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

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Cape Peninsula University of Technology
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by

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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\textsubscript{4} as a catalyst. They managed to synthesize 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\textsubscript{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:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>BnBr</td>
<td>benzyl bromide</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyl lithium</td>
</tr>
<tr>
<td>Br</td>
<td>bromine</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt; PPh&lt;sub&gt;3&lt;/sub&gt;Br</td>
<td>ethyltriphenylphosphonium bromide</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celcius</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>dichlorodicyanobenzoquinone</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Fe&lt;sub&gt;2&lt;/sub&gt;(CO)&lt;sub&gt;9&lt;/sub&gt;</td>
<td>diiron nonacarbonyl</td>
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<tr>
<td>Hex</td>
<td>hexane</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;4&lt;/sub&gt;</td>
<td>sulphuric acid</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
</tr>
<tr>
<td>KBr</td>
<td>potassium bromide</td>
</tr>
<tr>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminium hydride</td>
</tr>
<tr>
<td>Me</td>
<td>methyl group</td>
</tr>
<tr>
<td>MeI</td>
<td>methyl iodide/iodomethane</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>Mg&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>magnesium sulphate</td>
</tr>
<tr>
<td>MnO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>manganese dioxide</td>
</tr>
<tr>
<td>Mp</td>
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</tr>
<tr>
<td>Ms</td>
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</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;</td>
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</tr>
<tr>
<td>NaCl</td>
<td>sodium chloride</td>
</tr>
<tr>
<td>NaH</td>
<td>sodium hydride</td>
</tr>
<tr>
<td>NaOAc</td>
<td>sodium acetate</td>
</tr>
<tr>
<td>NMMO</td>
<td>N-methyl morpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxy group</td>
</tr>
<tr>
<td>OsO₄</td>
<td>osmium tetroxide</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on activated carbon</td>
</tr>
<tr>
<td>PdCl₂(CH₃CN)₂</td>
<td>bis(acetonitrile)dichloropalladium(II)</td>
</tr>
<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>titanium tetrachloride</td>
</tr>
<tr>
<td>Tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TsOH</td>
<td>toluene-p-sulphonic acid</td>
</tr>
</tbody>
</table>
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 an 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).

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.

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).

\[ \text{OMe} \quad \text{OPri}^i \quad \text{MeO} \quad \text{Br} \quad \text{O} \quad \text{O} \]

\[ \text{OMe} \quad \text{OPri}^i \quad \text{MeO} \quad \text{Br} \quad \text{OH} \]

Scheme 1:

Green et al.[32] demonstrated that reducing the steric environment at position 1 of the naphthyl dioxolane 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.
Naphtho[2,3-c]pyrans and their quinones form an extensive group of natural products which possess biological and pharmacological activities.\textsuperscript{[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\textsuperscript{[3,10]} 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\textsuperscript{[28]} (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\textsuperscript{[45]} proposed a mechanism for the biological activity of the pyranquinones, based on work done by Sartorelli,\textsuperscript{[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 bisquinone 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.\textsuperscript{[36]}
Hugo et al.\cite{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.\cite{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.
Benzo[c]pyranquinones\textsuperscript{[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.

Moore\textsuperscript{[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, compared to the quinones of the present study. An example of these are \textit{alpha}-lapachone\textsuperscript{[8]} 29, rhinacanthin-A\textsuperscript{[53]} 30, rhinacanthin-B\textsuperscript{[49]} 31, lambertillin\textsuperscript{[13]} 32 and erythrostominone 33,\textsuperscript{[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.\textsuperscript{[16, 30]}

\begin{align*}
29 & \quad R= H \\
30 & \quad R= OH \\
31 & \quad R= \text{OCOC=CHCH}_2\text{CH}_2\text{C=CHCH}_3 \\
32 & \\
33 &
\end{align*}

The concept of bioreductive alkylation proposed by Moore\textsuperscript{[45]} and earlier work by Sartorelli\textsuperscript{[43]} played a role towards this suspicion. Substitutions in the pyran ring have been shown to improve the naphthopyranquinones biological activities.\textsuperscript{[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.\textsuperscript{[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 \textit{et al.}\textsuperscript{[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\textsuperscript{34} and D\textsuperscript{35}, griseusin A\textsuperscript{36} and granaticin 37 are antimicrobial agents.\textsuperscript{[39]} The nanaomycins were reported to have excellent activities against mycoplasmas.\textsuperscript{[48]} The first total synthesis of racemic nanaomycins was achieved in 1978.

\begin{center}
\includegraphics[width=\textwidth]{nanaomycins.png}
\end{center}

Hongconin\textsuperscript{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.\textsuperscript{[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.\textsuperscript{[34]}

\begin{center}
\includegraphics[width=0.5\textwidth]{hongconin.png}
\end{center}

Kraus \textit{et al.}\textsuperscript{[40,41]} synthesized racemic hongconin with a low overall yield. In 1996 Green \textit{et al.}\textsuperscript{[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. 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 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. have established an efficient synthetic route to a series of these naphthopyranquinones antibiotics.
Chapter 4:

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

4.1. The synthesis of the aphid pigment (Protoaphins) derivatives.\textsuperscript{[15]}

In 1988 Elsworth \textit{et al.}\textsuperscript{[15]} described the racemic synthesis of Quinone A 5, Quinone A’ 6 and Deoxyquinone A 7 (scheme 7-11).

The naphthol 41 was oxidised to afford the quinone 42 which was allylated with allyltrimethylstannane in the presence of boron trifluoride, the resultant crude adduct was methylated with dimethyl sulphate and K\textsubscript{2}CO\textsubscript{3} in acetone to yield the allylnaphthalenone 43 in an overall yield of 61.0 %. The methyl from oxygen \textit{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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme7}
\caption{Scheme 7:}
\end{figure}
The compound 44 was treated with BnBr and anhydrous K$_2$CO$_3$ 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 %).

\[
\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
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\text{OMe} & \text{O} \quad \text{OMe} \\
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\end{align*}
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\end{align*}
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\end{align*}
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\end{align*}
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\text{OMe} & \text{O} \\
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\end{align*}
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\text{OMe} & \text{O} \quad \text{OMe} \\
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\text{OMe} & \text{O} \\
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\end{align*}
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\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
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\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
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\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
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\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
\]

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\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{OMe} & \text{O} \quad \text{OMe} \\
\text{Bn} & \text{O} \\
\text{OMe} & \text{O} \\
\text{Bn} & \text{O}
\end{align*}
\]

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 pseudoaxial epimer 50 as a minor product (5.0 %).
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.

![Chemical structure](image1)

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.

![Chemical structure](image2)
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.

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\textsuperscript{\[10\]} 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)
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 pseudoaxial 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 pseudoequatorial 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.[19] 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.

The main structural difference between Glucoside B 4 and Quinone A 5 is the absence of oxygen at position 5 in the former.
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 $^1$H 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 H¹ 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 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 H¹ 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.

In another conversion the alcohol 71\textsuperscript{[21]} (scheme 15) was subjected to oxidation and yielded the corresponding aldehyde 72, which was treated with ethyldene(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\textsubscript{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 \textit{trans}-stereochemistry was confirmed by the chemical shifts of the 3-H and 1-H protons in the H\textsuperscript{1} NMR spectrum, whose values were very close to those of the related naphthopyran 69. The C-5 aromatic singlet was at \textit{delta} 7.12 ppm.

\[ 75 + 76 \xrightarrow{\text{KOC(CH$_3$)$_3$, DMF}} 79 \]

\textbf{Scheme 16:}

There was no yield advantage on performing the ring closure to naphthopyran 79 using stereochemically pure \textit{trans}-olefinic precursors. These were obtained by conversion of the mixture of bromo olefins 73 and 74 into pure \textit{trans}-olefin 74 in high yield of 90.0 \%. This was achieved by treating the two olefins with \textit{bis}(acetonitrile)dichloropalladium(II).\textsuperscript{[20]} The pure bromo olefin 74 was converted into pure \textit{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 \textit{pseudo}equatorial alcohol 80 was 46.0 \%.

\[ 79 \xrightarrow{\text{KOC(CH$_3$)$_3$, DMF}} 79 \]

\[ 79 \xrightarrow{\text{KOC(CH$_3$)$_3$, DMF}} 80 + 81 \]

\textbf{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

The synthesis of naphthopyrans related to the aphin derived Glucoside B 4 led Giles et al. to the formulation of a new strategy for the construction of naphthopyrans through the stereoselective isomerisation of naphthyldioxolanes using TiCl₄ as a catalyst.

![Scheme 18](image)

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 pseudoaxial 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 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).
Scheme 19:

The alcohol 87 was subjected to oxidation using MnO\textsubscript{2} to afford the aldehyde 88. This was then treated with ethyldenetriphenylphosphorane in a Wittig reaction to yield a stereochemical mixture of the olefins 89 which were reacted with \textit{bis}(acetonitrile)dichloropalladium(II) to afford the \textit{trans}-isomer 90 as the sole product in high yield. The pure olefin in pyridine was reacted with OsO\textsubscript{4} in ether to afford the single racemate of the diol 91 in high yield (91.0 %) (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.

Preferential electrophilic attack on the dimethoxy-substituted aromatic ring rather than the olefin precluded the fascicle 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 TiCl₄ 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 R₇ compound was obtained in a yield of 39.0 %.
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 approximately 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).

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.
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).

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

Therefore it was shown that it is possible to isomerise naphthylidioxolanes into angular naphthopyrans.
Giles et al.\textsuperscript{[23]} attempted another isomerisation with a \textit{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:](image)

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 ethylidene phosphorane to yield the mixture of the \textit{trans}-olefin 105 and the \textit{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 \textit{erythro} selectivity. The resultant product was the \textit{erythro} adduct 107 obtained in a 42.0 % yield after repeated recrystallisation to separate the \textit{threo} adduct formed simultaneously. The diphenylphosphinate was eliminated under optimised conditions to provide the \textit{cis}-olefin 105 in a yield of 82.0 % from the \textit{erythro}-adduct 107. The \textit{trans}-olefin 106 was also obtained in small quantities of less than 10.0 %.
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.

**Scheme 25:**

**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 MnO₂ to afford the aldehyde 110. The 5-bromonaphthaldehyde 110 was subjected to a Wittig reaction, where it reacted with ethyldienetriphenylphosphorane 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-bromonaphthaldehyde 104 with ethyldienetriphenylphosphorane, 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). 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.

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.
The unpurified crude cis-olefin 111 in pyridine was reacted with OsO₄ 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.

The naphthydioxolane 8 was treated with 10 molar equivalents of TiCl₄, in dry DCM, at -78°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.
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).

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.
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.

These stereoisomers were then hydrogenolysed as in scheme 29 to yield the cis-1,3-dimethyl compound 123, which was stereoisomeric with product 120 (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 naphthylidioxolanes 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 \textit{alpha}-position rather than the \textit{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 \cite{30}

Hugo \textit{et al.} \cite{16} have reported the synthesis and biological activity of some benzopyran systems in 1993. Later on Hugo and Green \textit{et al.} \cite{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. \cite{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\cite{35} to yield the quinol 125. This was due to an \textit{ortho}-migration of the allyl group to the sterically disfavoured position\cite{4, 7} (scheme 32).

![Scheme 32](image)

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

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$_2$CO$_3$ 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$^{[16]}$ 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:](image)

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).
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.
Quinol 142 was dissolved in dry acetone containing iodomethane and K₂CO₃ 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 N₂, 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).

The relative configuration between the methyl groups at C-1 and C-3 was confirmed as trans in the H¹ NMR spectrum.

With Green et al. the introduction of the OH group at C-4 in pyran 145 was problematic, compared to the same introduction performed by other research groups. 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 %\(^\text{[34]}\) (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.

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 spectrum confirmed the desired product. The ketopyran 153 was then oxidatively demethylated to yield the pyranquinol 154 in a yield of 62.0 %.

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.
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\textsuperscript{[32]}

In 1997 Green \textit{et al.}\textsuperscript{[32]} studied the synthesis of a naphthyldioxolane and its isomerisation with TiCl\textsubscript{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\textsubscript{2}O 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.
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%.

Treatment of the acetate 160 with a methanolic solution of KOH resulted into the alcohol 162 whose subsequent oxidation with activated MnO₂ 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.
Green et al.\textsuperscript{[32]} attempted to improve the yield by adding 11 equivalents of hexamethylphosphoric triamide\textsuperscript{[11,12]} with the reaction at -78 °C. The yield improved to 66.0 % but the \textit{trans}/\textit{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 \textit{trans}/\textit{cis} ratio was 1:1. A solution of DCM containing the mixture and the \textit{bis}(acetonitrile)dichloropalladium(II)\textsuperscript{[20]} was heated under reflux to afford the pure \textit{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.

When the (1:1) \textit{trans}/\textit{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.
The epimeric mixture of dioxolanes 10 was treated with 2.4 equivalents of TiCl₄ in DCM at -78 °C and subsequently at 25 °C, under an atmosphere of N₂. 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).

\[
10 \xrightarrow{\text{TiCl}_4 \text{DCM} \ -78 \text{°C}} 10 + 167 + \text{11} + \text{12}
\]

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]
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).
Scheme 51:

The two new alcohols were also acetylated using pyridine and Ac\textsubscript{2}O to afford an easily separable mixture of the two acetates 174 and 175 in schemes 52 and 53.

Scheme 52:

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\textsubscript{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\textsuperscript{[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 \textit{alpha}- and \textit{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 \textit{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. \textit{The synthesis of dioxolanes and their isomerization to naphtho[3,4-\textit{c}]pyrans.}\textsuperscript{[28]} Giles \textit{et al.}\textsuperscript{[28]} had shown that phenyldioxolanes can be isomerized to benzopyrans.\textsuperscript{[24,25,26]} They found that all \textit{cis} 4-aryl-2,5-dimethyldioxolanes provided the 1,3-\textit{trans}-3,4-\textit{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.\textsuperscript{[24]} In the studied isomerization\textsuperscript{[23]} the corresponding dioxolanes were shown to yield angular naphthopyrans readily as the sole products of isomerization, after losing the \textit{peri}-substituted bromine atom, that was used as a blocking group, with an excess of the isomerization reagent. In 2004 Giles \textit{et al.}\textsuperscript{[28]} examined the rearrangement of a naphthylidioxolane bearing a blocking bromine atom \textit{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\textsubscript{2} to furnish the adduct 180 in scheme 54, as the sole product in a yield of 65.0 \%. 
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.

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.
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 TiCl₄ failed. The starting material and the diol 184 were recovered.

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 electrophilic 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 tert-butyldimethylsilyl ether 188 by treating it with imidazole and tert-butyldimethylsilyl chloride in scheme 56. Treatment of the dioxolane 188 with 2 equivalents of TiCl₄ at -78 °C under N₂ 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 naphthylidioxolane 194 in scheme 57.
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 $\text{Fe}_2(\text{CO})_9$ 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 %.

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 TiCl₄ 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.

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.
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 TiCl₄ 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.⁹⁵

4.7. The DDQ mediated cyclization of some naphthoquinones.⁹²
Ameer et al.⁹² have tried to synthesize molecules that could be transformed into naphthopyrans having similar structural features to the biologically active erythrostominone 33.¹³,²⁷
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.

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.

![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.

![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).]
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.

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 N₂. The resultant solution was heated and stirred under reflux, under N₂ to produce an oil. The unpurified oil 215 was then mixed with anhydrous NaOAc and boiled under reflux in Ac₂O overnight, under an atmosphere of N₂, 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.

![Scheme 65 cont.](image)

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\(_2\)Ph 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\(_2\)OH 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.

The benzyl alcohol 219 was acetylated by stirring its mixture with Ac\(_2\)O 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.

\[
\begin{align*}
\text{O} & \quad \text{MeO} & \quad \text{OH} \\
\text{MeO} & \quad \text{OAc} & \quad \text{Br} \\
\text{Br} & \quad \text{MeO} & \quad \text{OAc}
\end{align*}
\]

**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.

![Diagram of chemical reactions](image)

**Scheme 67:**

For the synthesis of the linear naphthopyrans the important product was the 4-bromonaphthol 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$_2$CO$_3$ 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\textsuperscript{[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\textsuperscript{[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\(_2\)OH 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.
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 N₂ 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'-CH₃, 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 OsO₄ 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 OsO₄ catalyzed hydroxylation of sterically hindered olefins proceed efficiently with trimethylamine N-oxide as an oxidizing agent in the presence of pyridine, and NMMO plus OsO₄ was shown to be highly successful with less hindered olefins.[52] NMMO was used to regenerate OsO₄ allowing glycolization to proceed whilst the OsO₄ was used as an oxidant.

The trans-olefin 166 was dissolved in acetone:water (2:1)[24] and treated with NMMO and OsO₄ 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'-CH₃, 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'-CH₃, 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.

\[
\begin{align*}
229 + 230 & \xrightarrow{2.4 \text{ mol TiCl}_4} \text{-78 °C dry DCM} & 231 + 3
\end{align*}
\]

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.

![Chemical Structure](image)
Chapter 7:

Experimental – General procedures:

NMR spectra were recorded using a VARIAN 200 spectrometer (H\textsuperscript{1}, 200 MHz; C\textsuperscript{13} 50 MHz) at UWC. All recorded spectra were run at ambient temperature in deuterated chloroform (CDCl\textsubscript{3}) solution, with CHCL\textsubscript{3} at delta 7.26 for H\textsuperscript{1} NMR spectra and at delta 77.00 for C\textsuperscript{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\textsubscript{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\textsubscript{4} and sodium pieces under N\textsubscript{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 phosphorus 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\textsubscript{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.

![Chemical Structure](image)

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 MgSO4, 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.

![Chemical Structure](image)

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 N2. 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). NaHCO3 (250 ml) was added to the DCM layer to neutralise any acetic acid formed. The DCM layer was then dried with MgSO4,
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), $\nu_{\text{max}}$ 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.

![Structure 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), $\nu_{\text{max}}$ cm$^{-1}$ 3375.28 (O-H) and 1714.21 (C=O). Delta H ppm, 9.15 (1H, s, D$_2$O 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-Benzylxy-6,8-dimethoxy-3-naphthoate 218.*

![Image of compound 218]

The naphthol 217 (480 mg; 1.83 mmol) in acetone (40 ml) was treated with BnBr (0.54 ml; 4.6 mmol) and K₂CO₃ (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, -CH₂Ph); 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-CH₂-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)c; 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 C₂₁H₂₀O₅; C, 71.6; H, 5.7 %; M, 352].

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

![Image of compound 219]

Into a slurry of LAH (56 mg; 1.48 mmol) in dry THF (5.6 ml) under N₂ 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 MgSO₄, 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, -CH₂OH); 5.18 (2H, s, -CH₂Ph); 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).

\[ \text{Delta C ppm, 55.3 and 56.1 (2 x OMe); 65.6 (CH}_2\text{OH); 71.3 (CH}_2\text{Ph); 98.9 (C-7), 99.0 (C-5); 105.2 (C-2); 113.2 (C-3); 117.9 (C-4); 127.0 (C-3'/5')^a; 127.6 (C-4'); 128.4 (C-2'/6')^a; 128.4 (C-1'); 137.7 (C-4a)^b; 138.3 (C-8a)^b; 156.8 (C-1)^c; 158.5 (C-8)^d and 158.6 (C-6)^d.} \]
Assignments with the same superscripts may be exchanged.

[Found: C 73.9; H, 6.1 %; M* 324. Cal. For C\textsubscript{20}H\textsubscript{20}O\textsubscript{4}; C; 74.0; H, 6.2 %; M, 324]

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

![Structural diagram of 220]

The benzyl alcohol 219 (190 mg; 0.59 mmol) in Ac\textsubscript{2}O (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\textsubscript{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), \[v_{\text{max}}\]/cm\textsuperscript{-1} 1743.87 (C=O). \[\text{Delta H ppm, 2.14 (3H, s, OAc); 3.89 and 3.92 (each for 3H, s, 2 x OMe); 5.18 (2H, s, CH}_2\text{OAc); 5.20 (2H, s, CH}_2\text{Ph); 6.52 (1H, d, J 2.2, 7-H); 6.71(1H, d, J 2.2, 5-H); 6.75 (1H, d, J 1.4, 2-H); 7.28 (1H, d, J 1.4, 4-H); 7.42 (3H, m, 3',4' and 5'-H) and 7.62 (2H, dd, 2'- and 6'-H).} \]

\[\text{Delta C ppm, 21.1 (OAc); 55.4 and 56.2 (2 x OMe); 66.5 (CH}_2\text{O); 71.4 (CH}_2\text{Ph); 99.1 (C-7)^a; 99.3 (C-5)^b; 106.3 (C-2); 113. 6 (C-3); 119.8 (C-4); 127.1 (C-2'/6')^b; 127.6 (C-4'); 128.4 (C-3'/5')^b; 134.8 (C-1'); 137.6 (C-4a)^c; 138.2 (C-8a)^c; 156.8 (C-1)^d; 158.6 (C-8)^d and 158.7 (C-6)^d.} \]
Assignments with the same superscripts may be exchanged.

[Found: C, 72.0 %; H, 5.9 %; M* 366. Cal. For C\textsubscript{22}H\textsubscript{22}O\textsubscript{5}; C, 72.1; H, 6.0 %; M, 366]

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

![Chemical structures of 221 and 222](image)

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\textsubscript{max} /cm\textsuperscript{-1} 3364.53 (O-H). \Delta C ppm, 22.7 (3-CH\textsubscript{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)\textsuperscript{a}; 138.6 (C-8a)\textsuperscript{a}; 154.4 (C-1)\textsuperscript{b}; 157.3 (C-6)\textsuperscript{b} and 157.9 (C-8)\textsuperscript{b}. Assignments with the same superscripts may be exchanged.  

[Found: C, 71.4; H, 6.2 %; M\textsuperscript{+} 218, C\textsubscript{13}H\textsubscript{14}O\textsubscript{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\textsubscript{max} /cm\textsuperscript{-1} 3359.60 (O-H) and 1737.01 (C=O). \Delta C ppm, 21.1 (OAc); 55.5, 56.3 (2 x OMe); 66.2 (CH\textsubscript{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)\textsuperscript{a}; 137.4 (C-8a)\textsuperscript{a}; 154.9 (C-1)\textsuperscript{b}; 157.2 (C-6)\textsuperscript{b}; 158.2 (C-8)\textsuperscript{b} and 170.95 (C=O). Assignments with the same superscripts may be exchanged.  

[Found: C, 65.0; H, 5.7 %, M\textsuperscript{+} 276 (75); 234 (55); 205 (100), calc. For C\textsubscript{15}H\textsubscript{16}O\textsubscript{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.

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\textsubscript{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\textsubscript{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), \(\nu_{\text{max}}/\text{cm}^{-1}\) 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\textsubscript{2}OAc); 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\textsubscript{2}-); 98.5 (C-7), 99.6 (C-5); 108.9 (C-2); 110.6 (C-3)b; 111.4 (C-4)b; 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=O). Assignments with the same superscripts may be exchanged. [Found: C, 50.8; H, 4.1%, M* 355: 357 (1:1) Calc. for C\textsubscript{15}H\textsubscript{15}BrO\textsubscript{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), \(\nu_{\text{max}}/\text{cm}^{-1}\) 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\textsubscript{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\textsubscript{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)b; 135.7 (C-8a)b; 151.2 (C-1)b; 156.3 (C-6)b; 158.4 (C-8)b and 170.7 (C=O). Assignments with the same superscripts may be exchanged.
9. 3-Acetoxymethyl-4-bromo-1,6,8-trimethoxynaphthalene 159.

![Chemical Structure of 159]

The 4-bromonaphthol 223 (100 mg; 0.28 mmol) in dry acetone (20 ml) was treated with K₂CO₃ (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). Δν ppm, 2.18 (3H, s, OAc); 3.94, 3.95 and 3.96 (9H, overlapping s, 3 x OMe); 5.36 (2H, s, CH₂OAc); 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).

ΔC ppm, 21.06 (OAc); 55.47, 56.63 (overlapping peaks 3 x OMe); 67.2 (CH₂OAc); 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 C₁₆H₁₇BrO₅: C, 52.0, H, 4.6 %, M, 368:370 (1:1)]

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

![Chemical Structure of 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 (MgSO₄) 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).

\[ ΔH \text{ ppm, (OH missing from the spec), 3.95, 3.96 and 3.97 (each 3H, s, 3 x OMe); 4.92 (2H, s, CH}_2\text{OH); 6.55 (1H, d, J 2.2, 7-H); 6.93 (1H, s, 2-H) and 7.25 (1H, d, J 2.2, 5-H).} \]

\[ ΔC \text{ ppm, 55.4 and 56.6 (overlapping peaks 3 x OMe); 66.3 (CH}_2\text{OH); 98.7 (C-7)\text{a}; 99.5 (C-5)\text{a}; 104.4 (C-2)\text{a}; 112.1 (C-3)\text{b}; 113.8 (C-4)\text{b}; 136.3 (C-4a)\text{c}; 139.2 (C-8a)\text{c}; 157.4 (C-1)\text{d}; 158.8 (C-6)\text{d} \text{ and 159.5 (C-8)\text{d}. Assignments with the same superscripts may be exchanged.} \]

[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.

\[ \text{OMe OMe} \]
\[ \text{MeO CHO} \]
\[ 226 \]

A mixture of the alcohol 225 (180 mg; 0.55 mmol) in benzene (30 ml) containing MnO₂ (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). \[ ΔH \text{ ppm, 3.96, 3.99 and 4.00 (each 3H, s, 3 x OMe); 6.71 (1H, d, J 2.2, 7-H); 7.17 (1H, s, 2-H); 7.46 (1H, d, J 2.2, 5-H) and 10.61 (1H, s, CHO).} \]

\[ ΔC \text{ ppm, 55.6, 56.5 and 56.8 (3 x OMe); 99.7 (C-2)\text{a}; 101.4 (C-5)\text{a}; 102.4 (C-7)\text{a}; 117.0 (C-3)\text{b}; 120.9 (C-4)\text{b}; 132.3 (C-4a)\text{c}; 136.4 (C-8a)\text{c}; 157.6 (C-1)\text{d}; 158.9 (C-6)\text{d}; 159.9 (C-8)\text{d} \text{ and 193.3 (C=O). Assignments with the same superscripts may be exchanged.} \]

[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.**

![Chemical Structure](image1)

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 N₂. 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 (elucent 5.0 % EtOAc:Hex) to afford a mixture of the *trans*- and *cis*- alkenes 227 as a yellow oil (990 mg; 81.05 %).

![Chemical Structure](image2)

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 (elucent 5.0 % EtOAc:Hex) to afford cream needles of the *trans*-olefin 166 (120 mg; 44.4 %), mp 123-125 °C (from Hex). \( \nu_{max} \text{ /cm}^{-1} \) 1617.32 (C=C). \( \Delta \text{H ppm,} \) 1.97 (3H, dd, \( J 6.6 \) and 1.8, 3'-CH₃); 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).
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 OsO₄ (1 mole % OsO₄) (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), $\nu_{\text{max}}$ /cm⁻¹ 3258.29 (O-H). Delta H ppm, 1.23 (3H, d, $J_{6.2}$, 3'-CH₃); 2.46 and 3.00 (each 1H, s, D₂O 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)$^{b}$; 113.0 (C-3)$^{b}$; 113.8 (C-4)$^{b}$; 133.3 (C-1'); 136.0 (C-4a)$^{c}$; 137.9 (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.

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

![Structural formulas of 229 and 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 NaHCO₃, 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), \( \nu_{\text{max}} \) cm\(^{-1}\) 1596.06 and 1200.62.

\( \Delta \delta \) 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, \( \nu \) 6.6 and 5.0, 5'-H); 5.32 (2H, d, \( \nu \) 5.6, 4'-H); 5.48 (1H, q, \( \nu \) 5.2, 2'-H, major isomer 229); 5.59 (1H, q, \( \nu \) 4.8, 2'-H, minor isomer 230); 6.57 (2H, d, \( \nu \) 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, \( \nu \) 2.2, 5-H).

\( \Delta \delta \) 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.

The TiCl₄ (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 N₂. The resultant dark solution was slowly warmed to room temperature and stirred for 1 hr. The addition of the saturated aqueous NaHCO₃ 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). ΔH ppm, 1.46 (3H, d, J 6.2, 3-CH₃); 1.61 (3H, d, J 6.2, 1-CH₃); 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).

ΔC ppm, 16.9 (3-CH₃); 19.7 (1-CH₃); 55.4, 56.3 and 62.0 (3 x OMe); 66.3 (C-3); 68.4 (C-1)ᵇ; 69.5 (C-4)ᵇ; 100.0 (C-8)ᵇ; 116.8 (C-10a)ᶜ; 120.2 (C-5)ᵃ; 127.9 (C-4a); 135.5 (C-5a)ᵈ; 135.7 (C-9a)ᵈ; 152.3 (C-7)ᵇ; 157.1 (C-9)⁹ and 158.9 (C-10)⁹. Assignments with the same superscripts may be exchanged.


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). ΔH ppm, 1.23 (3H, d, J 6.2, 3'-CH₃); 2.46 and 3.0 (each 1H, s, D₂O 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).

ΔC 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)ᵇ; 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.
References:


34. Hainan-Renmin Hospital Guanxinbin-Keyan-Xiaozu, Hainan-Weisheng, 1977, 43.


