2.42 with vicinal coupling of 17.6 Hz to the H-4e, *trans* coupling of 11.0 Hz with the axial H-3 and long range coupling of 1.8 Hz to the pseudoaxial H-1. On the other hand H-4e also appeared as a doublet of doublet of doublets but at δ 2.90 with the same vicinal coupling of 17.6 Hz to H-4a but with an expected smaller coupling of 3.0Hz to the H-3a due to the much smaller dihedral angle between H-4e and H-3e. The long range coupling to H-1a was 1.0 Hz in this instance being smaller since the coupling is due to H-4e and H-1a whereas in the former case of 1.8 Hz, coupling is due to H-4a and H-1a. [26] A single proton multiplet at δ 3.68 is assigned to H-3 while a single proton doublet of doublet of quartets at δ 4.85 with *J* 6.6, 1.8 and 1.0 Hz is assigned to H-1.

By contrast, the same pyran protons in the *trans* isomer **263** appeared as follows: H-4a appeared as a doublet of doublet of doublets at δ 2.37 with ^{2}J 17.6 Hz, ^{3}J to the H-3a of 9.4 Hz and long range coupling of 1.0 Hz to H-1e. H-4e appeared at δ 2.90 as a doublet of doublets with ^{2}J 17.6 Hz and ^{3}J 3.8 Hz to the H-3a. Long range coupling to H-1e is absent in this instance. H-3 appeared as a multiplet at δ 3.95 while H-1 appeared as a doublet of quartets at δ 4.95 with J 7.0 and 1.0 Hz.

By a similar separation the mixture of the *ortho*-pyranquinones **265** and **266** afforded the *cis* stereoisomer **265** in a yield of 21% as bright yellow crystals followed by the *trans* stereoisomer **266** in a yield of 24% also as bright yellow crystals. Both the IR spectra showed two carbonyl absorption peaks at 1660 cm^{-1} and 1709 cm^{-1}. It is noteworthy that the *para*-quinones elute prior to the *ortho*-quinones which appear a deeper yellow colour than the *para*-quinones. In addition the UV spectrum for the *para*-quinone **263** was determined and had $\lambda_{max.}$ values at 251, 286, and 259 nm while the corresponding *ortho*-quinone **266** had $\lambda_{max.}$ values at 260, 288 and 372 nm, the shift to longer wavelengths for the *ortho*-quinodical systems is described by Thomson.[2] This was further supported by the IR spectra in which the carbonyl stretching absorption bands at 1648 and 1689 cm^{-1} are ascribed to the *para*-naphthoquinones while those at 1660 and 1709 cm^{-1} are due to the *ortho*-naphthoquinones.[2]

The ^{1}H-nmr spectra of the two *ortho*-naphthoquinones **265** and **266** also differed in those hydrogens attached to the pyran ring as was described for the *para*-naphthoquinones. The *cis*-isomer **265** showed a doublet of doublet of doublets at

δ 2.38 for the pseudoaxial H-4 with vicinal coupling of 17.4 Hz to the H-4e, *trans* coupling of 9.8 Hz with the axial H-3 and long range coupling 1.5 Hz to pseudoaxial H-1. On the other hand the pseudoequatorial H-4 also appears as a doublet of doublet of doublets but at δ 2.85 with the same vicinal coupling of 17.4 Hz to H-4a but with an expected smaller coupling of 3.2 Hz to H-3a due to the much smaller dihedral angle between H-4e and H-3a. The long range coupling to H-1a was 1.5 Hz. A single proton multiplet at δ 3.68 is assigned to H-3 and a single proton unresolved multiplet at δ 4.86 is assigned to H-1. Overlapping signals due to the methylene protons of the benzyl group account for this.

In the *trans* isomer **266**, H-4a appeared as a doublet of doublet of doublets at δ 2.33 with ^{2}J 17.2 Hz, ^{3}J to the H-3a of 9.6 Hz and long range coupling of 1.0 Hz to H-1e. H-4e appeared at δ 2.86 as a doublet of doublets with ^{2}J 17.2 Hz and ^{3}J 3.2 Hz to the H-3a. Long range coupling to the H-1e is absent in this instance. H-3 appeared as a multiplet at δ 3.95 while H-1 appeared as a doublet of quartets at δ 5.02 with J 7.0 and 1.0 Hz.

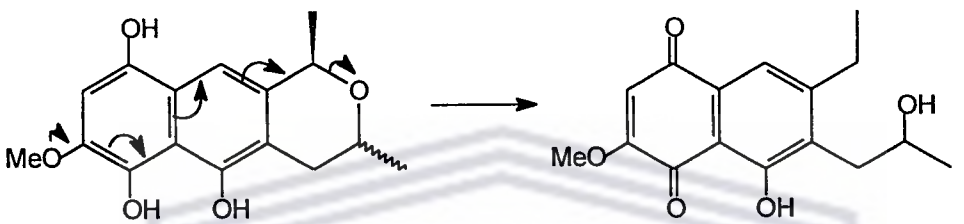
In an alternative oxidation procedure the stereoisomeric pyran mixture **260** and **261** was dissolved in dioxan and four molar equivalents of silver oxide was added to the stirring solution after which 6M nitric acid was dripped in and stirring continued for a further five minutes. Water was added to the reaction mixture and the organic material was extracted into dichloromethane and the residue obtained upon work-up was chromatographed on a PLC plate which

afforded starting material **260 / 261** (27%) and the quinone mixtures **262** and **263** (14%) and **265** and **266** (8%) as separate fractions. Due to the much lower yields obtained and that it became obvious that no advantage could be gained by utilising this procedure the former methodology was preferred.

Attempts to catalytically hydrogenalise the benzyl group from the mixture of *cis* and *trans* quinones **262** and **263** initially led to an over absorption of hydrogen resulting in the formation of the expected mixture of ventiloquinone F **29** and its isomer **264** in a yield of 43% as well as the pyran-ring-opened isomer **267** in a yield of 40%. In subsequent reactions the absorption of hydrogen was carefully monitored and after two molar equivalents had been absorbed the reduction was stopped. In this way none of the over-reduced isomer **267** was formed. Assignment of structure **267** to the over-reduced product was based on the following spectral data apart from the micro analysis which gave a molecular formula of $C_{16}H_{18}O_5$.

The IR spectrum showed a strong peak at 3402 cm^{-1} for an hydroxyl group while a sharp strong peak at 1651 cm^{-1} suggested the *para*-quinone functionallity.[2] The ^{1}H-nmr indicated two hydroxyl groups, one at δ 1.90 for an aliphatic alcohol while the other occurred at δ 12.32 demonstrating a strongly hydrogen-bonded phenolic hydroxyl group. The COSY spectrum demonstrated clear connectivity between a three-proton triplet at δ 1.25 (*J* 7.8) and a two-proton doublet of quartets at δ 2.80 (*J* 7.8 and 7.6) due to the diastereoisotopic nature of these protons. Furthermore the COSY showed connectivity of a three-proton doublet at

δ 1.32 (*J* 6.2) to a one-proton multiplet at δ 4.15 which in turn showed connectivity with a two proton doublet at δ 2.93 (*J* 6.6) for the 2'-hydroxypropyl side chain at C-3. A three-proton singlet at δ 3.90 accounted for the methoxy group while two one-proton singlets at δ 6.09 and 7.51 are assigned H-7 and H-1 respectively.

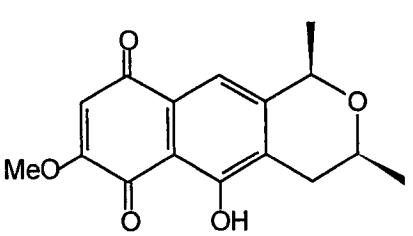


267

Scheme 53

The likely reason for the hydrogenolysis of the C-1-O bond would be the initial reduction of the initially formed quinone mixture **29** and **264** to the corresponding quinol in which the C-7 methoxy group would promote bond cleavage as depicted in **Scheme 53.**

Optimisation of the reduction methodology by strictly limiting the amount of hydrogen absorbed to two molar equivalents resulted in the target compound, ventiloquinone F **29** being isolated in a 44% yield and isoventiloquinone **264** in a 46% yield



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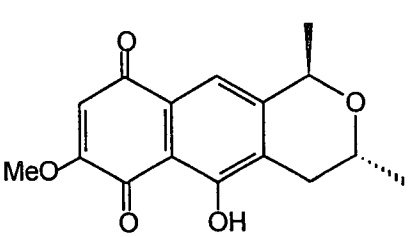
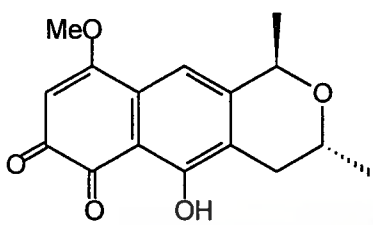


264

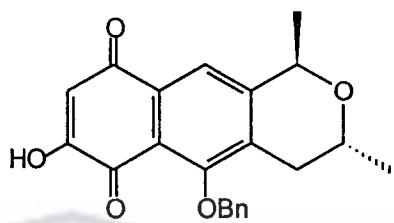
One of the most salient features of the ^{1}H-nmr spectra for ventiloquinone F **29** and isoventiloquinone F **264** lies in the signals of the pyran ring protons. Thus the signal for H-4a appeared as a doublet of doublets of doublets at δ 2.43 with ^{2}J of 17.5 Hz to H-4e, ^{3}J of 10.9 Hz to H-3a and long range coupling of 2.2 Hz to H-1a. On the other hand H-4e appeared as a doublet of doublets of doublets at δ 2.83 with ^{2}J of 17.5 Hz to H-4a, ^{3}J of 3.0 Hz to H-3a and long range coupling of 1.7 Hz to 1-Ha. The signal for H-3a appeared as a doublet of doublets of quartets at δ 3.75 with coupling of 6.2 Hz to the adjacent methyl group leading to the quartet while coupling to H-4a of 10.9 Hz and to He-4 of 3.0 Hz was also clearly evident. The *J* value of δ 3.75 indicated the *cis* 1,3-dimethyl stereochemistry of the pyran ring. The signal due to the H-1a appeared as a doublet of doublets of quartets at δ 4.77 with ^{3}J of 6.6 Hz while long range coupling of 2.2 Hz to H-4a and 1.7 Hz to H-4e were also evident.

The corresponding signals for isoventiloquinone F **264** are very similar with H-4a appearing as a doublet of doublets of doublets at δ 2.44 in which the long range coupling to H-1e was 1.0 Hz while H-4e appeared as a doublet of doublets at δ 2.91 showing no long range coupling. In this case H-3a appeared as a multiplet at δ 4.05 which supported the *trans* 1,3-dimethyl configuration of the pyran ring.

Attempts to hydrogenalise the *trans ortho*-quinone **266** in a similar manner as with the above did not afford the desired 6,7-dione analogue **268** of isoventiloquinone F **264**. Although hydrodgenation was sluggish, the reduction was stopped after two molar equivalents of hydrogen had been absorbed.



268



269

The initial product had the consistency of a yellow clay which decomposed during chromatography. A pure sample was however obtained by recrystallising the clay from ethanol which produced a yellow crystalline compound to which the 5-benzyloxy-7-hydroxy-naphthopyran structure **269** has been assigned based upon the following spectral data. The IR spectrum showed a strong band at 1667 cm^{-1} for the carbonyl groups whilst a broad stretch at 3500 cm^{-1} is assigned to the hydroxyl group at C-7. In the ^{1}H-nmr spectrum, the presence of the benzyl group was obvious from doublets at δ 4.92 and δ 5.00 (*J* 10.2) and the aryl ring protons at δ 7.40 – 7.52. In addition the methoxy group at δ 4.00 was absent and was replaced by an hydroxyl group at δ 7.69. Whilst it could be assumed that the initial demethylation had afforded the 9-hydroxy *ortho*-quinone, the UV spectrum with $\lambda_{max.}$ at 258, 281 and 355 supported the alternative 7-hydroxy *para*-quinone structure **269** suggested.[2] The trans nature of the pyran ring is

assigned based upon the position of the H-3 signal that appears as a multiplet at δ 3.94. This was the only product isolated from the clay-like crude material.

CONCLUSION

The target molecule ventiloquinone F **29** was successfully synthesised from 3,4,6-trimethoxy benzaldehyde **246** in 12 steps in an overall yield of 9.5% and isoventiloquinone F **264** was obtained in an overall yield of 10.0%.

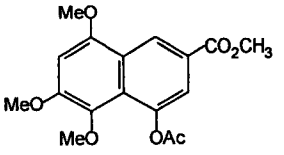
Oxidation of the stereoisomeric mixture of *cis* and *trans* 5-benzloxy-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran **260** and **261** led to the formation of the not only the desired benzyloxynaphthopranquinone precursors **262** and **263**, but also their *ortho* naphthoquinone analogues **265** and **266**.

Attempts to catalytically hydrogenalise the *trans ortho* quinone **266** afforded *trans*-5-benzyloxy-7-hydroxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-6,9-dione **269** as the only product in a yield of 33%.

2. EXPERIMENTAL METHODS

The general procedures used are identical to those described in Chapter 2.

***Methyl 4-acetoxy-5,6,8-trimethoxy-2-naphthoate* (249)**

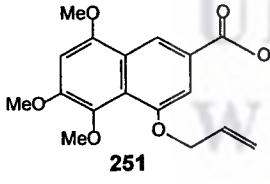


249

The aldehyde **246** (8 g, 40.8 mmol) and dimethyl succinate **247** (8 g, 54.8 mmol) were dissolved in hot absolutely dry tertiary butyl alcohol (80 ml) and this hot solution was added dropwise over 20 min to a rapidly stirring and refluxing solution of potassium tertiary butoxide [from potassium (2g, 53.1 mmol) in tertiary butyl alcohol (50 ml)], under a flow of nitrogen. The stirring and reflux of the mixture was continued for an additional 2h and then allowed to cool to 25°C and poured into water (600 ml), acidified with 5M hydrochloric acid and extracted with ether (3 × 200 ml). The ether layer was extracted with aqueous saturated sodium hydrogen carbonate (3 × 250 ml) and the combined bicarbonate extracts were acidified with 5M hydrochloric acid and then extracted with ether (3 × 200 ml). The residue obtained upon work-up of the ether extracts gave crude itaconic acid **248** (12.1g, 32.9 mmol, 96%). The itaconic acid **248** and sodium acetate (4.8 g, 58.8 mmol) were stirred in acetic anhydride (100 ml) under reflux under nitrogen for 6h. The cooled mixture was then thrown into ice water (800 ml) and the mixture stirred vigorously for 10 min and then left to stand. The product **249** precipitated and was collected by filtration (10.2 g) and washed with water. The filtrate was collected and extracted with dichloromethane, washed with saturated sodium bicarbonate and the residue obtained upon work-up

chromatographed (30% eluent) to obtain light yellow crystals (1.2 g), the combined yield being (11.4 g, 84%), mp 130 – 132°C; (Found: C, 61.26; H, 5.45. $C_{17}H_{18}O_7$ requires C, 61.08; H 5.39%); ν_{max} 1690 and 1705 cm^{-1} (C=O), δ_H 2.38 (3H, s, $OCOCH_3$), 3.82 (3H, s, CO_2CH_3), 3.95, 4.00, and 4.02 (each 3H, s, OCH_3), 6.70 (1H, s, H-7), 7.67 (1H, d, *J* 1.8, H-3) and 8.85 (1H, d, *J* 1.8, 1-H); δ_C 20.78 (CH_3CO), 52.28 (CO_2CH_3), 56.05, 56.86 and 61.95 (each OCH_3), 95.75 (C-7), 120.41 (C-3), 122.06 (C-4a)[a], 124.15 (C-1)[a], 124.45 (C-8a)[a], 124.85 (C-2)[a], 135.64 (C-4)[a], 145.18 (C-5)[b], 152.50 (C-6)[b], 154.28 (C-8)[b], 166.62 (C=O of aryl ester), and 169.86 (C=O of methyl ester) (assignments with the same superscript may be interchanged); *m/z* 334 (M^+, 40%), 292 (69), 277 (100), 261 (4), 249 (42), 231 (4), 217 (5), 203 (5), 145 (2), 115 (1), 77 (1) and 43 (1).

***Methyl 5,6,8-trimethoxy-4-(prop-2'-enyloxy)-2-naphthoate* (251)**



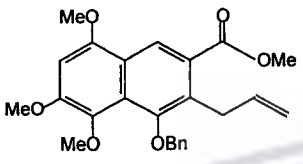
251

The acetate **249** (5g, 15.02 mmol) in a 1% methanolic potassium hydroxide solution (150 ml) was stirred under gentle reflux for 15 minutes. The reaction mixture was cooled to room temperature after which it was quenched with 50% hydrochloric acid and then extracted with dichloromethane. The residue obtained upon work-up was identified as the phenol **250** (4.14 g, 94.4%) as white crystals, mp 156 – 157°C (from ethanol)); (Found: C, 61.34; H, 5.86. $C_{15}H_{16}O_6$ requires: C, 61.64; H, 5.47%); $\nu_{max.}$ 3280 cm^{-1} (OH) and 1705 cm^{-1} (C=O); δ_H 3.94 (3H, s, CO_2CH_3), 4.02 (9H, s, 3 × OCH_3), 6.64 (1H, s, H-7), 7.43 (1H, d, *J* 1.4, H-3), 8.42 (1H, d, *J* 1.4, H-1) and 9.70 (1H, s, OH D_2O exchangeable); δ_C 52.15

(CO_2CH_3), 55.98, 57.13 and 62.31 (each OCH_3), 95.54 (C-7), 97.56 (C-4)[a], 110.46 (C-3), 116.67 (C-1), 120.68 (C-2)[a], 122.00 (C-4a)[a], 126.35 (C-8a)[a], 149.47 (C-5)[b], 153.40 (C-6)[b], 154.40 (C-8)[b] and 167.32 (CO_2CH_3) (assignments with the same superscript may be interchanged); *m/z* 292 (M^+, 60%), 277 (100), 261 (6), 249 (66) 234 (8), 217 (7), 203 (8), 190 (6), 175 (5), 145 (3), 117 (2), 91 (1), 77 (1) and 63 (1). The crude phenol **250** was dissolved in dry acetone (150 ml) and treated with dry potassium carbonate (9.9 g, 71.1 mmol) and allyl bromide (8.6 g 71.1 mmol) and the mixture vigorously stirred under reflux under nitrogen for 12h. The cooled mixture was filtered and the solvent evaporated under reduced pressure and the residue boiled in hexane (150 ml) and ethyl acetate (45 ml) solvent mixture. The resulting solution was decanted into a flat-bottomed flask leaving an amount of insoluble product in the original container flask. This latter solid material was dissolve and recrystallised from ethanol to afford the product **251**. The precipitate resulting from the cooling of the hexane / ethyl acetate solution was collected by filtration and this was also the correct product **251**. The combined material (4.6 g, 92%) appeared as light brown needles, mp 130 – 132°C, (Found: C, 65.25; H, 6.38. $C_{18}H_{20}O_6$ requires: C, 65.06; H, 6.02%); $\nu_{max.}$ 1715 cm^{-1} (C=O); δ_H 3.82 (3H, s, CO_2CH_3), 3.95 (3H, s, OCH_3), 4.01 (6H, s, 2 × OCH_3), 4.71 (2H, dm, *J* 5.0, H-1'), 5.33 (1H, dq, *J* 10.6 and 1.4, *cis* H-3'), 5.60 (1H, dq, *J* 17.2 and 1.4, *trans* H-3'), 6.21 (1H, m, H-2'), 6.72 (1H, s, H-7), 7.41 (1H, d, *J* 1.4, H-3) and 8.57 (1H, d, *J* 1.4, H-1); δ_C 52.18 (CO_2CH_3), 56.00, 57.39 and 62.13 (each OCH_3), 70.54 (C-1'), 96.30 (C-7), 107.83 (C-3), 117.66 (C-3'), 118.78 (C-1), 120.55 (C-2)[a], 122.36 (C-4a)[a], 124.75 (C-8)[a], 133.29 (C-2'), 137.91 (C-4), 152.39 (C-5)[b], 153.64 (C-6)[b], 154.70 (C-8)[b]

and 167.45 (CO_2CH_3) (assignments with the same superscript may be interchanged); *m/z* 332, (M^+, 79%), 317 (37), 302 (6), 285 (100), 271 (4), 257 (24), 243 (16), 229 (6), 215 (5), 128 (2), 77 (1) and 43 (1).

***Methyl 4-benzyloxy-5,6,8-trimethoxy-3-(prop-2'-enyl)naphthoate* (253)**



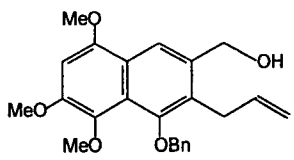
253

The naphthalene **251** (2.34 g, 7.04 mmol) was rapidly heated to 180°C and maintained at this temperature under nitrogen and stirred for 2h to give the black crude naphthol **252** (2.29 g, 98%) as light brown crystals, mp 94 – 96°C (from hexane / ethyl acetate), (Found: C, 65.19; H, 6.10. $C_{18}H_{20}O_6$ requires: C, 65.06; H, 6.02%); $\nu_{max.}$ 3270 cm^{-1} (OH) and 1705 cm^{-1} (C=O); δ_H 3.87 (2H, dt, *J* 5.8 and 1.5 H-1'), 3.90 (3H, s, CO_2CH_3), 3.98 (3H, s, OCH_3), 4.00 (6H, s, 2 × OCH_3), 4.97 (1H, dq, *J* 11.1 and 1.6, *cis* H-3'), 5.04 (1H, dq, 18.0 and 1.6, *trans* H-3'), 6.11 (1H, m, H-2'), 6.58 (1H, s, H-7), 8.24 (1H, s, H-1) and 10.08 (1H, s, OH, D_2O exchangeable); δ_C 30.17 (C-1'), 51.99 (CO_2CH_3), 55.90, 57.15 and 62.92 (each OCH_3), 95.03 (C-7), 114.38 (C-1)[a], 116.65 (C-3')[a], 119.63 (C-4)[b], 120.17 (C-3)[b], 121.25 (C-2)[b], 127.50 (C-4a)[b], 136.10 (C-8a)[b], 137.39 (C-2'), 149.28 (C-5)[c], 151.10 (C-6)[c], 153.92 (C-8)[c] and 168.48 (CO_2CH_3) (assignments with the same superscript may be interchanged); *m/z* 332 (M^+, 78%), 317 (37), 302 (5), 285 (100), 271 (4), 257 (22), 243 (15) 229 (6), 215 (6), 169 (2), 143 (2), 77 (1) and 43 (1). The naphthol was dissolved in dry acetone (110 ml) and treated with dry potassium carbonate (2.77 g, 20.04 mmol) and benzyl bromide (3.43 g, 20.05 mmol) and the mixture was stirred vigorously under reflux under

nitrogen for 24h. The mixture was allowed to cool to 20°C, filtered and the residue obtained upon work-up was chromatographed (40% eluent) to afford the product **253** (2.89 g, 97%) as off-white crystals, mp 94 – 95°C (from hexane / ethyl acetate); (Found: C, 71.47; H, 6.05. $C_{25}H_{26}O_6$ requires: C, 71.09; H, 6.16%); $\nu_{max.}$ 1705 cm^{-1} (C=O); δ_H 3.72 (3H, s, CO_2CH_3), 3.91 and 4.03 (each 3H, s, OCH_3), 4.04 (5H, sharp m, OCH_3 and H-1'), 4.88 (1H, dq, *J* 10.8 and 1.8, *cis* H-3'), 4.94 (2H, s, CH_2Ph), 5.00 (1H, dq, *J* 17.0 and 1.8, *trans* H-3'), 6.08 (1H, m, H-2'), 6.71 (1H, s, H-7), 7.25-7.62 (5H, m, CH_2Ph), 8.61 (1H, s, H-1); δ_C 30.50 (C-1'), 52.10 (CO_2CH_3), 56.00, 57.01, 62.47 (each OCH_3), 77.00 (CH_2-Ph), 94.94 (C-7), 114.90 (C-3'), 120.90 (C-3)[a], 122.53 (C-1)[a], 125.75 (C-2)[a], 126.62 (aryl ring)[a], 127.76 (C-4a)[a], 128.33 (aryl ring ×2), 128.40 (aryl ring ×2), 131.00 (aryl ring)[a], 136.14 (C-8a)[a], 138.11 (C-4), 138.23 (C-2'), 151.86 (C-5)[b], 152.24 (C-6)[b], 153.78 (C-8)[b] and 168.35 (CO_2CH_3) (assignments with the same superscript may be interchanged); *m/z* 422 (M^+, 17%), 407 (3), 395 (9), 381 (6), 363 (24), 343 (3), 331 (100), 299 (66), 285 (53), 272 (29), 257 (33), 243 (19), 229 (19), 213 (10), 199 (7), 128 (3), 91 (10) and 66 (1).

4-Benzyloxy-2-hydroxymethyl -5,6,8-trimethoxy-3-prop-2'-enylnaphthalene

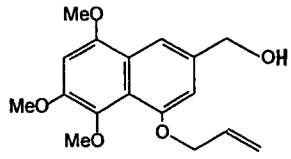
(254)



254

The naphthalene **253** (1.0 g, 2.4 mmol) was dissolved in dry tetrahydrofuran (25 ml) and dripped into a stirred slurry of lithium aluminium hydride (140 mg, 3.55 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. The reaction mixture was heated to 50°C and stirred for 30 minutes. The reaction was quenched by the careful addition of 15 drops of saturated ammonium chloride followed water (20 ml) and then extracted using dichloromethane (3 × 50 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford the product **254** (930 mg, 100%) as a colourless oil; (Found: C, 73.40; H, 6.90. $C_{24}H_{26}O_5$ requires: C, 73.10; H, 6.60%); $\nu_{max.}$ 3450 cm^{-1} (OH); δ_H 3.73 (3H, s, OCH_3), 3.77 (2H, dt, *J* 5.2 and 1.8, H-1'), 4.01 and 4.03 (each 3H, s, OCH_3), 4.81 (2H, s, CH_2OH), 4.87 (1H, dq, *J* 18.0 and 1.8 *trans* H-3'), 4.96 (2H, s, CH_2Ph), 5.05 (1H, dq, *J* 11.0 and 1.8 *cis* H-3'), 6.13 (1H, m, H-2'), 6.70 (1H, s, H-7), 7.26-7.57 (6H, m, CH_2Ph and O*H*) and 8.07 (1H, s, H-1); δ_C 25.69 (CH_2OH), 30.21 (C-1'), 55.95, 57.23 and 62.43 (each OCH_3), 77.00 (CH_2Ph), 95.10 (C-7), 115.35 (C-3')[a], 117.97 (C-3)[a], 123.64 (C-1)[a], 127.05 (C-2)[a], 127.70 (C-4a)[a], 128.34 (aryl ring)[a], 128.37 (aryl ring), 128.40 (aryl ring), 128.63 (aryl ring)[a], 129.78 (aryl ring)[a], 135.93 (C-8a)[a], 138.05 (C-2'), 138.18 (C-4), 150.22 (C-5)[b], 151.75 (C-6)[b] and 152.81 (C-8)[b] (assignments with the same superscript may be interchanged); *m/z* 394 (M^+, 38%), 304 (88), 289 (100), 271 (19), 261 (15), 243 (16), 233 (10), 213 (9), 183 (5), 115 (5), 91 (2) and 69 (1).

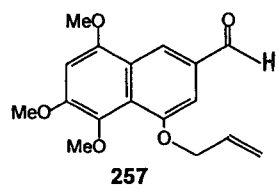
***2-Hydroxymethyl-5,6,8-trimethoxy-4-prop-2'-enyloxynaphthalene* (256)**



256

The naphthalene **251** (1.0 g, 3.0 mmol) was dissolved in dry tetrahydrofuran (25 ml) and dripped into a slurry of lithium aluminium hydride (170 mg, 4.5 mmol) in dry tetrahydrofuran (10 ml) while stirring and under nitrogen. The reaction mixture was heated to 50°C and stirred for 30 minutes after which time it was quenched by the careful addition of 15 drops of saturated ammonium chloride followed by water (20 ml) and then isolation of the organic components using dichloromethane (3 × 50 ml). The residue obtained upon work-up was chromatographed (40% eluent) to afford the product **256** (920 mg, 100%) as white crystals, mp 89 – 91°C (from hexane / ethyl acetate); (Found: C, 67.40; H, 6.91. $C_{17}H_{20}O_5$ requires: C, 67.11; H 6.56%); $\nu_{max.}$ 3453 cm^{-1} (OH); δ_H 3.82, 3.98, and 3.99 (each 3H, s, OCH_3), 4.66 (2H, dt, *J* 5.2 and 1.4, H-1'), 4.76 (2H, s, CH_2OH), 5.32 (1H, dq, *J* 10.6 and 1.4, *cis* H-3'), 5.57 (1H, dq, *J* 17.2 and 1.4, *trans* H-3'), 6.20 (1H, m, H-2'), 6.69 (1H, s, H-7), 6.91 (1H, d, *J* 1.2, H-3), 7.26 (1H, s, OH, D_2O exchangeable) and 7.75 (1H, d, *J* 1.2, H-1); δ_C 55.95, 57.83 and 62.06 (each OCH_3), 65.92 (CH_2OH) 70.64 (C-1'), 96.84 (C-7), 108.65 (C-3), 112.97 (C-1)[a], 117.47 (C-3'), 121.61 (C-2)[a], 123.46 (C-4a)[a], 133.55 (C-2'), 136.17 (C-8a)[a], 138.36 (C-4)[a], 150.02 (C-5)[b], 152.30 (C-6)[b] and 155.15 (C-8)[b] (assignments with the same superscript may be interchanged); *m/z* 304 (M^+, 79%), 289 (100), 271 (19), 261 (12), 243 (15), 233 (9), 213 (6), 141 (2), 115 (3), 91 (1), 69 (2) and 51 (1).

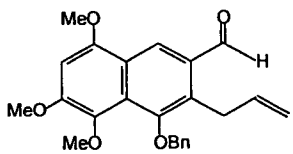
***5,6,8-Trimethoxy-4-prop-2'-enyloxy-2-naphthalene carbaldehyde* (257)**



257

The alcohol **256** (0.9 g, 2.96 mmol) was dissolved in dry benzene (100 ml) and treated with activated manganese dioxide (5 g) and stirred under reflux with a Dean Stark Trap under a nitrogen atmosphere for 18 h. The reaction mixture was the allowed to cool to room temperature and then filtered and the residue obtained upon solvent evaporation under reduced pressure was chromatographed (30% eluent) on a short column to afford the aldehyde **257** (500 mg, 56%) as yellow needles, mp 105 – 106°C (from hexane / ethyl acetate); (Found: C, 67.75; H, 5.86. $C_{17}H_{18}O_5$ requires: C, 67.55; H, 5.96%); $\nu_{max.}$ 1625 cm^{-1} (C=O); δ_H 3.82, 4.03, 4.04 (each 3H, s, OCH_3), 4.72 (2H, dt, *J* 3.6 and 1.6, H-1'), 5.34 (1H, dq, *J* 10.6 and 1.6, *cis* H-3'), 5.6 (1H, dq, *J* 17.2 and 1.6, *trans* H-3'), 6.20 (1H, m, H-2'), 6.75 (1H, s, H-7), 7.26 (1H, d, *J* 1.4, H-3), 8.31 (1H, d, *J* 1.4, H-1) and 9.99 (1H, s, CHO); δ_C 56.09, 57.23, and 62.15 (each OCH_3), 70.22 (C-1'), 96.31 (C-7), 102.94 (C-3), 117.81 (C-3'), 122.02 (C-1)[a], 124.26 (C-2)[a], 125.23 (C-4a)[a], 132.20 (C-4)[a], 133.03 (C-2'), 138.37 (C-8a)[a], 153.63 (C-5)[b], 153.83 (C-6)[b], 155.51 (C-8)[b] and 191.95 (C=O) (assignments with the same superscript may be interchanged); *m/z* 302 (M^+, 94%), 287 (100), 269 (7), 259 (23), 244 (25), 227 (58), 213 (5), 199 (9), 184 (3), 159 (4), 128 (4), 77 (1) and 51 (1).

***4-Benzyloxy-5,6,8-trimethoxy-3-prop-2'-enylnaphthalene-2-carbaldehyde* (255)**



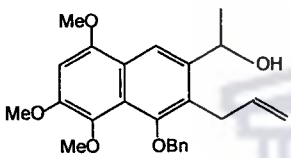
255

The alcohol **254** (2.57 g, 6.52 mmol) was dissolved in dry benzene (100 ml) and treated with activated manganese dioxide (15 g) and stirred under reflux with a Dean Stark Trap under a nitrogen atmosphere for 18 h. The cooled reaction mixture was filtered and the residue was chromatographed (30% eluent) on a short column to afford the aldehyde **255** (1.76 g, 69%) as yellow crystals mp 109 – 110°C (from hexane / ethyl acetate); (Found: C, 73.78; H, 6.41. $C_{24}H_{24}O_5$ requires: C, 73.47; H 6.12%); (Found: HRMS, 392.16374. $C_{24}H_{24}O_5$ requires 392.16237); $\nu_{max.}$ 1705 cm^{-1} (C=O); δ_H 3.72 (3H, s, OCH_3), 4.06 (6H, s, 2 × OCH_3), 4.09 (2H, dt, *J* 6.0 and 1.8, H-1', obscured by s at 4.06), 4.91 (1H, dq, *J* 17.6 and 1.8, *trans* H-3'), 4.96 (2H, s, C*H*$_2$Ph), 5.03 (1H, dq, *J* 10.2 and 1.8, *cis* H-3'), 6.14 (1H, m, H-2'), 6.73 (1H, s, H-7), 7.23-7.63 (5H, m CH_2*Ph*), 8.60 (1H, s, H-1) and 10.18 (1H, s, CHO); δ_C 29.15 (C-1'), 56.05, 56.88 and 62.53 (each OCH_3), 77.11 (*C*H$_2$Ph), 94.81 (C-7), 115.54 (C-3'), 120.95 (C-3), 126.74 (C-1)[a], 127.11 (C-4a)[a], 128.33 (aryl ring)[a], 128.44 (aryl ring)[a], 130.46 (C-2)[a], 130.63 (aryl ring)[a], 136.25 (C-8a)[a], 137.95 (C-2'), 138.04 (C-4), 151.89 (C-5)[b], 153.76 (C-6)[b], 154.55 (C-8)[b] and 192.32 (C=O) (assignments with the same superscript may be interchanged); *m/z* 392 (M^+, 19%), 301 (100), 286 (9), 271 (11), 258 (10), 243 (13), 242 (15), 213 (5), 133 (5) and 91 (16).

In an alternative route aldeyhyde **257** (840 mg, 2.8 mmol) was rapidly pyrolysed at 180°C under a nitrogen atmosphere for 2h. The Claisen Rearranged product **258** was dissolved in dry acetone (50 ml) and treated with potassium

carbonate (1.92 g, 14 mmol) and benzyl bromide (2.38 g, 14 mmol) and heated under reflux for 12h under nitrogen. The cooled mixture was filtered and the residue was chromatographed (40% eluent) to give the same aldehyde **255** (620 mg, 57%) as described above.

***4-Benzyloxy-2-(1'-hydroxyethyl)-5,6,8-trimethoxy-3-prop-2'-enylnaphthalene* (259)**

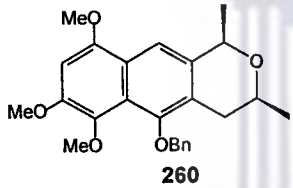


259

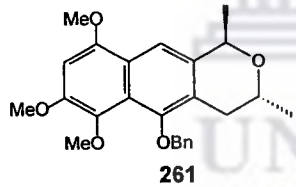
The aldehyde **255** (475 mg, 1.63 mmol) was dissolved in dry ether (25 ml) and dripped into a freshly prepared solution of methyl magnesium iodide, prepared from magnesium filings (88 mg, 3.64 mmol) and iodomethane (516 mg, 3.64 mmol) in ether (20 ml). The reaction mixture was then allowed to stir for 1h after which a saturated aqueous ammonium chloride solution was added dropwise to quench the reaction. Water (100 ml) was added and the organic layer was extracted into ether (3 × 100 ml). The residue obtained upon work-up was chromatographed (30% eluent) to afford the alcohol **259** (493 mg, 100%) as a clear oil, (Found: C, 74.52; H, 6.93. $C_{25}H_{27}O_5$ requires C, 73.71; H, 6.63%), $\nu_{max.}$ 3440 cm^{-1} (OH); δ_H 1.57 (3H, d, *J* 6.6, CHC*H*$_3$), 1.83 (1H, bs, OH), 3.70 (2H, dt, *J* 5.6 and 1.8, H-1'), 3.73 (3H, s, OCH_3), 4.02 (6H, s, 2 × OCH_3), 4.87 (1H, dq, *J* 17.8 and 1.8, *trans* H-3'), 4.96 (2H, s, C*H*$_2$Ph), 5.06 (1H, dq, *J* 10.2 and 1.8, *cis* H-3'), 5.21 (1H, q, *J* 6.6, C*H*CH$_3$), 6.15 (1H, m, H-2'), 6.69 (1H, s, H-7), 7.32 – 7.62 (5H, m, CH$_2$*Ph*) and 8.25 (1H, s, H-1); δ_C 24.68 (CH_3CH), 29.91 (C-1'), 55.88, 57.28 and 62.41 (each OCH_3), 66.79 (O*C*H$_2$Ph), 76.89 (CHOH), 95.01 (C-7), 114.85 (C-1)[a], 115.40 (C-3')[a], 112.48 (C-2)[b], 123.30 (C-4a)[b], 127.69 (aryl C), 128.35 (4 × aryl

C), 128.94 (aryl C), 136.35 (C-3)[b], 138.21(C-2'), 138.33 (C-8a)[b], 140.99 (C-4), 150.05 (C-5)[c], 151.43 (C-6)[c] and 152.82 (C-8)[c] (assignments with the same superscript may be interchanged); *m/z* 407 (M^+,%), 390 (60), 363 (100), 335 (35), 305 (6), 285 (9), 272 (4), 257 (5), 229 (4), 197 (3), 150 (4), 91 (5), and 69 (2).

***cis*-5-Benzyloxy-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran (260) and *trans*-5-benzyloxy-3,4-dihydro-6,7,9-trimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran (261)**



260



261

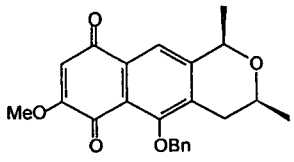
The alcohol **259** (640 mg, 1.57 mmol) was dissolved in THF (35 ml) and water (25 ml) was added. Mercuric acetate (498 mg, 1.56 mmol) was added and the reaction mixture was stirred at 20°C for 1h. 5M aqueous sodium hydroxide (12 ml) solution was added and the reaction mixture was stirred for a further 1h. An additional aliquot of 5M sodium hydroxide solution (12 ml) was added along with sodium borohydride (1541 mg, 34.8 mmol) and the reaction mixture was stirred for another 1h. Water (120 ml) was added to the stirred mixture which was extracted with ethyl acetate (3 × 100 ml) and the residue obtained upon work-up was chromatographed (30% eluent) to yield the product as an inseparable mixture of the two diastereoisomers **260** and **261** as a thick oil (456 mg, 71%) which later solidified as white cubes mp 91 – 93°C (from hexane), (found: C, 74.21; H, 7.06. $C_{25}H_{28}O_5$ requires C, 73.53; H, 6.86%); ν_{max} 1640 cm^{-1}

(aromatic C=C); δ_H 1.35 (3H, d, *J* 6.4, 3-CH_3), 1.40 (3H, d, *J* 6.4, 3-CH_3), 1.62 (3H, d, *J* 6.2, 1-CH_3), 1.69 (3H, d, *J* 6.2, 1-CH_3) 2.60 (1H, dd, *J* 16.8 and 10.0, pseudoaxial H-4), 2.66 (1H, dd, *J* 16.8 and 10.0 pseudoaxial H-4), 3.16 (1H, dd, *J* 16.8 and 3.0, pseudoequatorial H-4), 3.18 (1H, dd, *J* 16.8 and 3.0, pseudoequatorial H-4), 3.77 (6H, s, OCH_3), 3.80 (1H, m, *cis* H-3), 4.00 and 4.02 (each 6H, s, OCH_3), 4.05 (1H, m, *trans* H-3) 4.99 (4H, m, CH_2Ph), 5.20 (2H, q, *J* 6.2, H-1), 6.67 (2H, s, H-8), 7.37 – 7.63 (10H, m, Ph), 7.74 (1H, s, H-10) and 7.80 (1H, s H-10).

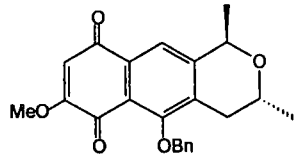
***cis / trans 5-Benzyloxy-3,4-dihydro-7-methoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione* (262 and 263) *and cis / trans 5-Benzyloxy-3,4-dihydro-9-methoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,7-dione* (265 and 266)**

Pyran mixture **260** and **261** (450 mg, 1.10 mmol) was dissolved in acetonitrile (80 ml) and water (25 ml) was added to the stirring solution. A solution of cerium (IV) ammonium nitrate (1.22 g, 2.22 mmol) in water (20 ml) was dripped in over 8 minutes and stirring was continued for an additional 10 minutes after which the whole solution was transferred to a separating funnel with water (800 ml). The organic material was extracted into dichloromethane (3 × 200 ml) and the residue obtained upon work-up was chromatographed on a column (40% eluent) to afford firstly a mixture of the *para*-naphthopyranquinones **262** and **263** (192 mg, 46%) followed by *ortho*-naphthopyranquinones **265** and **266** (171 mg 42%).

Purification of the products:



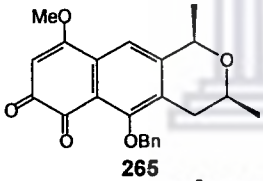
262



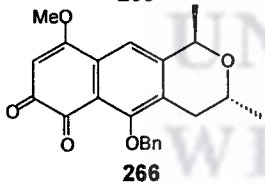
263

A. Separation of *para*-naphthopyranquinones **262** and **263**. The mixture (192 mg) was slowly chromatographed on 1m long column (20% eluent) to give the pure *cis* isomer **262** (92 mg, 22%) as yellow fluffy crystals, mp 191 – 193°C (from isopropanol); (Found: C, 73.26; H, 6.10. $C_{23}H_{22}O_5$ requires C, 73.02; H, 5.82%); $\nu_{max.}$ cm^{-1} 1648 and 1688 cm^{-1} (each C=O); δ_H 1.33 (3H, d, *J* 6.2, 3-CH_3), 1.61 (3H, d, *J* 6.6, 1-CH_3), 2.42 (1H, ddd, *J* 17.6, 11.0 and 1.8, pseudoaxial H-4), 2.90 (1H, ddd, *J* 17.6, 3.0 and 1.0, pseudoequatorial H-4), 3.68 (1H, m, H-3), 3.90 (3H, s, OCH_3), 4.85 (1H, ddq, *J* 6.6,1.8 and 1.0, H-1) 4.88 (1H, d, *J* 10.2, C*H*$_2$Ph), 5.02 (1H, d, *J* 10.2, CH_2Ph), 6.13 (1H, s, H-8), 7.38-7.61 (5H, m, CH_2*Ph*) and 7.73 (1H, s, H-10); δ_C 21.43 (3-CH_3)[a], 21.78 (1-CH_3)[a], 31.68 (4-C), 59.60 (CH_3O), 70.18 (C*H*$_2$Ph)[b], 73.23 (C-3)[b], 75.71 (C-1)[b], 108.58 (C-8), 119.13 (C-10), 121.28 (aryl C), 128.48, 128.63 and 128.79 (5 × aryl C), 131.92 (C-4a)[c], 136.51 (C-5a)[c], 136.86 (C-9a)[c], 148.21 (C-10a)[c], 157.03 (C-5), 160.97 (C-7), 178.86 (C=O) and 184.61 (C=O) (assignments with the same superscript may be interchanged). Further elution gave the pure *trans* **263** (98 mg, 24%) as yellow crystals, mp 208 – 210°C (from isopropanol); (Found: C, 73.25; H, 6.13. $C_{23}H_{22}O_5$ requires C, 73.02; H, 5.82%) (Found: HRMS, 378.14705. $C_{23}H_{22}O_5$ requires 37814672); $\nu_{max.}$ cm^{-1} 1649 and 1690 cm^{-1} (each C=O); $\lambda_{max.}$ (ethanol) 251 (Є 4.82), 286 (Є 4.08) and 359 (Є 3.55); δ_H 1.28 (3H, d, *J* 6.2, 3-CH_3), 1.56 (3H, d, *J* 7.0, 1-CH_3),

2.37 (1H, ddd, *J* 17.6, 9.4 and 1.0 pseudoaxial H-4), 2.90 (1H, dd, *J* 17.6 and 3.8, pseudoequatorial 4-H), 3.91 (3H, s, OCH_3), 3.95 (1H, m, H-3), 4.90 (1H, d, *J* 10.4, CH_2Ph), 4.95 (1H, dq, *J* 7.0 and 1.0, H-1), 5.00 (1H, d, *J* 10.4, CH_2Ph), 6.13 (1H, s, H-8), 7.37-7.60 (5H, m, Ph) and 7.66 (1H, s, H-10); δ_C 21.00 (3-CH_3)[a], 21.45 (1-CH_3)[a], 30.92 (4-C), 59.62 (CH_3O), 63.63 (C-3)[b], 70.66 (C-1)[b], 75.87 (CH_2Ph)[b], 108.59 (C-8), 119.13 (C-10), 119.86 (aryl C), 128.52, 128.65 and 128.84 (5 × aryl C), 131.82 (C-4a)[c], 135.80 (C-5a)[c], 136.86 (C-9a)[c], 148.00 (C-10a)[c], 157.31 (C-5), 161.04 (C-7), 178.86 (C=O) and 184.63 (C=O) (assignments with the same superscript may be interchanged); *m/z* 378 (M^+, 18%), 273 (5), 244 (8), 105 (4), 91 (100), 77 (4) and 65 (6).



265



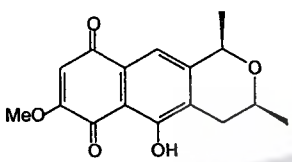
266

B. Separation of *ortho* naphthopyranquinones **265** and **266**. The mixture (171 mg) was slowly chromatographed on a 1m long column (20% eluent) to give the pure *cis* isomer **265** (21%) as bright yellow crystals, mp 191 – 193°C (from isopropanol); (Found: C, 73.36; H, 6.10. $C_{23}H_{22}O_5$ requires C, 73.02; H, 5.82%); $\nu_{max.}$ cm^{-1} 1660 and 1709 cm^{-1} (each C=O); δ_H 1.33 (3H, d, *J* 6.2, 3-CH_3), 1.59 (3H, d, *J* 6.6, 1-CH_3), 2.38 (1H, ddd, *J* 17.4, 9.8 and 1.5, pseudoaxial H-4), 2.85 (1H, ddd, *J* 17.4, 3.2 and 1.5, pseudoequatorial H-4), 3.68 (1H, m, H-3), 3.99 (3H, s, 9-OCH_3), 4.86 (1H, tq, *J* 6.6 and 1.5, H-1), 4.87 (1H, d, *J* 10.2, CH_2Ph), 5.00 (1H, d, *J*10.2 CH_2Ph), 5.96 (1H, s, H-8), 7.20 (3H, m, H-3', H-4', H-5' of aryl ring), 7.46 (1H, s, H-10) and 7.60 (2H, m, H-2' and H-6' of aryl ring); δ_C 21.21 (3-CH_3), 21.57 (1-CH_3), 30.62 (C-4),

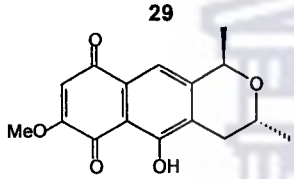
56.90 (OCH_3), 63.65 (C-3), 70.75 (C-1), 76.11 (CH_2Ph), 102.75 (C-8), 117.39 (C-4a)[a], 118.14 (C-10), 128.54 (aryl ring), 128,63 (aryl ring), 129.00 (aryl ring), 131.13 (aryl ring), 133.65 (aryl ring), 134.39 (C-10a)[a] 136.79 (C-9), 148.45 (C-9a)[a], 148.77 (C-5a)[a], 159.98 (C-5)[a], 178.85 (C=O) and 179.85 (C=O) (assignments with the same superscript may be interchanged). Further elution gave the pure *trans* isomer **266** (98 mg, 24%) as bright yellow crystals, mp 208 – 210°C (from isopropanol); (Found: C, 73.15; H, 6.13. $C_{23}H_{22}O_5$ requires C, 73.02; H, 5.82%); (Found: HRMS, 378.14762. $C_{23}H_{22}O_5$ requires 378.14672); $\nu_{max.}$ cm^{-1} 1660 and 1709 cm^{-1} (each C=O); $\lambda_{max.}$ (ethanol) 260 (Є 4.35), 288 (Є 3.90) and 372 (Є 3.50); δ_H 1.28 (3H, d, *J* 5.8, 3-CH_3), 1.56 (3H, d, *J* 7.0, 1-CH_3), 2.33 (1H, ddd, *J* 17.2, 9.6 and 1.0, pseudoaxial H-4), 2.86 (1H, dd, *J* 17.2 and 3.2, pseudoequatorial H-4), 3.95 (1H, m, H-3), 4.00 (3H, s, OCH_3), 4.89 (1H, d, *J* 10.4, C*H*$_2$Ph), 5.01 (1H, d, *J* 10.4, CH_2Ph), 5.02 (1H, dq, *J* 7.0 and 1.0, H-1), 5.97 (1H, s, H-8), 7.33-7.45 (3H, m, H-3', H-4', H-5' of aryl ring), 7.40 (1H, s, H-10) and 7.50-7.61 (2H, m, H-2' and H-6' of aryl ring); δ_C 21.22 (3-CH_3), 21.56 (1-CH_3), 30.62 (C-4), 56.85 (OCH_3), 63.63 (C-3), 70.69 (C-1), 76.00 (*C*H_2Ph), 102.63 (C-8), 117.38 (C-4a)[a], 118.14 (C-10), 128.53 (aryl ring), 128.61 (aryl ring), 128.95 (aryl ring), 131.12 (aryl ring), 133.59 (aryl ring), 134.37 (C-10a)[a] 136.77 (C-9), 148.43 (C-9a)[a], 148.67 (C-5a)[a], 159.72 (C-5)[a], 178.80 (C=O) and 179.84 (C=O) (assignments with the same superscript may be interchanged); *m/z* 378 (M^+, 17%), 363 (3), 350 (2), 259 (3), 245 (7), 216 (6), 115 (3), 91 (100) and 65 (6).

Alternative oxidation procedure for the formation of quinones 262, 263, 265 and 266. The pyran mixture **260** and **261** (90 mg, 0.22 mmol) was dissolved in dioxan (15 ml) and silver oxide (111 mg, 0.89 mmol) was added. To the stirred mixture was added 6M nitric acid (0.6 ml) over 4 min and the yellow solution was allowed to stir for a further 5 min. Water (100 ml) was added and the organic material was extracted into dichloromethane (3 × 50 ml). The residue obtained upon work-up was purified by PLC (40% eluent) to afford three fractions. Fraction 1 was starting material **260** and **261**, (24 mg, 27%), fraction 2 which comprised of the *cis* / *trans* mixture **262** and **263** naphthopyranquinones (12 mg, 73%) based on unrecovered starting material from which only the pure *trans* isomer **263** was obtained as light fluffy yellow needles, mp 208 – 210°C (from isopropanol) with identical spectral properties to the material isolated earlier. Fraction 3 was identified as the *ortho* naphthopyranquinone mixture **265** and **266** (6.4 mg, 39%) based on unrecovered starting material and the pure *trans* isomer was obtained as bright yellow needles, mp 208 – 210°C (from isopropanol) with identical spectral properties to the material isolated earlier.

***cis*-3,4-Dihydro-5-hydroxy-7-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-6,9-dione (Ventiloquinone F)** (29) **and *trans*-3,4-dihydro-5-hydroxy-7-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-6,9-dione (Isoventiloquinone F)** (264) ***and* 2-ethyl-4-hydroxy-6-methoxy-3-(2'-propanol)naphtho-5,8-dione** (267)

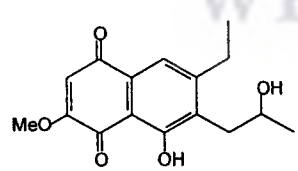


29



264

To the stereoisomeric quinone mixture **262** and **263** (192 mg, 0.51 mmol) in ethyl acetate (30 ml) was added the palladium catalyst (10% on C, 40 mg) and the resulting mixture vigorously stirred under an atmosphere of hydrogen for 24h. The colourless solution was filtered and rapidly became yellow on exposure to the atmosphere. The residue obtained by solvent removal was chromatographed (50% eluent) to afford two major fractions. The first comprised of a mixture of the *cis* and *trans* ventiloquinones **29** and **264** (63 mg, 43%). Further elution afforded the next fraction which was identified as the naphthoquinone **267** (58 mg, 40%) as yellow crystals, mp 142 – 144°C (from ethyl acetate); (Found: C, 66.40, H, 6.35; $C_{16}H_{18}O_5$ requires: C, 66.20, H, 6.25%); (Found: HRMS, 290.11632. $C_{16}H_{18}O_5$ requires 290.11542) $\nu_{max.}$ 3402 cm^{-1} (OH), 1651 (C=O); $\lambda_{max.}$ 251 (Є 4.05), 296 (Є 4.07) and 423 (Є 3.63); δ_H 1.25 (3H, t, *J* 7.8, CH_3CH_2), 1.32 (3H, d, *J* 6.2, $CH_3CH(OH)CH_2$), 1.90 (1H, s, aliphatic OH, D_2O exchangeable), 2.80 (2H, dq, *J* 7.8 and 7.6, CH_2CH_3), 2.93 (2H, d, *J* 6.6, $CH_3CH(OH)CH_2$), 3.90 (3H, s, OCH_3), 4.15 (1H, m,

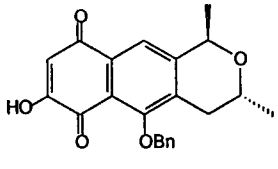


267

$CH_3CH(OH)CH_2$), 6.09 (1H, s, H-7), 7.51 (1H, s, H-1) and 12.32 (1H, s, OH); δ_C 14.02 (C-2'), 23.41 (C-3"), 26.40 (C-1'), 34.69 (C-1"), 56.00 (CH_3O), 67.46 (C-2"), 109.75 (C-7), 111.43 (C-4a)[a], 119.18 (C-1), 129.28 (C-2)[a], 131.74 (C-8a)[a], 153.25 (C-3)[a], 159.70 (C-4)[b], 160.42 (C-6)[b], 183.54 (C=O), and 184.15 (C=O) (assignments with the same superscript may be interchanged); *m/z* 290 (M^+, 8%), 258 (6), 246 (100), 231 (32), 217 (23), 216 (13), 203 (10), 161 (10), 115 (8), 77 (5) and 45 (16). In subsequent catalytic hydrogenation of the quinone mixture, reaction was stopped after 2 mol of hydrogen had been absorbed. Thus 360 mg, 0.96 mmol of the mixture of quinones **260** and **261** was hydrogenated and the residue obtained was chromatographed on a 1m long column (20% eluent) to afford ventiloquinone F **29** (121 mg, 44%) as fine yellow crystals, mp 197 – 199°C (from ethyl acetate / hexane), lit.[19], 213°C; (Found: C, 66.40, H, 5.35; $C_{16}H_{16}O_5$ requires: C, 66.66, H, 5.59%) (Found: HRMS, 288.10024. $C_{16}H_{16}O_5$ requires 288.09977); $\nu_{max.}$3696 cm^{-1} (OH), 1642 (C=O); δ_H 1.38 (3-H, d, *J* 6.2, 3-CH_3), 1.54 (3H, d, *J* 6.6, 1-CH_3), 2.43 (1H, ddd, *J* 17.5, 10.9 and 2.2, pseudoaxial H-4), 2.83 (1H, ddd, *J* 17.5, 3.0, and 1.7, pseudoequatorial H-4), 3.75 (1H, ddq, *J* 10.9, 6.2, and 3.0, H-3), 3.95 (3H, s, OCH_3), 4.77 (1H, ddq, *J* 6.6, 2.2 and 1.7, H-1), 5.87, (1H, s, H-8), 7.18, (1H,s, H-10) and 12.18 (1H, s, OH D_2O exchangeable); δ_C 21.14 (3-CH_3), 21.79 (1-CH_3), 30.61 (C-4), 56.62 (OCH_3), 70.00 (C-3), 73.29 (C-1), 110.53 (C-8), 111.93 (C-5a)[a], 115.30 (C-10), 116.09 (C-9a)[a], 129.52, (C-4a)[a], 130.11 (C-10a)[a], 159.88 (C-5)[c], 160.32 (C-7)[c], 184.11 (C=O), and 184.76 (C=O) (assignments with the same superscript may be interchanged); *m/z* 288 (M^+, 14%), 273 (34), 244 (100), 229 (13), 215 (16), 185 (4), 159 (9), 145 (6), 115 (10), 103 (5) and 77 (7). Further elution afforded

isoventiloquinone F **264** (126 mg, 46%) as fine yellow crystals, mp 225 – 226°C (from ethyl acetate / hexane); (Found: C, 66.41, H, 5.34; $C_{16}H_{16}O_5$ requires: C, 66.66, H, 5.59%); (Found: HRMS, 288.10033. $C_{16}H_{16}O_5$ requires 288.09977) $\nu_{max.}$3696 cm^{-1} (OH), 1642 (C=O); δ_H 1.36 (3H, d, *J* 6.4, 3-CH_3), 1.56 (3H, d, *J* 6.6, 1-CH_3), 2.44 (1H, ddd, *J* 17.6, 9.4 and 1.0, pseudoaxial H-4), 2.91 (1H, dd, *J* 17.6 and 3.4 pseudoequatorial H-4), 3.91 (3H, s, OCH_3), 4.05 (1H, m, H-3), 5.03 (1H, dq, *J* 6.6 and 1.0, H-1), 6.12 (1H, s, H-8), 7.33 (1H, s, H-10) and 12.16 (1H, s, OH D_2O exchangeable); δ_C 21.22 (3-CH_3), 21.38 (1-CH_3), 29.84 (C-4), 56.64 (OCH_3), 63.19 (C-3), 71.01 (C-1), 110.52 (C-8), 111.83 (C-5a)[a], 116.11 (C-10), 117.09 (C-9a)[a], 129.33, (C-4a)[a], 130.11 (C-10a)[a], 160.18 (C-5)[c], 160.38 (C-7)[c], 184.11 (C=O), and 184.74 (C=O) (assignments with the same superscript may be interchanged); *m/z* 288 (M^+, 16%) 273 (48), 255 (5), 244 (100), 229 (13), 215 (15), 214 (8), 189 (4), 159 (8), 145 (5), 115 (7) and 77 (6).

***<u>trans</u> 5-Benzyloxy-7-hydroxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran-6,9-dione* (269)**



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The quinone **266** (300 mg, 0.83 mmol) was dissolved in warm ethyl acetate (100 ml) and cooled to 25°C. Pd/C (10% wt/c) catalyst (90 mg) was added together with two drops of concentrated hydrochloric acid and the mixture was stirred under an atmosphere of hydrogen until 2 molar equivalents of hydrogen had been absorbed. The reaction mixture was filtered and evaporated to afford a clay like residue. This was carefully recrystallised from ethanol to afford fine olive yellow

crystals of the quinone **269** (100 mg, 33%), mp 195 – 196°C; (Found: C, 72.91; H, 5.63; $C_{22}H_{20}O_5$ requires: C, 72.53; H, 5.53%); (Found: HRMS, 364.13116. $C_{22}H_{20}O_5$ requires 364.13107) $\nu_{max.}$ 3550 cm^{-1} (OH), 1667 cm^{-1} (C=O); $\lambda_{max.}$ 258 (Є 4.18), 281 (Є 4.19) and 355 (Є 3.52); δ_H 1.29 (3H, d, *J* 6.2, 3-CH_3), 1.56 (3H, d, *J* 6.6, 1-CH_3), 2.36 (1H, dd, *J* 17.4 and 9.2, pseudoaxial H-4), 2.89 (1H, dd, *J* 17.4 and 3.2, pseudoequatorial H-4), 3.94 (1H, m, H-3), 4.92 (1H, d, *J* 10.2, C*H*$_2$Ph), 5.00 (1H, d, *J* 10.2 C*H*$_2$Ph), 5.07 (1H, q, *J* 6.6, H-1), 6.32 (1H, s, H-8), 7.41 (3H, m, H-3', H-4' and H-5' of aryl ring), 7.52 (2H, m, H-2' and H-6' of aryl ring) and 7.69 (2H, bs, H-10 and 7-OH which is D_2O exchangeable); δ_C 21.20 (CH_3), 21.51 (CH_3), 30.81 (C-4), 63.60 (*C*H_2Ph), 70.80 (C-3), 76.00 (C-1), 109.20 (C-8), 120.51 (C-10), 128.50 (C-3' and C-5')[a], 128.71 (C-2' and C-6')[a] 128.73 (C-4')[a], 132.60 (C-1'), 135.40 (C-10a and C-4a)[b], 136.70 (C-9a)[b], 149.41 (C-5a)[b], 156.91 (C-5)[c], 157 50 (C-7)[c], 180.31 (C=O) and 184.62 (C=O); *m/z* 364 (M^+, 66%), 349 (4), 336 (5), 320 (5), 292 (10), 273 (7), 259 (12), 230 (26), 201 (3), 115 (9), 91 (100) and 95 (28).

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