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A model route to a brominated hydroxy[2,3-c]pyran- a potential precursor to extended quinones

Mawonga N. Mei
Cape Peninsula University of Technology

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by

Mawonga N. Mei
BSc Hons, (Chemistry), (University of the Western Cape)

A thesis submitted in fulfilment of the requirements for the degree Magister Technologiae (Chemistry) in the Faculty of Applied Sciences, Department of Chemistry, Cape Peninsula University of Technology.

Supervisor: Prof. V. Hugo

Nov. 2008

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Declaration

I, Mawonga Newton Mei, declare that the contents of this thesis represent my own unaided work, and that the thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the Cape Peninsula University of Technology.

Signed Date

Abstract:

Green *et al*. attempted to synthesize linear naphthopyranquinones from a naphthyl dioxolane using a $TiCl_4$ as a catalyst. They managed to synthesise an angular naphthopyran as well as a linear naphthopyran in low yield. They showed that reducing the steric strain at position 1 of the naphthyl dioxolane afforded a low percentage yield of the linear naphthopyran plus an angular one.

This thesis describes the synthesis of linear naphthopyrans with an improved percentage yield using $TiCl_4$ as a catalyst. This was achieved by placing a OMe group of less steric hinderance at position 1 and a Br atom at position 4 of a naphthyl dioxolane. The OMe group at position 1 was to allow isomerisation to occur at position 2, and the Br atom was to inhibit isomerisation at position 4, thereby inhibiting the formation of the angular naphthopyran.

Acknowledgements:

I would like to thank the All Mighty for giving me strength and patience to complete my studies.

I would like to thank my supervisor Prof. Victor Hugo for his time, support, guidance and advice throughout these years.

My thanks also go to Prof. Ivan Green for his help and advice and to UWC Chemistry Department for allowing me to make use of the facilities at the Chemistry Department.

Thanks also to my friends and colleagues at CPUT and UWC for their assistance.

I would like to thank Wendell at UWC & Martin at Wits for their assistance in analysing my samples.

Many thanks to my family, brothers and sisters for their support, love, patience and encouragement over the years to complete my studies.

The financial assistance of CPUT and the Canon Collins Trust towards this research is acknowledged. Opinions expressed in this thesis and the conclusions arrived at, are those of the author, and are not necessarily to be attributed to the CPUT and Canon Collins Trust.

Abbreviations:

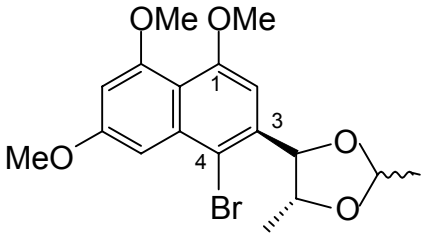
Ac_2O	- acetic anhydride
AcOH	- acetic acid
BnBr	- benzyl bromide
BuLi	- butyl lithium
Br	- bromine
$CH_3CH_2\overset{\oplus}{P}Ph_3\overset{\ominus}{Br}$	- ethyltriphenylphosphonium bromide
°C	- degrees Celcius
DCM	- dichloromethane
DDQ	- dichlorodicyanobenzoquinone
DMF	- dimethyl formamide
DMSO	- dimethylsulfoxide
EtOAc	- ethyl acetate
$Fe_2(CO)_9$	- diiron nonacarbonyl
Hex	- hexane
HCl	- hydrochloric acid
H_2SO_4	- sulphuric acid
IR	- infra red
KBr	- potassium bromide
K_2CO_3	- potassium carbonate
KOH	- potassium hydroxide
LAH	- lithium aluminium hydride
Me	- methyl group
MeI	- methyl iodide/iodomethane
MeOH	- methanol
m-CPBA	- *meta*-Chloroperbenzoic acid
Mg_2SO_4	- magnesium sulphate
MnO_2	- manganese dioxide
Mp	- melting point
Ms	- mass spectra
N_2	- nitrogen.
NaCl	- sodium chloride
NaH	- sodium hydride
NaOAc	- sodium acetate
NMMO	- N-methyl morpholine N-oxide
NMR	- nuclear magnetic resonance

OMe	- methoxy group
OsO_4	- osmium tetroxide
Pd/C	- palladium on activated carbon
$PdCl_2.(CH_3CN)_2$	- *bis*(acetonitrile)dichloropalladium(II)
Pyr	- pyridine
THF	- tetrahydrofuran
$TiCl_4$	- titanium tetrachloride
Tlc	- thin layer chromatography
TsOH	- toluene-p-sulphonic acid

Chapter 1:

Research aim and objectives:

The aim of my research was to synthesize linear naphtho[2,3-*c*]pyrans **2** and **3,** from a dioxolane **1** with a OMe group at position 1 and a Br atom at position 4. The Br was to prevent isomerization occurring at position 4, and the OMe group was to allow isomerization to occur at position 2, due to its less steric effect , compared to an isopropoxy group in previous attempts (refer to scheme 1).



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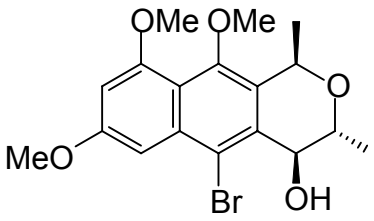

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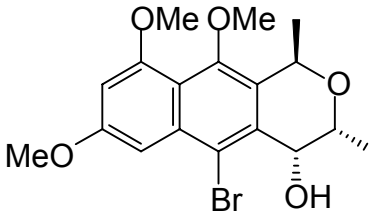
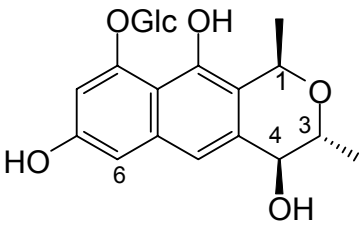


3

A further aim was to develop a model route to some linear naphtho[2,3-*c*]pyranquinones, related to glucoside B **4** (a constituent of the protoaphins, linked to quinone A **5** or A′ **6** via the C-6 atom). We foresee that further investigations in our laboratories using the methodology for the synthesis of **2** and **3** could afford compounds **4**, **5** and **6**, or their derivatives.



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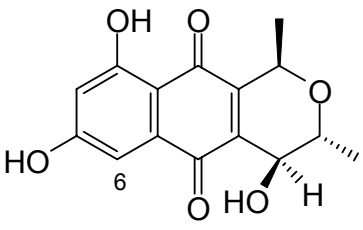

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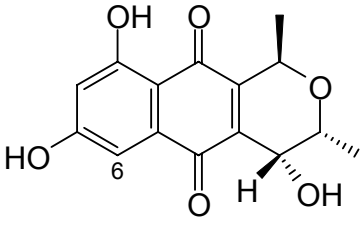


6

We also envisage that compounds **2** and **3** could lead to extended quinones of the type **13** and **14** on page 4.

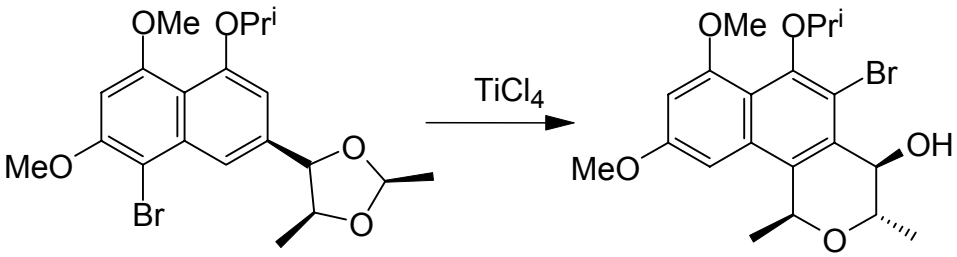
Chapter 2:

Introduction and background:

Previous experiments in the synthesis of linear naphthopyrans resulted in angular naphthopyrans.[23,28] Other experiments gave linear naphthopyrans with very low yields (scheme 2). In this research it is intended to replace the isopropoxy group at position 1 of the naphthyl dioxolane with a methoxy group, to offer less steric hindrance and to place a Br atom at position 4 to inhibit angular naphthopyran formation.

The naphthopyranquinones have a wide range of biological activities, for example, they are bioreductive alkylating agents[45] and are believed to cross-link the complementary strands of cellular DNA thereby inhibiting tumour growth/bacterial multiplication.
The naturally occurring naphthopyranquinones are obtained in minute quantities, this restricts studies of their mode of action, and therefore laboratory routes to such compounds or their derivatives are important.
The naphthopyranquinones are important subunits of antibiotics. Antibiotics are natural substances produced by certain microorganisms. In medicine they are used to kill/inhibit the growth of bacteria.

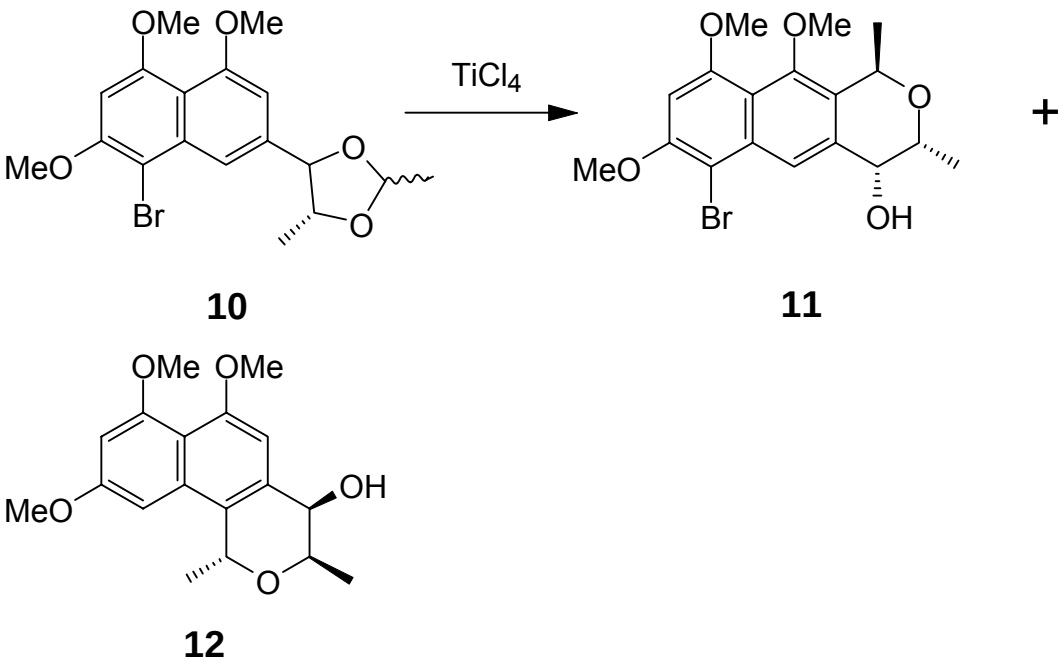
In the past Giles *et al.*[23] treated a 5-bromo dioxolane **8** with a powerful Lewis acid to derive the angular naphthopyran **9** (scheme 1).



8 **9**

Scheme 1:

Green *et al*.[32] demonstrated that reducing the steric environment at position 1 of the naphthyldioxolane afforded a very low yield of the linear naphthopyran **11** (scheme 2). The yields were based on their acetates, 13.0 % for naphthopyran **11** and 28.0 % for naphthopyran **12**.



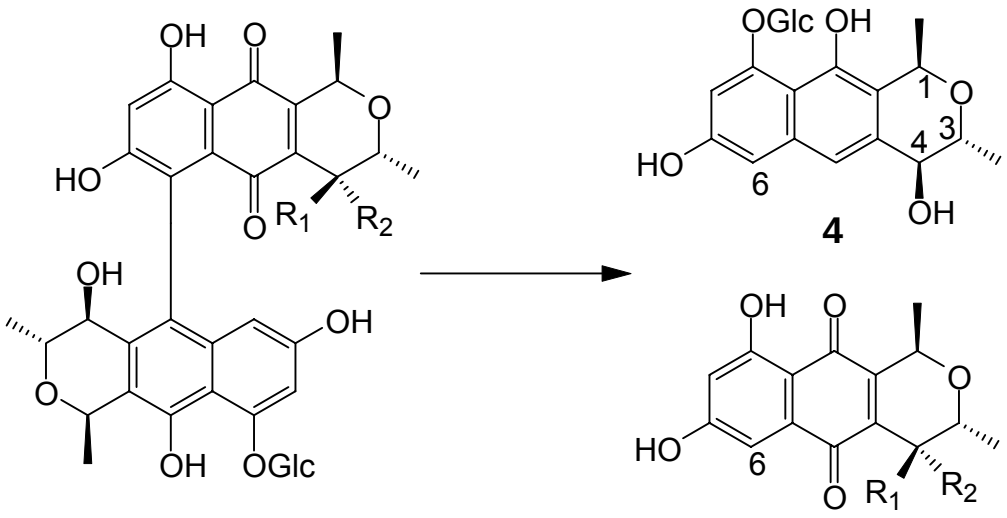
10 **11**

12

Scheme 2:

Naphtho[2,3-*c*]pyrans and their quinones form an extensive group of natural products which possess biological and pharmacological activities.[6,29,49] The synthesis of such naphthopyranquinones has received significant interest because a number of natural products possess this subunit.

Reductive cleavage of the aphid insect pigments the protoaphins-*fb* **13** and –*sl*[9,10] **14** afford glucoside B **4** in each case, and for the former quinone A **5** and for the latter quinone A′ **6** as shown in scheme 3. The deoxyprotoaphin **15** gives rise to the deoxyquinone A **7**[28] (scheme 3).



13 R_1 = OH R_2 = H **5**

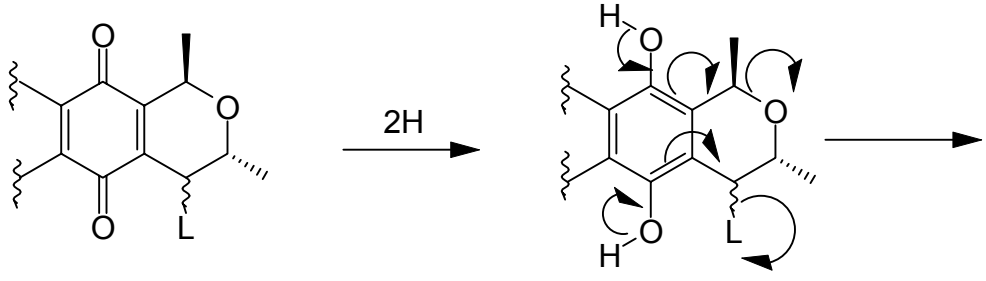
14 R_1 = H R_2 = OH **6**

15 R_1 = R_2 = H **7**

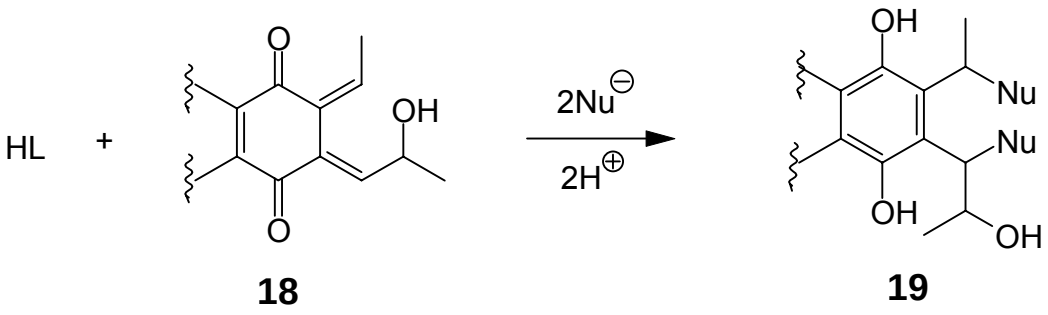
Scheme 3:

2.1. Bioreductive alkylation:

Bioreductive alkylating agents are compounds that become potent alkylating agents after undergoing a reduction *in vivo*. Such compounds may then alkylate DNA or RNA strands, resulting in effective cancer-inhibitory drugs. In 1977 Moore[45] proposed a mechanism for the biological activity of the pyranquinones, based on work done by Sartorelli,[43] e.g, **16** will undergo reduction *in vivo* to the quinol **17** which could open the ring as in scheme 4 to yield an active *bis*quinone methine **18**. This compound could then react with nucleophilic centres in DNA and RNA strands to modify the natural structures to compound **19**, thereby inhibiting tumour growth or bacterial multiplication.[36]



16 **17**



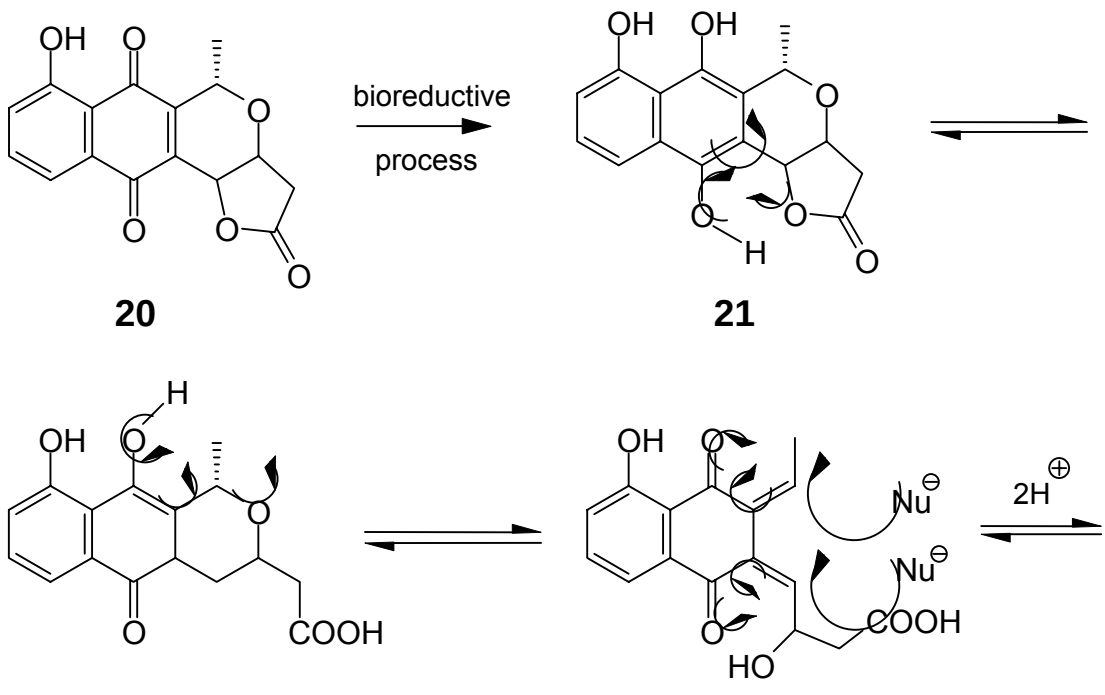
18 **19**

Scheme 4:

Hugo *et al.*[36] suggested that the most important structural feature for biological activity in such compounds is the aryl[2,3-*c*]pyranquinone nucleus and that a leaving group L at position 4 of the pyran ring would increase the activity.

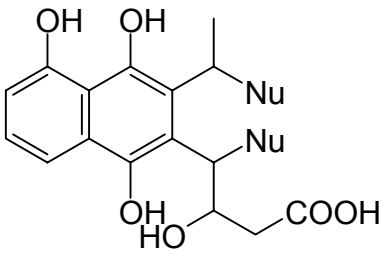
Nanaomycin D **20** containing the fused pyrano-*delta*-lactone moiety is biologically inactive but can be transformed by reduction *in vivo* to an active hydroquinone which functions as a *bis*-alkylating agent as in scheme 5.[51]

The quinone **20** is reduced *in vivo* to the hydroquinone **21** which undergoes two ring opening steps to afford the quinone methide **23** which could act as a Michael-type nucleophile (Nu^-) acceptor, that may be nucleophilic centres in the DNA and RNA strands thereby binding the nucleic acid as in **24**, preventing replication and cell growth.



20 **21**

22 **23**



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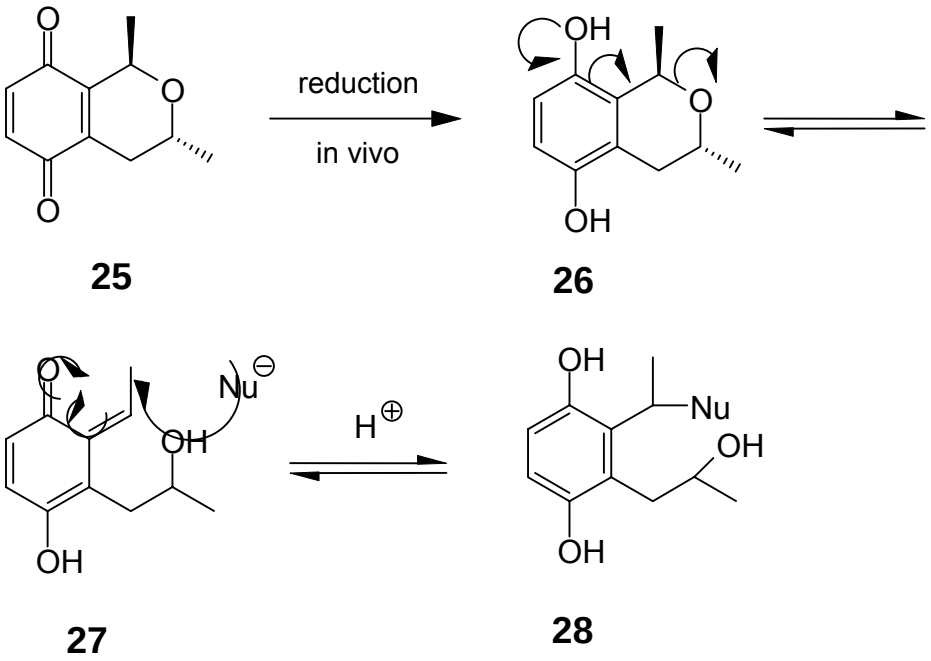
Scheme 5:

Benzo[*c*]pyranquinones[51] may have a similar behaviour to their naphthalene analogues and be able to act as bioreductive alkylating agents by the mechanism of quinone methide formation proposed in scheme 6.



25 **26** **27** **28**

Scheme 6:

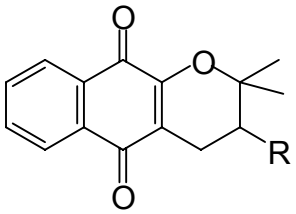
Moore[45] has listed a number of different examples of possible bioreductive alkylating agents such as mitomycin C, kinamycin C, anthracyclines and related compounds, nanaomycin D and related compounds, etc. etc..

Chapter 3:

Some naturally occurring antibiotics :

There are biologically active quinones found in nature that contain the naphtho[2,3-*b*]pyran ring system as part of their structures,[27] compared to the quinones of the present study. An example of these are *alpha*-lapachone[8] **29**, rhinacanthin-A[53] **30,** rhinacanthin-B[49] **31**, lambertillin[13] **32** and erythrostominone **33.**[14,16]

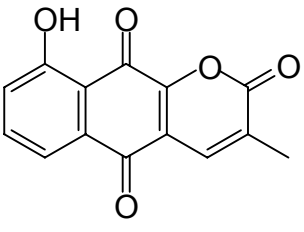
It has long been suspected that the pyran ring plays an important part in the biological activity of naphthopyranquinones and this was demonstrated by synthesizing and testing a wide range of benzo[*c*] pyranquinones.[16, 30]



29 R= H

30 R= OH

31 R= $OCOC(Me)=CHCH_2CH_2C(Me)=CHCH_3$



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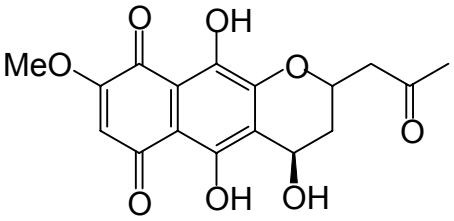
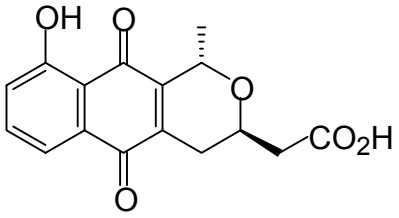


33

The concept of bioreductive alkylation proposed by Moore[45] and earlier work by Sartorelli[43] played a role towards this suspicion. Substitutions in the pyran ring have been shown to improve the naphthopyranquinones biological activities.[3,27] An example is the placement of the OH group at position 4 and the acetoxy group at position 2 in the erythrostominone analogues' pyran ring.[3]

Another class of biologically active quinones found in nature is that which contains the naphtho[2,3-*c*]pyran ring system as part of their structures. In 1995 Green *et al.*[30] reported a convenient synthetic route to antimicrobial benzo[*c*]pyranquinones, in which a general strategy was developed for the synthesis of benzo[*c*]pyran ring systems which were considered to be appropriate for microbial testing. They obtained encouraging results which led them to extend the methodology to include the naphthopyran ring systems.

The nanaomycins A **34** and D **35**, griseusin A **36** and granaticin **37** are antimicrobial agents.[39] The nanaomycins were reported to have excellent activities against mycoplasmas.[48] The first total synthesis of racemic nanaomycins was achieved in 1978.



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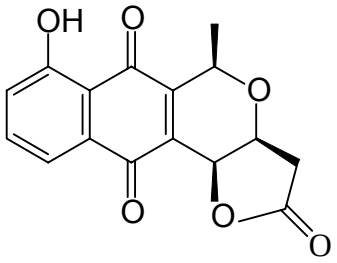

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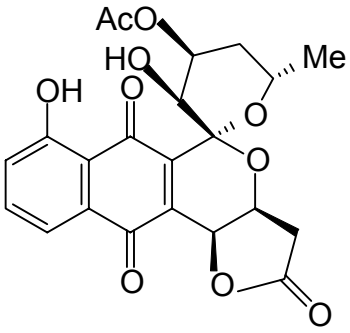

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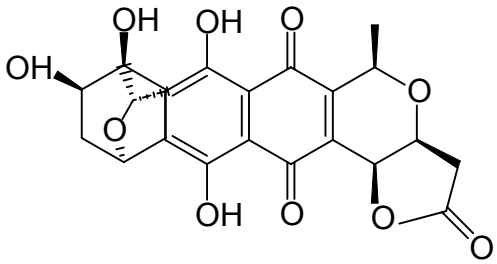
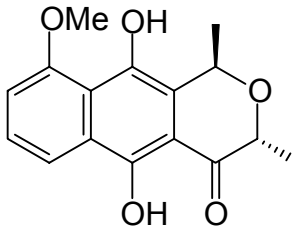


37

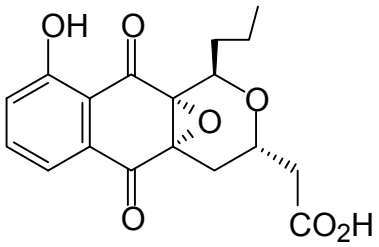
Hongconin **38** was isolated from the rhizome of Eleutherine Americana Merr. Et Heyne (Iridaceae), a herbal plant from southern China which has been used as a medicine.[41] Its structure was determined in 1986 and its natural occurrence is low, therefore generally the availability of these naphthopyranquinones for more testing is dependent on the development of a direct synthetic route. It has been shown to exhibit activity against angina pectoris in limited clinical trials.[34]



38

Kraus *et al.*[40,41] synthesized racemic hongconin with a low overall yield. In 1996 Green *et al*.[31] reported the synthesis of the hongconin with an improved yield.

Frenolicin **39**, and kalafungin **40** have been shown to be extremely active against Gram-positive bacteria, mycoplasmas and fungi.[50] They have a benzoisochromanquinone skeleton which plays an important role in the appearance of bioactivity. It has been suggested that *in vivo* reduction causes a transformation to an active hydroquinone form which functions as a *bis*-alkylating agent. Moore[45] suggested that these naphthopyranquinones may exhibit antitumour activity since the proposed mechanism of action resembles that of alkylating antibiotics such as the mitomycins. Uno *et al*. [50] have established an efficient synthetic route to a series of these naphthopyranquinones antibiotics.



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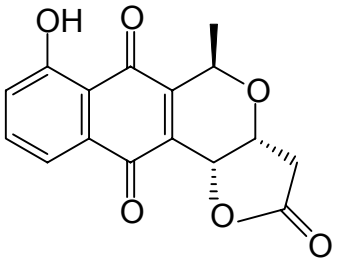

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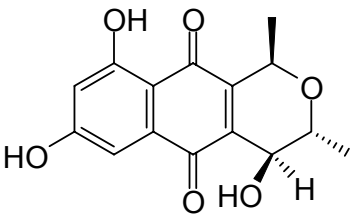
Chapter 4:

Some literature methods for the synthesis of naphthopyrans and benzo[*c*]pyranquinones.

4.1. The synthesis of the aphid pigment (Protoaphins) derivatives.[15]

In 1988 Elsworth *et al*.[15] described the racemic synthesis of Quinone A **5**, Quinone A' **6** and Deoxyquinone A **7** (scheme 7-11).



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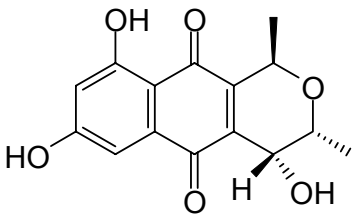

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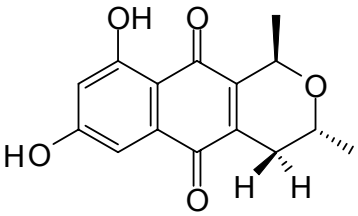
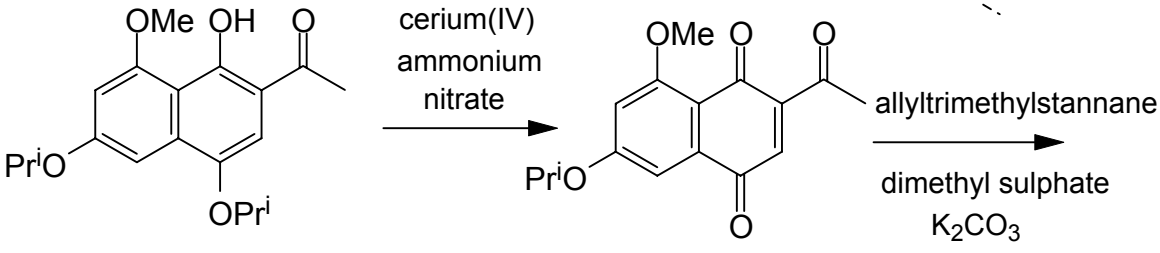
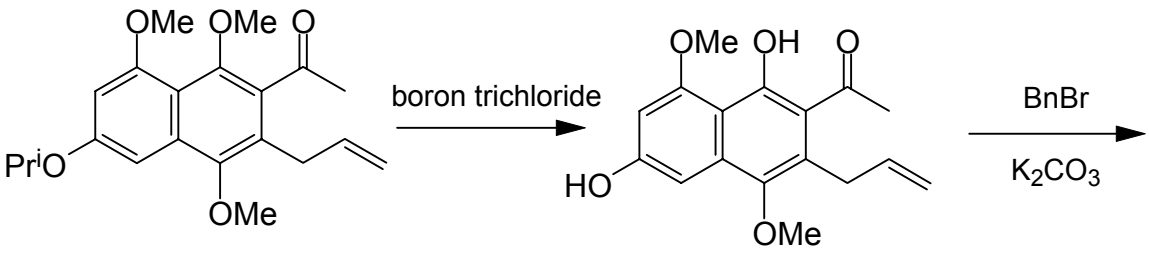


7

The naphthol **41** was oxidised to afford the quinone **42** which was allylated with allyltrimethylstannane in the presence of boron triflouride, the resultant crude adduct was methylated with dimethyl sulphate and K_2CO_3 in acetone to yield the allylnaphthalenone **43** in an overall yield of 61.0 %. The methyl from oxygen *ortho* to the acetyl group was removed by reacting the naphthalene **43** with boron trichloride in DCM at -78 °C, and the isopropoxy group was smoothly cleaved at 0 °C to afford the compound **44**.



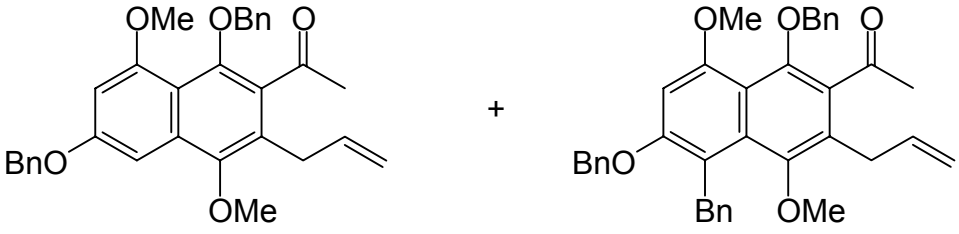
41 **42**



43 **44**

Scheme 7:

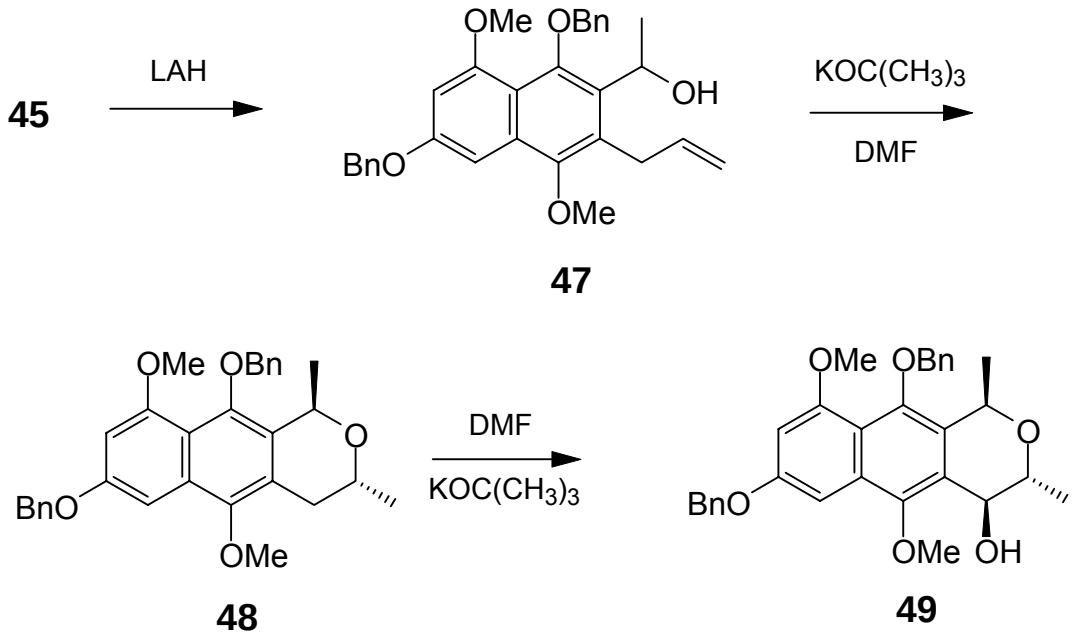
The compound **44** was treated with BnBr and anhydrous K_2CO_3 in acetone to yield the dibenzyl ether **45** as a major product together with the minor product of the C-benzyl derivative **46** (9.0 %).



45 **46**

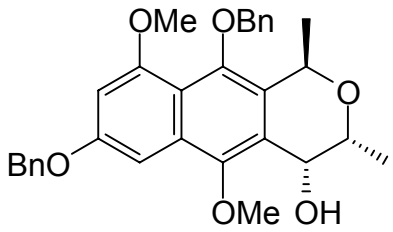
Scheme 7 cont.:

Compound **45** was then reduced by treating it with LAH to afford the alcohol **47**, which was cyclised with potassium *tert*-butoxide in dry DMF[18,19] to afford the *trans*-1,3-dimethylnaphtho[2,3-*c*]pyran **48** in 97.0 % yield. This naphthopyran **48** was oxygenated in DMF containing potassium *tert*-butoxide in the presence of air[[18,19] to yield the C-4 *pseudo*equatorial hydroxyderivative **49** in a 41.0 % yield, plus the *pseudo*axial epimer **50** as a minor product (5.0 %).



48 **49**

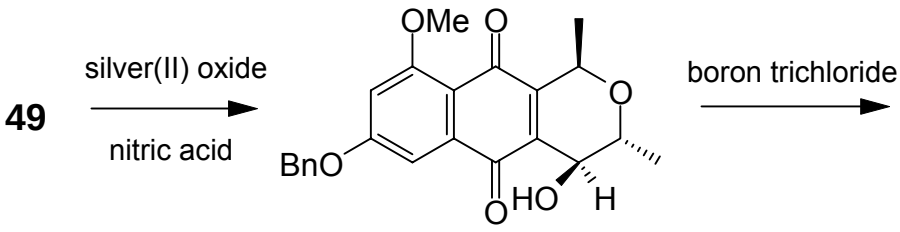
+



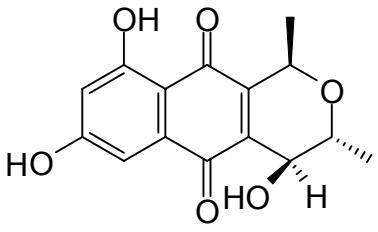
50

Scheme 8:

The naphthopyran **49** was oxidized with silver(II) oxide in 6M nitric acid to afford the 5,10-quinone **51** which was then deprotected with an excess of boron trichloride to remove the O-methyl and O-benzyl groups, to afford Quinone A **5.**



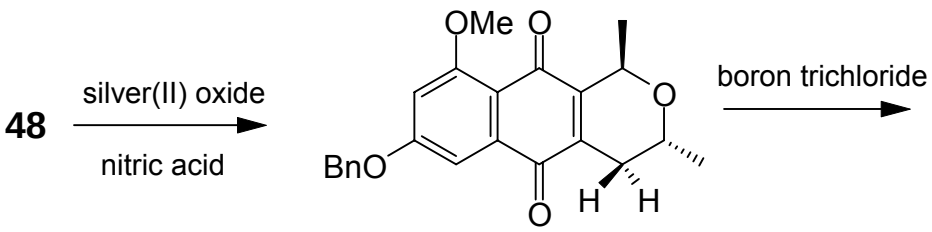
51



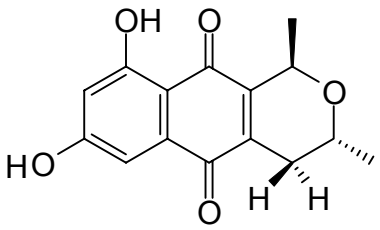
5

Scheme 9:

The naphthopyran **48** was subjected to oxidation by treating it with silver(II) oxide[47] in 6M nitric acid to afford the 5,10-quinone **52** in 86.0 % yield, after which it was deprotected to yield the deoxyquinone A **7.**



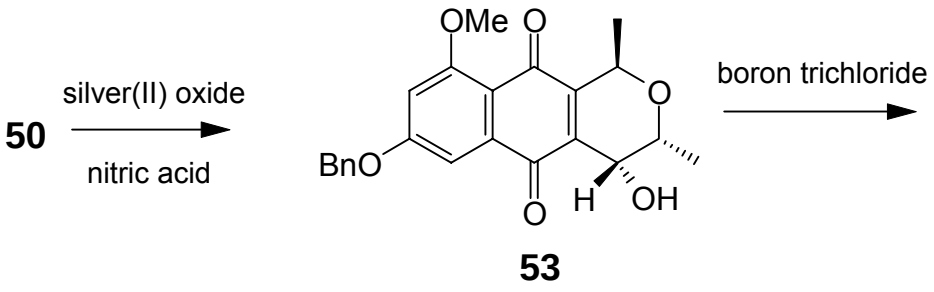
52



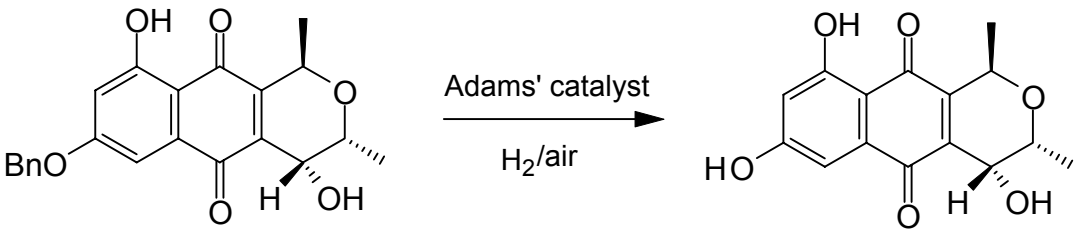
7

Scheme 10:

More of the compound **50** was synthesized to convert it into the quinone **53** by treating it with silver(II) oxide. This quinone was then demethylated with boron trichloride using 2 mole equivalents to give the Quinone A' benzyl ether **54** which was hydrogenolysed to yield the Quinone A' **6**.



53

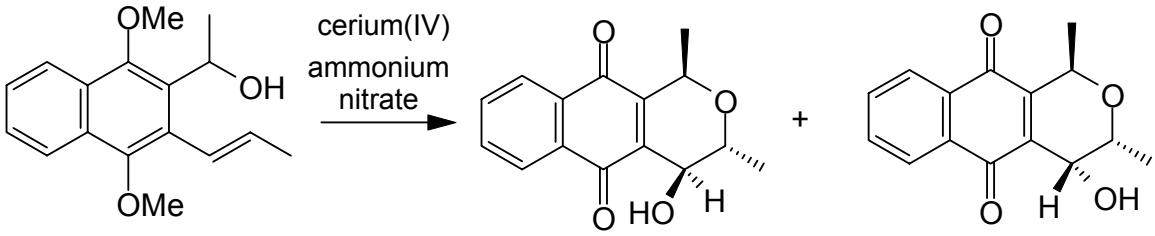


54 **6**

Scheme 11:

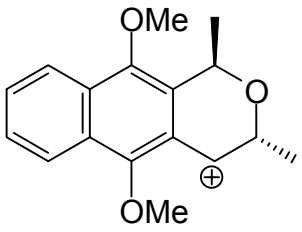
The above synthetic racemates were similar to the naturally derived products of Quinone A, Quinone A' and Deoxyquinone A in respect of their tlc behaviour, and their IR and proton NMR spectrums were closely similar.

The first synthesis[10] of the derivatives of Quinone A and A' involved the oxidative cyclisation with cerium(IV) ammonium nitrate of the naphthalene **55** affording the 7,9-dideoxy derivatives **56** and **57** respectively (scheme 12)



55 **56** **57**

Scheme 12:

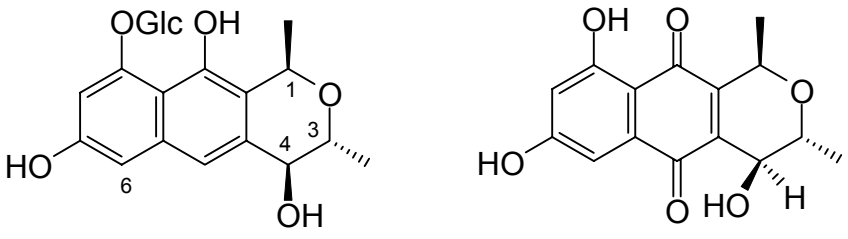


58

It was suggested that the carbocation **58** acted as an intermediate which was attacked by the nucleophile water, to yield the two naphthopyrans epimeric at position 4. The *pseudo*axial compound predominated and gave rise to the Quinone A' analogue **57** (major product) after oxidative demethylation, this was favoured because the *peri*-interactions with the neighbouring OMe group were less than in the alternative *pseudo*equatorial alcohol **56**.

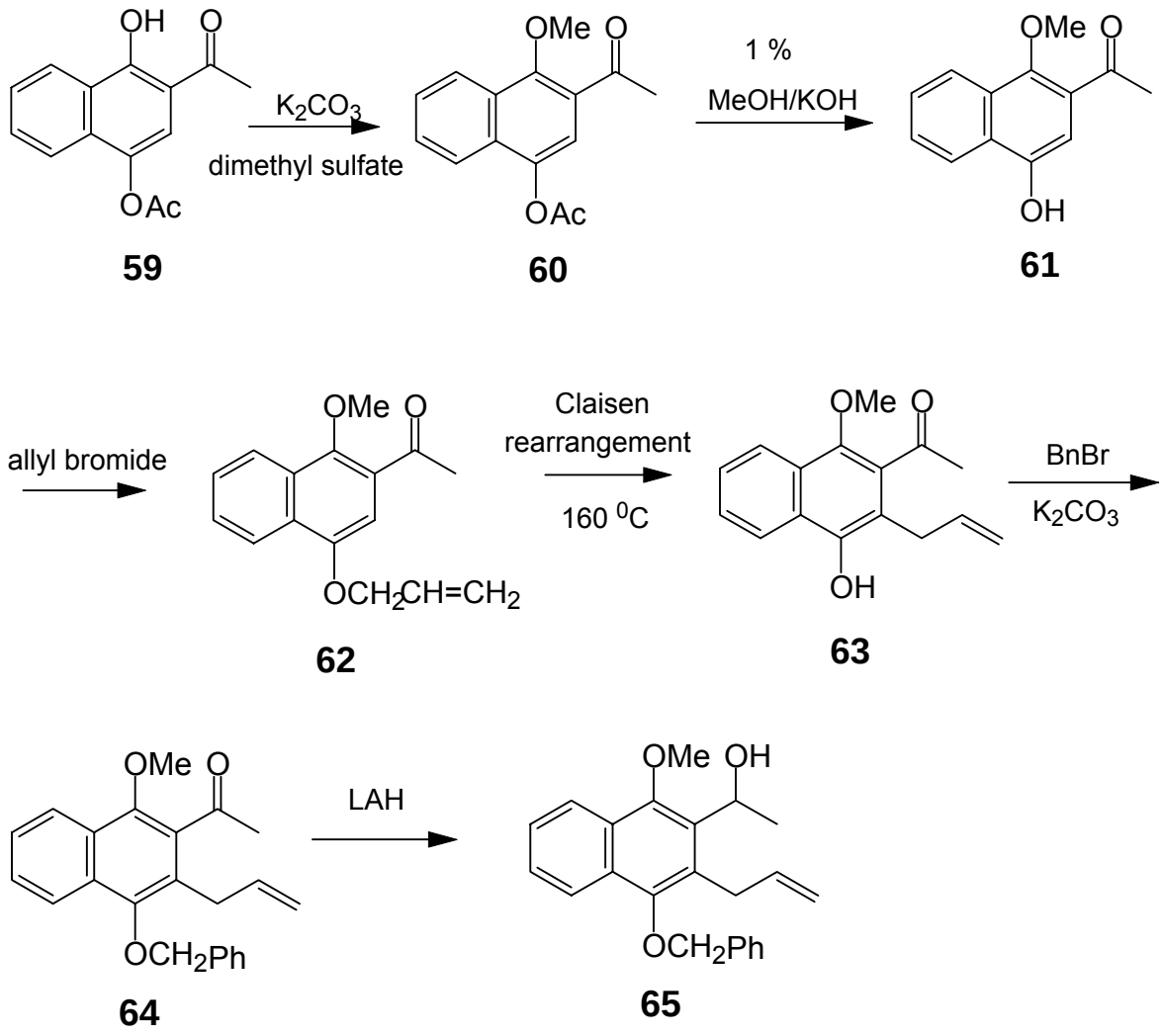
4.2. The conversion of naphthalenic precursors into naphthopyrans.[22]

The racemates of the three quinones **5**, **6** and **7** (scheme 3) were synthesised by Elsworth *et al*.[15] in 1988. In 1994 Giles *et al*.[22] investigated the possibility of assembling Glucoside B **4**, which possesses the same substitution and stereochemistry about the pyran ring as Quinone A **5**.



4 **5**

The main structural difference between Glucoside B **4** and Quinone A **5** is the absence of oxygen at position 5 in the former.



59 **60** **61**

62 **63**

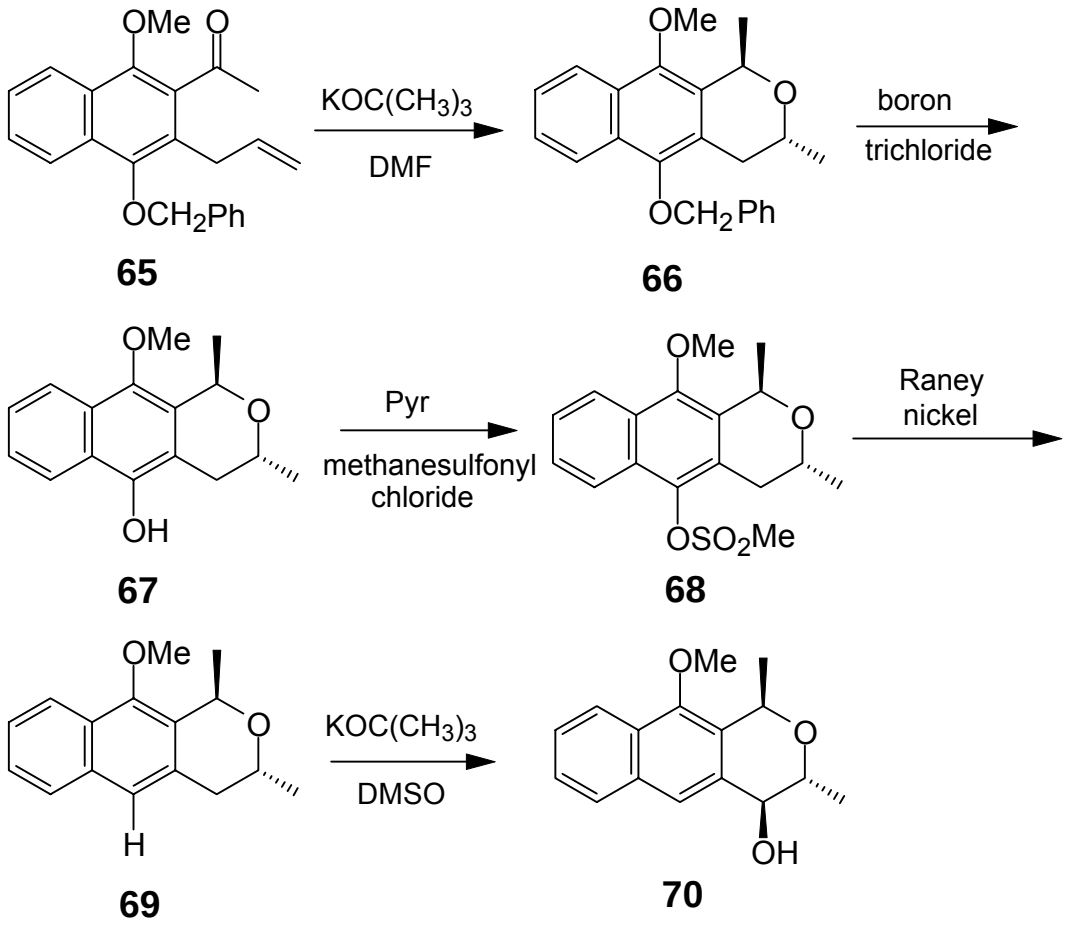
64 **65**

Scheme 13:

The starting material in Scheme 13, the naphthol **59**, was smoothly methylated with a dimethyl sulfate to afford the methyl ether **60**. The acetate group of this product was hydrolysed to yield the naphthol **61**, which was allylated with allyl bromide to give rise to the allyl ether **62**. This ether was subjected to a Claisen rearrangement at 160 °C to afford the C-allylnaphthol **63** as an unstable oil. The transformation was confirmed *inter alia* by the expected corresponding upfield shift in the H^1 NMR spectrum of the allyl methylene protons from *delta* 4.72 in **62** to *delta* 3.42 ppm in **63**. The naphthol **63** was immediately treated with benzyl bromide to form the benzyl ether **64** which was reduced with LAH to alcohol **65.** All the steps from naphthol **59** to product **65** were of high yield, and that for the overall process being 42.0 %.

In scheme 14 the alcohol **65** was treated with an excess of potassium *tert*-butoxide in dry dimethylformamide, under N_2, at room temperature, to yield the *trans*-naphthopyran **66** in a good yield of 72.0 %. Its benzyl group was removed by treating it with 2 equiv. of boron trichloride to afford the unstable phenol **67**. This compound was then converted to the

methanesulfonate ester **68** by reacting it with methanesulfonyl chloride and pyridine. Ester **68**'s structure was supported by the H^1 NMR spectrum in which there was a new methyl singlet at *delta* 3.38 ppm for the methanesulfonate group, and in its IR spectrum there were two absorption bands at 1339.01 and 1167.02 cm^{-1}, characteristic for this substituent.



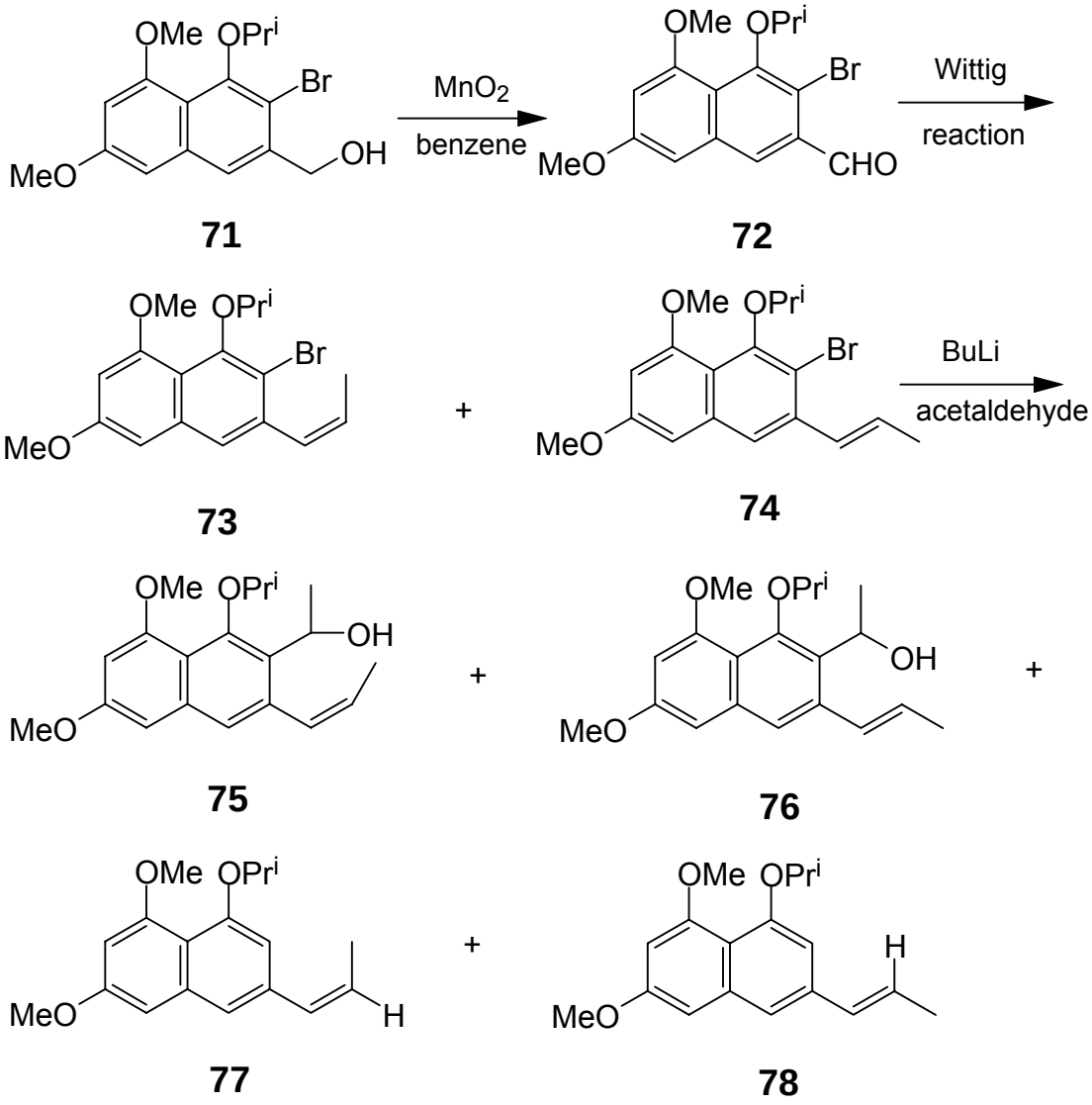
Scheme 14:

The aryl-oxygen bond of product **68** was selectively cleaved using the Raney nickel catalyst which left the sensitive benzylic C-O bond untouched, which was further activated in compounds **68** and **69** by the *peri*-methoxy substituent. Compound **69** was obtained with a reasonable yield of 66.0 % on using the solvent mixture, ethanol and water, in a ratio of 3:1. The *trans*- stereochemistry was confirmed by the characteristic appearance[15,17] of the new 3-H multiplet at *delta* 3.98-4.36 ppm and the 1-H quartet at *delta* 5.34 ppm in the H^1 NMR, while the presence of the derived C-5 proton was established by a one-proton singlet at *delta* 7.38 ppm.

Compound **69** was then dissolved in oxygenated dimethyl sulfoxide and treated with potassium *tert*-butoxide at room temperature to yield 67.0 % of the alcohol **70**. Oxygenations that were carried out on substrates carrying 5-methoxy substituents gave rise to both the

corresponding *pseudo*equatorial and *pseudo*axial C-4 epimeric alcohols. In the conversion of compound **69** to alcohol **70** no alternative *pseudo*axial alcohol was observed. This might be because of the absence of the *peri*-methoxy group at C-5, offering a less crowded reaction site.

Therefore the obtained alcohol **70,** had the stereochemistry required for Glucoside B **4**.

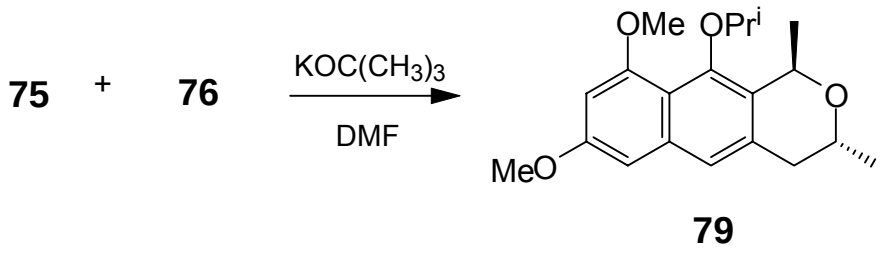


71 **72** **73** **74** **75** **76** **77** **78**

Scheme 15:

In another conversion the alcohol **71**[21] (scheme 15) was subjected to oxidation and yielded the corresponding aldehyde **72**, which was treated with ethylidene(triphenyl)phosphorane (Wittig reaction) to afford a mixture of the *cis*- and *trans*-olefins **73** and **74**. The mixture of these alkenes was treated with BuLi followed by acetaldehyde to yield the mixture of *cis*- and *trans*-olefinic alcohols **75** and **76**, plus a mixture of the debrominated isomeric olefins **77** and **78** as minor by-products.

On treating the mixture of the olefinic alcohols **75** and **76** with potassium *tert*-butoxide in dimethylformamide under N_2, a high yield of the naphthopyran **79** (83.0 %) in scheme 16, was obtained, as a single stereoisomer, thereby confirming that the stereochemistry of the product was not determined by that of the starting material. The *trans*-stereochemistry was confirmed by the chemical shifts of the 3-H and 1-H protons in the H^1 NMR spectrum, whose values were very close to those of the related naphthopyran **69**. The C-5 aromatic singlet was at *delta* 7.12 ppm.

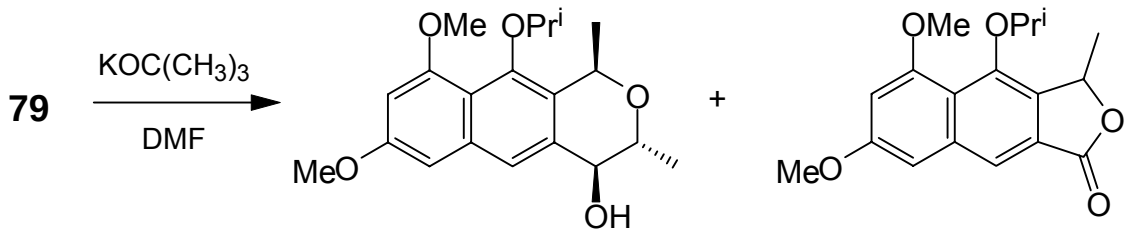


79

Scheme 16:

There was no yield advantage on performing the ring closure to naphthopyran **79** using stereochemically pure *trans*-olefinic precursors. These were obtained by conversion of the mixture of bromo olefins **73** and **74** into pure *trans*-olefin **74** in high yield of 90.0 %. This was achieved by treating the two olefins with *bis*(acetonitrile)dichloropalladium(II).[20] The pure bromo olefin **74** was converted into pure *trans*-olefinic alcohol **76** together with the pure compound **80** as a minor by-product. The product **76** was in turn, converted into the naphthopyran **79** in a yield of 83.0 % as before.

The naphthopyran **79** was then treated with potassium *tert*-butoxide to afford the alcohol **80** and the lactone **81** (scheme 17). Based on the unrecovered starting material the percentage yield of the *pseudo*equatorial alcohol **80** was 46.0 %.



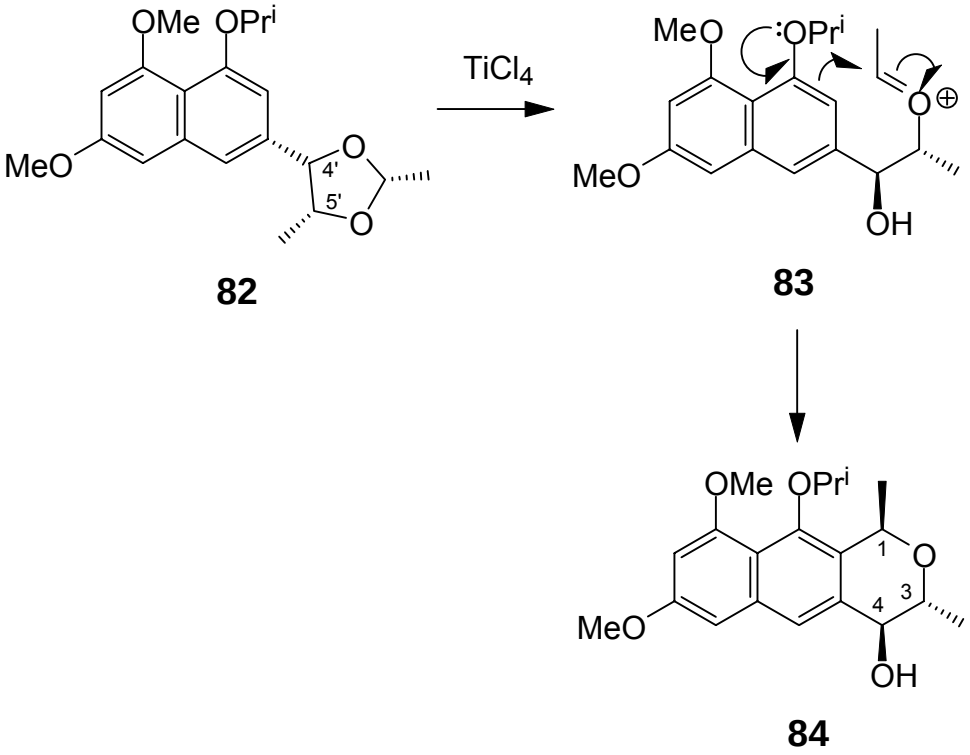
80 **81**

Scheme 17:

These experiments showed avenues and limitations to the assembly of products **70** and **80**.

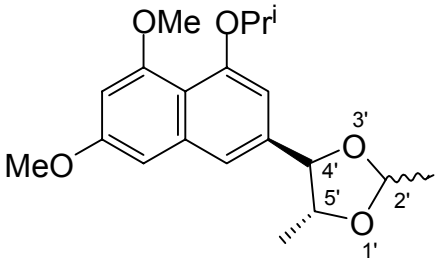
4.3. The formation of angular naphtho[3,4-*c*]pyrans.[23]

The synthesis of naphthopyrans related to the aphin derived Glucoside B **4** led Giles *et al*.[23] to the formulation of a new strategy for the construction of naphthopyrans through the stereoselective isomerisation of naphthyldioxolanes using $TiCl_4$ as a catalyst.

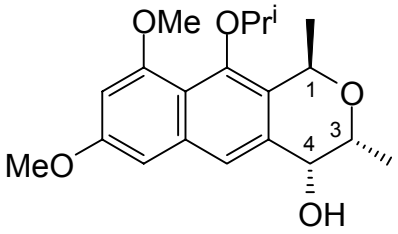


Scheme 18:

Scheme 18 depicts the desired isomerization in which the stereochemistry at C-4 and C-5 in the dioxolane **82** determines that established at C-3 and C-4 in the product naphthopyran **84**. The C-1 methyl in the naphthopyran **84** was expected to assume the *pseu*doaxial orientation through the intermediacy of the planar oxocarbenium ion **83** in order to minimize *peri* interaction with the neighbouring isopropoxy substituent. The C-10 oxygen was protected by the isopropyl group. It was intended to selectively remove it with boron trichloride and oxidise the derived phenol to the racemate of the dimethyl ether of Quinone A **5**[18] to confirm the structure of product **84** including the relative stereochemistry. The naphthyldioxolanes **85** were the synthetic targets because their relative stereochemistry at C-4 and C-5 which was deemed the easiest to construct, even though it was appreciated that the derived naphthopyran **86** , if formed, would have had the incorrect stereochemistry for the C-4 OH group of Glucoside B **4** (scheme 19).



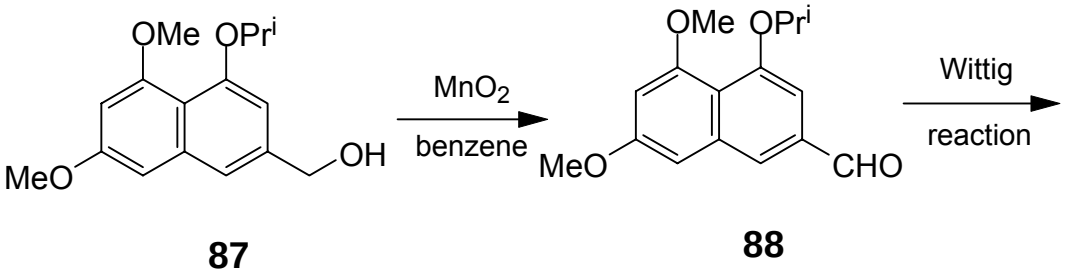
85



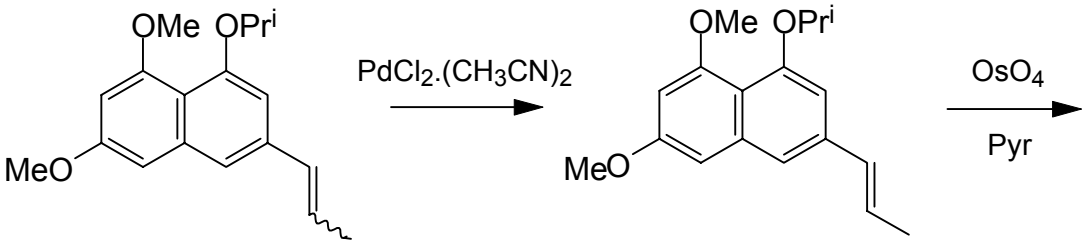
86

Scheme 19:

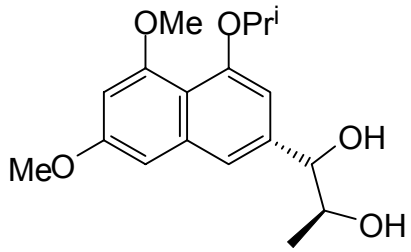
The alcohol **87** was subjected to oxidation using MnO_2 to afford the aldehyde **88**. This was then treated with ethylidenetriphenylphosphorane in a Wittig reaction to yield a stereochemical mixture of the olefins **89** which were reacted with *bis*(acetonitrile)dichloropalladium(II) to afford the *trans*-isomer **90** as the sole product in high yield. The pure olefin in pyridine was reacted with OsO_4 in ether to afford the single racemate of the diol **91** in high yield (91.0 %) (scheme 20).



87 **88**



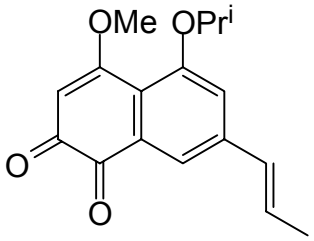
89 **90**



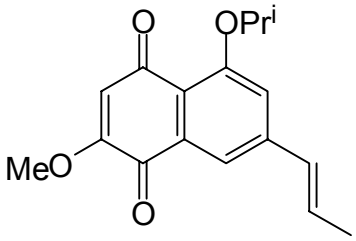
91

Scheme 20:

The attempts to convert the *trans*-olefin **90** into the corresponding epoxide failed when *meta*-chloroperbenzoic acid was used. Several products were formed, two of those were separated by chromatography from the mixture and gave rise to the 1,2- and 1,4-naphthoquinones **92** and **93**, in 13.0 and 10.0 % yields respectively.



92

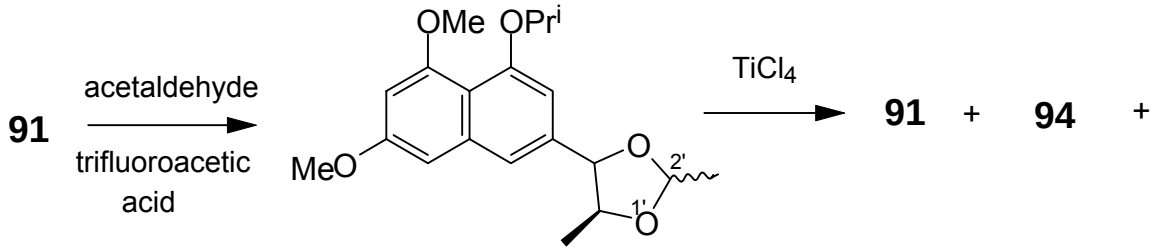


93

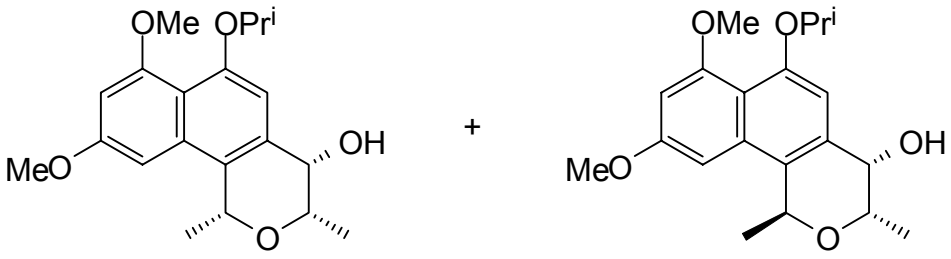
Preferential electrophilic attack on the dimethoxy-substituted aromatic ring rather than the olefin precluded the fascile formation of the desired epoxide, which could have been subjected to stereoselective ring opening to form the *erythro*-diol (*cf*. 35) required for the formation of the dioxolane **82**, and thence **84,** the Glucoside B **4** analogue.

The diol **91** (scheme 21) was reacted with acetaldehyde using trifluoroacetic acid in ether, which gave the product **94** in a yield of 63.0 %. In another reaction toluene-p-sulfonic acid in benzene was used and the same product **94** was formed with a better yield of 76.0 %. In both cases the dioxolane obtained was a single stereoisomer, although the relative stereochemistry at C-2 was not established. It was considered irrelevant if C-2 was to become planar in the subsequent reaction of the dioxolane **85.**

The dioxolane **94** was treated with an excess of both $TiCl_4$ and titanium tetraisopropoxide and two new products were obtained together with the starting dioxolane **94** and the diol **91**, its precursor. These were confirmed by their MS and NMR spectra. Compound **95** which was the higher R_F compound was obtained in a yield of 39.0 %.



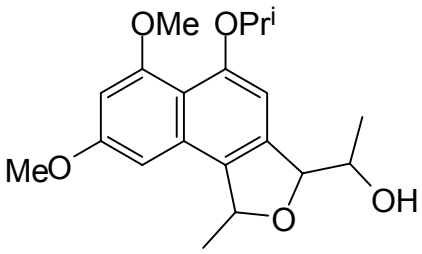
94



95 **96**

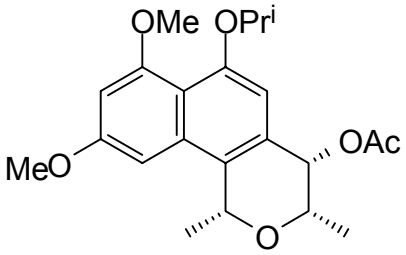
Scheme 21;

Compound **96**, the lower R_F compound, was obtained in a yield of 13.0 %. The OH group of each isomer was acetylated, in order to establish that each product was a naphthopyran rather than a naphthofuran of the general structure **97,** below. This resulted in the marked deshielding, by approximatetly 1.60 ppm in each case of the 4-H signals at *delta* 4.16 and 4.21 ppm in the compounds **95** and **96** respectively. Similar treatment of the isomeric naphthofurans **97** would have led to deshielding of the doublet of quartet (at *delta* 3.84 and 4.24 ppm).



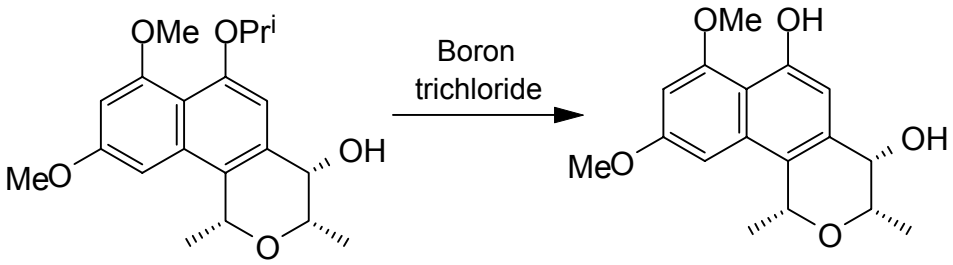
97

The confirmation of these two compounds, **95** (higher R_F, major) and **96** (lower R_F, minor), was through the X-ray crystallographic analysis on the crystalline acetate **98** (below) of the oily **95** and on the minor product, **96** itself.



98

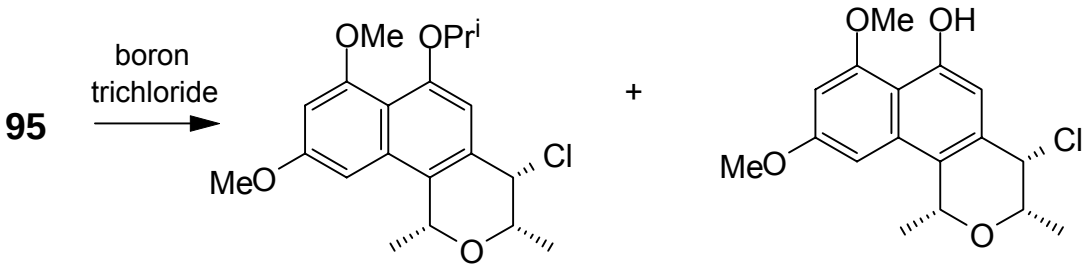
The compound **95** was deisopropylated by treating it with an excess of boron trichloride to yield four products (one the starting material), with the major one (30.0 %) as the naphthol **99** (scheme 22).



95 **99**

Scheme 22:

The chlorination of the same alcohol **95**, with boron trichloride in methylene dichloride gave rise to its C-4 *pseudo*axial chloro derivative **100** with a yield of 15.0 % and the corresponding chlorinated phenol **101** with a 15.0 % yield as well (scheme 23).

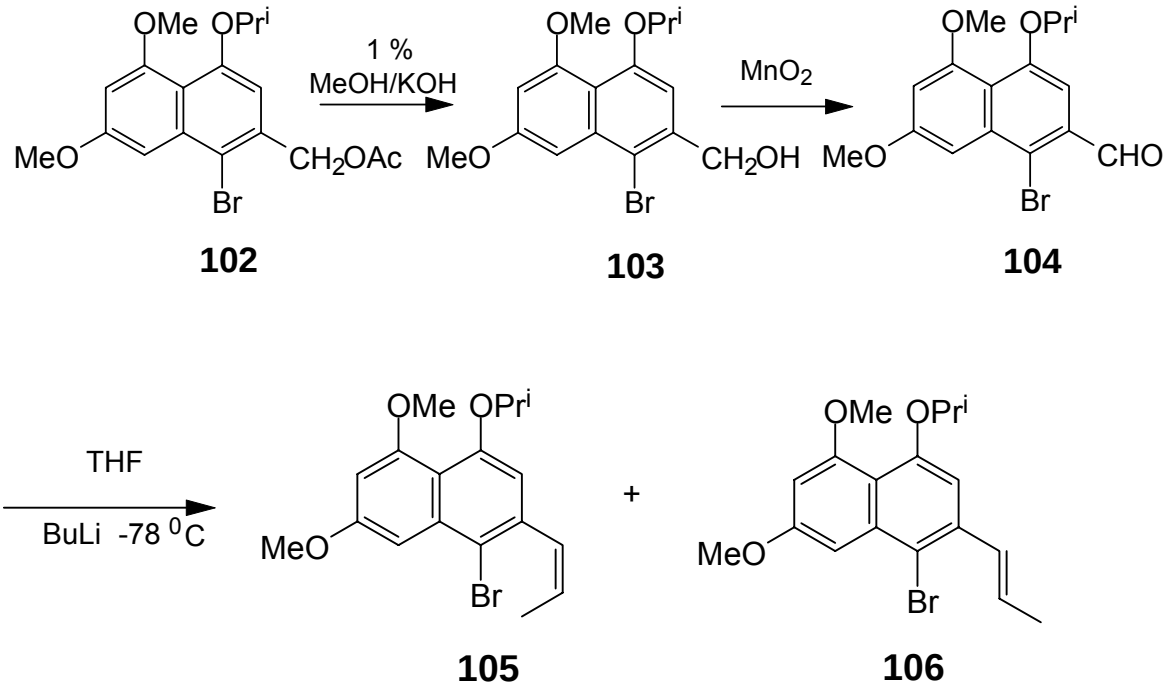


100 **101**

Scheme 23:

Therefore it was shown that it is possible to isomerise naphthyldioxolanes into angular naphthopyrans.

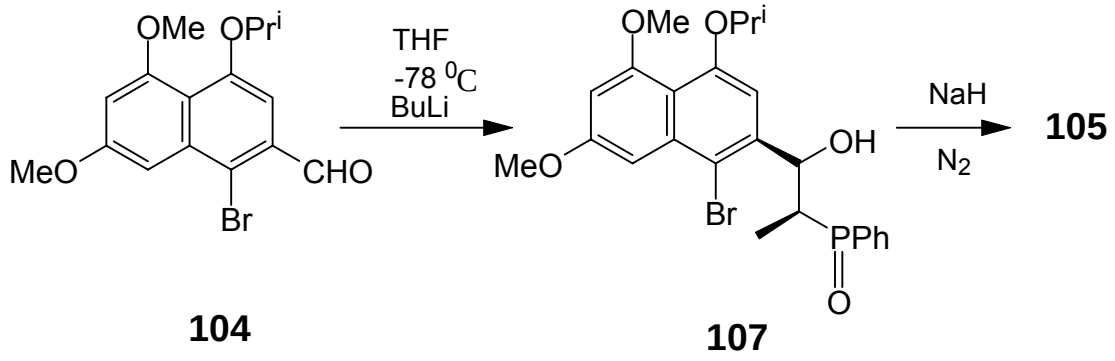
Giles *et al*.[23] attempted another isomerisation with a *cis*-4,5-disubstituted dioxolane related to compound **82**, this was to provide the correct relative stereochemistry at C-3 and C-4 required for Glucoside B **4.**



Scheme 24:

In compound **82** a bromine was attached at either of the unsubstituted positions 4 or 5 to discourage the formation of the angular naphthopyran through steric crowding. In scheme 24 the 4-bromonaphthyl acetate **102** was hydrolysed using a 1.0 % methanolic solution of KOH to yield the alcohol **103** in good yield. The alcohol **103** was then oxidised to afford the aldehyde **104** which was subjected to a Wittig reaction, treated it with the ethylidenephosphorane to yield the mixture of the *trans*-olefin **105** and the *cis*-olefin **106** in a ratio of 1:1.

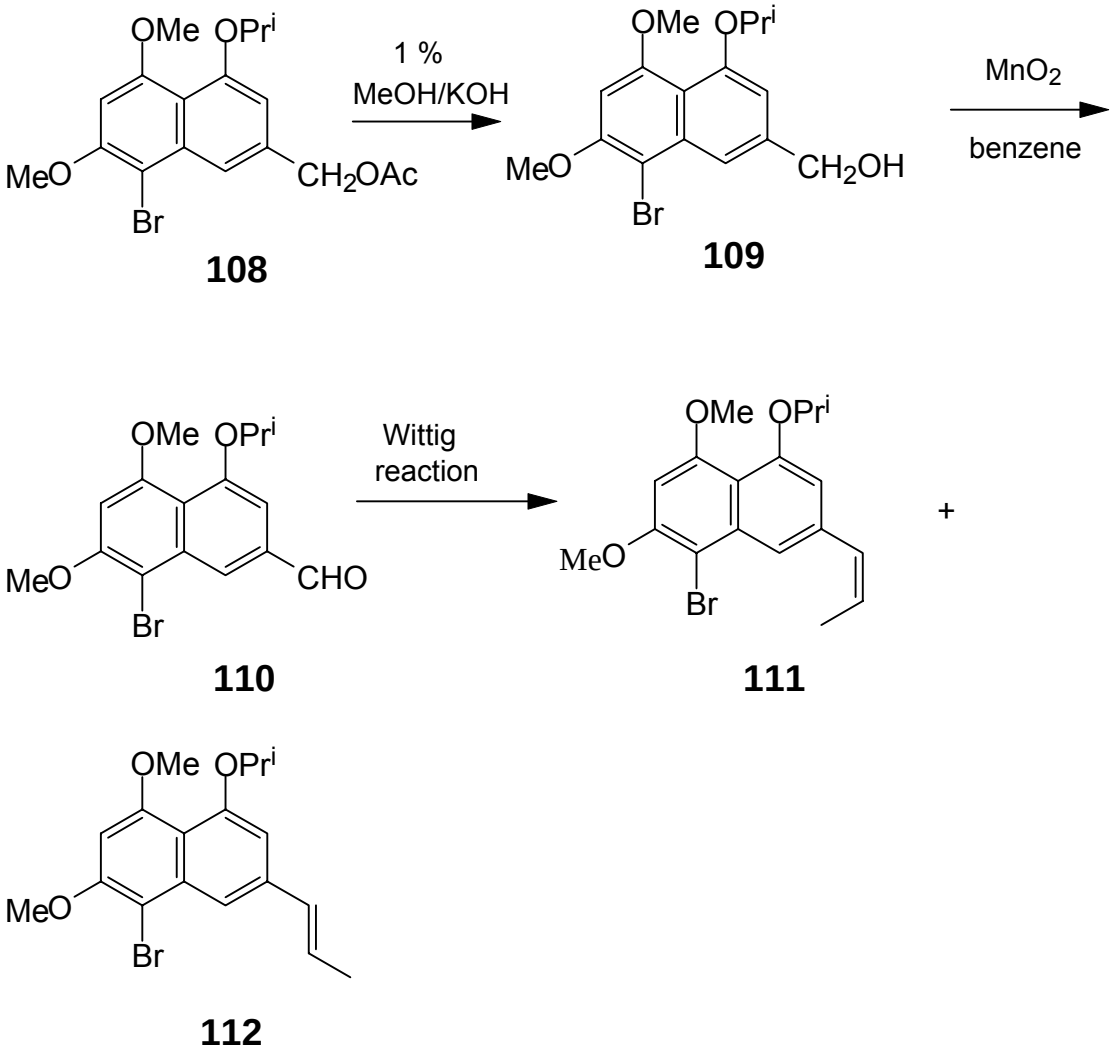
In another attempt the Horner-Wittig reaction was investigated (scheme 25). The 4-bromonaphthyldehyde **104** was treated with ethyldiphenylphosphine oxide under the reaction conditions stipulated for *erythro* selectivity. The resultant product was the *erythro* adduct **107** obtained in a 42.0 % yield after repeated recrystallisation to separate the *threo* adduct formed simultaneously. The diphenylphosphinate was eliminated under optimised conditions to provide the *cis*-olefin **105** in a yield of 82.0 % from the *erythro*-adduct **107**. The *trans*-olefin **106** was also obtained in small quantities of less than 10.0 %.



104 **107**

Scheme 25:

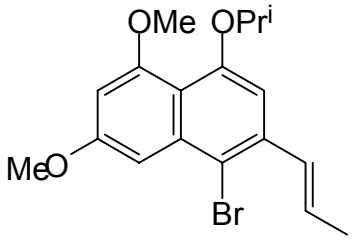
The modest yield of the pure *erythro* adduct **107** and other considerations had an influence against further investigations on the 4-bromonaphthalene series, and in favour of the isomeric 5-bromo analogues.



108 **109** **110** **111** **112**

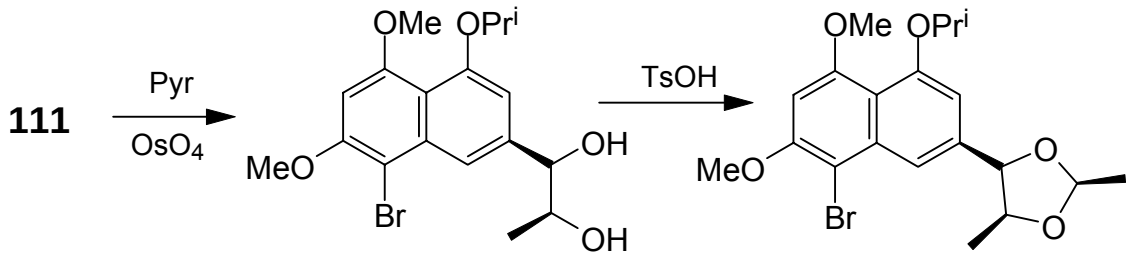
Scheme 26:

The 5-bromonaphthyl acetate **108** was treated with a 1.0 % methanolic potassium hydroxide solution to give rise to the alcohol **109**, which was dissolved in benzene and boiled with activated MnO_2 to afford the aldehyde **110**. The 5-bromonaphthaldehyde **110** was subjected to a Wittig reaction, where it reacted with ethylidenetriphenylphosphorane to yield largely the *cis*-olefin **111**, contaminated by only 8.0 % of the minor *trans*-olefin **112**. This was in contrast to the reaction of the 4-bromonaphthyldehyde **104** with ethylidenetriphenylphosphorane, whereby the product was the mixture of the *cis*- and *trans*-olefins **105** and **106**, in a 1:1 ratio. The assignments were based on the respective olefinic coupling constants of 13.0 and 15.6 Hz. The former value was at the upper limit for the *cis*-olefins, confirmation was sought through reaction with *bis*(acetonitrile)dichloropalladium(II).[20] In that 2 hours reaction the major product was converted into the minor product of the Wittig reaction, confirming the assignment. In another instance, longer reaction times converted the *trans*-olefin **112** into the *trans*-olefin **106**, where there was a migration of bromine from C-5 to C-4.[21]

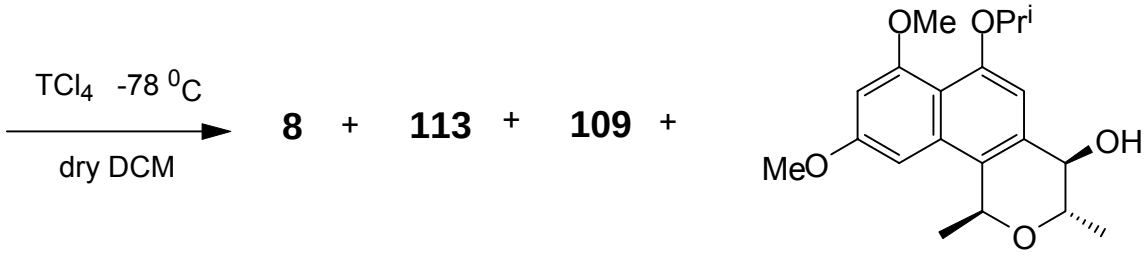


106

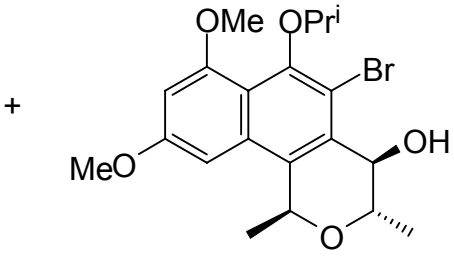
Migration also occurred by leaving the oily *cis*-olefin **111** in sunlight for 4 days, whereby the bromine migrated from C-5 to C-4 to afford **106**. Furthermore, purifying the *cis*-olefin **111** produced an olefin rich in the *trans*-olefin **112**.



113 **8**



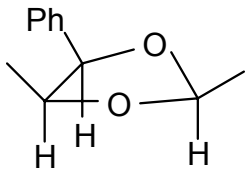
114



9

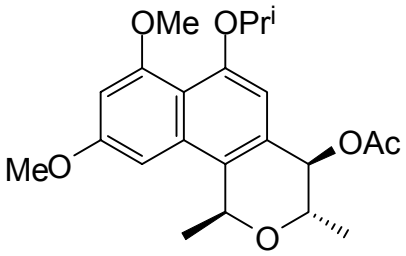
Scheme 27:

The unpurified crude *cis*-olefin **111** in pyridine was reacted with OsO_4 and sodium metabisulphite to afford the diol **113** in a yield of 59.0 %. This diol was then converted to the single diastereoisomer of dioxolane **8** using the acetaldehyde dimethyl acetal and TsOH. A Nuclear Overhauser effect difference spectrum was used to confirm this product. This isomer was favoured as the one with least nonbonded interactions, in the conformation **115**.

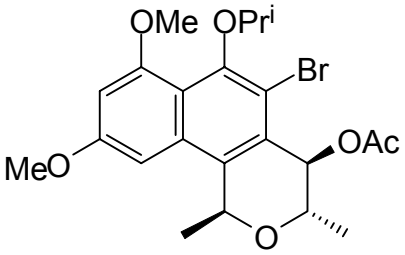


115

The naphthyldioxolane **8** was treated with 10 molar equivalents of $TiCl_4$, in dry DCM, at -78 ^{0}C. Five products were isolated from the reaction mixture, the starting dioxolane **8** (12.0 %), the diol **113** (14.0 %), the alcohol **109** (4.0 %), and the two new compounds, the debrominated angular naphthopyran **114** (45.0 %), and its 5-bromo derivative **9** (18.0 %). The percentage yields were based on the starting dioxolane consumed. The two new products were converted into their acetates **116** and **117**, to confirm that they were naphthopyrans instead of naphthofurans, whereupon the 4-H signal of each was deshielded by well over 1.00 ppm.



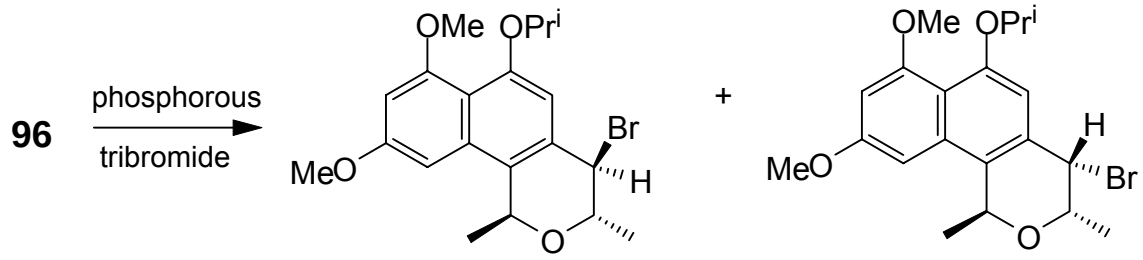
116



117

A method was sought to relate structures **114** and **9** to those of the stereoisomers **95** and **96** which were determined through X-ray crystallography. The angular naphthopyrans **95** and **96** were converted into their 4-deoxyderivatives.

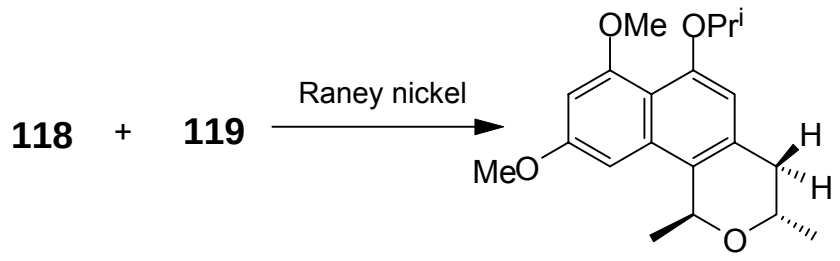
The compound **96** was reacted with phosphorus tribromide to produce a mixture of the two benzylic bromides **118** and **119** (scheme 28).



118 **119**

Scheme 28:

For product **118** the C-4 bromine was *pseudo*equatorial as the coupling constant between 3-H and 4-H was 8.5 Hz while that for the stereoisomer **119** was 2.0 Hz. The respective chemical shifts for the neighbouring 5-H aromatic protons were *delta* 6.92 and 6.65 ppm indicating the closer proximity of the bromine to 5-H in the former case.

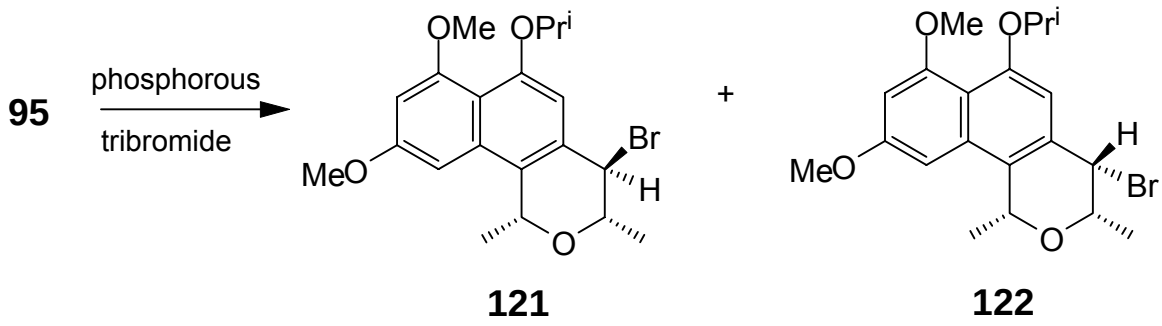


120

Scheme 29:

The mixture of these isomers, **118** and **119** was treated with an aqueous ethanolic Raney nickel catalyst to yield the *trans*-1,3-dimethylnaphthopyran **120** as a single product as in scheme 29.

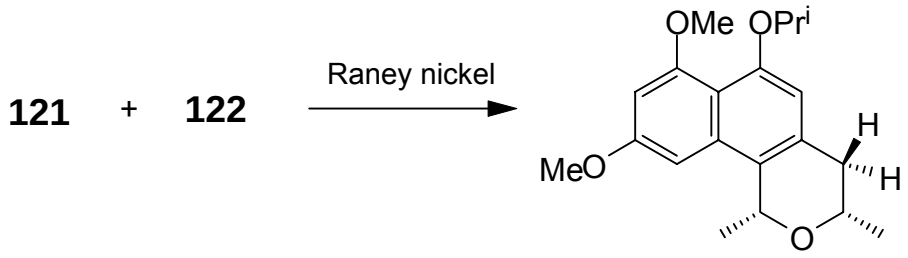
The product **95** was similarly reacted with the phosphorous tribromide to afford the two bromides, **121** and **122** (scheme 30). The stereochemistries of these products were assigned from the 4-H coupling constants and 5-H chemical shifts.



121 **122**

Scheme 30:

These stereoisomers were then hydrogenolysed as in scheme 29 to yield the *cis*-1,3-dimethylnaphthopyran **123**, which was stereoisomeric with product **120** (scheme 31)



123

Scheme 31:

The naphthopyran **114** was also reacted with phosphorous tribromide to give rise to the pair of isomeric bromides **118** and **119**, identical with those obtained from the epimeric alcohol **96**. The isomeric bromides were then hydrogenolysed to yield the *trans*-1,3-dimethyl compound **120**, as a result the stereochemistries of the pyrans **114** and **9** were confirmed.

In this study it was determined that appropriately substituted naphthyldioxolanes may be stereoselectively isomerised to angular naphthopyrans related to Glucoside B **4**. Steric crowding was thought to be the cause of the formation of angular naphthopyrans compared

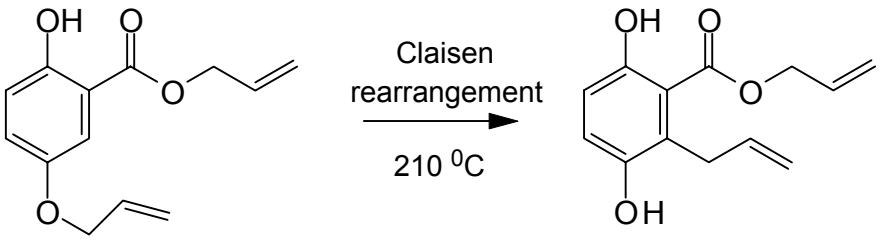
to the linear ones. Naphthalenes also prefer electrophilic substitution at the *alpha*-position rather than the *beta*-position.

It was also shown that the stereochemistry at C-3 and C-4 in the product could be controlled by the choice of stereochemistry at the vicinal centres C-4 and C-5 in the starting dioxolane.

4.4. The synthesis of the benzo[*c*]pyranquinones.[30]

Hugo *et al*.[16] have reported the synthesis and biological activity of some benzopyran systems in 1993. Later on Hugo and Green *et al*.[30] described fully the synthetic routes to these molecules and demonstrated how the methodology had been used in the synthesis of additional highly active benzo[*c*]pyran-5,10-quinones. In the past years the biological potential of the naphtho[2,3-*c*]pyran-5,10-quinones as antineoplastic antibiotics had been recognized and their synthesis had been successfully undertaken by different groups.[42,39,54] The most important structural feature for biological activity in these systems was considered to be the aryl-[2,3-*c*]pyranquinone nucleus and that the 4-OH group would increase the activity. The target compound was the racemic 3,4-dihydro-3-methyl-1H-benzo[*c*]pyran-5,8-dione **136**. This was to study the importance of the position of the oxygen in the pyran ring for antimicrobial activity.

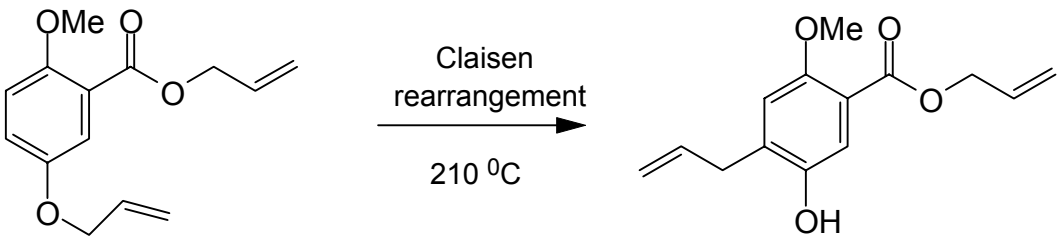
The ester **124** was pyrolysed via the Claisen rearrangement[35] to yield the quinol **125**. This was due to an *ortho*-migration of the allyl group to the sterically disfavoured position[4,7] (scheme 32).



124 **125**

Scheme 32:

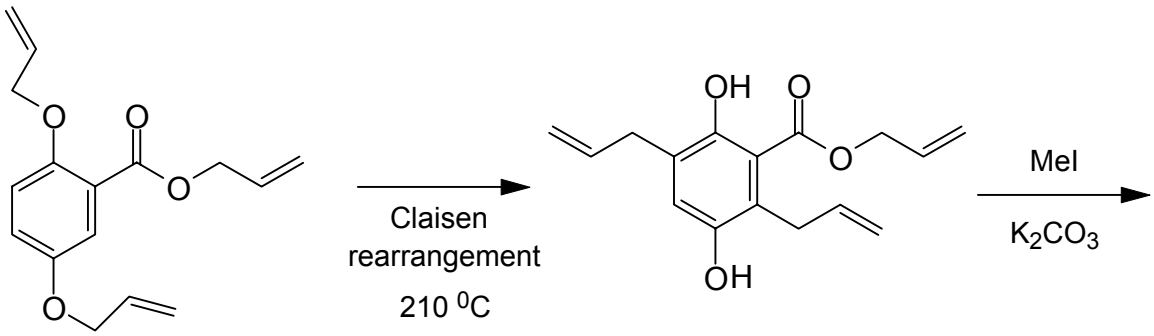
In scheme 33 subjection of the ether **126** to the same Claisen rearrangement conditions afforded phenol **127** as the sole product.



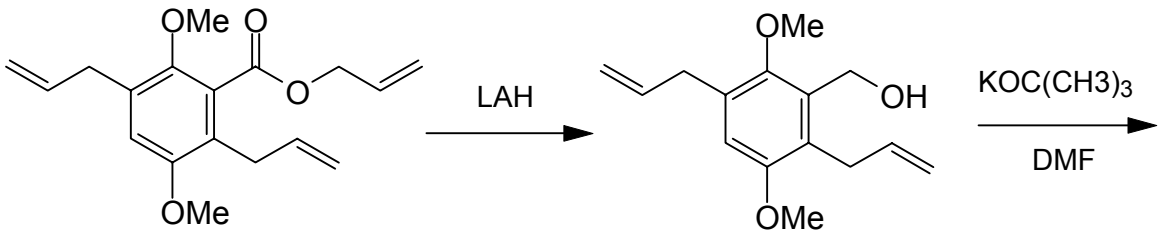
126 **127**

Scheme 33:

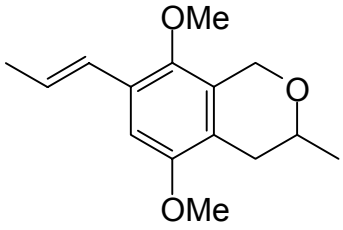
It was found that when hydrogen bonding between the ester carbonyl group and the OH group on C-2 was absent, migration of the allyl group was to the less crowded alternative *ortho* position at C-4.



128 **129**



130 **131**



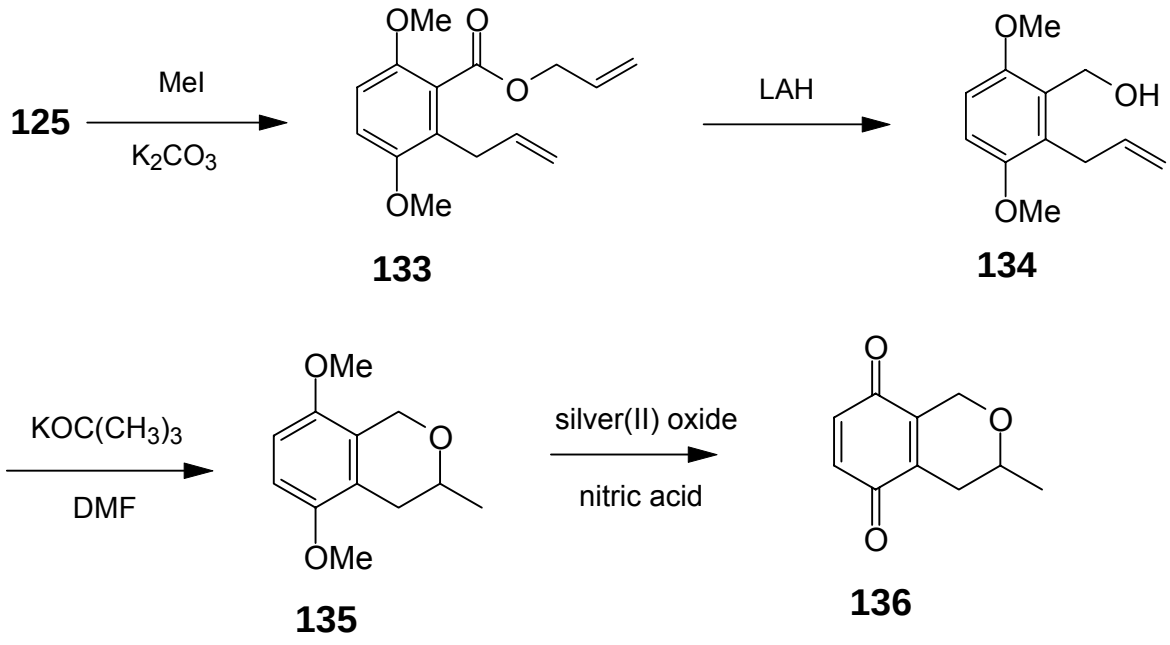
132

Scheme 34:

On pyrolysing the ester **128**, the sole product that was isolated was quinol **129**. That indicated that the allyl group at the C-5 ether position had migrated to the disfavoured

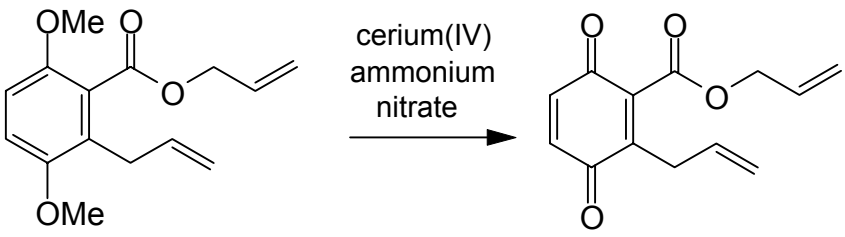
position at C-6. It was proposed that the first step in the rearrangement was prior migration of the allyl group from the C-2-O to C-3, whereby it allowed hydrogen bonding to be re-established, and in a way dictated the migration route of the allyl group from the C-5 to C-6. Quinol **129** was then treated with iodomethane and K_2CO_3 in boiling acetone to yield ether **130**, which was reduced by reacting it with LAH to afford the alcohol **131**. The alcohol **131** was base-catalysed under anaerobic conditions by treating it with potassium *tert*-butoxide to cyclize[18] to the benzopyran **132**. The propenyl group on C-3 had undergone conjugation that led to the formation of product **132**.

The benzopyran **132** was oxidised with cerium(IV) ammonium nitrate,[37] and in another instance silver(II) oxide[47] was used. In both reactions no quinone was obtained.



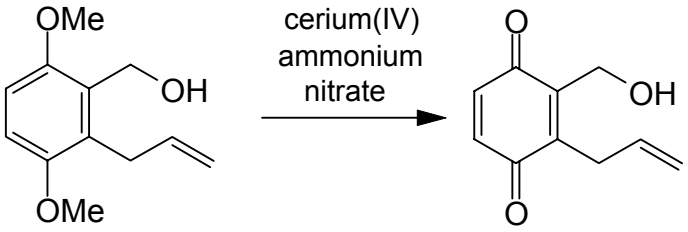
Scheme 35:

Similarly the quinol **125** in the above scheme 35 was methylated to yield ether **133** that was reduced using LAH to afford the alcohol **134**. Product **134** was then cyclized under base-induced conditions to the benzopyran **135**. Oxidative demethylation of this benzopyran using the silver(II) oxide in 6M nitric acid produced the racemic benzopyranquinone **136**.
In another reaction the oxidative demethylation of the ester **133** and the alcohol **134**, using cerium(IV) ammonium nitrate afforded the quinones **137** and **138**, (schemes 36 and 37).



133 **137**

Scheme 36:

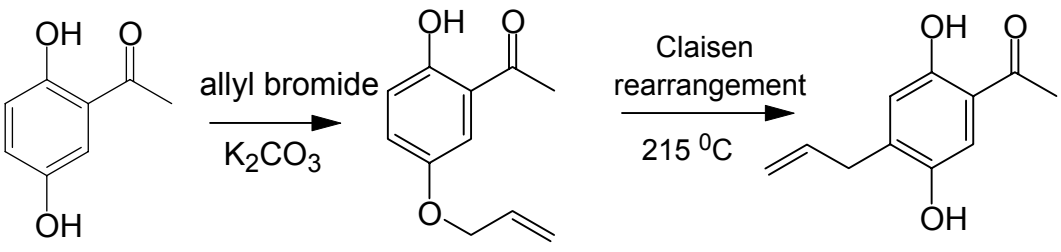


134 **138**

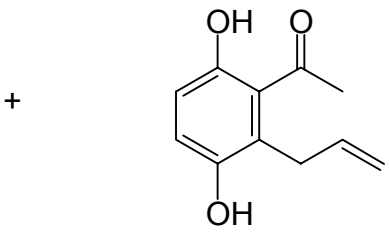
Scheme 37:

The research group then focused their attention on the synthesis of the OH benzopyranquinones **150** and **151** since they resembled models for the aphid pigments and degradative compounds, the benzo[*c*]pyran nucleus included in these systems.

A 2-acetyl-1,4-dihydroxybenzene **139** was monoallylated to give rise to the 5-allyloxy-2-hydroxyacetophenone **140**[4] in scheme 38, which was pyrolysed under N_2 to undergo the Claisen rearrangement to afford two compounds. Compound **141** was the minor (8.0 %) which was the first to elute from the column. Its allyl group at C-5-O had migrated to the less sterically crowded C-4 *ortho* position. The major compound **142** (82.0 %) had a H-bonding between the OH group at C-2 and the ketone carbonyl facilitated migration of the allyl group to C-6.



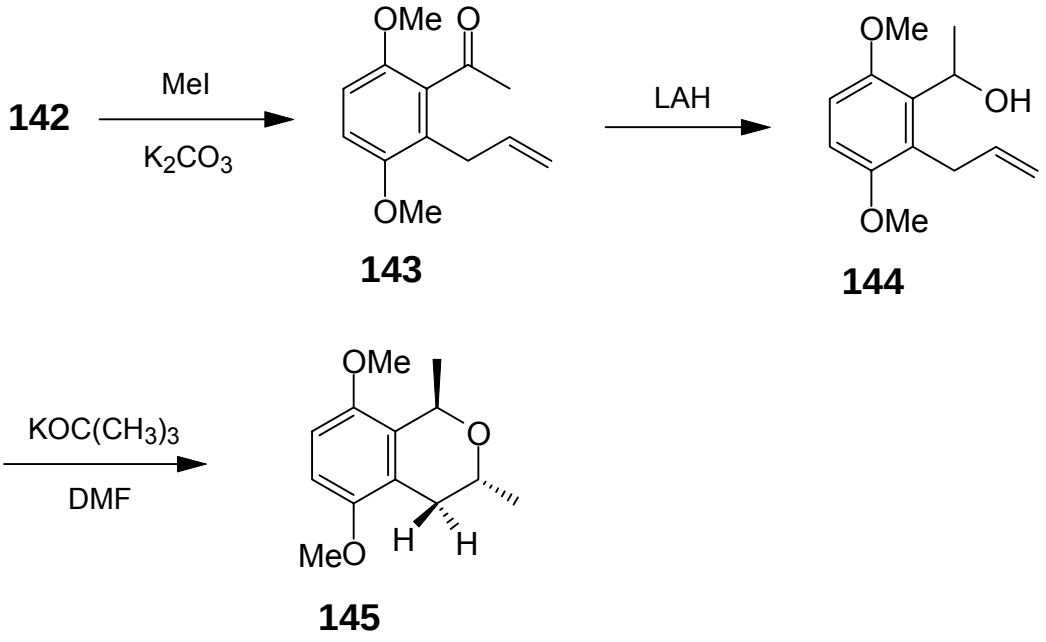
139 **140** **141**



142

Scheme 38:

Quinol **142** was dissolved in dry acetone containing iodomethane and K_2CO_3 to yield the dimethyl ether **143**, which was reduced using LAH to afford the alcohol **144** in a very high yield of 96.0 %. Anaerobic base-induced cyclisation of the alcohol **144** dissolved in dimethylformamide under N_2, was treated with potassium *tert*-butoxide to produce the racemic *trans*-1,3-dimethylbenzopyran **145** as the sole product in a high yield of 91.0 % (scheme 39).



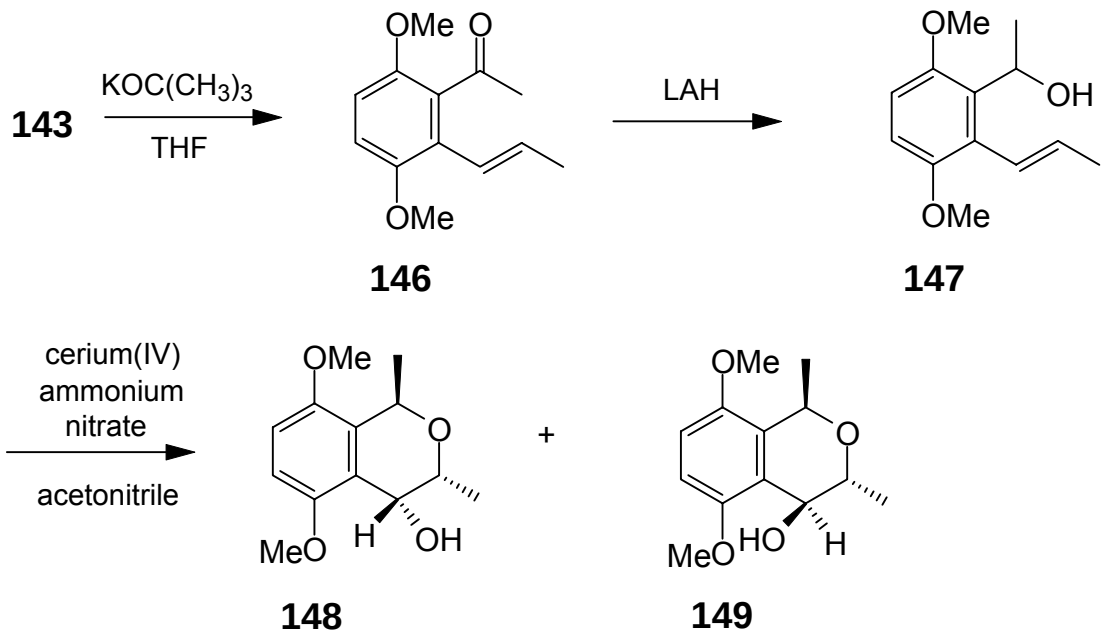
143 **144**

145

Scheme 39:

The relative configuration between the methyl groups at C-1 and C-3 was confirmed as *trans* in the H^1 NMR spectrum.

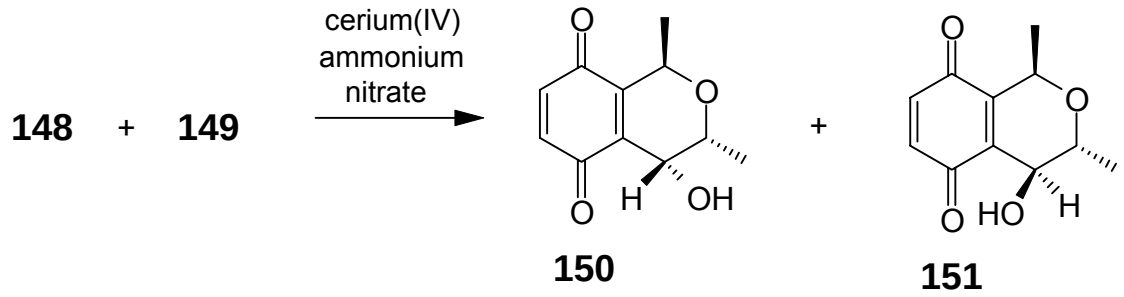
With Green *et al.*[30] the introduction of the OH group at C-4 in pyran **145** was problematic, compared to the same introduction performed by other research groups.[15,22] That led to them looking for an alternative route.



Scheme 40:

The ketone **143** was isomerised with potassium *tert*-butoxide in THF to afford the *trans*, conjugated analogue **146**, which was reduced to the corresponding alcohol **147** using LAH in diethyl ether with a 97.0 % yield. The alcohol **147** in aqueous acetonitrile was treated with 2 mol equivalents of cerium(IV) ammonium nitrate in aqueous acetonitrile to produce the two 4-hydroxypyran derivatives, **148** in a yield of 70.0 % and **149** in a yield of 21.0 %[34] (scheme 40). Confirmation of the stereochemistry about the pyran ring was evident from the proton NMR spectrum.

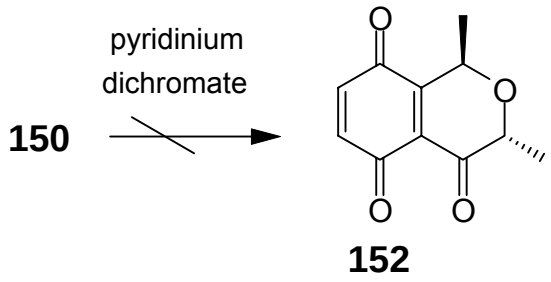
Similarly, treatment of the alcohol **147** with 4 mol equivalents of cerium(IV) ammonium nitrate in aqueous acetonitrile resulted in cyclisation, whose oxidative demethylation afforded the pyranquinones **150** (66.0 %) and **151** (15.0 %) in scheme 41.



Scheme 41:

The IR spectrum of **150** showed sharp bands confirming the presence of the alcohol and the quinone groups. The proton NMR spectrum displayed a close similarity to that of the pyran **148** whilst that of pyranquinone **151** and pyran **149** had confirmatory similarities in the

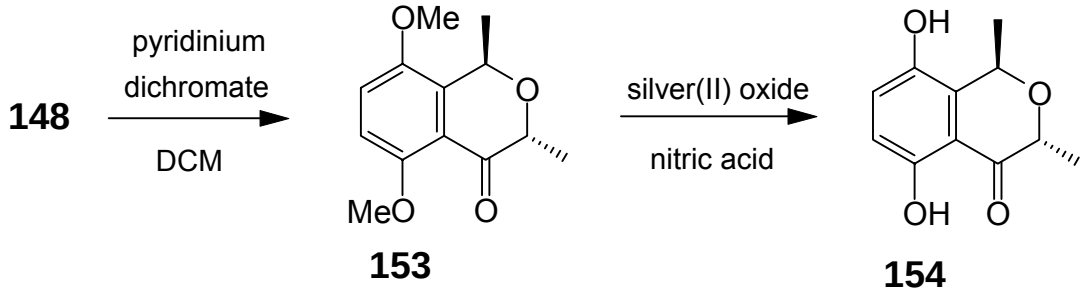
signals of the pyran ring protons, thereby establishing the assigned relative stereochemistries of the protons at C-1, C-3 and C-4 of the pyran ring.



Scheme 42:

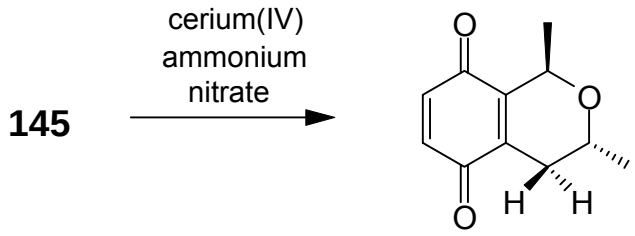
Failure of the oxidation of the pyranquinone **150** to the ketoquinone **152**, using pyridinium dichromate in scheme 42, forced the research group to look for an alternative route.

In scheme 43 the C-4 hydroxypyran **148** was oxidised to the C-4 ketopyran **153** using pyridinium dichromate in DCM, in a reasonable yield. The IR spetrum confirmed the desired product. The ketopyran **153** was then oxidatively demethylated to yield the pyranquinol **154** in a yield of 62.0 %.



Scheme 43:

In another oxidative demethylation, the pyran **145** without the C-4 carbonyl was successfully converted to the quinone **155** in scheme 44 in a yield of 90.0 %. Quinol **154** was reluctant to undergo oxidation to the corresponding quinone **152** due to the strong H-bonding stabilisation between the C-5 hydroxyl and C-4 carbonyl groups.



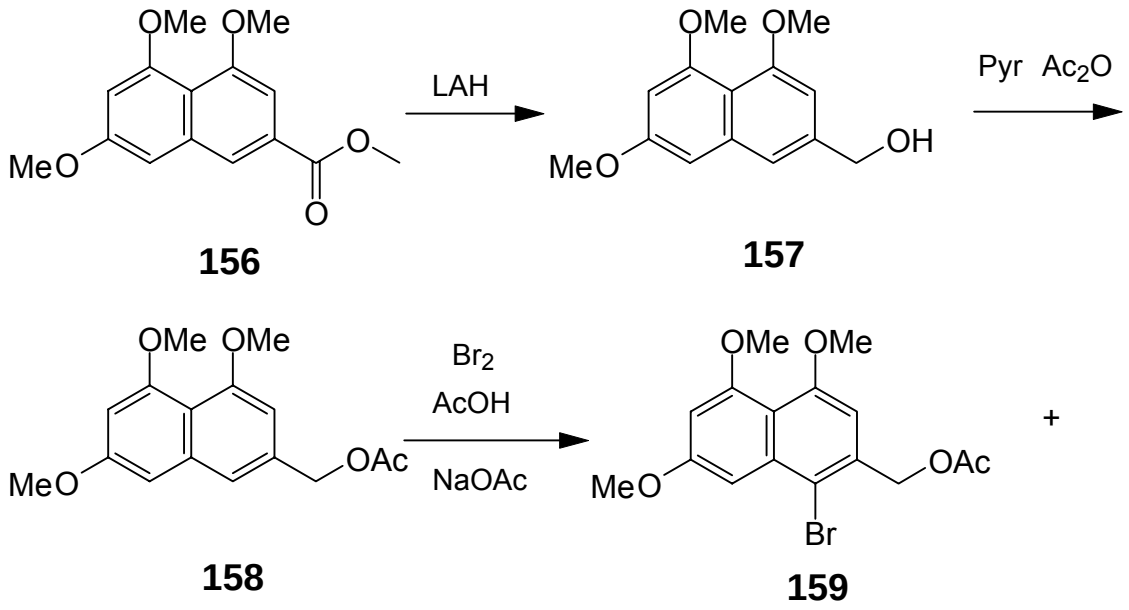
Scheme 44:

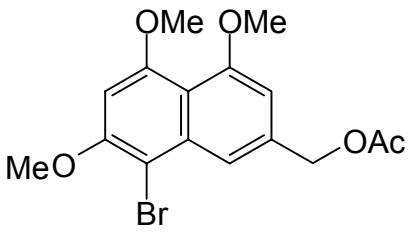
Therefore a general strategy was developed for the synthesis of benzo[*c*]pyran ring systems which were considered to be appropriate for microbial testing. The methodology needs to be investigated further, in order to include the naphthopyran ring systems.

4.5. The steric factors involved in the synthesis of naphthopyrans.[32]

In 1997 Green *et al*.[32] studied the synthesis of a naphthyldioxolane and its isomerisation with $TiCl_4$.

The alcohol **157** was obtained by reducing the ester **156** with LAH in diethyl ether in scheme 45 which was then converted into the acetate **158** by treating it with Ac_2O and Pyr. This was to facilitate subsequent brominations. Treating the acetate with 1 equivalent of bromine and 1.2 equivalents of NaOAc in AcOH, gave rise to the 4-bromo acetate **159** (8.0 %) and the 5-bromo analogue **160** (92.0 %). By omitting the NaOAc the 4-bromo acetate **159** was afforded.

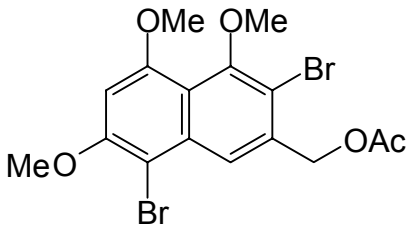




160

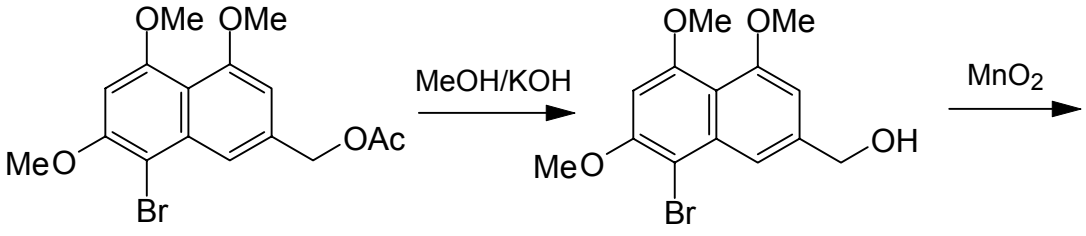
Scheme 45:

When the stoichiometry of bromine was increased to 2 equivalents, in the presence of NaOAc, the 2.5-dibromo acetate **161** was produced in a yield of 90.0 %.

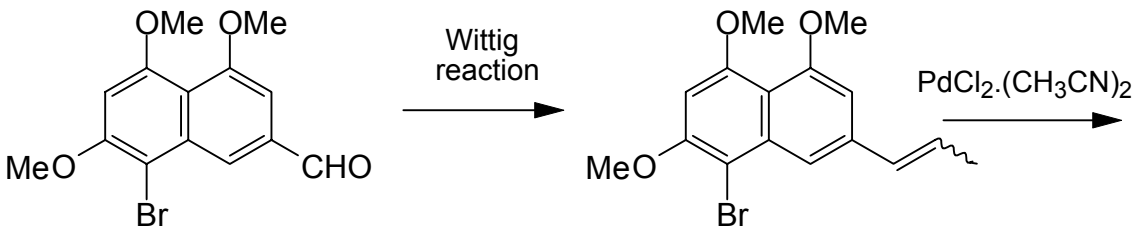


161

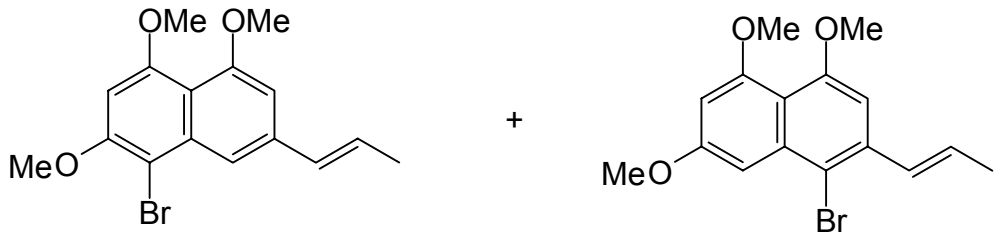
Treatment of the acetate **160** with a methanolic solution of KOH resulted into the alcohol **162** whose subsequent oxidation with activated MnO_2 yielded the aldehyde **163**. This was then subjected to a Wittig reaction where it was reacted with ethylidenetriphenylphosphorane at 20 °C to give a low yield (27.0 %) of the olefins **164**, whose *trans*/*cis* ratio was 7:3.



160 **162**



163 **164**

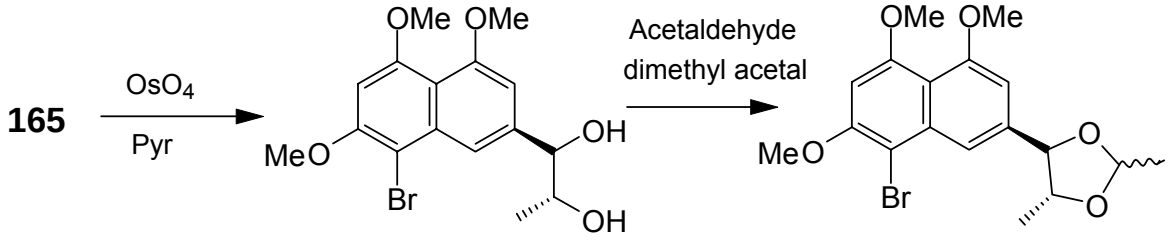


165 **166**

Scheme 46:

Green *et al.*[32] attempted to improve the yield by adding 11 equivalents of hexamethylphosphoric triamide[11,12] with the reaction at -78 °C. The yield improved to 66.0 % but the *trans*/*cis* ratio was still the same. The reaction was then conducted at 20 °C in the presence of the triamide and this improved the yield to 77.0 %, but the geometrical integrity was lost as the *trans*/*cis* ratio was 1:1. A solution of DCM containing the mixture and the *bis*(acetonitrile)dichloropalladium(II)[20] was heated under reflux to afford the pure *trans*-isomer **165** in a yield of 74.0 % and the bromo-olefin **166** in a 14.0 % yield (scheme 46).

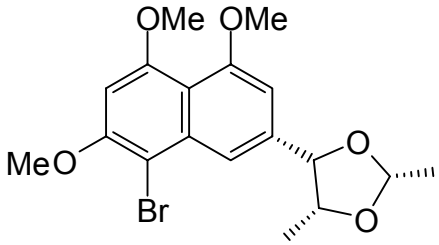
The olefin **165** in scheme 47 was reacted with OsO_4 in pyridine to produce the diol **167** (87.0 %) which was treated with the acetaldehyde dimethyl acetal to yield a mixture of inseparable epimeric (at C-2') dioxolanes **10**.



167 **10**

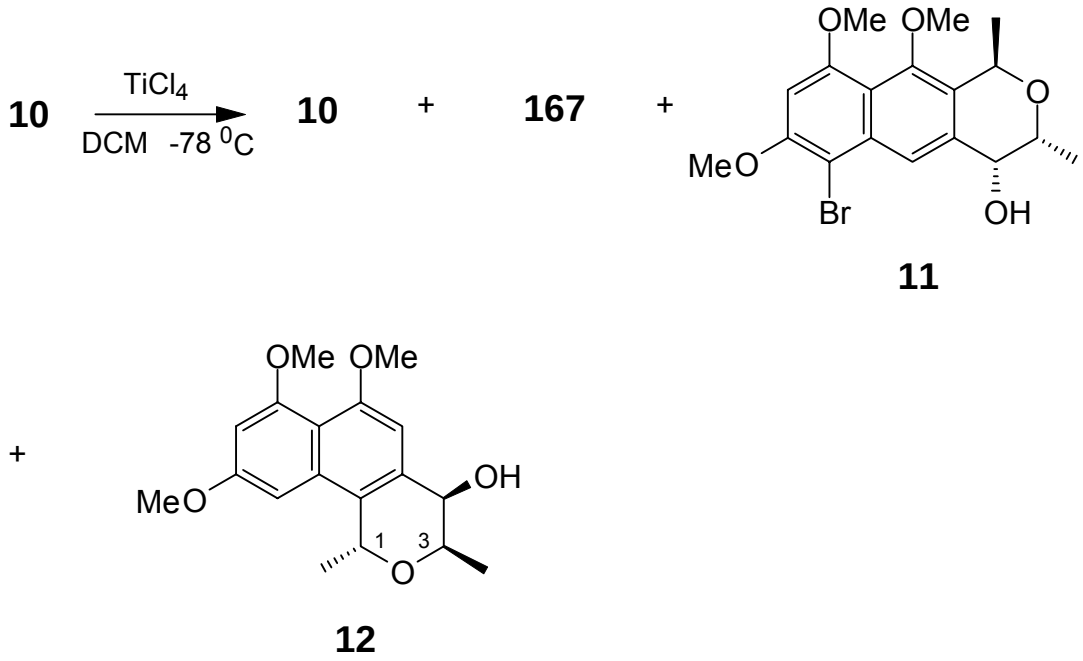
Scheme 47:

When the (1:1) *trans*/*cis* mixture of olefins **164** was reacted as above, a mixture of three inseparable dioxolanes was produced, the epimeric mixture **10** and **168** in a 1:1:2 ratio.



168

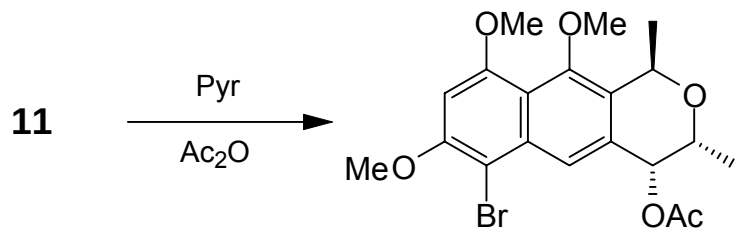
The epimeric mixture of dioxolanes **10** was treated with 2.4 equivalents of $TiCl_4$ in DCM at -78 °C and subsequently at 25 °C, under an atmosphere of N_2. Several products were isolated, the starting material **10** (27.0 %), the diol **167** (44.0 %), and the inseparable mixture of the hydroxynaphthopyrans **11** and **12** (scheme 48).



Scheme 48:

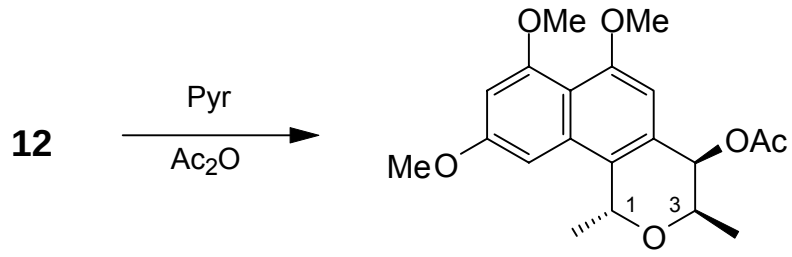
The two alcohols were then acetylated, in order to facilitate their separation, into the acetates **169** in a yield of 13.0 % and **170** in a yield of 28.0 % in schemes 49 and 50 below.

The minor product **169** represented the derivative of the desired linear naphthopyran **11**, and the major one **170** represented the angular naphthopyran **12**, which had similar signals with compounds that were isolated by Giles *et al*.[23]



169

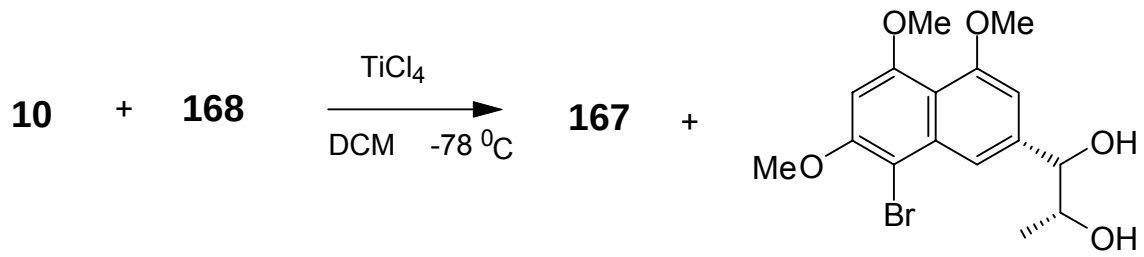
Scheme 49:



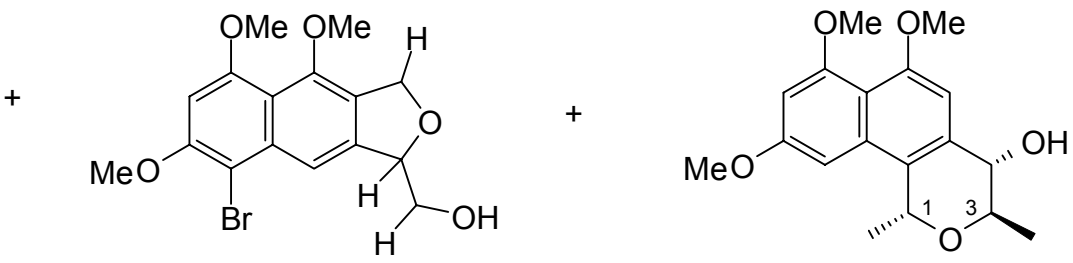
170

Scheme 50:

The mixture of the dioxolanes **10** and **168** was treated with 2 equivalents of $TiCl_4$ in DCM, at -78 °C and subsequently at 25 °C to yield a complex mixture of the starting material in a yield of 3.0 %, the diols **167** and **171** (22.0 %) and an inseparable mixture of the isomeric alcohols **172** and **173**, plus minor quantities of the previously isolated compounds **11** and **12** (scheme 51).



171

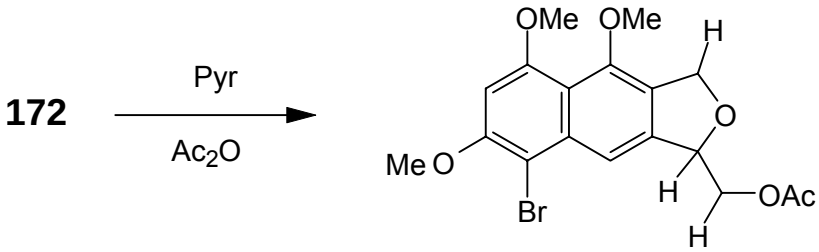


172 **173**

\+ **11** \+ **12**

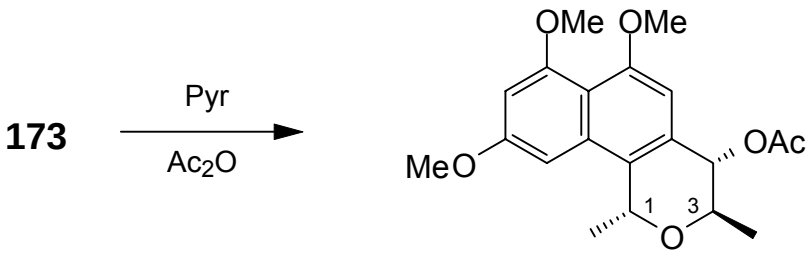
Scheme 51:

The two new alcohols were also acetylated using pyridine and Ac_2O to afford an easily separable mixture of the two acetates **174** and **175** in schemes 52 and 53.



174

Scheme 52:



175

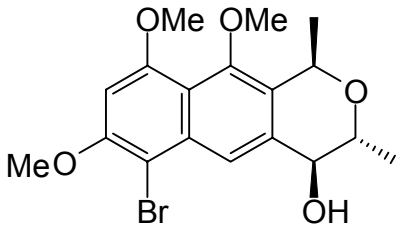
Scheme 53:

The major product **175** (11.0 % based on recovered material) was almost similar to acetate **170**, and the minor component (8.0 % based on recovered material) was the linear naphthofuran **174**.

The $TiCl_4$ –induced isomerisation of the dioxolanes **10** with a smaller methyl protecting group on the C-1 oxygen afforded the predicted linear naphthopyran **11** with the correctly predicted

stereochemistries at C-3 and C-4. In the angular naphthopyran **12**[23] the stereochemistry was also correct. The results therefore demonstrated that the steric size of the protecting group on the C-1 oxygen, enhanced the attack at C-2. The strong competition between attack at the *alpha*- and *beta*-positions was demonstrated by the angular naphthopyran **12** yield.

The angular naphthopyran **173** must have arisen from reaction of the dioxolane **168** since the stereochemistry of the hydrogens at C-3 and C-4 of the former was *trans*. The brominated linear naphthofuran **172** was believed to have arisen through the intermediacy of the linear naphthopyran **176**, which was initially formed at the lower temperature, but at higher temperatures underwent a second isomerisation induced by the Lewis acid and the combined influence of all the methoxy groups.

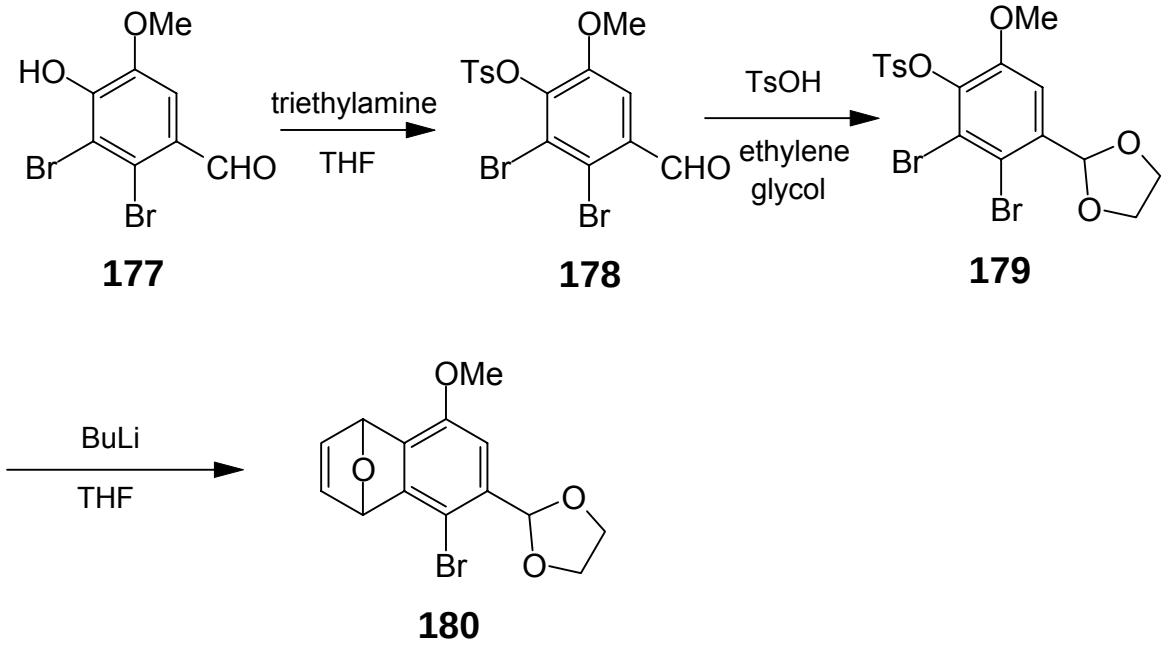


176

4.6. The synthesis of dioxolanes and their isomerization to naphtho[3,4-*c*]pyrans.[28]

Giles *et al.*[28] had shown that phenyldioxolanes can be isomerized to benzopyrans.[24,25,26] They found that all *cis* 4-aryl-2,5-dimethyldioxolanes provided the 1,3-*trans*-3,4-*trans* stereochemistry required for Glucoside B **4**, since the stereochemistries at C-4 and C-5 in the dioxolanes were transferred unaltered to C-4 and C-3 in the product benzo- and naphthopyrans.[24] In the studied isomerization[23] the corresponding dioxolanes were shown to yield angular naphthopyrans readily as the sole products of isomerization, after losing the *peri*-substituted bromine atom, that was used as a blocking group, with an excess of the isomerization reagent. In 2004 Giles *et al*.[28] examined the rearrangement of a naphthyldioxolane bearing a blocking bromine atom *ortho* to the dioxolane ring with a view to assembling linear naphthopyrans.

A solution of the toluene-p-sulfonyl chloride in THF was reacted with a solution of the dibromo phenol **177** and triethylamine in dry THF at zero degrees Celsius, after which the mixture was heated under reflux overnight to afford the product **178** (84.0 %). The aldehyde **178** together with ethylene glycol and TsOH in benzene were heated under reflux to yield the ethylene acetal **179**. A solution of n-BuLi in hexane was reacted with a solution of the dioxolane **179** and furan in dry THF at -78 °C under N_2 to furnish the adduct **180** in scheme 54, as the sole product in a yield of 65.0 %.

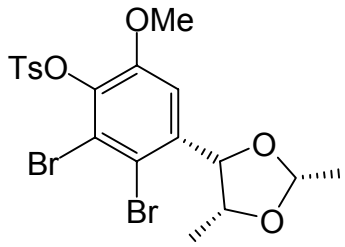


177 **178** **179**

180

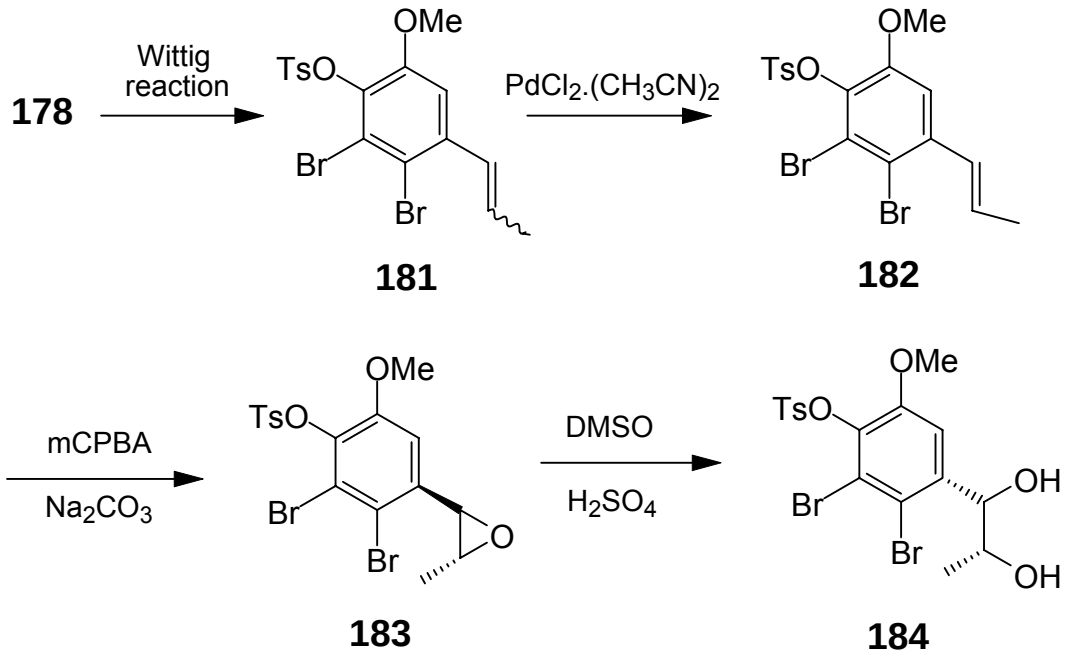
Scheme 54:

After it was established that the epoxynaphthalene **180** could be formed, the next step was to convert the aldehyde **178** into the all *cis*-dioxolane **186**.



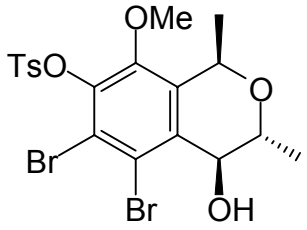
186

The aldehyde **178** (scheme 55) in dry THF was subjected to a Wittig reaction, where it was reacted with an ethyltriphenylphosphonium bromide and n-BuLi solution at -78 °C to furnish a mixture of the geometric isomers **181** (1:1). The mixture **181** was then treated with the *bis*(acetonitrile)dichloropalladium(II) to provide the pure *trans*-olefin **182** (79.0 %). This *trans*-olefin was then converted in 91.0 % yield into the *trans* epoxide **183** using the *m*-CPBA in the presence of anhydrous sodium carbonate. Basic hydrolysis of the epoxide **183** led to the cleavage of the sulfonate ester, whereas its acidic hydrolysis in aqueous DMSO led to the stereoselective ring opening of the epoxide **183** to afford solely the *erythro*-diol **184** in 86.0 % yield, after recrystallization.



Scheme 55:

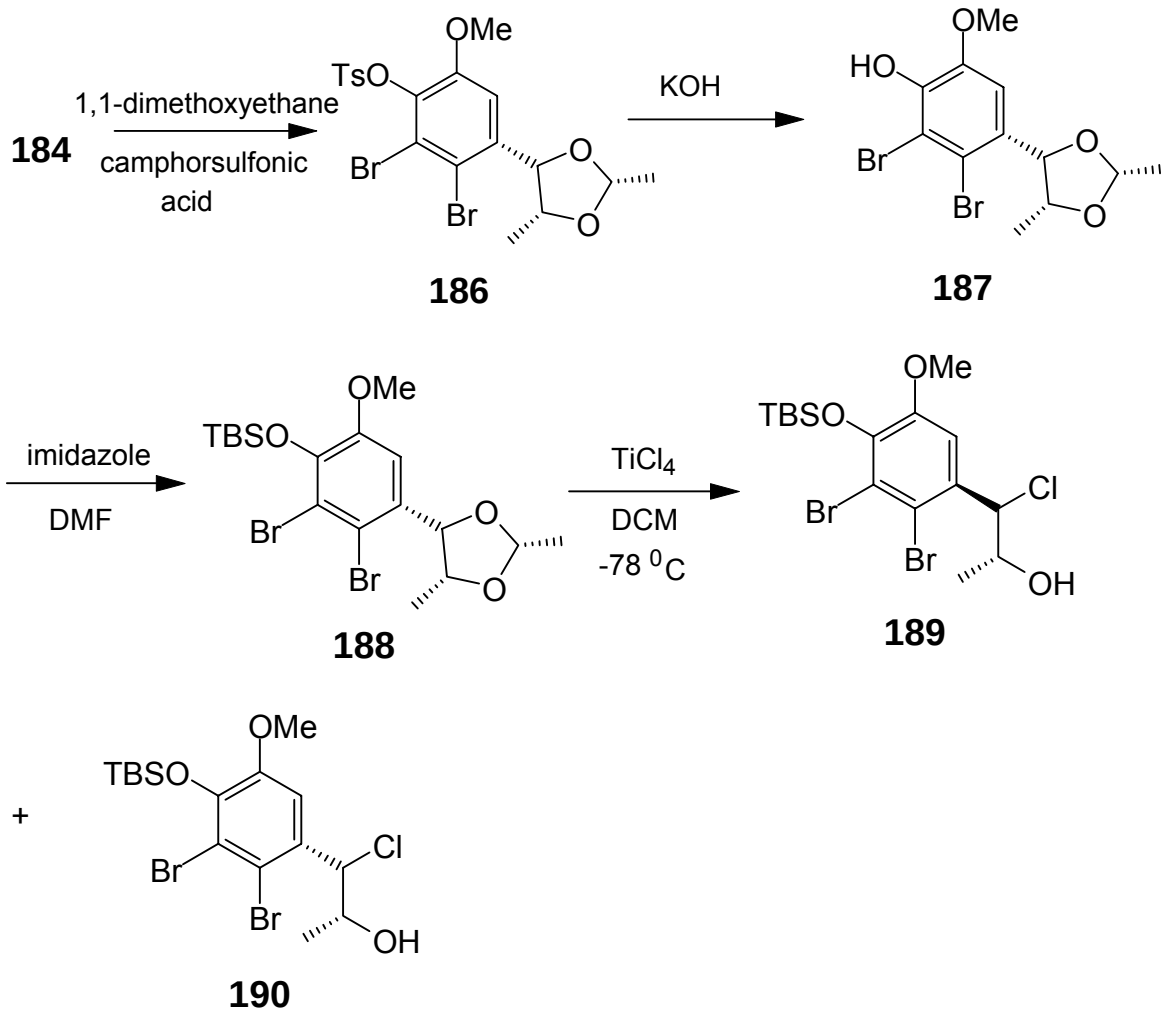
The diol **184** was treated with an excess of 1,1 –dimethoxyethane in the presence of (+/-)-camphorsulfonic acid under reflux to afford the all *cis*-dioxolane **186** as the sole product (96.0 %). Isomerization of the aryldioxolane **186** to the benzo[*c*]pyran **185** at -78 °C, using 2 equivalents of $TiCl_4$ failed. The starting material and the diol **184** were recovered.



185

Another reaction at -30 °C and 0 °C was attempted but the expected benzo[*c*]pyran **185** was not produced, instead there were increasing quantities of the diol **184** that were produced as the temperature of the reaction was raised. The failure of the reaction was thought to be due to the poor electron availability on the aromatic ring for the required electrphilic substitution to occur, or was due to the crowded nature of the aromatic ring of the target benzo[*c*]pyran **185**. The electron density on the aromatic ring was increased by removing the tosyl group through basic hydrolysis to derive the phenol **187**, which was converted into its *t*-butyldimethylsilyl ether **188** by treating it with imidazole and *t*-butyldimethylsilyl chloride in scheme 56. Treatment of the dioxolane **188** with 2 equivalents of $TiCl_4$ at -78 °C under N_2 resulted into

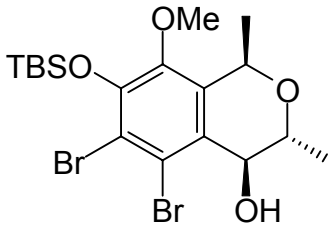
the unwanted diastereoisomeric chlorohydrins **189** (major) and **190** (minor) in a combined yield of 83.0 %, in a ratio of approximately 2:1.



Scheme 56:

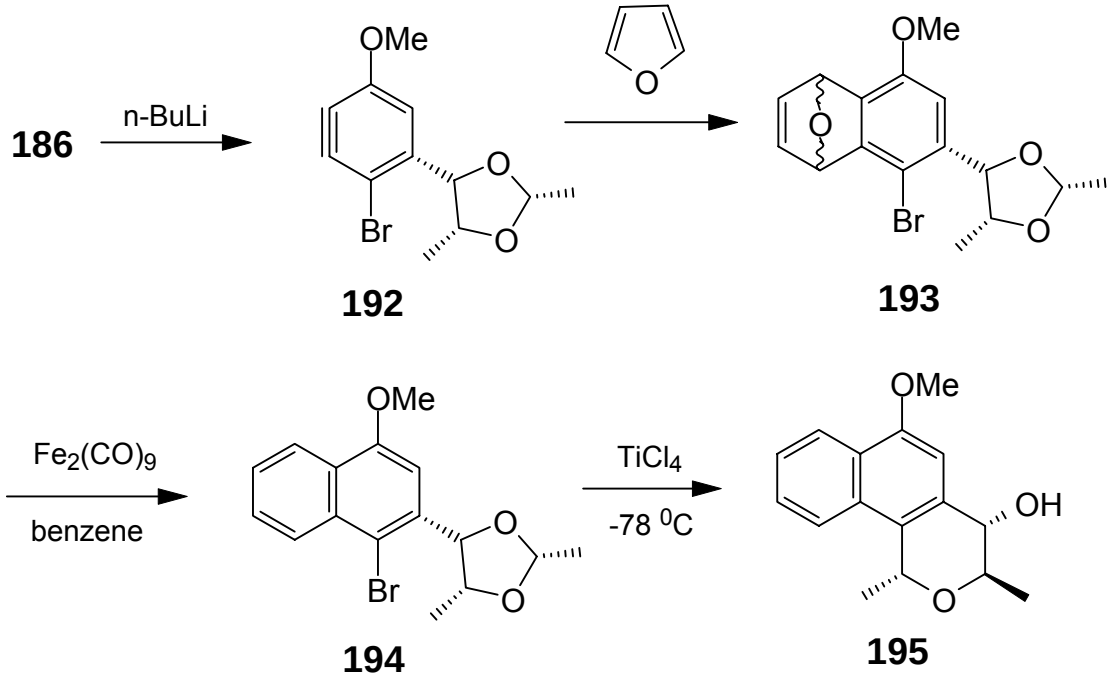
Their stereochemistries were based on the chemical shifts and associated coupling constants of the benzylic protons.

As it was impossible to isomerise the two phenyldioxolanes **186** and **188** to the corresponding benzo[*c*]pyrans **185** (above) and **191** (below), the dioxolane **186** was then converted into the nahphthyldioxolane **194** in scheme 57.



191

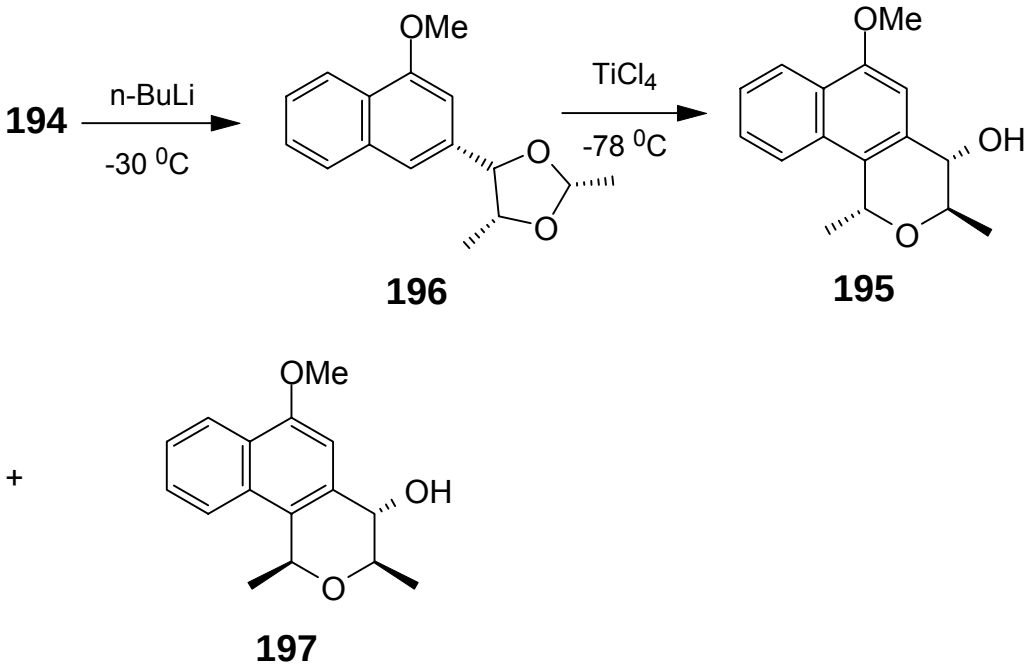
The benzyne **192** was generated by treating the dioxolane **186** with BuLi, which was converted into the diastereoisomeric epoxides **193** (1:1 ratio) in the presence of an excess of furan (87.0 %). These epoxides were deoxygenated by reacting them with $Fe_2(CO)_9$ in benzene, according to the method of Wage and co-workers,[5,44] to afford the target naphthyldioxolane **194** as a single diastereoisomer in a yield of 86.0 %.



Scheme 57:

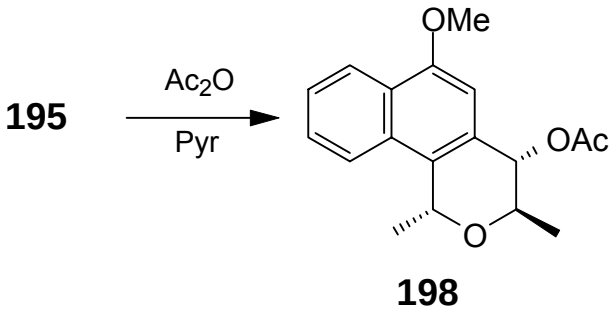
Isomerization of the naphthyldioxolane **194** with 2 equivalents of the $TiCl_4$ at -78 °C yielded the angular naphthopyran **195** in a very low yield of 6.0 % (naphthalenes prefer to undergo electrophilic substitutions at the *alpha*- rather than at the *beta*-position, particularly at low temperatures), plus the starting material. The ring closure to afford the starting material was because of the low reaction temperature and the bulk of the bromine atom, to discourage the displacement of bromine through electron substitution.

In scheme 58 the bromine atom was removed using BuLi at -30 °C to yield the naphthyldioxolane **196** in a yield of 74.0 %, after which it was isomerised with $TiCl_4$ at -78 °C to furnish the two angular naphthopyrans **195** (minor, 14.0 %) and **197** (major, 46.0 %). The naphthopyran **195** was similar to the one obtained from the isomerisation of the brominated naphthyldioxolane **194**. Isomerisation of the naphthyldioxolane **196** was also attempted at -95 °C and -30 °C to determine if the change in temperature would have an effect on the ratio of the products, and yet there was no effect.

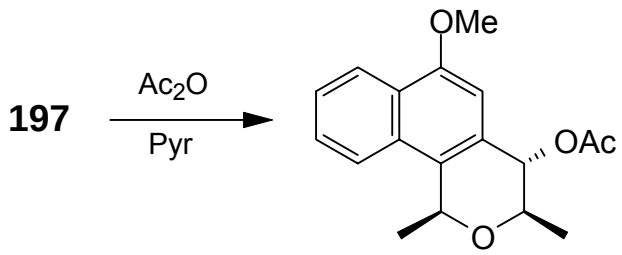


Scheme 58:

These naphthopyrans were then acetylated (schemes 59 and 60), to produce the acetylated naphthopyrans **198** and **199**, to confirm that they were naphthopyrans instead of the naphthofuran **200** below.

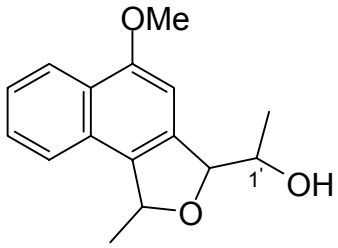


Scheme 59:



199

Scheme 60:

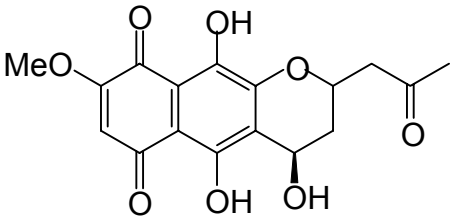


200

Benzynes were generated from the 1,2-dibromo-3-tosylates **179** and **186** through the elimination of the *ortho*-bromotosylate rather than the *ortho*-dibromo substituents. The phenyldioxolane did not isomerise to the benzo[*c*]pyran **185**, because the aromatic ring of **186** was not electron rich or **185**'s aromatic system was going to be crowded. The more electron rich analogue **188** underwent cleavage on reacting with $TiCl_4$ producing unwanted chlorohydrins **189** and **190**. The naphthyldioxolane **194** gave a very low yield of the angular naphthopyran **195**. Isomerisation of the naphthyldioxolane **196** led to the formation of two angular naphthopyrans **195** and **197** in good yield. The vicinal stereochemistry at C-4 and C-5 of the dioxolanes was transferred unaltered to C-4 and C-3 of the product benzo[*c*]pyrans. The substituents at C-1 and C-4 were *trans* related in the major isomer **197**, which differed from all earlier observations.[25]

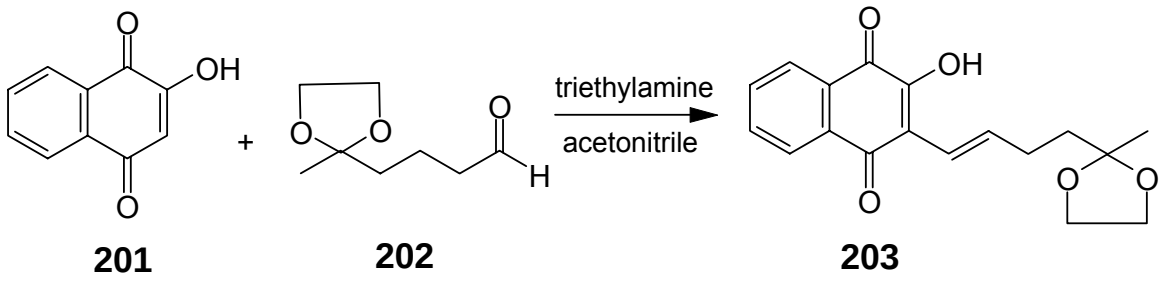
4.7. The DDQ mediated cyclization of some naphthoquinones.[2]

Ameer *et al*.[2] have tried to synthesize molecules that could be transformed into naphthopyrans having similar structural features to the biologically active erythrostominone **33**.[13,27]

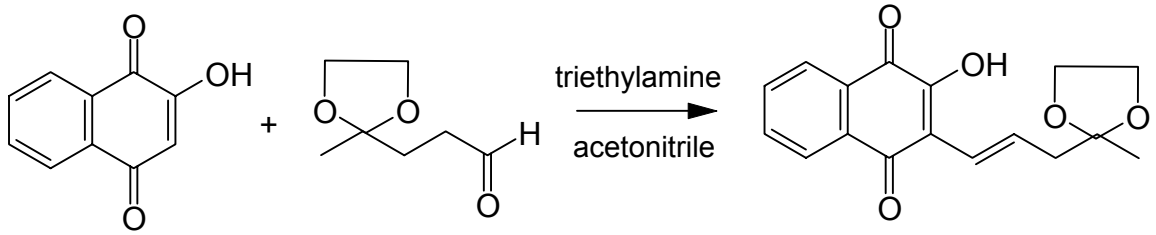


33

A condensation reaction between the aldehyde **202** and the lawsone **201** in acetonitrile at 75 °C, in the presence of triethylamine afforded the alkenyl condensation product **203** in 56.0 % yield. The quinone **205** (60.0 %) was the result of a condensation reaction between lawsone **201** and the aldehyde **204** as depicted in scheme 61.



201 **202** **203**

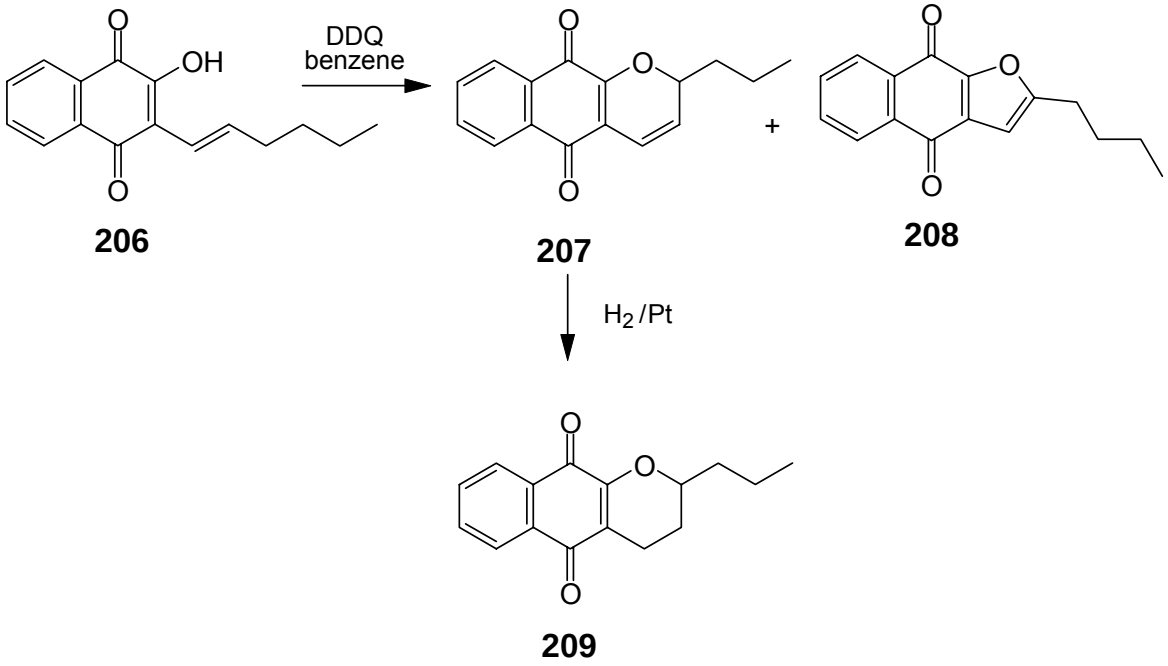


201 **204** **205**

Scheme 61:

Quinone **206**[1] was treated with 1.2 mol equivalents of the DDQ in benzene, at 60 °C for 2 hours to yield the dehydronaphthopyranquinone **207** as a minor (5.0 %) and the naphthofuranquinone **208** as a major (70.0 %) (scheme 62). Repeating the reaction at 25 °C for 18 hours resulted into the formation of the pyranquinone **207** in 42.0 % yield and the furanquinone **208** in 43.0 % yield. Performing the reaction at 8 °C for 36 hours gave rise to the sole product of the pyranquinone **207** in 78.0 % yield. It was speculated that thermodynamic factors were of greater significance than kinetic ones at the lowest temperature.

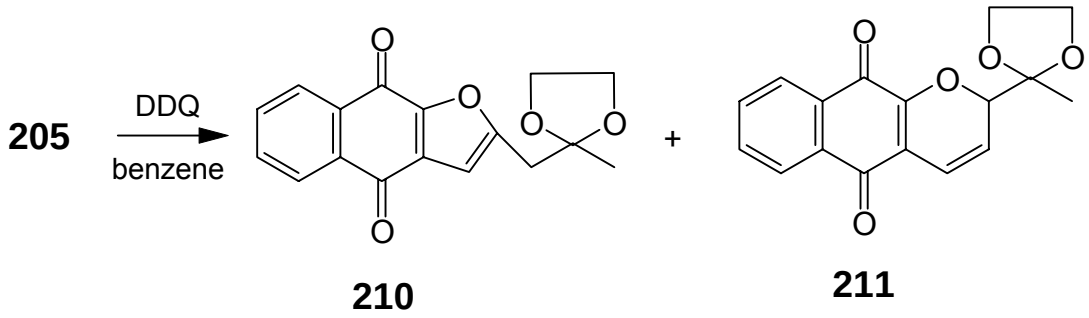
The double bond of the dehydropyran ring was easily reduced by catalytic hydrogenation of the dehydronaphthopyranquinone **207** into the corresponding naphthopyranquinone **209**.



206 **207** **208** **209**

Scheme 62:

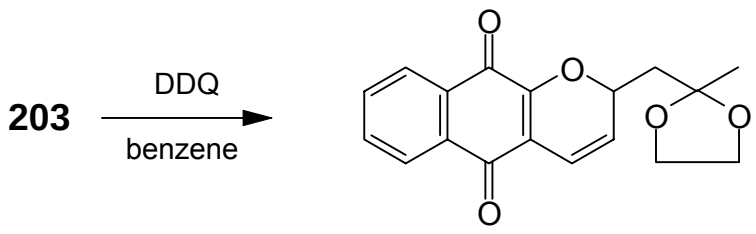
Treatment of the alkenyl quinone **205** with 1.2 mol equivalents of the DDQ in benzene at 60 °C for 2.5 hours afforded two products, the naphthofuranquinone **210** as a major (54.0 %) and the minor product as the dehydronaphthopyranquinone **211** (24.0 %) (scheme 63). The same reaction at 8 °C for longer hours improved the yield of the pyranquinone **211**, 38.0 % for the quinone **210** and 32.0 % for the quinone **211**. It was assumed that the near proximity of the dioxolane ring to the tricyclic ring system might have had an effect on the ratio.



210 **211**

Scheme 63:

On treating the alkenyl quinone **203** with 1.2 mol equivalents of the DDQ in benzene, at 25 °C for 12 hours gave rise to the sole product of the dehydronaphthopyranquinone **212** in a 68.0 % yield. At a higher temperature of 60 °C for 2 hours in benzene , the reaction afforded the same product **212** in 60.0 % yield (scheme 64).



212

Scheme 64:

Therefore a new strategy was developed for the synthesis of the intermediates **209**, **211** and **212** which could be transformed into the trideoxyerythrostominone analogues to be used for biological evaluations.

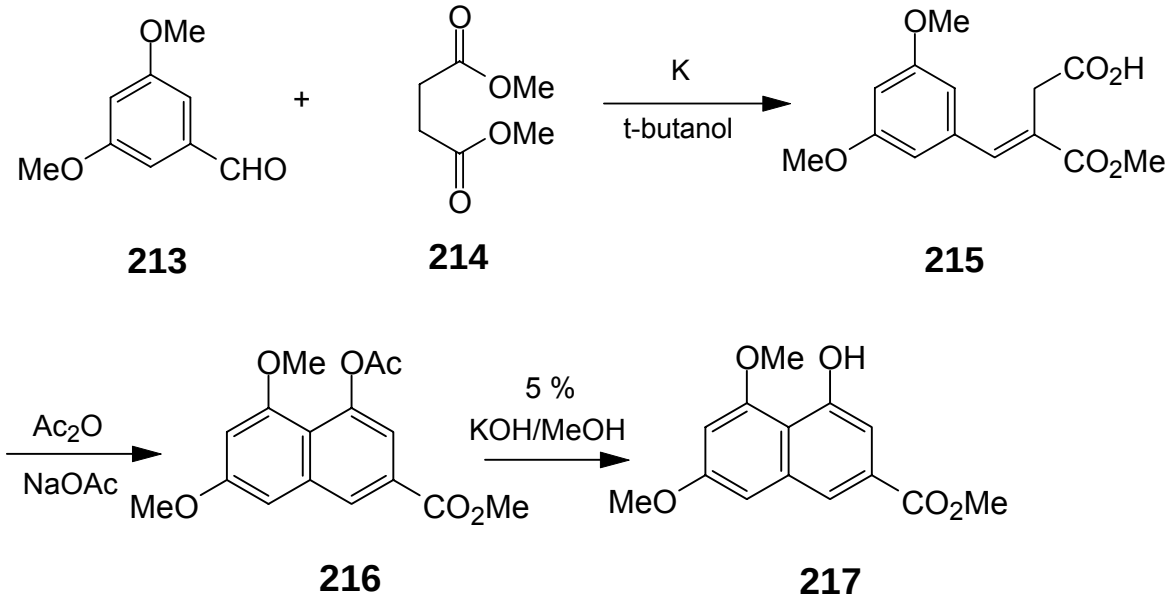
Chapter 5:

Our approach to linear naphtho[2,3-*c*]pyrans: Results and discussion:

In the light of the difficulties in some cases described earlier in chapter 4 to obtain linear naphtho[2,3-*c*]pyrans rather than angular pyrans, we started on a new approach for the synthesis of some linear pyrans.

Our strategy was to place a methoxy group at position 1 and a bromine atom at position 4 of a naphthyldioxolane **1**.

The starting materials for the synthesis of the target linear naphthopyran **3** were the commercially available 3,5-dimethoxybenzaldehyde **213** and the dimethyl succinate **214**.



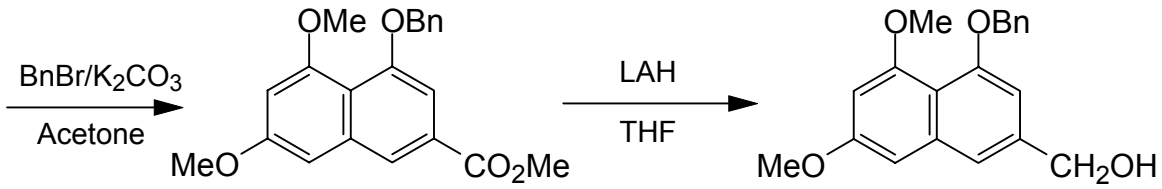
Scheme 65:

A solution of the aldehyde **213** and dimethyl succinate **214** in dry *tert*-butanol was dripped into a refluxing solution of potassium in dry *tert*-butanol under an atmosphere of N_2. The resultant solution was heated and stirred under reflux, under N_2 to produce an oil. The unpurified oil **215** was then mixed with anhydrous NaOAc and boiled under reflux in Ac_2O overnight, under an atmosphere of N_2, to yield the naphthoate **216**, in a low yield of 26.9 % (scheme 65).

It was noted [21,23,32] that the J^4 coupling constant for the naphthyl protons 5- and 7-H is 2.2 Hz, while 2- and 4-H is 1.4 Hz, and this fact has been used for *inter alia* assigning structures to the different products of the synthesis. The proton NMR spectrum of the acetate displayed

four 1-proton signals in the aromatic region, J^4 coupling (*meta* coupled) between the 7- and 5-H to be 2.2 Hz, at 6.59 ppm, a doublet, and 6.84 ppm, a doublet, respectively, and between the 4- and 2-H to be 1.4 Hz at 7.48 ppm, a doublet, and 8.31 ppm, a doublet, respectively. The 7-H was shielded compared to the 5-H due to the two electron donating OMe groups next to it, compared to one OMe group next to the 5-H. The same applied to the 2-H, which was deshielded compared to the 4-H, because it was next to two electron withdrawing groups, and the 4-H was next to one electron withdrawing group. This fact was going to assist in assigning structures to the bromination products later on in the synthesis. The presence of the methoxy and methyl protons were also confirmed by the proton NMR spectrum. The IR spectrum showed a strong signal at 1725.00 cm^{-1} due to the carbonyl (C=O) stretch of the acetate group. The MS had the expected M^+ signal at m/z 304.

Chemoselective removal of the phenolic acetate ester group was performed by dissolving the acetyl acetate **216** in hot MeOH, and then adding the KOH/MeOH mixture. The whole mixture was stirred at room temperature for 4 hours to afford the naphthol **217** in a reasonable yield of 89.3 %. The proton spectrum showed, the absence of the acetate signal at 2.36 ppm, the presence of the OH signal at 9.15 ppm, a proton signal at 7.29 ppm, a doublet due to 2-H, and a proton signal at 7.93 ppm, a doublet due to 4-H. The 2-H signal was shielded due to the electron donating group OH next to it, and the 4-H signal was deshielded due to the electron withdrawing group next to it. All the other signals corresponded to those of the starting material. The IR spectrum displayed the OH signal at 3375.28 cm^{-1} and the C=O signal at 1714.21 cm^{-1} . The MS had the M^+ peak at m/z 262, confirming the produced naphthol.



218 **219**

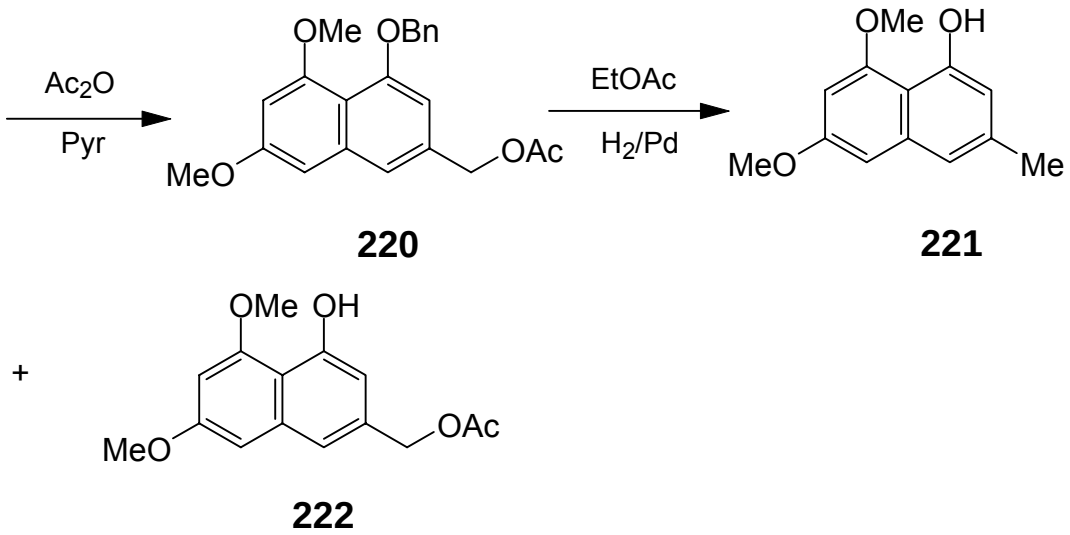
Scheme 65 cont.:

The naphthol **217** was then dissolved in acetone and treated with four mole equivalents of benzyl bromide (BnBr) and excess potassium carbonate. The mixture was heated and vigorously stirred under reflux for 24 hours to yield the benzyl ester **218** in a very high yield of 98.0 %.

The proton NMR showed a notable singlet of 2H at 5.26 ppm due to the -CH_2Ph of the benzyl group at position 1, substituting the hydrogen of the OH group that was in the naphthol. The

5 aryl-protons of the phenyl group were noted at 7.39 ppm. The IR also indicated the absence of the OH group in its region of the IR spectrum, and the presence of the C=O at 1716.91 cm^{-1}. The M^+ signal of the MS at m/z 352 confirmed the benzyl ester **218**.

The benzyl ester **218** in dry THF was reduced by treating it with the LAH in dry THF under N_2 at room temperature, to yield the benzyl alcohol **219** (60.0 %). The disappearance of the C=O peak and the appearance of the OH peak at 3515.50 cm^{-1} in the IR spectrum confirmed that the reduction was successful. In the proton NMR spectrum there was an absence of the third OMe peak due to reduction, and the appearance of a singlet, for 2H at 4.76 ppm which was due to the -CH_2OH group at position 3. There was a little shift in the 2-H, 4-H, 5-H and 7-H signals' positions probably due to the change in the functional group at position 3. The MS produced the expected M^+ signal at m/z 324, confirming the reduction.

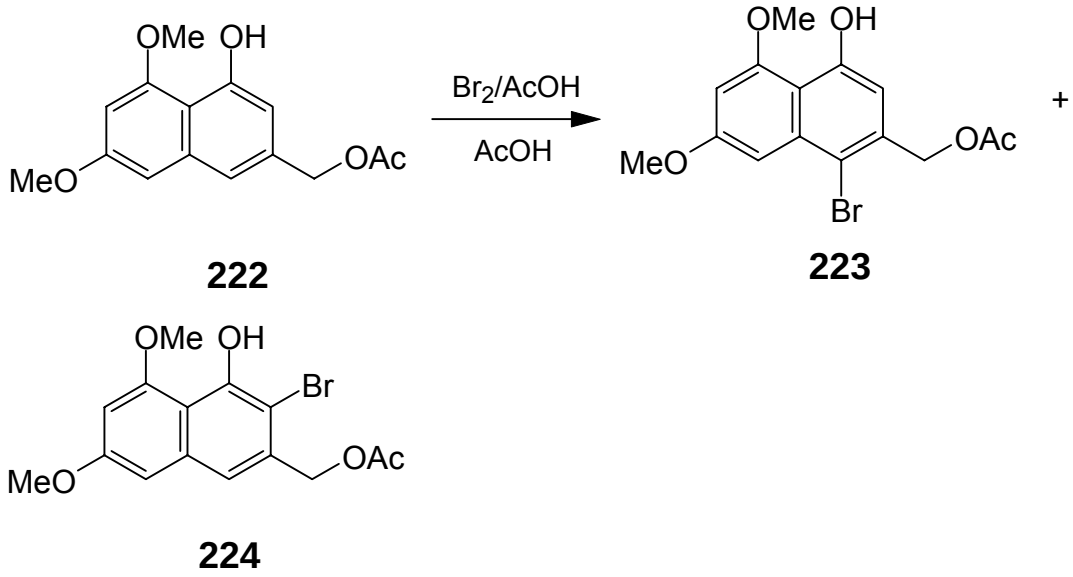


Scheme 65 cont.:

The benzyl alcohol **219** was acetylated by stirring its mixture with Ac_2O and pyridine for 24 hours to give rise to the benzyl ester **220** in a good yield of 88.0 % (scheme 51). The tlc plate showed the occurrence of a reaction, and the IR spectrum showed the C=O peak at 1743.87 cm^{-1} and the absence of the OH peak. The proton NMR spectrum displayed a singlet of 3H which was due to the OAc protons at 2.14 ppm. The molar mass was confirmed by the MS signal at m/z 366 for the ester. A mixture of the benzyl ester **220** in EtOAc containing Pd/C and concentrated HCl was catalytically hydrogenated at atmospheric pressure to get rid of the benzyl group at position 1. The resultant product was a mixture of the 3-methyl naphthol **221**, in a 17.4 % yield, which was due to overhydrogenation of the ester.. The second naphthol was the naphthol **222** obtained in a yield of 90.0 %. The MS, IR and the NMR spectra confirmed the differentiation of the two products. The IR spectrum of the naphthol **221** showed the absence of the C=O signal (OAc) and the OH signal at 3363.53 cm^{-1}, whilst

that of the naphthol **222** showed the C=O signal at 1737.01 cm^{-1} and that of the OH group at 3359.60 cm^{-1}.

The proton NMR of the naphthol **221** had a singlet, for 3H at 2.39 ppm for the 3-CH_3 functional group whilst that of the naphthol **222** had a singlet, for 3H, at 2.13 ppm for the OAc functional group and a singlet, for 2H at 5.14 ppm for the CH_2-OAc group. The MS had the M^+ signal at m/z 218 for the naphthol **221** and M^+ signal at m/z 276 for the naphthol **222**. The important naphthol for the synthesis was the 3-acetoxymethyl-6,8-dimethoxy-1-naphthol **222**.



222 **223**

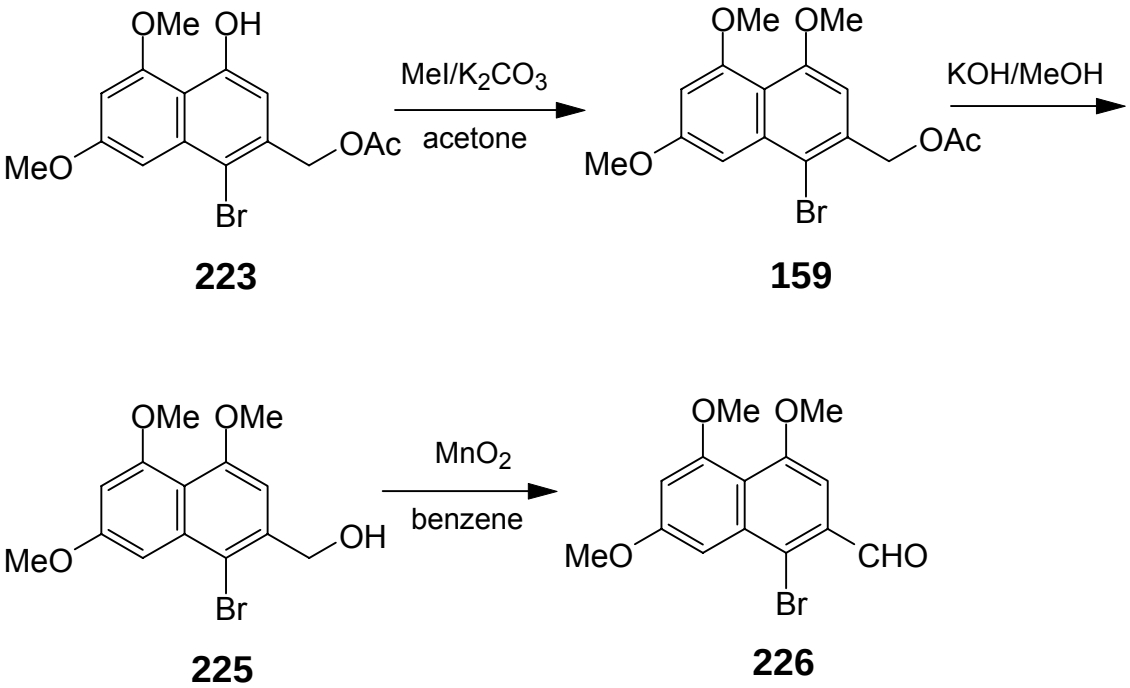
224

Scheme 66:

Bromination of the naphthol **222**, in scheme 66, was by adding bromine in AcOH to a stirred solution of the naphthol **222** in AcOH, in a ratio of 1:1,[32,33] under N_2 , and the mixture was stirred for about 50 minutes. The resultant product was a mixture of the 4- and the 2-bromo naphthols, which were difficult to separate by column chromatography. The first to elute was the 4-bromonaphthol **223** in a yield of 54.2 %, and the second was the 2-bromonaphthol **224** in a yield of 36.1 %, in a ratio of about 5:3.

The proton NMR spectrum of the 4-bromonaphthol **223** displayed a singlet, for 1H at 6.81 ppm for the 2-H, indicating that the proton that used to couple with at position 4 had been displaced by the Br, whilst that of the 2-bromonaphthol **224** displayed a singlet, for 1H at 7.24 ppm for the 4-H, indicating that the proton at position 2 had been displaced by the bromine, since there was no coupling between the two protons. The 7-H doublet signal for the 4-bromonaphthol **223** was at 6.52 ppm (*J* 2.2 Hz) and that for the 2-bromonaphthol **224** at 6.50 ppm (*J* 2.2 Hz). In the former naphthol the 5-H signal had been deshielded, by about 0.58

ppm, due to the bromine at position 4. The 5-H doublet signal was at 7.21 ppm (*J* 2.2 Hz) for the 4-bromonaphthol **223** and was at 6.69 ppm (*J* 2.2 Hz) for the 2-bromonaphthol **224**. The OH signal of the 4-bromonaphthol **223** was at 9.28 ppm and that of the 2-bromonaphthol **224** at 9.89 ppm, indicating the deshielding effect of the bromine at position 2 for the 2-bromonaphthol **224**. The molecular ions observed for the two brominated naphthols **223** and **224** were at m/z 355 and 357 . The almost 1:1 (M^+ and $M^+ + 2$) ratio indicated the presence of the bromine atoms in the two structures.



Scheme 67:

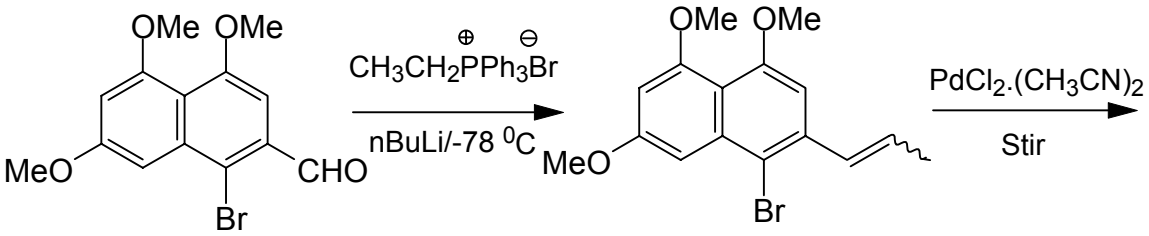
For the synthesis of the linear naphthopyrans the important product was the 4-bomonaphthol **223**, since one of the objectives was to have a dioxolane with a bromine atom at position 4 and a OMe group at position 1. The next step was to get the OMe group at position 1 as in scheme 67.

The 4-bromonaphthol **223** was dissolved in dry acetone and reacted with K_2CO_3 and iodomethane (methyl iodide), after which the whole mixture was vigorously stirred under reflux for 24 hours to afford the trimethoxy acetate **159** in a good yield of 86.5 %. This was confirmed by the presence of the third OMe group signal in its proton NMR spectrum at either of the three peaks, 3.94, 3.95 or 3.96 ppm as singlets, and the absence of the OH signal. The IR spectrum also exhibited the absence of the OH absorption. The molecular ion was observed at m/z 368:370 (1:1), confirming the trimethoxynaphthalene.

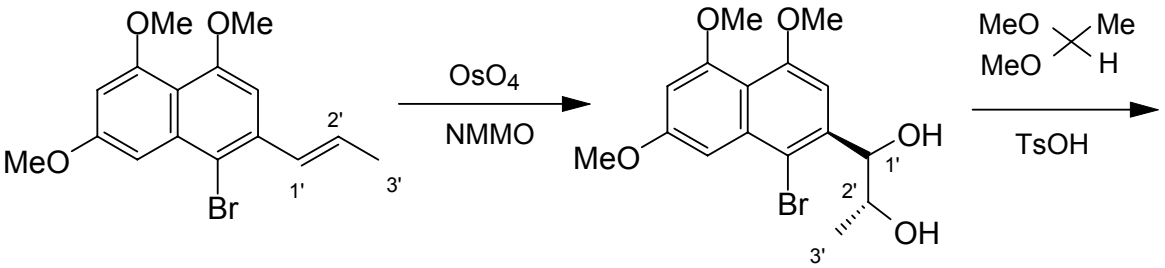
The 4-bromoacetate **159** was reacted with a methanolic solution[32] of KOH to afford the alcohol **225** in a good yield of 90.2 %. Assignment of the structure was based on the IR spectrum displaying the OH peak at 3292.41 cm^{-1}, the absence of the C=O (OAc) peak, and the M^+ signal of the alcohol at m/z 326:328 (1:1). In the proton NMR spectrum the OH peak was absent.

The alcohol **225** in benzene containing MnO_2 was stirred and heated under reflux[32] to yield the aldehyde **226** in a reasonable yield of 83.9 %.

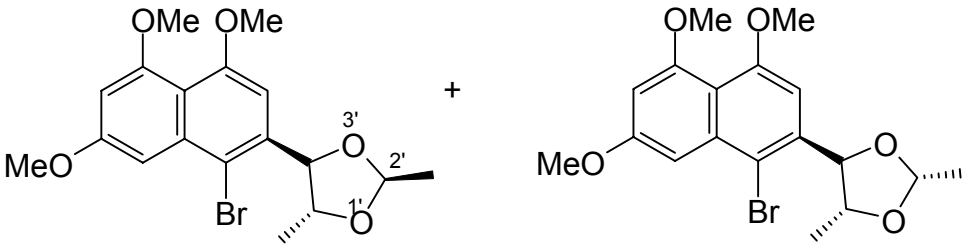
The proton NMR spectrum exhibited the deshielded singlet, for 1H, at 10.61 ppm for the CHO group and there was no CH_2OH peak. The 2-H signal was deshielded from 6.93 to 7.17 ppm due to the electron withdrawing group, the CHO at position 3. The IR spectrum exhibited the presence of the C=O (CHO) signal at 1672.59 cm^{-1} and the absence of the OH signal. The MS had the expected M^+ signal at m/z 324:326 (1:1), confirming the molecular formula of the aldehyde **226**.



226 **227**



166 **228**



229 **230**

Scheme 67 cont.:

The aldehyde **226** was subjected to a Wittig reaction,[32] by adding its solution in dry THF into a stirred suspension of ethyltriphenylphosphonium bromide in dry THF containing nBuLi under N_2 at -78 °C. The product was a mixture of the *cis*- and *trans*-olefins **227** which was treated with *bis*(acetonitrile)dichloropalladium(II)[20] to convert the *cis*- to the *trans*-olefin **166** in a low yield of 44.4 %.

The IR spectrum displayed the absence of the C=O stretch and the presence of the C=C stretch at 1617.32 cm^{-1}. The proton NMR spectrum showed the absence of the deshielded CHO peak, the presence of the new peaks, a doublet of a doublet for 3H, *J* 6.6 and 1.8 Hz at 1.97 ppm due to the 3'-CH_3, a doublet of a quartet for 1H, *J* 15.8 and 6.6 Hz at 6.27 ppm due to the 2'-H, and a doublet of a quartet for 1H, *J* 15.4 and 1.8 Hz at 6.98 ppm due to 1'-H. The singlet 2-H peak was also shielded in the *trans*-olefin from 7.17 ppm in the aldehyde to 6.54 ppm. The molecular ion observed was at m/z 336:338 confirming the olefin structure.

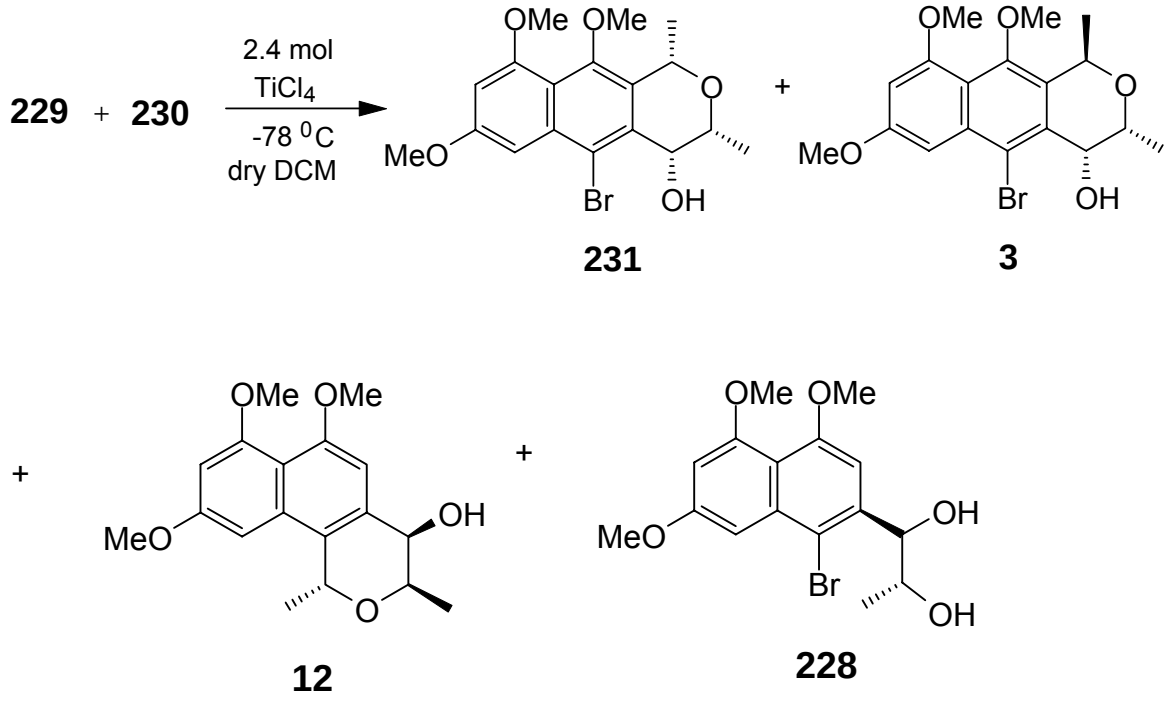
In 1976 Van Rheenen *et al*.[52] showed that the reaction of an olefin with OsO_4 is the most reliable method for *cis*-dihydroxylation of a double bond, and the presence of NMMO gives a faster reaction rate. Later on in 1980 Ray *et al*.[46] demonstrated that the OsO_4 catalyzed hydroxylation of sterically hindered olefins proceed efficiently with trimethylamine N-oxide as an oxidizing agent in the presence of pyridine, and NMMO plus OsO_4 was shown to be highly successful with less hindered olefins.[52] NMMO was used to regenerate OsO_4 allowing glycolization to proceed whilst the OsO_4 was used as an oxidant.

The *trans*-olefin **166** was dissolved in acetone:water (2:1)[24] and treated with NMMO and OsO_4 in *tert*-butanol at 0 °C and stirred at room temperature to afford the diol **228** in a very high yield of 99.2 %. The IR spectrum exhibited the presence of the OH stretch at 3258.29 cm^{-1}. The proton NMR spectrum displayed the doublet for 3H, *J* 6.2 Hz, at 1.23 ppm for the 3'-CH_3, the two OH signals, each 1H as a singlet, at 2.46 and 3.0 ppm, a doublet of a quartet for 1H, *J* 6.6 and 6.2 Hz, at 4.06 ppm for the 2'-H and a doublet for 1H, *J* 6.6 Hz, at 5.18 ppm for the 1'-H. The MS had the expected M^+ signal at m/z 370:372 (1:1) for the diol.

A solution of the diol **228**, acetaldehyde dimethyl acetal and TsOH[23] in benzene was heated under reflux in a Dean-Stark apparatus to yield a mixture of the dioxolanes **229** and **230**, epimeric at position 2', in a 99.8 % yield. These were found to be in a ratio of (2:1). The mixture displayed the following proton NMR signals, doublets for 12H, at 1.48 – 1.60 ppm assigned to the 2'- and 5'-CH_3, singlets for 18H, at 3.95, 3.96 and 3.97 ppm assigned to 6 x OMe and 5'-H obscured by the OMe signals, a doublet of a quartet for 1H, *J* 6.6 and 5.0 Hz, at 4.11 ppm assigned to the 5'-H, a doublet for 2H, *J* 5.6 Hz at 5.32 ppm assigned to the 4'-

H, a quartet for 1H, *J* 5.2 Hz at 5.48 ppm assigned to the 2'-H of the major isomer **229**, a quartet for 1H, *J* 4.8 Hz at 5.59 ppm assigned to the 2'-H of the minor isomer **230**, a doublet for 2H, *J* 2.2 Hz at 6.57 ppm assigned to the 7-H, a singlet for 1H, at 6.84 ppm assigned to the 2-H of the minor isomer **230,** a singlet for 1H, at 6.96 ppm assigned to the 2-H of the major isomer **229**, and a doublet for 2H, *J* 2.2 Hz at 7.30 ppm assigned to the 5-H.

The IR spectrum displayed two peaks at 1596.06 and 1200.62 cm^{-1}due to C=C and C-O-C functionalities. The MS had the expected M^+ signals at m/z 396:398 (1:1), supporting the molecular formula of the dioxolanes **229** and **230**.



Scheme 67 cont.:

The mixture of the dioxolanes **229** and **230** in dry DCM[32] was treated with $TiCl_4$ at -78 °C, under an atmosphere of N_2, to afford four products as indicated by tlc. These in our opinion could be **3**, **12**, **228** and **231** as shown in scheme 67. Due to the low yields of some of these products, only compounds **3** and **228** could properly be characterised.

Chromatography and purification afforded the alcohol **3** in a yield of 53.0 %. The IR spectrum showed a peak at 3454.50 cm^{-1} due to the OH. The proton NMR spectrum showed the following signals, 3-protons, a doublet, *J* 6.2 Hz, at 1.46 ppm assigned to the 3-CH_3, 3-protons, a doublet, *J* 6.2 Hz, at 1.61 ppm assigned to the 1-CH_3, 1-proton, a broad singlet, at 1.76 ppm assigned to the OH group, 9-protons, 3 x singlets, at 3.80, 3.96 and 3.98 ppm assigned to the three OMe groups, 1-proton, a doublet of a quartet, *J* 1.4 and 6.2 Hz, at 4.19 ppm, assigned to the 3-H, 1-proton, a doublet, *J* 1.4 Hz, at 4.77 ppm assigned to the 4-H, 1-

proton, a quartet, *J* 6.2 Hz, at 5.32 ppm assigned to the 1-H, 1-proton, a doublet, *J* 2.6 Hz, at 6.59 ppm assigned to the 8-H, and 1-proton, a doublet, *J* 2.6 Hz, at 7.32 ppm assigned to the 6-H. The molecular ion was observed at m/z 396:398 (1:1), confirming the molecular formula of the linear naphthopyran **3**, as well as the diol **228** (36.5 %) whose retention time on the tlc plate was the same as the one produced in scheme 67. The IR, NMR and MS results were also the same as for the diol **228** in scheme 67.

Chapter 6:

Conclusion:

The Br atom at position 4 of dioxolanes **229** and **230** did assist in forcing isomerization to occur at position 2, to obtain a linear naphthopyran **3**.

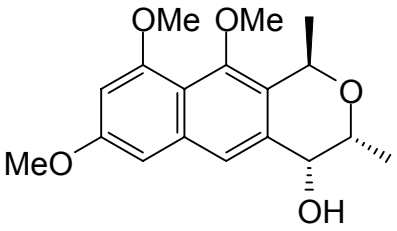
The OMe group at position 1 of dioxolanes **229** and **230**, due to its less steric hindrance, compared to the isopropoxy group of the dioxolanes **8** and **94**, allowed isomerization to occur at position 2.

Therefore the objectives of the research were met with an improved percentage yield of the linear naphthopyran **3**.

Further work:

We are envisaging to use pyran **3** in a model route to afford an extended quinone of the type **13** or **14** shown earlier.

It is also envisaged to debrominate **3** to afford pyran **232** and to use this compound or its derivative in a coupling reaction with a suitable naphthopyranquinone to afford an extended quinone.



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Chapter 7:

Experimental – General procedures:

NMR spectra were recorded using a VARIAN 200 spectrometer (H^1, 200 MHz; C^{13} 50 MHz) at UWC. All recorded spectra were run at ambient temperature in deuterated chloroform ($CDCl_3$) solution, with $CHCL_3$ at *delta* 7.26 for H^1 NMR spectra and at *delta* 77.00 for C^{13} spectra as internal standards. Coupling constants (*J*) are given in Hz. The splitting patterns s, d, t, q and m indicate singlet, doublet, triplet, quartet and multiplet.

IR spectra were measured as Nujol mulls for solids and as thin films between KBr plates for oils using a PERKIN ELMER FT-IR Spectrometer, Spectrum 1000. High resolution mass spectra were performed at Wits. Melting points were determined on a Fischer-John apparatus. Residue obtained upon work-up refers to the material that remains when the organic layer has been separated, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure.

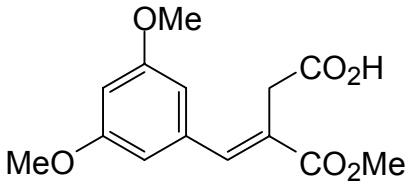
The solvents used for the reactions and column chromatography were distilled prior to use. *Tert*-butanol was dried using distillation, $MgSO_4$ and sodium pieces under N_2. THF was heated under reflux over NaH, distilled and heated under reflux with benzophenone and sodium to dry, distilled and stored over molecular sieves . The DCM was dried by refluxing over phosphorous pentoxide, distilled and stored over molecular sieves.

Chromatography was carried out on dry columns using Merck Silica gel 60 (0.2-0.5 mm) for preadsorption and Merck Silica gel 60 (0.063-0.2 mm) as the stationary phase. Mixtures of the EtOAc and Hex in different ratios were used as the mobile phase. Merck Silica gel 60 F_{254} TLC aluminium sheets (20 x 20 cm) were used for thin layer chromatography. Compounds were routinely visualised under short wavelength (254 nm) and long wavelength (365 nm) ultraviolet light.

Chapter 8:

Experimental Procedures:

1. *E and Z-methoxycarbonyl-4-(3', 5'-dimethoxyphenyl) but-3-enoic acid* ***215****.*

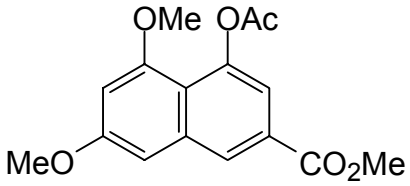


215

The 3,5-dimethoxybenzaldehyde **213** (10.06 g; 60.6 mmol) in dry *tert*-butanol (25 ml) containing the dimethyl succinate **214** (10 ml; 76.5 mmol) was dripped into a refluxing solution of potassium (2.71 g; 69.4 mmol), in dry *tert*-butanol (75 ml) under nitrogen. The resultant solution was heated and stirred under reflux, under nitrogen for a further 30 minutes. The yellow mixture was then allowed to cool and then water (400 ml) was added, followed by concentrated HCl (10 ml) until the solution was acidic (to litmus paper).

The mixture was extracted into DCM (3 x 80 ml) and the solvent evaporated to produce an oil. The oil was dissolved in saturated aqueous sodium hydrogen carbonate, washed with diethyl ether (1 x 150 ml), the bicarbonate solution was acidified with concentrated HCl. The oil that separated was extracted into DCM (3 x 80 ml), dried with Mg_2SO_4, filtered and evaporated to a dark yellow oily product **215** (8.38 g; 49.4 %).

2. *Methyl 1-Acetoxy-6,8-dimethoxy-3-naphthoate* ***216****.*



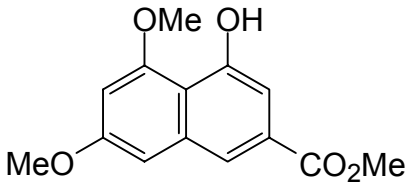
216

The unpurified oil **215** (7.75 g; 27.7 mmol) was mixed with sodium acetate (5,21 g; 63.5 mmol) and boiled under reflux in acetic anhydride (60 ml) overnight under N_2. The cooled solution was added to 620 ml of ice cold water (oil separated). This was transferred into a separating funnel and extracted into DCM (3 x 70 ml). $NaHCO_3$ (250 ml) was added to the DCM layer to neutralise any acetic acid formed. The DCM layer was then dried with $MgSO_4$,

filtered and evaporated to a residue. This was chromatographed using EtOAc:Hex (3:7) as an eluent to obtain the acetate **216** as yellow crystals (2.27 g; 26.9 %), mp 154-155 °C (from EtOH), ν_{max}/cm^{-1} 1725.00 (C=O). *Delta* H ppm, 2.36 (3H, s, OAc); 3.89 (6H, s, 2 x OMe); 3.94 (3H, s, OMe); 6.59 (IH, d, *J* 2.2, 7-H); 6.84 (IH, d, *J* 2.2, 5-H); 7.48 (IH, d, *J* 1.4, 4-H) and 8.31 (IH, d, *J* 1.4, 2-H).

[Found: C, 63.1; H, 5.1 %; M^+ 304(25); 262 (100); 219 (38), Calc. For $C_{16}H_{16}O_6$; C, 63.2; H, 5.3 %; M, 304]

3. *Methyl 1-Hydroxy-6,8-dimethoxy-3-naphthoate **217**.*



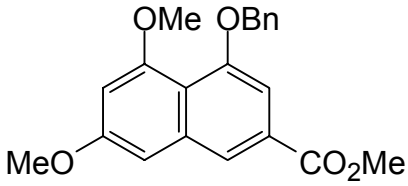
217

The acetyl acetate **216** (1.0 g; 3.29 mmol) was dissolved in MeOH (30 ml) and 5.0 % KOH/MeOH (4 ml) was added. The mixture was heated and stirred to dissolve the solids after which it was stirred at room temperature for 4 hrs. The mixture was then acidified with concentrated HCl and diluted with water (400 ml). The resultant solids were filtered and the cake dried. The filtrate was extracted with DCM (3 x 100 ml), dried with $MgSO_4$, filtered and evaporated to a residue of the fine light yellow solids of the naphthol **217** (0.77 g; 89.3 %), mp 158-163 °C (from EtOH), ν_{max}/cm^{-1} 3375.28 (O-H) and 1714.21 (C=O). *Delta* H ppm, 9.15 (1H, s, D_2O exchangeable 1-OH); 3.89, 3.94 and 4.03 (each 3H, s, 3 x OMe); 6.55 (IH, d, *J* 2.2, 7-H); 6.81 (IH, d, *J* 2.2, 5-H); 7.29 (IH, d, *J* 1.6, 2-H) and 7.93 (IH, d, *J* 1.6, 4-H).

Delta C ppm, 52.3, 55.5 and 56.4 (3 x OMe); 99.8 (C-7); 100.7 (C-5)[a]; 108.1 (C-2)[a]; 113.1 (C-3)[a]; 120.6 (C-4)[a]; 129.8 (C-4a)[b]; 136.8 (C-8a)[b]; 154.8 (C-1)[c]; 157.1 (C-8)[c]; 158.3 (C-6)[c]; 167.2 (C=0). Assignments with the same superscripts may be exchanged.

[Found: C, 64.0, H, 5.2 %; M^+ 262 (100); 219 (60); 204 (30); 189 (50). Calc. For $C_{14}H_{14}O_5$; C, 64.1; H; 5.3 %; M 262]

4. *Methyl 1-Benzyloxy-6,8-dimethoxy-3-naphthoate* ***218****.*

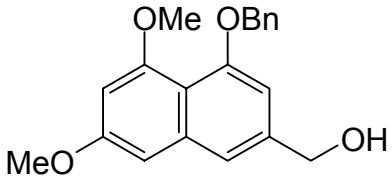


218

The naphthol **217** (480 mg; 1.83 mmol) in acetone (40 ml) was treated with BnBr (0.54 ml; 4.6 mmol) and K_2CO_3 (632 mg; 4.58 mmol) and the mixture was heated and vigorously stirred under reflux for 24 hrs, cooled and filtered. The residue obtained on evaporation was chromatographed using EtOAc:Hex (3:7) as an eluent to yield the benzyl ester **218** as white crystals (630 mg; 98.0 %), mp 123-128 °C (from Hex), ν_{max} /cm^{-1} 1716.91 (C=O). *Delta* H ppm, 3.91, 3.93 and 3.97 (each 3H, s, 3 x OMe); 5.26 (2H, s, -CH_2-Ph); 6.61 (IH, d, *J* 2.2, 7-H); 6,82 (IH, d, *J* 2.2, 5-H); 7.39 (5 aryl-H, m, hiding 2-H) and 8.06 (IH, d, *J* 1.2, 4-H).

Delta C ppm, 52.4, 55.43 and 56.19 (3 x OMe); 71.2 (O-CH_2-Ph); 100.12 (C-7); 101.05 (C-5); 104.96 (C-2); 113.6 (C-3); 123.23 (C-1); 127.02 (C-2'/6')[a]; 127.6 (C-4'); 128.46 (C-3'/5')[a]; 128.51 (C-1'); 137.45 (C-4a)[b]; 137.492 (C-8a)[b]; 156.68 (C-1)[c]; 158.48 (C-8)[c]; 158.8 (C-6)[c] and 167.32 (C=0). Assignments with the same superscripts may be exchanged.
[Found: C, 71.5; H, 5.6 %, M^+ 352, Calc for $C_{21}H_{20}O_5$; C, 71.6; H, 5.7 %; M, 352].

5. *1-Benzyloxy-3-hydroxymethyl-6,8-dimethoxynaphthalene* ***219****.*



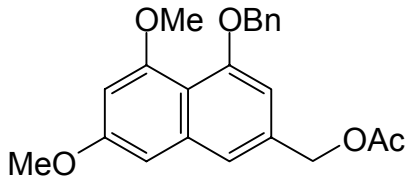
219

Into a slurry of LAH (56 mg; 1.48 mmol) in dry THF (5.6 ml) under N_2 was dripped a solution of the benzyl ester **218** (200 mg; 0.57 mmol) in THF (8.5 ml) at room temperature and stirring was continued until reduction was complete (tlc). Saturated ammonium chloride was added (3 drops) to destroy the excess of LAH and the residue obtained after adding DCM, drying with $MgSO_4$, filtering and evaporating was chromatographed using EtOAc:Hex (2:3) as an eluent to give the benzyl alcohol **219** as white crystals (110 mg; 60.0 %), mp 154-157 °C (from EtOH), ν_{max} /cm^{-1} 3515.50 (O-H). *Delta* H ppm, 1.65 (1H, s, -OH); 3.89 and 3.92 (each 3H, s, 2 x OMe); 4.76 (2H, s, -CH_2OH); 5.18 (2H, s, -CH_2Ph); 6.50 (IH, d, *J* 2.2, 7-H); 6.69

(IH, d, *J* 2.2, 5-H); 6.79 (IH, d, *J* 1.6, 2-H) and 7.42 (2H, 3H, m, aryl-H, and 4-H hidden in the aryl-H).

Delta C ppm, 55.3 and 56.1 (2 x OMe); 65.6 (CH_2OH); 71.3 (CH_2Ph); 98.9 (C-7), 99.0 (C-5); 105.2 (C-2); 113.2 (C-3); 117.9 (C-4); 127.0 (C-3'/5')[a] ; 127.6 (C-4'); 128.4 (C-2'/6')[a] ;128.4 (C-1'); 137.7 (C-4a)[b]; 138.3 (C-8a)[b]; 156.8 (C-1)[c]; 158.5 (C-8)[c] and 158.6 (C-6)[c]. Assignments with the same superscripts may be exchanged.
[Found: C 73.9; H, 6.1 %; M^+ 324. Cal. For $C_{20}H_{20}O_4$; C; 74.0; H, 6.2 %; M, 324]

6. *3-Acetoxymethyl-1-benzyloxy-6,8-dimethoxynaphthalene* ***220****.*

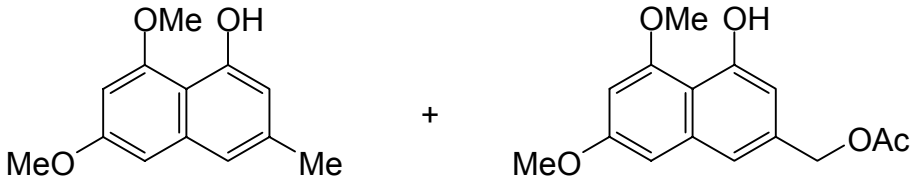


220

The benzyl alcohol **219** (190 mg; 0.59 mmol) in Ac_2O (2.0 ml) and Pyr (0.7 ml) was stirred at room temperature for 24 hrs, after which water (80 ml) was added, and the mixture extracted with ether (3 x 50 ml). The extract was rinsed with 0.1 M HCl followed by water, dried in $MgSO_4$, filtered, evaporated and chromatographed using EtOAc:Hex (1:5) as an eluent to give the benzyl ester **220** as cream crystals (190 mg; 88.0 %), mp 85-87 °C (from Hex), ν_{max} /cm^{-1} 1743.87 (C=O). *Delta* H ppm, 2.14 (3H, s, OAc); 3.89 and 3.92 (each for 3H, s, 2 x OMe); 5.18 (2H, s, CH_2OAc); 5.20 (2H, s, CH_2Ph); 6.52 (1H, d, *J* 2.2, 7-H); 6.71(1H, d, *J* 2.2, 5-H); 6.75 (1H, d, *J* 1. 4, 2-H); 7.28 (1H, d, *J* 1.4, 4-H); 7.42 (3H, m, 3',4' and 5'-H) and 7.62 (2H, dd, 2'- and 6'-H).

Delta C ppm, 21.1 (OAc); 55.4 and 56.2 (2 x OMe); 66.5 (CH_2O); 71.4 (CH_2Ph); 99.1 (C-7)[a]; 99.3 (C-5)[a]; 106.3 (C-2); 113. 6 (C-3); 119.8 (C-4); 127.1 (C-2'/6')[b]; 127.6 (C-4'); 128.4 (C-3'/5')[b]; 134.8 (C-1'); 137.6 (C-4a)[c]; 138.2 (C-8a)[c]; 156.8 (C-1)[d]; 158.6 (C-8)[d]; 158.7 (C-6)[d] and 170.9 (C=0). Assignments with the same superscripts may be exchanged.
[Found: C, 72.0 %; H, 5.9 %; M^+ 366. Calc. For $C_{22}H_{22}O_5$; C, 72.1; H, 6.0 %; M, 366]

7. *3-Acetoxymethyl-6,8-dimethoxy-1-naphthol* ***222,*** *and 6,8-Dimethoxy-3-methyl-1-naphthol* ***221.***



221 **222**

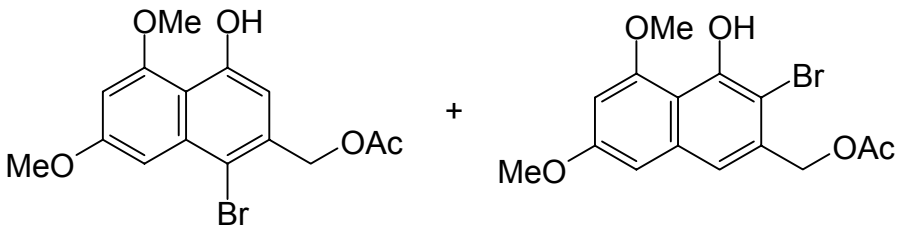
A mixture of the ester **220** (4.82 g; 13.17 mmol) in EtOAc (200 ml) containing Pd/C (400 mg of a 5.0 % mixture) and concentrated HCl (3-4 drops) was hydrogenated at atmospheric pressure and 21 °C and monitored for the uptake of 1 mol equivalent of hydrogen. The filtered solution was evaporated and the residue chromatographed using EtOAc:Hex (3:7) as an eluent to afford the 6,8-Dimethoxy-3-methyl-1-naphthol **221**, as a yellow powder (0.5 g; 17.4 %), mp 77-80°C (from Hex), ν_{max} /cm^{-1} 3364.53 (O-H). *Delta* H ppm, 2.38 (3H, s, 3-CH_3); 3.88 and 4.01 (each 3H, s, 2 x OMe); 6.38 (1H, d, *J* 2.2, 7-H); 6.58 (1H,d, *J* 1.4, 2-H); 6.63 (1H, d, *J* 2.2, 5-H); 6.97 (1H, d, *J* 1.4, 4-H) and 9.03 (1H, s, D_2O exchangeable, 1-OH).

Delta C ppm, 22.7 (3-CH_3) 55.4 (OMe); 56.2 (OMe); 96.9 (C-7); 99.1 (C-5); 109.1 (C-3); 110.5 (C-2); 117.6 (C-4); 137.7 (C-4a)[a]; 138,6 (C-8a)[a]; 154.4 (C-1)[b]; 157.3 (C-6)[b] and 157.9 (C-8)[b]. Assignments with the same superscripts may be exchanged.
[Found: C, 71.4, H, 6.2 %; M^+ 218, $C_{13}H_{14}O_3$, requires C, 71.6; H, 6.4 %; M, 218].
This naphthol was due to the overhydrogenation of the ester.

Further elution gave rise to the second naphthol **222** as cream needles (3.29 g; 90.0 %), mp 90-94 °C (from Hex), ν_{max} /cm^{-1} 3359.60 (O-H) and 1737.01 (C=O). *Delta* H ppm, 2.13 (3H, s, OAc); 3.88 and 4.01 (each for 3H, s, 2 x OMe); 5.14 (2H, s, CH_2OAc); 6.45 (1H, d, *J* 2.2, 7-H); 6.71 (1H, d, *J* 2.2, 5-H); 6.70 (1H, d, *J* 1.4, 2-H); 7.15 (1H, d, *J* 1.4, 4-H) and 9.13 (1H, s, 1-OH).

Delta C ppm, 21.1 (OAc); 55.5, 56.3 (2 x OMe); 66.2 (CH_2-); 98.1 (C-7); 99.7 (C-5); 108.1 (C-2); 110.6 (C-3); 117.1 (C-4); 136.3 (C-4a)[a]; 137.4 (C-8a)[a]; 154.9 (C-1)[b]; 157.2 (C-6)[b]; 158.2 (C-8)[b] and 170.95 (C=O). Assignments with the same superscripts may be exchanged.
[Found: C, 65.0; H, 5.7 %, M^+, 276 (75); 234 (55); 205 (100), calc. For $C_{15}H_{16}O_5$; C, 65.2; H, 5.8 %; M, 276]

8. *3-Acetoxymethyl-4-bromo-6,8-dimethoxy-1-naphthol* ***223*** *and 3-Acetoxymethyl-2-bromo-6,8-dimethoxy-1-naphthol* ***224****.*



223 (5:3) **224**

Bromine (199.7 mg; 1.25 mmol) in AcOH (3.5 ml) was added to a stirred solution of the naphthol **222** (344.5 mg; 1.25 mmol) in AcOH (25 ml), and stirring was maintained at room temperature under N_2 for 50 minutes, after which water (300 ml) was added and the products extracted into DCM. The organic extract was rinsed with saturated $NaHCO_3$, and the residue obtained upon workup was chromatographed using EtOAc:Hex (1:4) as an eluent to afford the 4-bromonaphthol **223** as white clusters (240 mg; 54.2 %), mp 143-144 °C (from EtOH), v_{max} /cm^{-1} 3364.53 (O-H) and 1737.01 (C=O). *Delta* H ppm, 2.18 (3H, s, OAc); 3.94 and 4.04 (each for 3H; s; 2 x OMe); 5.31 (2H, s, -CH_2OAc); 6.52 (IH, d, *J* 2,2, 7-H); 6.81 (IH, s, 2-H); 7.21 (IH, d, *J* 2.2, 5-H) and 9.28 (IH, s, 1 -OH).

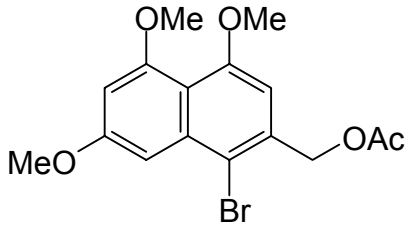
Delta C ppm, 21.0 (OAc); 55.6 and 56.6 (2 x OMe); 66.6 (CH_2-); 98.5 (C-7), 99.6 (C-5); 108.9 (C-2); 110.6 (C-3)[a]; 111.4 (C-4)[a]; 135.6 (C-4a)[b]; 136.1 (C-8a)[b]; 154.6 (C-1)[c]; 157.4 (C-6)[c]; 159.1 (C-8)[c]; and 170.7 (C=0). Assignments with the same superscripts may be exchanged.

[Found: C, 50.8; H, 4.1%, M^+ 355: 357 (1:1) Calc. for $C_{15}H_{15}BrO_5$; C; 50.7; H, 4.2 %; M, 355:357 (1:1)]

Further elution afforded the 2-bromonaphthol **224** as brown rosettes (160 mg; 36.1 %), mp 149-152 °C (from EtOH), v_{max} /cm^{-1} 3280.03 (O-H) and 1739 (C=O). *Delta* H ppm, 2.18 (3H, s, OAc); 3.88 and 4.03 (each for 3H, s, 2 x OMe); 5.28 (2H, s, CH_2-); 6.50 (IH, d, *J* 2.2, 7-H); 6.69 (IH, d, *J* 2.2, 5-H); 7.24 (IH, s, 4-H) and 9.89 (IH, s, 1-OH).

Delta C ppm, 21.1 (OAc); 55.5 and 56.6 (2 x OMe); 66.3 (CH_2-); 98.9 (C-7); 99.8 (C-5); 102.9 (C-2); 110.8 (C-3); 118.3 (C-4); 135.0 (C-4a)[a]; 135.7 (C-8a)[a]; 151.2 (C-1)[b]; 156.3 (C-6)[b]; 158.4 (C-8)[b] and 170.7 (C=0). Assignments with the same superscripts may be exchanged.

9. *3-Acetoxymethyl-4-bromo-1,6,8-trimethoxynaphthalene* ***159****.*

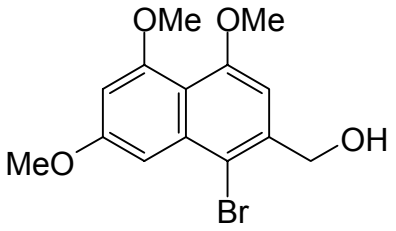


159

The 4-bromonaphthol **223** (100 mg; 0.28 mmol) in dry acetone (20 ml) was treated with K_2CO_3 (200 mg; 1.45 mmol) and iodomethane (0.17 ml; 2.69 mmol) and the mixture was vigorously stirred under reflux for 24 hrs. The cooled reaction mixture was filtered and the solvent removed under reduced pressure to leave a residue that was chromatographed using EtOAc:Hex (1:4) as an eluent to yield the acetate **159** as white crystals (90 mg; 86.5 %), mp 110-113 °C (from EtOH), ν_{max} /cm^{-1} 1744.02 (C=O). *Delta* H ppm, 2.18 (3H, s, OAc); 3.94, 3.95 and 3.96 (9H, overlapping s, 3 x OMe); 5.36 (2H, s, CH_2OAc); 6.57 (1H, d, *J* 2.6, 7-H); 6.78 (1H, s, 2-H) and 7.27 (1H, d, *J* 2.6, 5-H).

Delta C ppm,, 21.06 (OAc); 55.47, 56.63 (overlapping peaks 3 x OMe); 67.2 (CH_2OAc); 99.1 (C-7); 99.8 (C-5); 105.1 (C-2); 113.8 (C-3); 127.6 (C-4); 134.6 (C-4a)[a]; 136.4 (C-8a)[a]; 157.3 (C-1)[b]; 158.8 (C-6)[b]; 159.6 (C-8)[b] and 170.8 (C=O). Assignments with the same superscripts may be exchanged.
[Found: C, 51.90, H, 4.4 %, M$^+$ 368:370 (1:1). Calc. for $C_{16}H_{17}BrO_5$: C, 52.0, H, 4.6 %, M, 368:370 (1:1)]

10. *4-Bromo-3-hydroxymethyl-1,6,8-trimethoxynaphthalene* ***225****.*



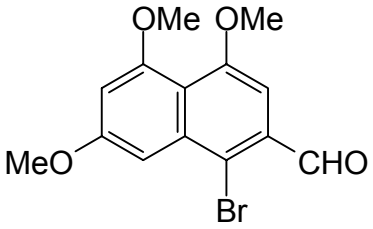
225

The 4-bromoacetate **159** (640 mg; 1.73 mmol) was treated with a methanolic solution of KOH (34 ml MeOH containing 150 mg KOH) and the resulting solution was stirred at room temperature for 30 minutes. Dilute HCl (5 ml of a 0.1 M solution) and water (50 ml) were added and the resulting mixture was extracted with DCM. The dried ($MgSO_4$) organic extract

was chromatographed using EtOAc:Hex (3:7) as a mobile phase to yield the white needles of the alcohol **225** (510 mg; 90.2 %), mp 150-152 °C (from EtOH), ν_{max} /cm^{-1} 3292.41 (O-H). *Delta* H ppm, (OH missing from the spec), 3.95, 3.96 and 3.97 (each 3H, s, 3 x OMe); 4.92 (2H, s, CH_2OH); 6.55 (1H, d, *J* 2.2, 7-H); 6.93 (1H, s, 2-H) and 7.25 (1H, d, *J* 2.2, 5-H).

Delta C ppm, 55.4 and 56.6 (overlapping peaks 3 x OMe); 66.3 (CH_2OH); 98.7 (C-7)[a]; 99.5 (C-5)[a]; 104.4 (C-2)[a]; 112.1 (C-3)[b]; 113.8 (C-4)[b]; 136.3 (C-4a)[c]; 139.2 (C-8a)[c]; 157.4 (C-1)[d]; 158.8 (C-6)[d] and 159.5 (C-8)[d]. Assignments with the same superscripts may be exchanged.
[Found: C, 51.3, H, 4.4 %, M^+, 326:328 (1:1). Calc. for $C_{14}H_{15}BrO_4$: C, 51.4, H, 4.6 %, M, 326:328 (1:1)].

11. *4-Bromo-1,6,8-trimethoxy-3-carboxaldehyde **226**.*

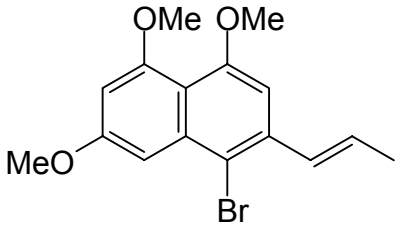


226

A mixture of the alcohol **225** (180 mg; 0.55 mmol) in benzene (30 ml) containing MnO_2 (750 mg; 8.62 mmol) was vigorously stirred under reflux for 3 hrs. The cooled mixture was filtered and the filtrate dried in rotavapor, chromatographed using EtOAc:Hex (3:7) as a mobile phase to yield yellow crystals of the aldehyde **226** (150 mg; 83.9 %), mp 144-146 °C (from EtOH), ν_{max} /cm^{-1} 1672.59 (C=O). *Delta* H ppm, 3.96, 3.99 and 4.00 (each 3H, s, 3 x OMe); 6.71 (1H, d, *J* 2.2, 7-H); 7.17 (1H, s, 2-H); 7.46 (1H, d, *J* 2.2, 5-H) and 10.61 (1H, s, CHO).

Delta C ppm, 55.6, 56.5 and 56.8 (3 x OMe); 99.7 (C-2)[a]; 101.4 (C-5)[a]; 102.4 (C-7)[a]; 117.0 (C-3)[b]; 120.9 (C-4)[b]; 132.3 (C-4a)[c]; 136.4 (C-8a)[c]; 157.6 (C-1)[d]; 158.9 (C-6)[d]; 159.9 (C-8)[d] and 193.3 (C=O). Assignments with the same superscripts may be exchanged.
[Found: C, 51.8, H, 3.8 %, M^+, 324:326 (1:1). Calc. for $C_{14}H_{13}BrO_4$: C, 51.7, H, 4.0 5, M, 324:326 (1:1)].

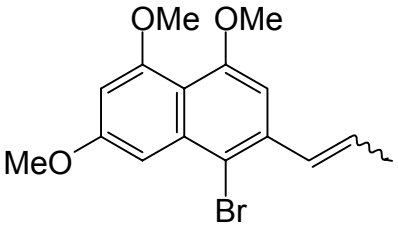
12. *Trans-1'-(4-Bromo-1,6,8-trimethoxynaphthalen-3-yl)prop-1'-ene* ***166****.*



166

To a stirred suspension of ethyltriphenylphosphonium bromide (2.51 g; 6.76 mmol) in dry THF (62.75 ml) at -78 °C, was added dropwise nBuLi (1.45 M solution in Hex; 4.67 ml; 6.76 mmol) under an atmosphere of N_2. The resultant orange solution was stirred at 0 °C for 5 minutes and then again cooled to -78 °C. An aldehyde **226** (940 mg; 2.89 mmol) in dry THF (50 ml) was added dropwise to the reaction mixture. The resultant solution was stirred at -78 °C for 15 minutes, allowed to warm to room temperature and then stirred for another 3 hrs.

The reaction mixture was quenched with water and extracted with diethyl ether. The extract was washed several times with aqueous NaCl, dried and evaporated to give a yellow oil, which was chromatographed (eluent 5.0 % EtOAc:Hex) to afford a mixture of the *trans*- and *cis*- alkenes **227** as a yellow oil (990 mg; 81.05 %).



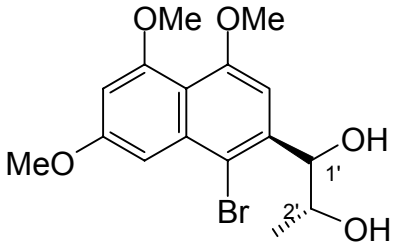
227

The mixture of the olefins (*trans*/*cis*) **227** (270 mg; 0.80 mmol) in dry DCM (30 ml) was stirred with *bis*(acetonitrile)dichloropalladium(II) (58.51 mg; 0.23 mmol) overnight at room temperature after which it was filtered. The residue obtained upon evaporation of the filtrate was chromatographed (eluent 5.0 % EtOAc:Hex) to afford cream needles of the *trans*-olefin **166** (120 mg; 44.4 %), mp 123-125 °C (from Hex), ν_{max} /cm^{-1} 1617.32 (C=C). *Delta* H ppm, 1.97 (3H, dd, *J* 6.6 and 1.8, 3'-CH_3); 3.94, 3.95 and 3.96 (each 3H, s, 3 x OMe); 6.27 (1H, dq, *J* 15.8 and 6.6 , 2'-H); 6.54 (1H, d, *J* 2.2, 7-H); 6.84 (1H, s, 2-H); 6.98 (1H, dq, *J* 15.8 and 1.8, 1'-H) and 7.32 (1H, d, *J* 2.2, 5-H).

Delta C ppm, 18.9 (C-3'); 55.4, 56.6 and 56.61 (3 x OMe); 99.3 (C-2)[a]; 99.8 (C-5)[a]; 102.9 (C-7)[a]; 113.6 (C-3)[b]; 113.7 (C-4)[b]; 129.6 (C-1')[c]; 131.7 (C-2')[c]; 136.5 (C-4a)[c]; 136.6 (C-8a)[c]; 156.8 (C-1)[d]; 158.7 (C-6)[d] and 159.4 (C-8)[d]. Assignments with the same superscripts may be exchanged.

[Found: C, 57.2, H 5.2 %, M^+, 336:338 (1:1). Calc. for $C_{16}H_{17}BrO_3$; C, 57.0, H, 5.0 %, M, 336:338 (1:1)].

13. *1'-(4-Bromo-1,6,8-trimethoxynaphthalen-3-yl)propan-1',2'-diol* ***228***.



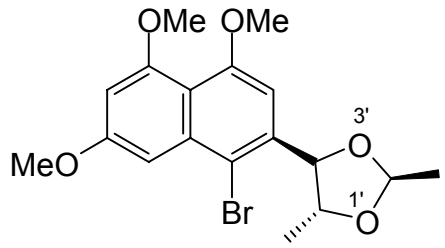
228

The *trans*-alkene **166** (100 mg; 0.297 mmol) in acetone:water (2:1; 1.36 ml) was treated with NMMO (40.71 mg; 0.348 mmol) and OsO_4 (1 mole % OsO_4) (0.75 mg; 0.00295 mmol) in *tert*-butanol (0.15 ml) at 0 °C. After stirring for 24 hrs, acetone was removed under vacuum at room temperature and the remaining aqueous layer mixed with diluted HCl (2M; 0.75 ml). The organic materials were extracted into EtOAc (5 x 20 ml) and the combined extracts washed with brine. The residue obtained gave rise to cream crystals of the diol **228** (109.2 mg; 99.2 %), mp 164-165 °C (from EtOAc:Hex), ν_{max} /cm^{-1} 3258.29 (O-H). *Delta* H ppm, 1.23 (3H, d, *J* 6.2, 3'-CH_3); 2.46 and 3.00 (each 1H, s, D_2O exchangeable, 2 x OH); 3.94 (9H, s, 3 x OMe); 4.06 (1H, dq, *J* 6.6 and 6.2, partially obscured by the OMe signals, 2'-H); 5.18 (1H, d, *J* 6.6, 1'-H); 6.55 (1H, d, *J* 2.2, 7-H); 6.81 (1H, s, 2-H) and 7.22 (1H, d, *J* 2.2, 5-H).

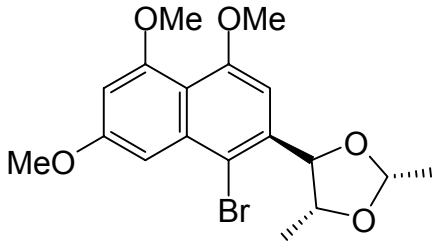
Delta C ppm, 18.8 (C-3'); 55.3, 56,4 and 56.5 (3 x OMe); 71.7 (C-2'); 99.5 (C-2)[a]; 99.6 (C-5)[a]; 103.3 (C-7)[a]; 113.0 (C-3)[b]; 113.8 (C-4)[b]; 133.3 (C-1'); 136.0 (C-4a)[c]; 139.7 (C-8a)[c]; 157.1 (C-1)[d]; 158.6 (C-6)[d] and 159.3 (C-8)[d]. Assignments with the same superscripts may be exchanged.

[Found: C, 51.6, H, 5.2 %, M^+, 370:372 (1:1). Calc. for $C_{16}H_{19}BrO_5$: C, 51.75, H, 5.1 %, M, 370:372 (1:1)].

14. *(+/-)-2',5'-Dimethyl-4'-(4-Bromo-1,6,8-trimethoxynaphthalen-3-yl)dioxolanes **229** and **230**.*



229



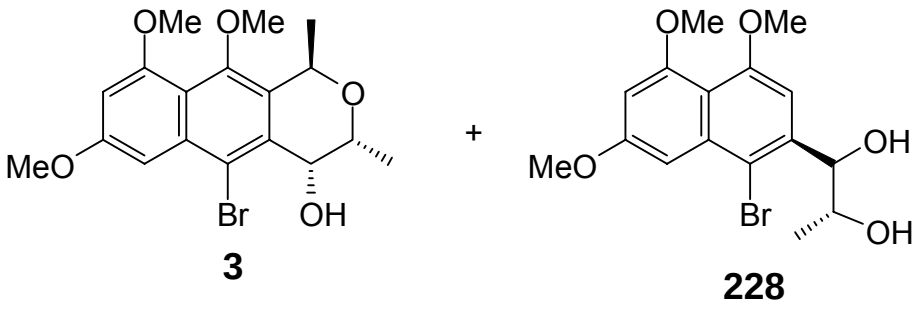
230

A solution of the diol **228** (61.3 mg; 0.165 mmol), acetaldehyde dimethyl acetal (0.052 ml) (44.09 mg; 0.489 mmol) and TsOH (22.7 mg; 0.12 mmol) in benzene (20 ml) was heated under reflux in a Dean-Stark apparatus for 30 minutes. The cooled solution was washed with aqueous $NaHCO_3$, followed by water, and the residue obtained upon workup was chromatographed using EtOAc:Hex (3:7) as an eluent to yield the dark yellow powder of a mixture of the dioxolanes (2:1), epimeric at position 2', **229** (the major isomer) and the minor isomer **230** (65.4 mg; 99.8 %), mp 128-132 °C (from Hex), ν_{max} /cm^{-1} 1596.06 and 1200.62.

Delta H ppm, 1.48-1.60 (12H, overlapping 4 x d, each 3H, 2'- and 5'-CH_3); 3.95, 3.96 and 3.97 (18H, 6 x s, 6 x OMe and 5'-H, the latter obscured by the OMe signals); 4.11 (1H, dq, *J* 6.6 and 5.0, 5'-H); 5.32 (2H, d, *J* 5.6, 4'-H); 5.48 (1H, q, *J* 5.2, 2'-H, major isomer **229**); 5.59 (1H, q, *J* 4.8, 2'-H, minor isomer **230**); 6.57 (2H, d, *J* 2.2, 7-H); 6.84 (1H, s, 2-H, minor isomer **230**); 6.96 (1H, s, 2-H, major isomer **229**) and 7.30 (2H, d, *J* 2.2, 5-H).

Delta C ppm, 18.5 (2'-CH_3)[a]; 20.3 (5'-CH_3)[a]; 55.3, 56.3 and 56.5 (3 x OMe); 75.7 (C-2')[b]; 80.1 (C-4')[b]; 84.2 (C-5')[b]; 99.2 (C-2)[c]; 99.5 (C-5)[c]; 100.8 (C-7)[c]; 102.9 (C-3)[d]; 112.3 (C-4)[d]; 136.1 (C-4a)[e]; 138.4 (C-8a)[e]; 157.4 (C-1)[f]; 158.7 (C-6)[f] and 159.4 (C-8)[f]. Assignments with the same superscripts may be exchanged.
[Found: C, 54.1, H, 5.0 %, M^+, 396:398 (1:1), Calc. for $C_{18}H_{21}BrO_5$: C, 54.4, H, 5.3 %, M, 396:398 (1:1)].

15. *5-Bromo-3,4-dihydro-4-hydroxy-7,9,10-trimethoxy-1,3-dimethyl-1H-naphtho[2,3-c]pyran* ***3****, and 1'- (4-Bromo-1,6,8-trimethoxynaphthalen-3-yl)propan-1',2'-diol* ***228****.*



3 **228**

The $TiCl_4$ (0.08 ml; 0.76 mmol) was added to the mixture of the dioxolanes **229** and **230** (2:1) (126.2 mg; 0.32 mmol) in dry DCM (30 ml) at -78 °C under an atmosphere of N_2. The resultant dark solution was slowly warmed to room temperature and stirred for 1 hr. The addition of the saturated aqueous $NaHCO_3$ quenched the reaction and the organic material was extracted with DCM. The residue obtained upon workup was chromatographed using EtOAc:Hex (3:7) as an eluent to yield four products, 2 of which could not be properly characterised.

Pyran **3** (44.0 mg; 53.0 %) as a light yellow caked solids, ν_{max} /cm^{-1} 3454.50 (O-H). *Delta* H ppm, 1.46 (3H, d, *J* 6.2, 3-CH_3); 1.61 (3H, d, *J* 6.2, 1-CH_3); 1.76 (1H, br s, 4-OH); 3.80, 3.96 and 3.98 (each 3H, s, 3 x OMe); 4.19 (1H, dq, *J* 1.4 and 6.2, 3-H); 4.77 (1H, d, *J* 1.4, 4-H); 5.32 (1H, q, *J* 6.2, 1-H); 6.59 (1H, d, *J* 2.6, 8-H) and 7.32 (1H, d, *J* 2.6, 6-H).

Delta C ppm, 16.9 (3-CH_3); 19.7 (1-CH_3); 55.4, 56.3 and 62.0 (3 x OMe); 66.3 (C-3); 68.4 (C-1)[a]; 69.5 (C-4)[a] ; 99.1 (C-6)[b]; 100.0 (C-8)[b]; 116.8 (C-10a)[c]; 120.2 (C-5)[c]; 127.9 (C-4a); 135.5 (C-5a)[d]; 135.7 (C-9a)[d]; 152.3 (C-7)[e]; 157.1 (C-9)[e] and 158.9 (C-10)[e]. Assignments with the same superscripts may be exchanged.
[Found: M^+, 396:398 (1:1), Calc. for $C_{18}H_{21}BrO_5$: C, 54.5, H, 5.3 %, M, 396:398 (1:1).]

Diol **228** (43.4 mg; 36.5 %) as cream crystals, mp 164-165 °C (from EtOAc:Hex), ν_{max} /cm^{-1} 3258.29 (O-H). *Delta* H ppm, 1.23 (3H, d, *J* 6.2, 3'-CH_3); 2.46 and 3.0 (each 1H, s, D_2O exchangeable, 2 x OH); 3.94, (9H, s, 3 x OMe); 4.06 (1H, dq, *J* 6.6 and 6.2, partially obscured by the OMe signals, 2'-H); 5.18 (1H, d, *J* 6.6, 1'-H); 6.55 (1H, d, *J* 1.8, 7-H); 6.81 (1H, s, 2-H) and 7.22 (1H, d, J 2.2, 5-H).

Delta C ppm, 18.8 (C-3'); 55.3, 56,4 and 56.5 (3 x OMe); 71.7 (C-2'); 99.5 (C-2)[a]; 99.6 (C-5)[a]; 103.3 (C-7)[a]; 113.0 (C-1')[b]; 113.8 (C-4)[b]; 133.3 (C-3)[c]; 136.0 (C-4a)[c]; 139.7 (C-8a)[c]; 157.1 (C-1)[d]; 158.6 (C-6)[d] and 159.3 (C-8)[d].

[Found: C, 51.6, H, 5.2 %, M^+, 370:372 (1:1). Calc. for $C_{16}H_{19}BrO_5$: C, 51.75, H, 5.1 %, M, 370:372 (1:1)].

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