SYNTHESES OF THE ENANTIOPURE QUINONES A AND A’ AND THEIR C-1 EPIMERS.

THIS THESIS IS PRESENTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY OF MURDOCH UNIVERSITY

BY

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Masters Degree in Technology (Cape Technikon)
2002
I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary educational institution.

Francois Jacobus Oosthuizen

August 2002
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ABSTRACT

The 3,4-dihydro-1H-naphtho[2,3-c]pyran ring system is found in many natural products as the 5,10- or 6,9-quinones. These compounds have been synthesized by various research groups as a result of their wide range of biological activities. This thesis describes several investigations directed towards syntheses of compounds in this general area. Quinone A (16) and quinone A’ (17), derived from the naturally occurring aphid insect pigments protoaphin-fb and protoaphin-sl respectively, were of particular interest.

The first chapter describes the previous syntheses of some naphtho[c]pyrans including those relating to the aphid pigment derivatives, followed by the isolation and identification of the aphid pigments. Also described was the ability of these naphthopyranquinones to act as potential bioreductive alkylating or dealkylating agents. The latter part of the chapter deals with the syntheses of the racemates of the aphid pigment derivatives quinones A and A’ and deoxyquinone as well as model studies toward the non-quinonoid cleavage product, glucoside B. The chapter concludes with the progress made towards the first asymmetric synthesis of these compounds.

Chapter 2 reports the establishment of conditions which led to ortho or para regioselectivity in the intramolecular cyclisation of tethered lactaldehydes to form benzo[c]pyrans. This regioselectivity depended on whether either benzyl or t-butyldimethylsilyl was used as protecting group. This chapter also described a model for the control of stereochemistry leading to quinone A’.

Chapter 3 describes the syntheses of naphthalenes as potential precursors to the naphthopyranquinones derived from the aphid insect pigments. This followed after problems were encountered in previous work with inappropriate protection in the oxidation of halogenated benzopyrans.

Chapter 4 develops the first successful syntheses of enantiopure quinone A and quinone A’ with the correct absolute stereochemistry. This involved the regioselective addition of 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene to
selectively halogenated benzopyranquinones. The latter were obtained through complementary series of highly diastereoselective transformations based on 2,5-dihydroxyacetophenone as starting material and (R)-lactate from the chiral pool as the source of asymmetry.
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ACKNOWLEDGMENTS

My sincere thanks and appreciation to my supervisor and friend Robin Giles for his time, advice, guidance and encouragement throughout the whole of this project.

Thanks also to the following persons:

* Ivan Green from the University of the Western Cape and Victor Hugo from the Cape Technikon for all their help and valuable advice during my studies and for setting me on my way.

* Doug Clarke and the rest of the technical staff at Murdoch University for their invaluable assistance in the use of instrumentation.

* Dr. A. Reeder of the University of Western Australia for providing high and low resolution mass spectra.

* Murdoch University for financial support as well as Karin Olkowski and Anne Randell at the Research Office for all their friendly advice and help.

* My colleagues Richard, Peter, Chris, Kim, Celestine, Franky, Jason, Danielle and Yolanta for all the humorous and sometimes helpful discussions in the laboratory.

* Special thanks to my parents for all their love and support throughout all the years of my studies.
To my wife Annie
1.0 General Introduction

A wide variety of quinones occur naturally and have been isolated from various microorganisms, fungi, higher plants and animals. The largest subgroup of natural quinones are the naphthoquinones, of which over 350 are found in nature, the majority being microbial in origin. Naphthoquinones have been comprehensively reviewed until 1997.\textsuperscript{1,2,3}

A significant number of these naphthoquinones possess the naphtho[2,3-\textit{c}]pyran ring system and occur commonly as the 5,10-quinones (1) with carbon substituents at C-1 and C-3.

In some members of this group an additional $\gamma$-lactone ring fused to the dihydropyran moiety is present, as in structure (2). Others possess a carboxylic acid side chain (3) caused by ring opening of the $\gamma$-lactone.\textsuperscript{4}
Three major groups of naphtho[2,3-c]pyrans can be identified from these compounds, based on degree of oxidation of analogous polyketide precursors. The simpler and more common 5,10-quinones with C-1 and C-3 methyl substitution represent the first class of naphtho[2,3-c]pyrans. Examples include eleutherin (4) and isoeleutherin (5), which were first isolated from the tubers of Eleutherine bulbosa by Schmid and co-workers. Other examples include ventiloquinone A (6) and B (7) isolated from the roots of Ventilago maderaspatana.

A number of the 5,10-quinones display a range of interesting biological activities, showing significant antibiotic and antimicrobial behaviour. Further examples of naphthopyran-5,10-quinones of microbial origin include nanaomycin A (8), nanaomycin D (9) and kalafungin (10) isolated from Streptomyces rosa var. notoensis. Nanaomycin D (9) and kalafungin (10) are enantiomers elaborated by different microorganisms.
Other 5,10-quinones of microbial origin include deoxyfrenolicin (11),\textsuperscript{12,13} granaticin (12)\textsuperscript{14} and griseusin A (13),\textsuperscript{15} isolated from the cultures of \textit{Streptomyces roseofulvus},\textsuperscript{16} \textit{Streptomyces olivaceus}\textsuperscript{17} and \textit{Streptomyces griseus} respectively.\textsuperscript{18} The structurally related nanaomycin D (9) and griseusin A (13) would be ideally suited to function as bioreductive dialkylating agents by virtue of a pyrano-$\gamma$-lactone moiety fused to a 5-hydroxynaphthoquinone skeleton\textsuperscript{19} (discussed later in the chapter).

The second class of naphtho[2,3-\textit{c}]pyrans includes the isomeric 6,9-quinones, which are not as widely found in nature. Ventilagone (14), isolated from the root of \textit{Ventilago
*viminalis* \(^{20,21}\) is an example of this group. The third class is represented by non-quinonoid systems such as the naphthopyran karwinaphthol B (15)\(^ {22,5}\).

Our main focus of interest centres around a group of naphthopyranquinones, namely the protoaphin-derived insect pigment derivatives quinone A (16), quinone A’ (17), deoxyquinone A (18) and glucoside B (19) and our attempts at the first syntheses of these compounds in enantiopure form.

A short review of the isolation and syntheses of some of the most relevant naphthopyranquinones will be discussed in *Section 1.1*, followed by the isolation and structure determination of the aphid pigments in *Section 1.2*. The potential of these compounds to act as bioreductive alkylating and dialkylating agents will be discussed in
Section 1.3, followed by the racemic syntheses of quinone A (16), quinone A’ (17) and deoxyquinone (18), as well as exploratory studies directed towards the synthesis of glucoside B (19) in Section 1.4. Section 1.5 dealing with recent attempts at the asymmetric syntheses of (16), (17), (18) and (19) will conclude the introduction.

1.1 Isolation and Syntheses of Selected Naphtho[2,3-c]pyrans Related to the Aphid Pigment Derivatives.

1.1.1 The Eleutherins

Isolation:
The epimeric eleutherin (4) and isoeleutherin (5) were the first members of the naphtho[2,3-c]pyran-5,10-quinone family to be isolated and identified. In 1950 Schmid and co-workers\textsuperscript{6a,c} reported the isolation of eleutherin (4) as yellow rods from the tubers of Eleutherine bulbosa (Mill.) Urb. (Iridaceae). The plant, also known as Eleutherine americana, originates from tropical America where its elongated red tubers have been used by the local inhabitants to treat numerous medical conditions. It has since been cultivated in Javanese gardens and can now be found in the wild, particularly in rubber plantations in Java.

\[
\begin{array}{c}
\text{(4)} \\
\text{(5)}
\end{array}
\]

In 1981, Japanese and Chinese researchers isolated eleutherin (4) and isoeleutherin (5) from the rhizome Eletherine americana Merr. et Heyne (Iridaceae), together with related naphthopyrans, namely the ketones, hongconin (20)\textsuperscript{23} and eleutherol (21).\textsuperscript{24}
Recently two new compounds have been isolated from the same plant, namely the naphthoquinone, elecanacin (22) and the naphthalene isoeleutherol (23), the enantiomer of eleutherol (21), by Imakura and co-workers.\textsuperscript{25}

This herbal plant is widely cultivated in Hainan Island, South China for ornamental and medicinal purposes. The tubers are used as a folk medicine for the treatment of coronary disorders,\textsuperscript{23,24} together with eleutherin (4) and isoeleutherin (5). Hongconin has shown the effect of increasing coronary flow on isolated guinea pig heart and was confirmed by pharmacological tests to exhibit cardioprotective activity against angina pectoris.\textsuperscript{25,26,27}

The presence of eleutherin (4) and isoeleutherin (5) in \textit{Eleutherine subaphylla Gagnep}\textsuperscript{28} was also reported by Vietnamese scientists.

In 1975 two substituted eleutherins, 7-methoxyeleutherin (24) and 6-hydroxy-7-methoxy eleutherin (25) were isolated from the seeds of a desert plant \textit{Karwinska humboldtiana} of the Rhamnaceae family growing in Southern Texas, California, Mexico and parts of central America.\textsuperscript{29}
Two closely related naphthopyrans namely karwinaphthol A (26) and karwinaphthol B (27) were isolated from the ground roots of the same plant. Oxidation with Fremy’s salt to yield eleutherin (4) and 7-methoxyeleutherin (24) gave confirmation of the structures of (26) and (27).

Syntheses:
Various methods have been reported for the syntheses of the naphtho[2,3-c]pyrans. The syntheses of eleutherin (4) and isoeleutherin (5) were first reported in 1958 by Eisenhuth and Schmid and started with the conversion of 5-methoxy-1-naphthol into the allylquinone (28). Reduction to the hydroquinone (29) and subsequent cyclisation gave the furan (30), which was reoxidised to give the hydroxypropylquinone (31).

Scheme 1 (contd. over)
The key step in the synthesis involved the reduction of quinone (31) to the quinol (32) followed by a condensation reaction using acetaldehyde to give a separable racemic mixture of the epimeric eleutherin (4) and isoeleutherin (5) as their racemates.

Cameron\textsuperscript{31} used a similar approach and also found that in the reduction of the hydroxypropyl quinone (33) to form the quinol (34), by using an excess of zinc and hydrochloric acid in tetrahydrofuran followed by atmospheric reoxidation, a mixture of
the naturally occurring (±)-pyranquinone 7-methoxyeleutherin (24) and the derivative deoxyquinone A dimethyl ether (35) was obtained (Scheme 2).

\[
\begin{align*}
(33) & \quad \rightarrow \quad (34) \\
(24) & \quad + \quad (35)
\end{align*}
\]

Scheme 2

A high yielding synthesis of the racemic eleutherins (4) and (5) was reported by Naruta et al.\textsuperscript{32} 1,5-Dimethoxynaphthalene (36) was acetylated to give the acetate (37) which then underwent a Fries rearrangement on treatment with boron trifluoride diethyl etherate to afford the corresponding 3-acetyl derivative. This underwent oxidative demethylation with cerium(IV) ammonium nitrate to yield the naphthoquinone (38). Nucleophilic addition of allyltrimethylstannane\textsuperscript{32,33} to (38) in the presence of boron trifluoride diethyl etherate followed by methylation and reduction resulted in the formation of the intermediate (39) with the allyl group directly introduced to the C-2 position (Scheme 3). The key step involved an oxymercuration demercuration\textsuperscript{34,35} reaction of the naphthylcarbinol (39) which led to intramolecular cyclisation to yield an equal mixture of the two diastereoisomers (40) and (41). These were chromatographically separated and each diastereoisomer oxidised with cerium(IV)
ammonium nitrate to afford the pure cis (4) and trans (5) isomers in a high overall yield of 38% and 34% respectively.32

Scheme 3
Yoshii and co-workers\textsuperscript{35} described a different route to the strategic naphthylcarbinol (39) starting with the oxidative alkylation of 3-bromo-5-methoxy-1,4-naphthoquinone (42) with vinyl acetic acid in the presence of persulphate and silver nitrate (Scheme 4) to form 2-allyl derivative (43). This was reduced and then methylated to give the trimethoxynaphthalene (44). Treatment of (44) with \( n \)-butyl lithium and subsequent addition of acetaldehyde afforded the key benzylic alcohol (39). Cyclisation of (39) was effected as previously described (Scheme 3).

\[ \text{CH}_2=\text{CHCH}_2\text{CO}_2\text{H} \quad \begin{array}{c} \text{K}_2\text{S}_2\text{O}_8 \\ \text{AgNO}_3 \end{array} \rightarrow \text{OMe} \quad \text{Br} \quad \begin{array}{c} \text{OMe} \\ \text{OMe} \\ \text{OMe} \\ \text{Br} \end{array} \]

(42) \quad (43)

(39) \quad (40) \quad (41)

(5) \quad (4)

\[ \begin{array}{c} 1. \text{Na}_2\text{S}_2\text{O}_4 \\ 2. \text{CH}_3\text{CHO} \end{array} \rightarrow \text{OMe} \quad \text{OMe} \quad \begin{array}{c} \text{OMe} \\ \text{OMe} \end{array} \]

(44)

Scheme 4

In contrast to these earlier methods, Giles \textit{et al.}\textsuperscript{36} developed a completely diastereoselective method to cyclise the unconjugated alkenyl alcohol (39) to afford the \textit{trans} isomer (5) exclusively as the sole product in high yield. When compound (39) was treated with potassium \( t \)-butoxide in dimethylformamide it resulted in a stereoselective intramolecular nucleophilic attack on the activated double bond to provide solely the cyclised product (40) in 88\%. Oxidation with cerium(IV) ammonium nitrate then gave isoeleutherin (5). This methodology was also applied by the Giles group\textsuperscript{36b} to convert the
individual alcohols (45) and (46) into deoxyquinone A dimethyl ether (35) and demethoxyisoeleutherin (47) respectively.

Recently Cameron and colleagues\(^5\) published the first synthesis of the non-quinonoid naphthopyran, karwinaphthol B (15) through which an alternative route to 7-methoxyeleutherin (24) was developed. Their approach utilised acylation and Michael addition methodology. 3,5-Dimethoxyphenylnitromethane (49) was acylated with the \textit{cis}-acid chloride (48) used as the pyran ring precursor to give the enone (50). This underwent intramolecular Michael addition in the presence of methanolic Triton B, to produce the tricyclic ketone (51) in high yield. Nitrous acid was thermally eliminated from the ketone (51) by boiling in \textit{p}-cymene to produce the target compound (15).
The position of the \( O \)-methyl groups could be established by oxidising natural (+)-karwinaphthol B (15) to yield (+)-7-methoxyleuetherin (24).\(^2\) This alternative route\(^5\) was brought about by conversion of the nitro group in the tricyclic ketone (51) to form a carbonyl group by means of the Nef reaction, using aqueous titanium trichloride. The resulting intermediate dihydronaphthalenedione (52) was readily tautomerised to the corresponding quinol, which underwent aerial oxidation during work-up to give racemic 7-methoxyleuetherin (24).\(^5\)

Kobayashi \textit{et al.}\(^{39}\) recently reported a one-pot preparation of 1H-naphtho[2,3-\(c\)]pyran-5,10-diones and its application to a concise total synthesis of (±)-eleutherin and (±)-isoeleutherin.
By reacting the 2-(1-hydroxyethyl)-8-methoxy-1,4-naphthoquinone (53) with imine (54) the 1H-naphtho[2,3-c]pyran-5,10-dione (55) was isolated in a 55% yield. Subsequent reduction with triethylsilane in trifluoroacetic acid at room temperature gave a 1:5 mixture of racemic eleutherin (4) and isoeleutherin (5).\textsuperscript{39}

\[
\begin{align*}
\text{(53)} & \quad \text{OH} \\
\text{(54)} & \quad \text{Me} \\
\text{1. toluene, Argon, rt} & \quad \text{Me} \\
\text{2. air, SiO}_2 & \\
\end{align*}
\]

\[
\begin{align*}
\text{(55)} & \quad \text{Et}_3\text{SiH} \\
\text{TFA} & \\
\end{align*}
\]

\[
\begin{align*}
\text{(4)} & \quad 1 : 5 \\
\text{+ (5)} & \\
\end{align*}
\]

Scheme 5

It was concluded that (4) had isomerized to (5) under the reaction conditions. The reaction was repeated at -20 °C and gave eleutherin (4) as the sole diastereoisomer in moderate yield. Higher yields of analogues of the 5,10-dione (55) are obtained when enamines (56) are used but these are described\textsuperscript{39} as harder to prepare than the corresponding imines (54).

\[
\begin{align*}
\text{(56a)} & \quad R^1, R^2 = (\text{CH}_2)_3 \\
\text{(56b)} & \quad R^1, R^2 = (\text{CH}_2)_4 \\
\text{(56c)} & \quad R^1 = \text{Et, } R^2 = \text{Me} \\
\end{align*}
\]
In 1996 two publications appeared simultaneously dealing with the enantioselective synthesis of hongconin (20). Baker and co-workers prepared both enantiomers of hongconin in optically pure form, from L-quinoval and D-fucal diacetates, using cyanophthalide annulation chemistry.

Swenton and colleagues reported a total synthesis of (-)-hongconin (20) in six steps, the key step involving the annelation of readily available levoglucosenone (58). The annelation reaction of levoglucosenone (58) with a methoxy-substituted cyanophthalide anion (57) yielded the stable, crystalline naphthohydroquinone (59) in good overall yield (74%). Reductive ring opening of (59) with zinc/copper in tetrahydrofuran and acetic acid gave (60) as the sole product in a yield of 85%. The primary alcohol group on the naphthopyran (60) was converted into the mesylate, followed by reaction with sodium iodide in acetone to afford the iodide (61), which was then reduced with tri-n-butylstannane. Chromatography gave an 89% yield of (62) contaminated with 10% tin residue. It proved essential to rid the product of tri-n-butyltin contamination in order to continue the synthesis. Treatment with potassium fluoride, chromatography and recrystallization did not give a pure product, however, methylation with dimethyl sulfate gave the product (63) which could easily be purified by chromatography. Treatment with lithium tetramethylpiperidide (LiTMP) followed by methyl iodide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) afforded ketone (64). Oxidative demethylation of (64) with silver(II) oxide followed by reducton with sodium dithionite gave (-) hongconin in 85% yield.

Scheme 6 (contd. over)
Baker et al.\textsuperscript{40a} also reported the chiral synthesis of (−)-hongconin. The unnatural configuration (20b) was also reported, with all physical data identical except for the expected opposite sign for the optical rotation.
Green\textsuperscript{41} and Kraus\textsuperscript{42} have both reported total syntheses of racemic hongonin.

1.1.2 Kalafungin and the Nanaomycins

Isolation:
In 1968 M.E. Bergy from the Upjohn Company Research Laboratories (U.S.A.) reported the isolation of kalafungin,\textsuperscript{10} previously patented by the company under the name kalamycin (U-19,718).\textsuperscript{43a,b} This broad spectrum antibiotic was isolated as orange crystals from the fermentation broth of \textit{Streptomyces tanashiensis} strain Kala.\textsuperscript{10} The organisms \textit{S. tanashiensis} NRRL B-1692 and an alkalophilic actinomycete \textit{Nocardiopsis dassonvillei} subsp. \textit{prasina} were also later identified as producers of kalafungin.\textsuperscript{43c}

The structure and related configuration of this antimicrobial compound (10) were subsequently determined by X-ray crystallographic analysis.\textsuperscript{44} Chemical transformations, spectroscopic studies and determination of the absolute configuration of its three stereochemical centres from optical rotary dispersion (ORD) comparisons with eleutherin (4) and isoeleutherin (5) confirmed the structure of kalafungin.\textsuperscript{11}
Kalafungin (10) was found to display high in vitro activity against a number of pathogenic fungi, yeasts, protozoa, Gram-positive bacteria and, to a lesser extent, Gram-negative bacteria. More recently, it was found to be cytotoxic, showing a marked inhibitory activity against mouse leukemic cells in vitro, and it also proved to be an anthelmintic.

Omura and co-workers were the first to discover the nanaomycins, a series of very important antibiotics, whilst in the process of screening Steptomyces culture filtrates for antimycoplasmal antibiotics. Of the ten different nanaomycins isolated, five were from Streptomyces rosa var. notoensis and five from Streptomyces sp. OM-173. Only five of these compounds are naphtho[2,3-c]pyranquinones and will be discussed subsequently in this section.

Nanaomycin A (8) was first isolated in 1974 as orange needles from cultures of Streptomyces rosa var. notoensis. Assignment of the structure and relative stereochemistry, followed by the determination of the absolute configuration, was determined in the following two years.

Nanaomycin A (8) has been shown to possess inhibitory activity against mycoplasmas, fungi and Gram-positive bacteria. It also exhibited some inhibition towards the platelet aggregation agent adenosine diphosphate (ADP), in a study of anti-platelet activities of isochromanquinone antibiotics. Most recently it was found that nanaomycin A (8) inhibits in vitro growth of the human malaria parasite Plasmodium falciparum through the action of heme-dependent radical generation.
Further examination of the culture extracts of *S. rosa* var. *notoensis* led to the discovery of nanaomycin C (65), isolated as orange needles.\(^9\),\(^{47}\)

![Chemical structure of nanaomycin C (65)](attachment:image)

Nanaomycin C, an amide of nanaomycin A, has also been shown to exhibit comparable activity against Gram-positive bacteria, but was weaker against fungi and mycoplasmas.\(^{47}\)

In 1976, Omura and co-workers reported yet another antibiotic from *S. rosa* var. *notoensis*, identified as nanaomycin D (9).\(^9\) Comparisons of spectroscopic and optical rotary dispersion data showed nanaomycin D (9) to be the enantiomer of kalafungin (10) with almost identical antimicrobial activities.\(^{48}\)

![Chemical structure of nanaomycin D (9)](attachment:image)

Nanaomycin D exhibited a very high anti-platelet activity with the inhibition activity moderately strong for kalafungin, indicating that absolute configuration is not crucial for inhibition of platelet aggregation.\(^{49}\)

It was further reported by the same research group that nanaomycin A (8) was converted into nanaomycin D (9) by aerial oxidation in a methanolic solution.\(^{8a,9}\) Consequently, all syntheses of (±)-nanaomycin A constitute formal syntheses of nanaomycin D (9) and kalafungin (10).
A different strain of *Streptomyces* was found to produce nanaomycin-type antibiotics. Two derivatives of nanaomycin A were isolated from the fermentation broth of *Streptomyces* sp. OM-173. Nanaomycin αA (66), a relatively non-polar yellow powder, was found to be the methyl ester of nanaomycin A. The second derivative, nanaomycin βA (67), isolated as yellow crystals, was described as an analogue of nanaomycin A, in which the carboxylic acid group had been reduced to the corresponding alcohol. Nanaomycin A and nanaomycin βA were also isolated as minor components from the fermentation broth of *Streptomyces roseofulvus* AM-3867. The structural elucidation of compound (67) was reported in a subsequent paper.

The antimicrobial activities of these compounds (66) and (67), where the carboxylic acid group has been modified, were less than those of nanaomycin A. The carboxylic acid functionality could thus be the key factor in determining strong antibacterial activity.

More recently, a Japanese research group produced two main compounds from a culture of the *Nocardia* YS-02931K species. The first active compound, named 2931-α, was found to be kalafungin (10). The other antibiotic, a yellow powder named 2931-β (YS-02931KB) had spectroscopic and analytical data identical to those of nanaomycin A except for the optical rotation being the opposite sign, and this was subsequently simply called (+)-nanaomycin A (68).
Treatment of 2931-β with silver(I) oxide in pyridine produced kalafungin (10), proving the absolute stereochemistry of the two chiral centres in the starting material to be opposite to (-)-nanaomycin A isolated from *Streptomyces rosa.* var. *notoensis.* (+)-Nanaomycin A showed similar antimicrobial behaviour to that of (-)-nanaomycin A.

**Syntheses:**
There have been many interesting synthetic routes to kalafungin, the nanaomycins and their derivatives since these compounds were first isolated and identified as having significant antimicrobial properties. A few of the most relevant and interesting of these approaches will be discussed in the following section.

The first syntheses of the racemate of kalafungin (10) and nanaomycins A (8) and D (9) were reported by Li and Ellison in 1978. They used the same methodology developed by Schmid for the synthesis of the eleutherins. 2-Allyl-5-methoxy-1,4-naphthoquinone (28) was also used as starting material.

![Scheme 6](contd. over)
Scheme 6 (contd. over)
Scheme 6 (contd.)

Quinone (28) was reduced with aqueous sodium dithionite to the hydroquinone and methylated with dimethyl sulfate to give the trimethyl ether (69). This was followed by a two step oxidative cleavage of the double bond using osmium tetroxide and potassium chlorate to afford the aldehyde (70) in high yield. A catalytic amount of titanium tetrachloride was added to a mixture of (70) and ketene ethyl tert-butylidemethylsilyl acetal (71) to form the hydroxy ester (72). Cerium(IV) ammonium nitrate induced oxidative demethylation of (72) then gave the quinone (73). Reduction of (73) with zinc and hydrochloric acid in tetrahydrofuran and subsequent reaction with acetaldehyde produced the intermediate pyran (74). Oxidation with silver(I) oxide and O-demethylation with aluminium chloride afforded the naphthopyranquinone (75). The cis-stereochemistry for substituents at C-1 and C-3 was determined by $^1$H NMR spectroscopic studies. C-1 epimerisation was achieved by treatment of (75) with concentrated sulfuric acid to form the trans and cis isomers (76) in a 2:1 ratio.
respectively and the individual diastereoisomers were separated by fractional recrystallisation. Racemic nanaomycin A (8) was obtained by hydrolysis of the ethyl ester group of the trans isomer (76) with concentrated hydrochloric acid. Treatment of nanaomycin A with aerated methanol gave a mixture of racemic nanaomycin D (9) and kalafungin (10).

In 1995 Kraus et al.\textsuperscript{55} reported a much shorter route to (±)-kalafungin via a highly regioselective Diels-Alder reaction, which is outlined by Scheme 7. The starting diol (77) was treated with palladium acetate and cupric chloride in an atmosphere of carbon monoxide to give the pyranolactone (78) in moderate yield, after which oxidation with silver(II) oxide afforded quinone (79). Treatment of (79) with 1-trimethylsilyloxy-1,3-butadiene in dichloromethane followed by Jones oxidation yielded (±)-kalafungin (10) in a 63\% yield from the lactone (78). The spectral data matched the spectra of a sample made via a completely different route.\textsuperscript{56,57}

In 1985, Tatsuta and co-workers\textsuperscript{58} published the first syntheses of the enantiopure members of the benzoisochromanquinone family of antibiotics, namely (-)-nanaomycin
A, (+)-nanaomycin D and kalafungin, via an “enantiodivergent strategy” from a common optically active intermediate.

The key step in the syntheses was the construction of the optically active intermediate, methyl 3,4,6-trideoxy-\(\alpha\)-L-glycero-hex-3-enopyranosid-2-ulose (85) from a carbohydrate precursor as depicted in Scheme 8.

Commercially available L-rhamnose (80) was converted into methyl-\(\alpha\)-L-rhamnoside (81). Reaction of (81) with trichloromethyl chloroformate in pyridine followed by the addition of tosyl chloride afforded the cyclic carbonate (82) in a one-pot procedure. Treatment of (82) with zinc powder and sodium iodide under reflux in aqueous acetonitrile afforded a mixture of the desired 3,4-unsaturated alcohol (83) and the
isomeric 2,3-unsaturated alcohol (84) in a 2:1 ratio respectively. The process presumably proceeds through the removal of the carbonate protecting group and formation of the 3,4-epoxide. Ring opening of the epoxide with sodium iodide followed by elimination with zinc powder would then give the olefin. Subsequent oxidation of alcohol (83) with pyridinium chlorochromate afforded the stable α,β-unsaturated ketone (85) in high yield (86%).

Mesylation of the rearranged isomeric alcohol (84) followed by exposure to potassium carbonate in aqueous tetrahydrofuran again produced alcohol (83) as a mixture of epimers at C-2. This mixture could be oxidized to the key intermediate (85) in a similar manner.

The preparation of the ketone (85) (Scheme 9) was reported earlier in 1977\textsuperscript{61} by Paulsen and Koebernick but in considerably lower yield. The epoxy alcohol (86), derived from L-rhamnose (81)\textsuperscript{62} was treated with acetic anhydride and pyridine to form the acetate (87) which was subsequently treated with sodium iodide followed by phosphorus oxychloride to give the olefin (88). Hydrolysis and subsequent oxidation then produced the optically active synthon (85) in 46% yield, compared to the 57% overall yield of Tatsuta\textsuperscript{58} (including recycling of isomer (84) from L-rhamnose).

\[ \text{Scheme 9} \]
The phthalide annulation methodology developed by Hauser\(^\text{63}\) has been extensively applied in the syntheses of racemic benzoisochromanquinone antibiotics\(^\text{2}\) and used by Tatsuta \textit{et al.}\(^\text{58}\) for the construction of the napthopyran ring system (Scheme 10). Condensation of the chiral intermediate (85) with the lithium \(t\)-butoxide-generated anion of the sulfonylphthalide (89) produced the napthopyran (90) with the correct stereochemistry.\(^\text{63}\) Dimethylation followed by stereoselective reduction afforded the alcohol (91) of \textit{syn} hydride delivery owing to the directing influence of the pyrano oxygen atom.\(^\text{58}\) Acid hydrolysis of the acetal (91) produced the key intermediate hemiacetal (92) without racemisation at C-1 and C-4. A Wittig reaction then furnished the two desired compounds (93) and (94) in 53 and 41\% yields respectively. The lactone (93) was formed \textit{via} an intramolecular conjugate addition of the Wittig \(\alpha,\beta\)-unsaturated ester and concomitant lactonisation. Conjugate addition without lactonisation afforded the 3,4-\textit{trans} hydroxy ester (94).\(^\text{63}\) Oxidation and demethylation of the lactone (93) produced (-)-nanaomycin D (9), identical to the natural antibiotic.\(^\text{58}\)

\textbf{Scheme 10} (contd. over)
Scheme 10 (contd. over)
Similar treatment of the hydroxy ester (94) produced the quinone (95). Treatment with sulphuric acid in benzene followed by completion of the lactonisation in boiling toluene furnished (+)-kalafungin (10). In this case the favoured epimerisations at C-1 and C-4 were effected through keto-enol tautomerism with the quinone functionality and controlled by the stereochemistry at C-3 to give the preferred 1,3-trans configuration.\textsuperscript{58}

The (+)-kalafungin (10) was identical to an authentic sample of the natural product. Hydrogenolysis of (-)-nanaomycin D (9) and (+)-kalafungin (10) gave near quantitative yields of (-)-nanaomycin A (8) and (+)-nanaomycin A (68) respectively.\textsuperscript{58} The overall yields obtained for the chiral syntheses of (-)-(9) and (+)-(10) from methyl α-L-rhamnoside were 18 and 13% respectively.

This elegant “enantiodivergent” strategy could also be applied to the synthesis of both antipodes of many other naphthopyranquinone antibiotics, and was indeed applied in 1990 by the same group for the synthesis of the two enantiomers of medermycin (96) and (97).\textsuperscript{64} Only enantiomer (96) has been found in nature.\textsuperscript{65-69} Both the natural product (96) and the unnatural compound (97) were found to have similar antibacterial activities\textsuperscript{64} in the antimicrobial spectra as was observed for the other two pairs of enantiomers, kalafungin and nanaomycin D,\textsuperscript{49} and (+)-nanaomycin A and (-)-nanaomycin A.\textsuperscript{52,53} This suggests that the absolute stereochemistry at the chiral centres does not have a significant effect on the nature of their biological activity.
1.1.3 The granaticins

Isolation:
A new antibiotic pigment (98) isolated from the cultures of *Streptomyces olivaceus* (Waksman) Waksman and Henvici was reported in 1957.16 The deep red crystals were named granaticin. Another microorganism, *Streptomyces violaceoruber* (Waksman and Curtis) Waksman sensu Waksman and Katzner, was found to produce a mixture of granaticin (98) and granaticin B (99), a glycoside of granaticin.70

The sugar moiety of granaticin B was identified as L-rhodinose70 attached as the α-glycoside.15

Granaticin has also been detected in the following actinomycetes: *Streptomyces litogenes*71, *S. lateritus* ZIMET 43 627,72 *S. thermoviolaceus* subsp. *pingens* var. WR-
The structures of granaticin (98) and granaticin B (99) were determined in 1968 by Keller-Schierlain\textsuperscript{14} and confirmed by x-ray crystallography and detailed spectroscopic analysis.\textsuperscript{77} An interesting and unique feature of the structure is the attachment of a 2-oxabicyclo[2.2.2]oct-5-ene moiety, derived biosynthetically from C-glucoside,\textsuperscript{78} to the naphthopyranquinone nucleus. It is interesting to note that the benzoquinone antibiotic sarabucin A (U58431) (100) isolated from \textit{Streptomyces} strain JA 2861 and \textit{S. helicus} (UC-5837), also possesses this unique structural feature.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{granaticin.png}};
\end{tikzpicture}
\end{center}

Granaticin (98) was found to be highly active against Gram-positive bacteria\textsuperscript{16,74} and protozoa and also exhibited some activity against P-388 lymphocytic leukemia in mice as well as cytotoxicity against KB cells. It showed limited effect, however, against Gram-negative bacteria, yeasts and fungi.\textsuperscript{71,74} The synthesis of RNA in bacteria and to a lesser extent of DNA and protein, were inhibited by granaticin.\textsuperscript{79} The cytotoxicity of (98) was partly attributed to inhibition of ribosomal RNA maturation.\textsuperscript{80} Further reports have claimed that granaticin inhibits the DNA polymerase activity of RNA tumour viruses involved in some forms of human cancer such as leukemia.\textsuperscript{81} Granaticin B (99), the glycoside of granaticin (98), shows distinct inhibition of various transplanted tumours in rodents after intraperitoneal application.

Granaticin acid (101) exhibited similar but overall weaker antibiotic properties compared with granaticin.\textsuperscript{75} Dihydrogranaticin (102) inhibited the proliferation of leukemic cells \textit{in vitro} equal to granaticin but five times less toxic in mice by i.v. application.\textsuperscript{82} Granaticin B and the L-rhodinoside (probable $\alpha$-configuration) of
dihydrogranaticin (103) showed high activity against Gram-positive bacteria but limited activity against Gram-negative organisms.\textsuperscript{83}

Syntheses:
Yoshii and co-workers\textsuperscript{84} were the first to achieve the challenging total synthesis of granaticin with its unique structural feature, the 2-oxabicyclo[2.2.2]oct-5-ene moiety. The first total synthesis of (±)-granaticin was reported in 1987 followed by the synthesis of optically active natural granaticin in 1989.\textsuperscript{84,85}

In an attempt to make a suitable carbohydrate precursor from which to derive the optically active synthon for the pyrano-\(\gamma\)-lactone ring it was decided to start with commercially available di-\(O\)-acetyl-L-rhamnal (104).\textsuperscript{86} Reaction of (104) with ketene methyl \(t\)-butylidimethylsilyl acetal in the presence of boron trifluoride diethyl etherate, followed by \(O\)-deacetylation, produced the \(C\)-glycoside (105) and its C-1 epimer which could be separated chromatographically to give yields of 38 and 26\% respectively. Silica gel chromatography produced an intramolecular S\(_{N}2\) reaction to transform the \(O\) -methanesulphonyl derivative of (105) into the \(\gamma\)-lactone (106). Aminolysis followed by pyridinium chlorochromate oxidation yielded the optically active \(\gamma\)-ketocarboxamide (107).\textsuperscript{86}
The optically active alcohol (108), needed for the synthesis of the other chiral fragment, was obtained by resolution of the racemic form through the \((-\)-\(N-(1\)-phenylethyl)carbamate). The absolute configuration was determined by the exciton chirality method. The chiral synthon (108) was then transformed into the cyanophthalide (109) via a synthetic sequence developed by the same group for the preparation of the racemate.

Through phthalide annulation methodology, the chiral fragments (107) and (109) were joined in the presence of an excess of lithium dimsylate to give the naphthopyran (110) in moderate yield (50%). Methylation followed by reduction of the ketone functional...
group with lithium tri-sec-butylborohydride afforded mainly the 3,4-cis-hydroxy carboxamide. Lactonization with chlorotrimethylsilane in wet dichloromethane followed by oxidative demethylation (CAN) and subsequent treatment of the crude product with aluminium chloride-diethyl sulfide complex afforded optically active granaticin (98).  

By incorporating an acetamide derivative at C-3 within the chiral fragment (107), this method required less steps to assemble the natural product than the method used by Tatsuta et al. for the synthesis of asymmetric naphtho[2,3-c]pyranquinones, where the precursor corresponding to (107) was the methoxy analogue (85).

1.1.4 The Griseusins

Isolation: Griseusin A (111) and griseusin B (112), antibiotics of the pyranonaphthoquinone group, were first isolated by Tsuji and co-workers from the metabolites of Streptomyces griseus K-63 found in a soil sample collected in Peru.  

\[
\text{Griseusin A (111) and griseusin B (112)}
\]

\[
\text{Griseusin A (111) and griseusin B (112)}
\]
Griseusin A and B have been shown to be effective against Gram-positive bacteria, pathogenic fungi and yeasts and have been proposed to act as bioreductive alkylating agents.\textsuperscript{19,90} The griseusins are of particular interest since they contain a unique 1,7-dioxaspiro[5.5]undecane ring system fused to a 5-hydroxy-1,4-naphthoquinone (juglone) moiety which distinguishes them from less complex members of the family such as kalafungin and nanaomycins A and D.\textsuperscript{90}

The structures of griseusins A and B were established in 1976.\textsuperscript{90,91} In 1982\textsuperscript{92} the chiral synthesis of (+)-9-deoxygriseusin B (113) was reported which possessed the same absolute configuration that had been assigned to the naturally occurring griseusin A and B.

On comparison of the CD spectra of the three compounds it was found that griseusins A and B (114) and (115) are the enantiomers of the originally assigned structures (111) and (112) respectively.
The molecular structures and absolute configurations of the griseusins were again confirmed by Tsuji through x-ray analysis of the 6,8-dibromo derivatives (116) and (117).93

![Chemical structures](image)

**Syntheses:**
Up to date only one total synthesis for each of the compounds of (+)-griseusin A (111) and (+)-B (112), the enantiomers of the naturally occurring materials, has been reported by Yoshii and co-workers in 1983.92,94,95 The key step involved an assembly of the spiroacetal moiety of the griseusins via intramolecular ketalization of a δ,δ'-dihydroxyketone in which the oxygenated substituents of the spiroketal ring system were derived from a carbohydrate precursor.

3-Bromo-5-hydroxy-1,4-naphthoquinone (118) was used as starting material since it could serve as the basis for the pyranojuglone moiety. Reaction of (118) with 3-butenoic acid in the presence of silver nitrate and ammonium persulphate afforded the 2-allyl-3-bromojuglone (119) and subsequent reduction with an excess of sodium hydrosulfite gave the unstable hydroquinone. Immediate treatment with acetone and 2,2-dimethoxypropane in the presence of perchloric acid and subjection to O-methylation with dimethyl sulphate afforded the acetonide (120) in a 63% overall yield. Compound (120) was treated with tert-butyl lithium in tetrahydrofuran at low temperature after which addition of the L-gulose derivative (121) gave the epimeric carbinols (122). Subsequent slow oxidation with PCC gave compound (123) in moderate yield and recovery of some unreacted starting material (122). Reaction of the olefinic bond of
(123) with HOBr, followed by selective removal of the acetonide protective group on the sugar moiety with hydrochloric acid, produced a mixture of (124a) and (124b) in a ratio of 1:2 respectively. These diastereomers could be separated through preparative layer chromatography and the structures confirmed by \(^1\)H NMR spectroscopy.

Scheme 12 (contd. over)
Scheme 12 (contd. over)
The diastereomeric mixture of (124a) and (124b) was then reacted with sodium cyanide in dimethyl sulphoxide to give the diastereomeric nitriles (125) in a combined yield of 83%. These were hydrolyzed with ethanolic potassium hydroxide in the presence of hydrogen peroxide to afford the carboxylic acid (126) as a single stereoisomer in moderate yield (61%). This epimerization at the C-3 centre from a 3S to a more stable 3R configuration under basic conditions has been reported previously.\textsuperscript{94}

Acetylation of (126) followed by selective removal of the methoxymethyl group with hydrochloric acid in dimethoxyethane gave product (127) after which oxidation with silver(II) oxide in nitric acid\textsuperscript{96} afforded (+)-griseusin B (112). Aerial oxidation produced the γ-lactone, thereby yielding (+)-griseusin A (111) in 63% yield.

Spectral data and TLC behaviour of the synthetic (+)-griseusin A were identical to the naturally occurring (-)-griseusin A and their CD spectra were mirror images in shape and amplitude.
1.2 Isolation and Structure Determination of the Aphid Insect Pigments.

1.2.1 The Aphins

An in-depth investigation of these unique compounds has been carried out over a period of twenty years by Lord Todd, D.W. Cameron and their colleagues.\textsuperscript{1,97} The first report was published in 1948.\textsuperscript{98} Prior to that Sorby\textsuperscript{99} described a fascinating series of interrelated pigments originating from the “red Aphides” found in “downy patches” on apple bark.\textsuperscript{99} In 1936 Blount\textsuperscript{100} isolated two pigments, namely lanigerin (now chrysoaphin-\textit{fb}) from the common woolly aphid \textit{Eriosoma lanigerum} Hausmann\textsuperscript{99} as well as the red pigment strobinin, isolated from the \textit{Adelges (Pineus) strobi}.\textsuperscript{97} Schulz\textsuperscript{101} also recorded some observations on the pigments of \textit{Eriosoma lanigerium} (Börner). Both were apparently unaware of the earlier work of Sorby. Both pigments displayed some interesting colour reactions, similar to those observed by the Cambridge group in preliminary investigations of the crude extracts of the black aphids (\textit{Aphis fabae}).\textsuperscript{98,100}

A study showed that these colouring matters, given the name aphins, were present in at least twenty species of aphids.\textsuperscript{98,99}

These protoaphins are also found as a yellow, water-soluble pigments in the haemolymph of living aphid insects. Isolation of the aphins was complicated by the fact that, after death, they are attacked by an accompanying enzyme system, which rapidly converts each protoaphin into a yellow, fat-soluble, unstable xanthoaphin. This changes further, on standing, into the still unstable, orange coloured chrysoaphin, which was then converted into the stable end-product, the red erythroaphin.\textsuperscript{102,103}

The protoaphins were isolated by washing the insects of the host plant with hot water (70 °C), which kills both the aphids and renders the enzymes inactive, without damaging the protoaphins themselves.\textsuperscript{102,98} Two protoaphins were isolated, namely protoaphin-\textit{fb} from the common bean aphid, \textit{Aphis fabae} Scop., and protoaphin-\textit{sl}, a stereoisomeric pigment, from the haemolymph of the large brown willow aphid, \textit{Tuberolachnus salignus} Gmelin. These protoaphins gave rise to a stereoisomeric series of xanthoaphins, chrysoaphins and erythroaphins.
The pigments of these brown-yellow protoaphins, being hygroscopic and acidic (pKₐ 6.2), ionise at biological pH producing violet-red anions which are mainly responsible for the dark colour of the haemolymph. Addition of sodium hydroxide caused deep violet colours indicating the presence additional phenolic groups. For each protoaphin, one quinonoid unit per molecule was confirmed by gentle hydrogenation (1 molar equivalent) and aerial reoxidation; each protoaphin afforded a deca-acetate and each leuco-compound a dodeca-acetate, the latter absorbing light in the naphthalenic region. D-glucose and an unstable aglucone were obtained by mild acid hydrolysis. The latter could only be isolated under nitrogen and could be converted by acid treatment into the corresponding erythroaphin.

In 1962, Lord Todd presented the structure and absolute stereochemistry of the aphins in a lecture at the second International Symposium on the Chemistry of Natural Products in Prague (Czechoslovakia) and formally published these in 1964.

Structure determination of the protoaphins relied heavily on the fact that mild reduction, either by dithionite or by catalytic hydrogenolysis in aqueous buffer at pH 6.6, followed by aerial oxidation, gave in each case an acidic quinone and a naphthalenic glucoside. Specifically, protoaphin- yielded the orange acidic quinone A and a colourless glucoside, glucoside B. Reductive fission of protoaphin- afforded quinone A’, stereoisomeric with quinone A, and the same glucoside B.

From the derivatives formed and a detailed analysis of its spectroscopic properties (ultraviolet-visible, infra-red and ¹H NMR spectroscopy) involving a comparison with those of the eleutherins, the structure and relative stereochemistry of quinone A were determined. The absolute configurations at the chiral centres in the pyran ring were determined by mild chromic acid oxidation of quinone A to give D,D-(+)-dilactic acid (128) of known absolute stereochemistry. ¹H NMR spectroscopy was also used to determine the stereochemistry at C-4 of the pyran ring of quinone A dimethyl ether. This showed a mutual coupling constant of 8 Hz between 3-H, appearing as a doublet of quartets, and the doublet 4-H which indicated a near trans relationship between 3-H and 4-H. Thus the C-3 methyl substituent was equatorial and the C-4 hydroxy group
pseudoequatorial. From the structure of D,D-(+)-dilactic acid, it follows that the C-1 methyl is pseudoaxial. Long range homoallylic coupling of the type between H-1 and H-4 is known to be largest when the two protons are pseudoaxial, smaller when one is pseudoaxial and the other pseudoequatorial, and smallest when both are pseudoequatorial. In the case of quinone A, a long range coupling constant of 1.5 Hz between 1-H and 4-H was consistent with the former being pseudoequatorial and the latter pseudoaxial, which was in agreement with the proposals above that the C-1 methyl was pseudoaxial and the C-4 hydroxy pseudoequatorial. The structure of quinone A (16) was also confirmed by X-ray crystal structure determination.

Quinone A’ was found to be very similar to quinone A and also gave D,D-(+)-dilactic acid (128) upon mild chromic acid oxidation. The $^1$H NMR spectrum of quinone A’ dimethyl ether also showed a doublet for the C-4 proton, but, in this case, with a coupling constant of 2.0 Hz, confirming that the 3-H and 4-H protons are cis to one another, i.e. that 3-H is axial and 4-H is pseudoequatorial. The small long range coupling constant (<0.5 Hz) between 1-H and 4-H showed that these two protons are both pseudoequatorial and therefore that both the methyl substituent at C-1 and the hydroxy group at C-4 are pseudoaxial. The structure (17) was therefore assigned to quinone A’ and differed from quinone A (16) only in the configuration of the C-4 hydroxy group.
The oxidation of glucoside B with Fremy’s salt at pH 6 gave two naphthoquinones, one being a sugar-containing quinone which was easily hydrolysed to quinone A. Structure (129) was therefore assigned to it.

\[
\text{Glucose} \quad \begin{array}{c}
\text{O} \\
\text{HO}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{HO}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array} \\
\text{O}
\]

\[(129)\]

The other sugar-free quinone was more acidic and was determined to be (130) from spectroscopic studies.\textsuperscript{104} The formation of quinones (129) and (130) from glucoside B led to the conclusion that the structure of glucoside B must therefore be (19).

\[
\text{Glucose} \quad \begin{array}{c}
\text{O} \\
\text{OH}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{HO}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\]

\[(19)\]

The anomic configuration of the glucose moiety was determined through treatment of glucoside B with a β-glucosidase (almond emulsion). Virtually complete hydrolysis occurred to yield its aglucone. The same reaction using α-glucosidase (horse serum) was without effect, indication a β-configuration for the sugar linkage of glucoside B.\textsuperscript{110} In later work, glucoside B was also found in the bright orange aphid *Aphis nerii*, accompanied by a related yellow pigment, neriaphin (131).\textsuperscript{111}
Knowledge of the structures of quinone A, quinone A’ and glucoside B was then utilised to determine the structures of protoaphins-fb and –sl. It seemed that conditions of mild reduction had indeed cleaved the binaphthyl linkage to give rise to derivatives. Thus, protoaphin-fb and protoaphin-sl were formulated as (132) and (133) respectively since these were the only structures that could explain their further transformation into erythroaphin.\textsuperscript{104,105}

It is likely that the formation of the protoaphins \textit{in vivo} includes a coupling reaction between the quinone and glucoside. Cameron and Chan have achieved this \textit{in vitro} by leaving quinone A and glucoside B standing at room temperature in a slightly acidic aqueous solution (pH 6.6). A yield of only 2% of the protoaphin-fb was achieved. The major product was a symmetrically coupled analogue of protoaphin-fb. A higher yield of 18% was obtained when the reaction was performed at 80 °C. A similar coupling reaction between epimeric quinone A’ and glucoside B gave protoaphin-sl in a yield of
5%. Therefore by synthesising quinone A, quinone A’ and glucoside B the formation of protoaphin-fb and –sl may be achieved.

A new aphid pigment, deoxyprotoaphin from the Dactynotus aphid species *Dactynotus circii* L. and *D. jaceae* L. was reported by Banks and Cameron in 1972. Cleavage of the binaphthyl link was obtained through catalytic hydrogenation to afford deoxyquinone A (18) and once again, glucoside B (19).

![Image of molecular structure (18)](image)

Treatment of deoxyprotoaphin A (18) with aqueous enzymic extracts gave a more coupled pigment, similar to chrysoaphin-fb. This, together with the spectroscopic data for deoxyquinone A, confirmed the structure of deoxyprotoaphin as (134), differing from protoaphin-fb and –sl in that it lacks the hydroxyl group at C-4.

![Image of molecular structure (134)](image)

Deoxyprotoaphin is also present in many other aphid species. Banks and Cameron, after having developed specialised chromatographic techniques for identification of
these pigments, were able to confirm that *Aphis fabae* Scop. and *Tuberolachnus salignus* Gmelin each contain only one protoaphin. However there are some species that contain both the \(-fb\) and \(-sl\) stereoisomers.

1.2.2 *The Dactynaphins*

During the examination of the aphid species *Dactynotus jaceae* L. and *D. cirsii* L., Cameron and co-workers observed the presence of dactynaphin glucosides. These pigments were also observed in the North American species *D. rudbeckiae* Fitch, *D. ambrosiae* Thomas and *D. nigrotuberculatus* Thomas Olive. These pigments were also detected in the related genus *Macrosiphoniella*.

As with the protoaphins, death of the insects led to enzymic conversion of these dactynaphin glucosides into related aglycones. In order to inactivate these enzymes, living specimens were crushed in acetone. Hot water, as used in the isolation of the protoaphins, could not be used, because of the relative thermal instability of the dactynaphin glucosides. Improved chromatographic techniques resulted in the separation and characterization of protorhododactynaphin-\(jc\)-1 (135) and protorhododactynaphin-\(jc\)-2 (136).

![Chemical structures](image-url)
The structures for the remaining two dactynaphins, protoxanthodactynaphin-\(jc\)-1 and protoxanthodactynaphin-\(jc\)-2 were determined to be (137) and (138) respectively.

\[
\text{(137) } R = \text{OH} \\
\text{(138) } R = \text{H}
\]

1.3 Naphthopyranquinones as Potential Bioreductive Alkylating or Dialkylating Agents.

The term bioreductive alkylating agents refers to those types of compounds which become potent alkylating agents after they undergo reduction in vivo. Such reactive species may then alkylate DNA/RNA and/or other biomolecules resulting in potentially effective cancer-inhibitory drugs.

Moore\(^{19}\) suggested four simple models to catalogue potential bioreductive alkylating agents: (1) activated enamines; (2) vinylogous quinone methides; (3) simple quinone methides and (4) \(\alpha\)-methylene lactones or lactams as key alkylating agents in vivo.

Sartorelli’s group have found that naphthoquinone derivatives which have the potential to form \textit{ortho}-quinone methides after in vivo reduction to the unstable hydroquinone derivatives show distinct antineoplastic activity.\(^{115}\)
It was also found that the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependant enzyme system, which reduces naturally occurring quinones such as coenzyme Q and the mitomycins, is relatively non-specific and thus various structural modifications of the quinone alkylating agents may be accommodated.\(^{115}\)

Quinones can be activated by a reductive mechanism and therefore offer potential for development as hypoxia-selective cytotoxins. Since the aim of this project is to synthesise quinone A and quinone A' in asymmetric form, the former will also be used to demonstrate the mechanism for bioreductive alkylation. \textit{In vivo} reduction of quinone A to the hydroquinone (139) from which the quinone methide (140) is formed produces an electron rich environment. Subsequent expulsion of the remaining leaving group, which is also benzylic to the phenolic system, results in a potent dialkylating agent (141). The two \(\alpha,\beta\)-unsaturated ketone moieties of the derived diquinone methide can then alkylate certain nucleophilic centres (Nu') in the DNA or RNA molecule, which binds the nucleic acid, as in (142), thereby preventing cell growth. Thus for example, quinone A (16) and quinone A' (17) may both be classified as potential bioreductive dialkylating agents.

![Scheme 13 (contd. over)](image-url)
Moore\textsuperscript{19} includes the eleutherins, \(\gamma\)-actinorhodin, granaticin, kalafungin, the nanaomycins D, A and C, \(\gamma\)-naphthocyclinone and the protoaphins in a list of examples of possible bioreductive alkylating agents.

Through the reductive thioalkylation of a pyranonaphthoquinone, Brimble and co-workers\textsuperscript{116,117} provided the first experimental evidence that this class of compounds may indeed act as bioreductive alkylating agents.

Pyranonaphthoquinone (143) was dissolved in a 1:1 mixture of tetrahydrofuran and methanol and subsequently treated with aqueous sodium dithionite under argon. This was followed by the addition of the nucleophile, thiocresol, to afford a polar product which proved difficult to isolate. Treatment of this compound with ethereal diazomethane afforded a less polar product which could be purified by flash chromatography. \(^{1}\)H NMR spectroscopy showed a 3.1:1 mixture of thioadducts (144):(145) (Scheme 14) which was separated by preparative HPLC to give a yield of 40\% and 13\% respectively.
A variety of different reducing agents and nucleophiles were used. Only sodium dithionite and 4-methoxyphenylhydrazine with thiocresol as nucleophile gave one major product (albeit a mixture of stereoisomers).

The intermediacy of the hydroquinone (146) was confirmed by reductive acetylation to the diacetate (147). Reaction of pyranonaphthoquinone (143) with thiols after reduction with dithionite therefore presumably occurs via the intermediacy of the hydroquinone.

**Scheme 15** suggests two pathways available for the introduction of the thiol at C-4.
Scheme 15 (contd.over)
Pathway A suggests that the initial hydroquinone (146) rearranges to a quinomethane intermediate which undergoes nucleophilic attack by the thiocresol at C-4 to afford a hydroquinone (148) that is readily oxidised to the final quinonoid (144) and (145).

In pathway B, the lactone moiety of the hydroquinone (146) undergoes nucleophilic addition to yield a thioester which loses water to form a quinomethane. Addition of thiol and hydrolysis of the thioester also affords intermediate (148) as in pathway A.

Brimble et al.\textsuperscript{116-118} carried out the experiments in such a way that reduction to the hydroquinone preceded the thioalkylation step. It was noted, however, that when the kalafungin analogue (143) was treated with thiocresol without the reducing agent, thioalkylation products (144) and (145) were formed together with di-p-tolyl disulphide. This suggests that the thiol may effect initial reduction of the quinone to a semi-quinone with thioalkylation proceeding \textit{via} a semi-quinone radical-thiyl radical coupling.

This work done by Brimble and colleagues\textsuperscript{116-118} supports the argument that naturally occurring pyranonaphthoquinones such as kalafungin (10) and the aforementioned quinone A (16) and quinone A’ (17) may undergo similar reductive thioalkylations, mediated by an enzyme \textit{via} a similar mechanism originally proposed by Moore and Czerniak.\textsuperscript{19} However the precise mechanism of thioalkylation still remains open for discussion.
1.4 Racemic Syntheses of Quinone A, Quinone A′ and Deoxyquinone A. Synthetic Efforts Toward Glucoside B.

Since our main area of interest is focused on the aphid pigment derivatives, it is useful to the rest of my work to discuss the only racemic synthesis of quinone A (16) and quinone A′ (17) and deoxyquinone A (18). The synthetic attempts towards glucoside B (19) will also be discussed.

In 1988 Giles and co-workers published two papers\textsuperscript{119,120} describing the successful syntheses of quinones (16), (17) and (18) and these are outlined in Scheme 16. The sequence started with a Diels-Alder reaction between Brassard’s diene (149) and 1,4-benzoquinone, and the resulting intermediate adduct was alkylated, followed by acylation to produce the naphthol (150) in a 48% overall yield. Oxidation of this naphthol (150) afforded the quinone (151) in excellent yield (90%). Allylation and subsequent methylation produced the allylnaphthalene (152) in a 61% yield from the original naphthol (150). The next step was to remove the methyl from the oxygen ortho to the acyl group with an excess of boron trichloride at –78 °C, while the isopropyl group was removed with this reagent at 0 °C,\textsuperscript{121} and this was followed by benzylation of the resulting naphthalenediol to give the dibenzyl ether (153). This change of the protecting group at C-7 from isopropyl to benzyl was necessary in order to facilitate its removal in the concluding steps of the synthesis, since this was shown not to occur with isopropyl. On the other hand, lower yields arose through initial benzylation, to give the dibenzyl analogue of naphthol (150). The change in the protecting group was, therefore, economical. Reduction of the ketone entity with lithium aluminium hydride afforded the alcohol (154).
The key step in the synthesis was a completely diastereoselective, base-induced cyclisation where the alcohol (154) was treated briefly with potassium t-butoxide in dimethylformamide to produce solely the trans-1,3-dimethylnaphtho[2,3-c]pyran (155) in 97% yield.\(^{36}\) This reaction was unique in that the mechanism appears to involve intramolecular nucleophilic attack on an unactivated double bond.\(^{36a,b,e}\) It is interesting to note that none of the cis-isomer was formed in contrast to cyclisations of the corresponding tetramethoxy analogues,\(^{36b}\) where the cis stereoisomer was formed if the reaction was allowed to continue for longer periods. The reason could be attributed to greater steric hindrance owing to the bulky benzyloxy protecting group rather than the
methoxy substituent at C-10, thus discouraging the C-1 methyl from assuming the more crowded pseudoequatorial configuration\textsuperscript{119} where strong \textit{peri} interactions arise between the C-1 and C-10 substituents.

Oxidation of naphthopyran (155) with silver(II) oxide followed by deprotection with an excess of boron trichloride afforded racemic deoxyquinone A (18) as shown in Scheme 17. Oxygenation\textsuperscript{36b,c} of the naphthopyran (155) by stirring with potassium \textit{t}-butoxide in dry dimethyl sulphoxide in the presence of dry oxygen produced the favoured C-4 psuedoequatorial hydroxy derivative (156) together with the pseudoaxial epimer (157) in yields of 60\% and 24\% respectively. Oxidation and subsequent deprotection of the naphthopyran (156) in a similar manner to the pyran (155) then gave racemic quinone A (16).

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme17.png}
\end{center}
\end{scheme}

\textit{Scheme 17 (contd. over)}
The epimeric alcohol (157) was similarly oxidised to the quinone (158), however similar deprotection using an excess of boron trichloride led to decomposition. This may be as a result of the elimination of water through the axial and pseudoaxial configurations of the adjacent hydrogen and hydroxy at C-3 and C-4 respectively. The O-methyl group was removed using a limited amount of boron trichloride, followed by debenzylation through hydrogenolysis, after which (±)-quinone A’ (17) was formed by the aerial re-oxidation of the resulting hydroquinone.119

In theory, chiral reduction of the ketone (153) could afford the (R)-alcohol of the type (154), which could lead to the formation of pure enantiomers of quinones A and A’, and deoxyquinone A. The method used for this transformation, however, involved
enantioselective Corey-Bakshi-Shibata reduction, where model studies have indicated that the carbon-carbon double bond would be subjected to hydroboration in preference to the desired reduction of the crowded carbonyl group in compound (153).\(^{122}\)

Thus the three racemic aphid pigment derivatives (16), (17) and (18) were successfully synthesised from a single intermediate (155).\(^{119}\) In order to achieve now the total synthesis of the naturally occurring aphid pigments, protoaphin-fb, protoaphin-sl and deoxyprotoaphin, attention was turned to the preparation of glucoside B.\(^{104,105,119}\) In doing so Giles and colleagues synthesised a 7,9-dideoxy derivative of the aglucone of glucoside B (Scheme 18).\(^{123}\)

![Scheme 18](contd.over)
The chosen target molecule (165) was synthesised over six steps from starting material (159) in an overall yield of 42%. Stereoselective base-induced cyclisation of the alcohol was obtained by treatment of (161) with potassium t-butoxide to give solely the trans-naphthopyran (162). Subsequent treatment of (162) with boron trichloride afforded an unstable intermediate naphthol through selective debenzylation, which was converted directly into the methanesulphonate ester (163). Selective cleavage of the aryl-oxygen bond at C-5 of compound (163) was achieved with Raney nickel catalyst to afford the trans-1,3-dimethylnaphthopyran (164), which, after treatment with potassium tert-butoxide in dry dimethyl sulfoxide containing oxygen afforded the target molecule (165), with the correct relative stereochemistry, in a 67% yield.

Thus, hydroxylation in the absence of an oxygen substituent at C-5 of the naphthopyran ring afforded only the pseudoequatorial alcohol at C-4, whereas naphthopyrans containing an oxygen substituent at C-5 produced a mixture of epimeric alcohols as observed in the synthesis of quinone A and A’ (Scheme 17). This methodology would thus be useful for the synthesis of glucoside B which only possesses the pseudoequatorial alcohol.

Having successfully made the 7,9-dideoxy analogue (165), Giles and co-workers attempted to use the same methodology to construct a glucoside B derivative without the oxygen at the C-5 position (Scheme 19).

After oxidising the starting material (166) to the aldehyde (167), it was subsequently subjected to a Wittig reaction by treatment with ethyltriphenylphosphonium bromide. The resulting mixture of cis- and trans-olefins (168) was treated with butyl lithium and acetaldehyde to give the corresponding mixture of olefinic cis- and trans-alcohols (169).
which was then treated with base to induce stereoselective cyclisation to give only the trans-naphthopyran (170) in 83% yield. This proved that the stereochemistry of the product pyran was not determined by that of the olefinic double bond of the starting material. Hydroxylation\textsuperscript{119} of (170) furnished the target compound (171) in a poor yield of 33%\textsuperscript{123}. Difficulty in controlling the reaction led to over-oxidation and the formation of lactone (172) as a by product as shown in Scheme 19.

Scheme 19 (contd. over)
Recently Giles and colleagues\textsuperscript{124} have developed a novel approach for the formation of the naphtho[2,3-\textit{c}]pyran ring system. This involved the stereoselective isomerisation of phenyl- and naphthyl-dioxolanes through the use of titanium tetrachloride \textit{via} an intramolecular version of the Mukaiyama reaction.\textsuperscript{125}

This methodology was used by the Giles group\textsuperscript{126} in model studies to demonstrate the titanium tetrachloride induced stereo- and regioselective isomerisation of 2,5-dimethyl-4-(2'-naphthyl)dioxolanes (173) and (174) to produce two angular glucoside B analogues (176) and (177) (Scheme 20).
This could be as a result of steric crowding leading to ring closure of the intermediate oxonium ion (175) at the position para, rather than ortho, to the large isopropoxy group. Another reason may be the preference for electrophilic substitution at the $\alpha$- rather than the $\beta$-position of naphthalenes.$^{126}$

The isomerism of the 8'-bromodioxolane (178) was investigated by the same group$^{126}$ in an attempt to determine whether the bromine would provide the steric bulk to facilitate the formation of the desired linear naphthopyrans.
Treatment of (178) with titanium tetrachloride afforded the debrominated angular pyran (179) (45%) as a single stereoisomer, as well as derivative (180) (18%) arising from migration of bromine (Scheme 21).

It was thus shown that the all cis dioxolane stereochemistry in dioxolane (178) indeed gave the correct stereochemistry for glucoside B at C-1, C-3 and C-4 of the naphthopyran products (179) and (180). However, a preference for the angular rather than the desired linear products, where ring closure must take place at the C-3' position, was still observed.

Further attempts at the formation of linear naphthopyrans lacking oxygen at C-5, through isomerisation of dioxolanes, have not yet met with success.

### 1.5 Progress Toward the Asymmetric Syntheses of Benzo[c]pyrans Related to the Aphid Pigments.

Following the preparation of racemic quinone A (16) and quinone A’ (17) and deoxyquinone A (18), Giles et al. have embarked upon the development of asymmetric syntheses of these naphthopyranquinones. An important practical factor is that a combination of any of these enantiomers with the correct enantiomer of glucoside B (19) would provide the corresponding protoaphins as single stereoisomers.

Giles and Joll have developed a new approach for this asymmetric synthesis of the aphid pigment derivatives. This differs from the chiral syntheses of naphthopyranquinone antibiotics, described in Section 1.1, which involved the construction of the optically active pyran ring from a commercially available carbohydrate precursor, and the optically active naphtho[2,3-c]pyran skeleton was then formed by coupling the pyran compound with an aromatic derivative.

The strategy that was now used involved an intramolecular reaction between metal phenolates and chiral aldehydes. Benzyl bromide (185) was prepared over five steps from the starting hydroquinone (184) in excellent (86%) overall yield (Scheme 22).
Asymmetry was achieved through use of lactate from the chiral pool. This provided the required chirality at C-3 of the derived benzopyran ring. Initial model studies used the cheaper commercially available ethyl (S)-lactate (181), rather than the more expensive (R)-lactate (182). This would afford the enantiomer (183) of the model for quinone A.

![Chemical structures](image)

Reaction of the lactate (181) with benzyl bromide (185) in the presence of silver trifluoroacetate afforded an inseparable mixture of esters (186) and (187).

![Chemical structures](image)

Scheme 22 (contd. over)
Reduction of the ethyl esters (186) and (187) with lithium aluminium hydride gave a 55:45 ratio of the alcohols (188) and (189), which were separated chromatographically. Alcohol (188) was oxidised to the corresponding aldehyde (190) in high yield using Swern methodology, after which hydrogenolysis afforded the unstable phenolic aldehyde (191). Intramolecular cyclisation of the asymmetric phenolic lactaldehyde (191) was achieved with titanium tetrapropoxide in dry dichloromethane under ultrasonic irradiation to afford the benzopyran (192). The crude product was subjected to $^1$H NMR spectroscopy, which indicated a large coupling constant ($J$) of 8.6 Hz indicative of the near trans-diaxial arrangement of the adjacent protons 3-H and 4-H of the erythro epimer (192). This confirmed that the C-3 methyl was equatorial and the C-4 hydroxy pseudoequatorial.

The diol (192) was then immediately acetylated to afford the more stable diacetate (193) in 71% overall yield from (191). The chemical shift of 3-H ($\delta$ 3.89) in (192), together
with deshielding of 4-H from $\delta$ 4.55 in (192) to $\delta$ 5.75 in (193), and the coupling constant of 4.8 Hz between 3-H and 4-H in the diacetate (193) are consistent with reported results for analogous compounds.\textsuperscript{105,131}

The formation (≥ 97\%) of only one diastereoisomeric diacetate (193) indicated that the cyclisation was highly diastereoselective and that no racemisation occurred at the carbon centre $\alpha$ to the aldehyde moiety in precursor (191).\textsuperscript{128a,b}

The diastereomeric phenol (194) obtained in the same way from alcohol (189) was similarly ring closed with the titanium reagent and subsequently acetylated to give the diacetate (195) and its C-4 epimer (196) in a ratio of 3:1, respectively.

The coupling constant for (195) between 3-H and 4-H was 7.8 Hz, while that for the axial 3-H and pseudoequatorial 4-H in (196) was only 1.3 Hz. Since the only difference between the epimers (191) and (194) was the difference in stereochemistry of the benzyl methyl groups, the reduced diastereoselectivity could be the result of increased \textit{peri} interactions between the C-8 methoxy and the C-1 pseudoequatorial substituent (Chapter 2).\textsuperscript{128}

After having purified and characterised the more stable diacetate (193), the diol was regenerated from it by treatment with lithium aluminium hydride and immediately subjected to oxidative demethylation with silver(II) oxide to give the asymmetric quinone (183).\textsuperscript{128c} This represented the first synthesis of an asymmetric compound with the correct absolute stereochemistry of the substituents about the pyran ring for the enantiomer of the aphid insect pigment-derived quinone A (16).
Having successfully completed the asymmetric synthesis of the benzo[2,3-\textit{c}]pyran diacetate (192), Giles et al.\textsuperscript{128b} suggested that a related naphthol bearing a tethered aldehyde derived from an (\textit{R})-lactate (182) should lead to a naphtho[2,3-\textit{c}]pyran which could then be converted into enantiomERICALLY pure quinone \textit{A} (16).

This procedure would also be very relevant in the asymmetric syntheses of the eleutherins and ventiloquiones.\textsuperscript{1}

Giles and Taylor\textsuperscript{132} envisaged the enantioselective synthesis of quinone \textit{A} (16) by utilising the regioselective Diels-Alder reaction between brominated quinone (199) and 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene (200)\textsuperscript{133} (Scheme23). The purpose of the bromine atom at C-7 was to control the regioselectivity of the Diels-Alder reaction of the quinone (199) with the diene (200).

Using the (\textit{R})-lactate required for the correct enantiomer, the diacetate (198) was synthesised with absolute stereochemistry reversed in comparison with that found for the diacetate (193).\textsuperscript{128} The purified diacetate (198) was deprotected to give back the less stable diol (197). This was treated with the usual oxidising reagents, \textit{viz.} cerium(IV) ammonium nitrate and argentic oxide, in an attempt to obtain the required brominated benzopyranquinone (199), but this was not achieved in either case. Further alternative oxidants were investigated without success.\textsuperscript{132}
Since the related oxidation of the benzopyran (192) to yield the corresponding quinone (183) occurred in high yield (91%), it was assumed that the additional C-7 bromine created sufficient steric congestion at C-8 (between the C-7 bromine and the C-1 methyl substituent) that the required oxidation at C-8 could not occur. It was therefore proposed that the bromine be replaced by chlorine because of its smaller steric demand. Chlorine would also have a similar directing effect on the final Diels-Alder reaction. However, when the corresponding chlorinated phenolic aldehyde (202) was prepared,\textsuperscript{132} it was not
possible to cyclise it to the diol (203), even with an increased proportion of titanium reagent and longer reaction times.

![Diastereomeric ring closure reaction](image)

**Scheme 24**

Other cyclisation procedures were also attempted without success.\textsuperscript{132} It appeared that the presence of a chlorine substituent at the 3′-position inhibits the hydroalkylation reaction in contrast with a bromine substituent in the same position. This type of intramolecular diastereomeric ring closure reaction is therefore relatively susceptible to electron availability at the site of annelation. Chlorine, being more electronegative than bromine, is presumably able to reduce the electron density on the aromatic ring sufficiently to prevent cyclisation.\textsuperscript{129,132}

Giles and Joll\textsuperscript{134} also investigated the synthesis of naphtho[2,3-c]pyrans relating to aphid pigments using the intermolecular methodology developed by Casirighi and co-workers.\textsuperscript{129} Casirighi et al. examined some intermolecular reactions between metal phenolates and chiral aldehydes and found the process to be highly diastereoselective. The titanium phenolates were found to give the products of \textit{anti} addition whereas the magnesium phenolates resulted in the \textit{syn} addition mode. The methodology has since been developed to include a variety of different chiral aldehydes.\textsuperscript{135}

The strategy used by Giles and co-workers was to apply this protocol to a suitably substituted naphthol (204), such that C-arylation of a chiral aldehyde (205) would give diastereoselective control of the newly created chiral centre at C-1 in the adduct. This would provide compounds (206) and (207) with the correct chirality and functionality from which to synthesise quinone A (16) and quinone A′ (17) respectively (Scheme 25).
Reaction of the titanium phenolate of naphthol (204) with the aldehyde (205) produced the required addition product (206) in 43% yield. The mixture of diastereoisomers at C-1’ proved to be inseparable, but the exclusive formation of a single diastereoisomer at C-1 indicated that complete diastereoselectivity (anti addition mode) was achieved. $^1$H NMR spectroscopy confirmed the formation of the erythro epimer (206).

The alternative complete diastereoselectivity, leading to the syn addition product (207) (78%), was achieved through preparation of the bromomagnesium phenolate of naphthol (204), followed by addition of the aldehyde (205). The two products (207), diastereoisomeric at C-1’, were separated by chromatography, in a 1:1 ratio. $^1$H NMR spectroscopy confirmed the threo configuration at C-1.

In order to complete the syntheses of enantiopure quinone A and quinone A’ by this latter route, subsequent cyclisation of (206) and (207), using an intramolecular Lewis acid-catalysed Mukaiyama reaction$^{125}$ of the aryl ether and acetyl functions would be required. The stereochemistry of the derived C-1 methyl would need to be controlled.$^{124}$ Oxidation and deprotection would then afford quinone A and quinone A’ respectively from the precursors (206) and (207).

1.6 Concluding Remarks

The stage was therefore set for the asymmetric syntheses of quinone A and quinone A’, by either the intra - or the intermolecular route.
Chapter 4 of this thesis describes the research carried out in the present study which leads successfully to these syntheses using the intramolecular method.
CHAPTER 2

2.0 Introduction

In previous studies undertaken by Giles et al.\textsuperscript{128} leading up to intramolecular metal-induced cyclisations of \textit{meta}-hydroxybenzyl protected lactaldehydes, all substrates had a substituent at both the C-2 and C-5 positions. This meant that arylation of the aldehyde (191) could take place only \textit{ortho} to the phenolic substituent to afford the benzopyran-4,5-diol (192), a process which was achieved with complete diastereoselectivity.

![Chemical structures](image1.png)

The main aim of the work described in this chapter was to determine whether cyclisation of the aldehyde (208), without a substituent at C-2, would occur exclusively \textit{ortho} to the phenolic substituent to afford the benzopyran-4,5-diol (209), or \textit{para} to afford the benzopyran-4,7-diol (210). It was hoped that cyclisation using titanium tetraisopropoxide would occur with complete regio- and stereoselectivity to yield solely the 4,5-diol through coordination by titanium to both the phenolic and aldehydic oxygens.

![Chemical structures](image2.png)

The initial synthetic target was therefore the phenolic lactaldehyde (208), the demethoxy analogue of Joll’s lactaldehyde (191),\textsuperscript{128c} and that methodology was used, by and large.
In particular, benzylic protection of the phenolic substituent was used as before, in view of its previous success.

2.1 The Sequence Using Benzyl Protection of the Phenol.

2.1.1 Synthesis of Diastereomeric Esters (214) and (215)

The first part of the synthetic sequence is indicated in Scheme 26. Commercially available 3-hydroxyacetophenone (211) in dimethylformamide was treated with benzyl bromide and potassium carbonate to afford the benzyl ether (212) in high yield. Reduction of the ketone carbonyl (212) with lithium aluminium hydride then gave the alcohol (213).

![Scheme 26](image)

The next step was to convert the alcohol (213) into the esters (214) and (215). Several literature methods exist for this type of process. Previous literature\textsuperscript{128c,136} shows
extensive use of bromo compounds being treated with silver(I) compounds, such as silver(I) oxide. Danheiser et al.\textsuperscript{137} used a silver salt such as silver nitrate or silver(I) trifluoroacetate to achieve nucleophilic substitution (Scheme 27).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme27}
\caption{Scheme 27}
\end{scheme}

Giles and Joll\textsuperscript{128} treated the benzyl alcohol (216) with phosphorus tribromide to form the benzyl bromide (185). Subsequent addition of ethyl (S)-lactate in the presence of an excess of silver(I) trifluoroacetate gave a mixture of diastereoisomers (186) and (187) in a ratio of 55:45 respectively.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme28}
\caption{Scheme 28 (contd. over)}
\end{scheme}
As mentioned before, the cheaper ethyl (S)-lactate (181) was used in order to first optimise the conditions for the eventual synthesis of the quinone A and quinone A' precursors using the (R)-form of the lactate (182).

The same methodology was therefore applied to the synthesis of compounds (214) and (215). Benzyl alcohol (213) was treated with phosphorus tribromide in benzene to give the benzyl bromide (217) in a yield of 86%.
Compound (217) was subsequently dissolved in dry acetonitrile and ethyl (S)-lactate (181) added. Subsequent treatment of the reaction mixture with silver(I) trifluoroacetate gave a mixture of products, the main products being styrene (218) and trifluoroacetate (219), possibly owing to the silver trifluoroacetate not being added slowly enough.

\[
\text{O} \quad \text{Bn} \\
(218)
\]

\[
\text{F}_3\text{C} = \text{O} \\
\text{Bn} \\
(219)
\]

With the aim of obtaining a better yield for the assembly of the lactates (214) and (215), an alternative method was conceived. This involved the formation of trichloroacetimidate (220)\(^{138}\) by treating the alcohol (213) with sodium hydride (60% dispersion in oil) and trichloroacetonitrile followed by acid catalysed etherification.\(^{139}\) This method has previously been developed for the benzylation of hydroxy groups in carbohydrate derivatives, and it has been extended to \(\beta\)-hydroxy esters.\(^{140}\)

\[
\text{O} \\
\text{Bn} \\
(220)
\]

Giles and Taylor\(^{132}\) successfully utilised this methodology to react the benzyl alcohol (221) with sodium hydride and trichloroacetonitrile to give the imidate (222) in 77% yield.
Giles and Gruchlik\textsuperscript{127} also achieved success in forming the trichloroacetimidate (224) from the benzyl alcohol (223) in good yield.

Alcohol (213) in tetrahydrofuran was thus treated with a catalytic amount of sodium hydride and the mixture added under nitrogen to a solution of the trichloroacetonitrile at 0 °C (inverse addition)\textsuperscript{138} and stirred at that temperature for a further 4 h. None of the product (220) was formed and some starting material (213) was recovered. However, when the direct addition method\textsuperscript{138} was used, which involved the trichloroacetonitrile being added to a suspension of alcohol (213) and sodium hydride in tetrahydrofuran, the imidate (220) was obtained in a yield of 85%.

![Scheme 30](image-url)
A sample submitted for high resolution mass spectroscopy gave the correct molecular ion peak at m/z 373 (C_{17}H_{16}^{35}Cl_{2}^{37}ClNO_{2}). The infrared spectrum of the imidate (220) showed the presence of the N-H stretch at 3340 cm\(^{-1}\) and this was confirmed by a broad singlet at \(\delta\) 8.30 in the \(^1\)H NMR spectrum. The infrared spectrum also showed a C=N stretch at 1662 cm\(^{-1}\) and the imidate carbon atom (C-1) resonated at \(\delta\) 161.5 in the \(^{13}\)C NMR spectrum. A downfield shift was also observed in the \(^{13}\)C NMR spectrum for the signal of the benzylic carbon (C-1) from \(\delta\) 70.2 in the alcohol (213) to 76.9 (C-\(\alpha'\)) in the imidate. \(^1\)H NMR spectroscopy showed that conversion of the alcohol (213) into the imidate (220) caused noticeable deshielding of the quartet for the benzylic proton from \(\delta\) 4.80 (1-H) to \(\delta\) 5.95 (\(\alpha'\)-H). The methyl group appeared as a doublet at \(\delta\) 1.62 (\(J\) 6.6 Hz), downfield from the corresponding signal in the alcohol (213) at \(\delta\) 1.44 (\(J\) 6.5 Hz). These shifts downfield would be the result of greater polarisation of the C-O bond through the attachment of the imidate moiety.

Employing the literature procedure,\(^{139a,141}\) also successfully used by Gruchlik\(^{127}\) and Taylor,\(^{132}\) a solution of the imidate (220) and ethyl (S)-lactate (181) in a hexane:dichloromethane (2:1) solution was treated with a catalytic amount of boron trifluoride diethyl etherate. After stirring the mixture in an atmosphere of nitrogen for one hour, this gave an inseparable mixture of diastereoisomers (214) and (215) in a combined yield of 75% and a ratio of 7:5 respectively.

\[ \text{OBn} \quad \text{EtO}_2\text{C} \]
\[ \text{O} \]
\[ \alpha' \]
\[ \text{OBn} \quad \text{EtO}_2\text{C} \]
\[ \text{O} \]
\[ 2 \]

(214)

(215)

It was assumed, owing to earlier work undertaken on derivatives of these compounds,\(^{127,132}\) that no racemisation occurred at the \(\alpha\)-carbon of the lactate in the conversion of racemic benzyl alcohol (213) into the pair of \(O\)-benzyl lactate ethers (214) and (215).
These were not separated using GC-MS and a molecular ion of m/z 328 was obtained for the mixture. The ester carbonyl stretch was apparent at 1746 cm\(^{-1}\) in the infrared spectrum and the carbonyl carbon atoms resonated at 173.1 and \(\delta\) 173.7 (C-1) in the \(^{13}\)C NMR spectrum.

2.1.2 *Synthesis of the Two Phenolic Aldehydes, Diastereomeric at C-\(\alpha\).*

Having successfully synthesised the ester mixture (214) and (215) *via* the imidate (220), the methodology was further applied to the synthesis of the key phenolic aldehyde intermediates (208) and (229) (Scheme 31). As a preliminary summary, the ester mixture was reduced to the alcohols (225) and (226), which were separated and individually oxidised to the benzylic aldehydes (227) and (228). Hydrogenolysis of (227) and (228) then afforded the key phenolic aldehydes (208) and (229).

![Scheme 31 (contd. over)](image-url)
Exposure of the diastereomeric esters (214) and (215) to lithium aluminium hydride gave the corresponding diastereomeric alcohols (225) and (226) in a combined yield of 92%. Confirmation of the stereochemistry of each particular diastereomer was obtained upon examination of the \(^1\)H NMR spectra of the cyclisation products obtained later in the synthesis and these must be assumed at this point.\(^{128b,c}\)
The alcohols were separated at this level through repeated radial chromatography. The compound of higher R\textsubscript{F} proved difficult to separate from an unknown impurity. Previous work\textsuperscript{127,128,132} all suggested separation at this stage, as the subsequent aldehydes proved inseparable. The alcohols (225) and (226) were separated in a ratio of 56:44 respectively.

The lower R\textsubscript{F} alcohol (225) was purified and a correct microanalysis was obtained. The mass spectrum showed a molecular ion peak at m/z 286 and the base peak at m/z 91. The aliphatic hydroxy group was obvious from the OH stretch at 3436 cm\textsuperscript{-1} in the infrared spectrum and at $\delta$ 1.99 in the $^1$H NMR spectrum. The two diastereotopic protons attached to C-1 and the signal for 2-H were not well resolved and appeared as a 3-proton multiplet in the region $\delta$ 3.43-3.69.

The mass spectrum of the higher R\textsubscript{F} alcohol (226) showed the molecular ion peak at m/z 286 and the base peak at 91. The infrared spectrum showed the OH stretch of the aliphatic alcohol group at 3435 cm\textsuperscript{-1}, and it resonated at $\delta$ 2.24 in the $^1$H NMR spectrum. As in the case of the previous diastereomer (225), the two diastereomeric C-1 protons and the 2-H proton appeared as a multiplet.

Even though the higher R\textsubscript{F} alcohol (226) possesses methyl groups with different relative stereochemistry to those reported in the aphid pigment derivatives, the cis-dimethyl arrangement about the pyran ring does occur in other natural products such as the eleutherins and the ventiloquinones. Thus a comparative investigation of the intramolecular cyclisation of the desired phenol would be a relevant pursuit. Comparison to the cyclisation of phenolic aldehyde (208) derived from alcohol (225) will provide useful information and structures of the derived benzopyrans which in turn will be useful for confirming the stereochemistry of the alcohols (225) and (226).

At this stage it was important to determine the enantiomeric purity of these two diasteroisomeric alcohols (225) and (226) to observe whether any racemisation had occurred at the carbon atom $\alpha$ to the ester group either during benzylation of the lactate or reduction of the esters to the alcohols.
The use of the chiral lanthanide NMR shift reagents to determine enantiomeric purity of optically active compounds has been widely recognised. The reagent Eu(hfc)$_3$, a camphor derivative of europium, was chosen as the chiral shift reagent since this had been successful with similar compounds.

The respective enantiomeric alcohols (230) and (231) first had to be synthesised in order to assist in the interpretation of the $^1$H NMR spectra resulting from the addition of the NMR shift reagent to the individual alcohols (225) and (226).

This was achieved by first making the diastereomeric esters (232) and (233) by reacting the imidate (220) with methyl ($R$)-lactate (182).

Reduction of the ester mixture with lithium aluminium hydride then gave the alcohols (230) and (231) in roughly the same ratio as their enantiomers (225) and (226).
The optical rotations of the alcohols (225) and (226) were measured and these compared well with their enantiomers (230) and (231) as shown in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>[α]_D (c 1.0, CHCl₃)</th>
</tr>
</thead>
<tbody>
<tr>
<td>225</td>
<td>-38.1 °</td>
</tr>
<tr>
<td>230</td>
<td>+36.2 °</td>
</tr>
<tr>
<td>226</td>
<td>+67.2 °</td>
</tr>
<tr>
<td>231</td>
<td>-70.8 °</td>
</tr>
</tbody>
</table>

**Table 1:** Optical Rotations of the Alcohols (225), (230), (226) and (231)

With the four alcohols (225), (226), (230) and (231) prepared, the optically purities of (225) and (226) were determined using the chosen chiral shift reagent. Good separation of many of the signals in the ^1^H NMR spectrum was achieved by the addition of 15 mol% of the shift reagent to a 60:40 mixture of the enantiomer alcohols (225) and (230) respectively. For example, the respective signals (230; 225) for 2-CH₃ occurred at δ 2.13 and δ 2.17, for α′–CH₃ at δ 2.24 and δ 2.27, for Ar-OCH₂ at δ 5.25 and δ 5.26 and for α′-H at δ 5.76 and δ 5.84. From this information, when the same procedure was applied to a sample of pure (225), the appropriate regions of the spectrum could be
examined for signals due to the enantiomer (230). However, no signals resulting from the enantiomer (230) were detected.

To obtain any reasonable separation in any signals in the \(^1\text{H}\) NMR spectrum of a 60:40 mixture of (226) and (231), it was necessary to use 25 mol% of Eu(hfc)$_3$. Separation was achieved for three signals: for 2-CH$_3$ at \(\delta\) 2.28 and \(\delta\) 2.31 (231; 226), for \(\alpha'\)-CH$_3$ at \(\delta\) 2.78 and \(\delta\) 2.84 (226; 231) and for Ar-OCH$_2$ at \(\delta\) 5.27 and \(\delta\) 5.28 (226; 231). When 25 mol % Eu(hfc)$_3$ was applied to the solution of the pure enantiomer (226), no signals for the alternative enantiomer (231) were observed.

From the results of this experiment, it was concluded that the diastereoisomeric alcohols (225) and (226) were optically pure within the limits of this NMR spectroscopic technique, i.e. they had enantiomeric excesses (e.e.) > 98%. Thus no observed racemisation occurred at the chiral centre of ethyl (S)-lactate during the reduction of the esters to the alcohols or in their formation from the trichloroacetimidate (220). These results, together with results previously obtained,$^{127,128\textbf{b}}$ further support the generalality of this reaction in the preparation of benzyl ethers of chiral alcohols.

The enantiomerically pure alcohols (225) and (226) were then individually oxidised to the corresponding aldehydes (227) and (228) via the Swern oxidation method.$^{130}$ Alcohol (225) was treated with a mixture of oxalyl chloride and dimethyl sulfoxide at –70 °C, followed by base treatment to give a 75% yield of the aldehyde (227).

\[
\begin{align*}
\text{(227)} & \\
\text{(228)} &
\end{align*}
\]

The infrared spectrum showed a strong signal at 1733 cm$^{-1}$ due to the C=O stretch of the aldehyde. In the \(^1\text{H}\) NMR spectrum the aldehydic proton resonated as a doublet at \(\delta\) 9.66 \((J 1.8\text{ Hz})\) while in the \(^{13}\text{C}\) NMR spectrum the aldehydic carbon signal appeared at \(\delta\) 203.1. The mass spectrum exhibited a molecular ion at m/z 284 and a base peak at 91.
Alcohol \(226\) was converted in the same way to afford the aldehyde \(228\) in 80% yield. The C=O stretch remained nearly unchanged at 1736 cm\(^{-1}\) in the infrared spectrum. The aldehydic signal in the \(^1\)H NMR spectrum showed a doublet at \(\delta\) 9.41 with the coupling constant of 1.3 Hz, which is slightly smaller than that of the aldehyde \(227\). The aldehydic carbon signal resonated at \(\delta\) 204.1 in the \(^{13}\)C NMR spectrum. The mass spectrum gave the same molecular ion at m/z 284.

To prove that there was no loss of enantiomeric purity during the oxidation procedure the aldehydes \(227\) and \(228\) were individually reduced with lithium aluminium hydride back to their respective alcohols \(225\) and \(226\). Thin layer chromatography and \(^1\)H NMR spectroscopy showed no evidence of more than one diastereomeric alcohol, from which it was inferred that no racemisation had occurred at the carbon atom \(\alpha\) to the aldehyde group during the oxidation step.

The next step was to remove the benzyl ether protecting group of the aldehydes \(227\) and \(228\) in order to synthesize the intermediate phenol \(208\) and its benzylic epimer \(229\). This was achieved by dissolving either one of the benzylic aldehydes in ethyl acetate, adding 10% palladium on carbon catalyst (mass ratio 100%) and subjecting the suspension to an atmosphere of hydrogen for 1.5 hours.

The biggest problem encountered during this step was the sulfurous residue from the Swern oxidation, which has to be removed completely before introducing the catalyst for hydrogenation. This adventitious sulphur had the effect of poisoning the catalyst rendering it inactive. The benzylic aldehydes \(227\) and \(228\) had to be chromatographed several times in order to remove this residue. The alternative removal of the poisoned catalyst after a relatively short period and addition of fresh catalyst
either gave no product or a complicated mixture. Success was achieved when the aldehyde was dissolved in ethyl acetate and the suspension stirred vigorously for 24 hours at room temperature after which the catalyst was filtered and a fresh portion added and the solution subjected to hydrogenation. The phenolic aldehyde (208) was obtained in this way in a yield of 72%.

The infrared spectrum of (208) showed the C=O stretch of the aldehyde functionality at 1730 cm\(^{-1}\) and the OH stretch at 3389 cm\(^{-1}\). The \(^1\)H NMR spectrum showed no signal for the benzyl group observed in the spectrum of aldehyde (227) and showed a broad singlet at \(\delta\) 6.29 for the OH. The aldehydic proton resonated as a doublet (\(J\) 1.8 Hz) at \(\delta\) 9.68. The mass spectrum showed the molecular ion peak at m/z 194 and a base peak at 121 arising from the benzylic carbocation after cleavage of the benzyl-lactaldehyde oxygen bond.

The same procedure was used to convert the aldehyde (228) into the phenol (229) in a 71% yield. The infrared spectrum showed a C=O stretch and OH stretch at 1729 cm\(^{-1}\) and 3378 cm\(^{-1}\) respectively. The \(^1\)H NMR spectrum showed the absence of the benzyl group. A broad singlet relating to the phenolic proton appeared at \(\delta\) 2.06 with the aldehyde proton resonating as a doublet at \(\delta\) 9.45 with a 1-H to 2-H coupling constant of 1.5 Hz. The mass spectrum in this case produced a ‘molecular’ ion peak of m/z 193 (M-H\(^+\)) with the same base peak at 121.

The desired phenol (208) and its C-\(\alpha\)' diasteriomer (229) could therefore be prepared in good yields from the benzylic aldehydes (227) and (228) respectively.

\[2.1.3 \textbf{Intramolecular Titanium-Mediated Cyclisation of Phenolic Aldehyde (208)}\]

The intramolecular approach to cyclisations is well known in the literature.\(^{129,135}\) Our approach, as discussed in \textbf{Section 1.5}, was to employ this methodology of intramolecular diastereoselective C-arylation of chiral carbonyl compounds. This type of intamolecular cyclisation has been extensively used in the synthesis of anthracyclinones. Krohn\(^{143}\)
reported the use of the Marschalk reaction in the syntheses of anthracyclinones (Scheme 32).

**Scheme 32**

Stereoselectivity of the α-hydroxy aldehyde cyclisation can be directed by the reaction conditions. *Cis/trans* ratios can vary from 3:1 in NaOH/THF to 1:10-15 under phase transfer conditions using Triton B as catalyst. Krohn\(^{143}\) suggested that this stereochemical outcome can be explained in terms of chelation versus non-chelation control (Scheme 33). He also suggested that less protic conditions (e.g. THF) favour a chelated transition state (I) leading to the *cis* diol with the sodium ion probably surrounded by many solvent molecules so that it is difficult for nucleophilic attack to occur at this face of the molecule.

**Scheme 33** (contd. over)
A non-chelating counter ion, such as Triton B, results in the natural trans-diol (transition state (II)).

Guanti et al.\textsuperscript{144b,c,d} reported cyclisation through a metal-mediated completely regioselective intramolecular hydroxyalkylation reaction under basic conditions. The carboxylic ester (234) was treated with a 1 M solution of diisobutyl aluminium hydride (DIBAL-H) in dichloromethane at -78 °C and quenched with ammonium chloride to achieve regioselective intramolecular cyclisation to the diol (236) via the aldehyde (235) (Scheme 34).
The diol (236) proved to be unstable and was treated with acetic anhydride and dimethylaminopyridine (DMAP) to afford the stable diacetate (237). Regioselectivity was achieved by coordination of the aluminium complex with both oxygens. The aluminium atom can also act as a Lewis acid with respect to the carbonyl group of the aldehyde as soon as this function is released by aqueous quenching with ammonium chloride leading to the ortho cyclised product. This method, however, was very substituent specific and only occurred for a limited range of substrates. Specifically benzo[c]pyran-4,5-diols could not be prepared by this method.

Casiraghi et al.\textsuperscript{129} investigated the intermolecular addition of aldehydes to phenolic systems. Stereochemical control over the hydroxy group is reported to be achieved by choice of the metal in the phenolates. These have the advantage of being Lewis acids as well as providing a nucleophilic aromatic ring. This was shown when a bromomagnesium phenolate was generated, when the syn addition product (238) was obtained. However, the anti addition product (239) was formed when the titanium phenolate was generated (Scheme 35) (discussed in Section 1.5).

Scheme 35

The alternative diastereoselectivity achieved in the case of the magnesium phenolate relies on the additional chelation of magnesium to the $\alpha$-oxygen of the reactant.\textsuperscript{145}
Giles and co-workers\textsuperscript{127,128b,132} have successfully applied the methodology developed by the above groups to achieve intramolecular cyclisation, involving the titanium phenolate of asymmetric phenolic aldehydes, with the eventual aim of synthesising the aphindervived quinone A and quinone A'.

The phenolic aldehyde (208) was cyclised with titanium tetraisopropoxide using ultrasonication. This was essential to ensure complete consumption of starting material. The cyclisation was found to proceed with complete diastereoselectivity to afford the benzopyran-4,5-diol (209) as the sole product in a yield of 73%.

Analysis of (209), a yellow oil, by TLC (30% ethyl acetate-hexane) revealed the presence of only one product. The mass spectrum gave the correct molecular ion at m/z 194 while the infrared spectrum showed an OH stretch at 3319 cm\(^{-1}\) and as a broad singlet at \(\delta\) 7.98 in the \(^1\)H NMR spectrum. \(^1\)H NMR spectroscopy confirmed the presence of only one product and showed the absence of the aldehyde peak previously observed at \(\delta\) 9.68. The large coupling constant of 7.0 Hz between the 3-H and 4-H indicated a near \textit{trans}-dixial arrangement of these protons. It also confirmed that the intramolecular cyclisation\textsuperscript{129} process indeed afforded the pseudoequatorial alcohol (209) equivalent to the product of \textit{anti} addition \textit{i.e.} the \textit{erythro} epimer. The likely conformation of this benzopyran (209) is drawn in Scheme 36 and shows the axial/pseudoaxial relationship of 3-H and 4-H.
This conformation is favoured since the methyl group at C-3 has the preferred equatorial configuration and the C-1 methyl group is in the pseudoaxial position, even though there is no bulky C-8 substituent present to cause peri-interactions. The chemical shift of 3-H (δ 3.93), appearing as a doublet of quartets, is consistent with values reported for similar compounds having a trans-1,3-dimethyl substitution pattern,\textsuperscript{105,131} and is characteristically downfield of the signal (δ 3.54) for 3-H in the corresponding cis-dimethyl compound (245) (vide infra).\textsuperscript{35b,36c,126} The 4-H proton resonated as a doublet at δ 4.56 (J 7.0 Hz) and 1-H appeared as a quartet at δ 4.90 (J 6.7 Hz). Two methyl doublets for the C-3 and C-1 methyl groups were also observed at δ 1.34 (J 6.3 Hz) and δ 1.49 (J 6.7 Hz) respectively. The presence of only three aromatic protons confirmed that cyclisation had taken place. The aromatic protons 6-H and 8-H appeared as doublets at δ 6.55 (J 7.9 Hz) and δ 6.69 (J 7.9 Hz) respectively. The aromatic proton 7-H appeared as a triplet at δ 7.12 (J 7.9 Hz).

The potentially unstable diol (209) was immediately acetylated to the corresponding diacetate (240) in an overall yield of 53\% from the phenolic aldehyde (208).

The infrared spectrum of the diacetate (240) showed the C=O stretch of the acetate groups at C-4 and C-5 at 1770 and 1733 cm\(^{-1}\). The \(^1\)H NMR spectrum showed two singlets for the acetate methyls at δ 2.09 and δ 2.27, respectively. The chemical shift (δ
4.25) of the proton 3-H was typical of a trans arrangement of the methyl substituents, supporting a trans-dimethyl substitution pattern. A noticeable deshielding of the 4-H doublet from δ 4.56 in the diol (209) to δ 5.72 in the diacetate (240) was observed. However, the unexpectedly small coupling constant of 2.0 Hz between 3-H and 4-H in compound (240) was inconsistent with that of the diacetate (193), for which the larger coupling constant of 4.8 Hz was observed. Thus 3-H and 4-H were almost certainly no longer axial and pseudoaxial, respectively.

**Scheme 37** shows the results of nOe difference spectroscopy on Joll’s diacetate (193). Irradiation of the pseudoaxial methyl group signal attached to C-1 gave nOe enhancement for the proton attached to C-1 and for the substituents on C-3 and C-4 which were located on the same side of the ring system as the C-1 methyl, namely 3-H and the protons of the acetate group at C-4.

This indicates the spatial proximity of the C-1 methyl group to the axial 3-H proton and to the pseudoequatorial acetate at C-4. It is also further support for the C-4 acetate group being pseudoequatorial, rather than pseudoaxial, and thus for the fact that the titanium reaction gave the product of anti addition. This was entirely consistent with results reported for analogous compounds.
In the 4,5-diacetate (240), however, the coupling constant between 3-H and 4-H was 2.0 Hz, for which the most likely explanation was that the half chair had inverted into the alternative half chair conformation in order to minimise peri interactions between the two sterically demanding acetate substituents (Scheme 38). This would require the C-1 and C-3 methyl groups to adopt pseudoequatorial and axial orientations respectively. The adoption of pseudoequatorial stereochemistry for the C-1 methyl group would be acceptable since, in diacetate (240), the C-8 substituent is hydrogen. Peri-interactions between this C-8 hydrogen and the C-1 methyl would be minimal. This steric crowding would be less than that experienced in diacetate (193), where more significant peri interactions operate between the C-1 methyl and the C-8 methoxy groups.

![Scheme 38 (240)](image)

Thus, for the diacetate (193), the C-1 methyl remains pseudoaxial, and the stereochemistry annotated on structure (192) is retained on formation of its diacetate (193). The alternative possibility that the stereochemistry of the C-4 substituent is reversed from pseudoequatorial to pseudoaxial on conversion of the diol (209) into its corresponding diacetate (240), while retaining the stereochemistry, including the same half-chair conformation, throughout this transformation was excluded when the diacetate (240) was reduced with lithium aluminium hydride to give back the same 4,5-diol (209), for which the coupling between 3-H and 4-H was 7.0 Hz.

The mass spectrum gave the correct molecular ion at m/z 278. The loss of CH$_3$CO$_2$H produced a fragment ion at m/z 218 with a further loss of a methyl radical affording the oxonium ion of mass m/z 203$_{124}^{124}$(Scheme 39).
Additional peaks at m/z 236 and m/z 234 correspond to the loss of ketene and loss of acetaldehyde in a retro Diels-Alder reaction respectively.

We can thus conclude that when phenol (208) is treated with titanium tetraisopropoxide, cyclisation occurs ortho to the phenolic function at C-3’ to give benzopyran (209).

We can also conclude that there was no racemisation at the chiral centre α to the aldehyde functionality of phenol (208) during the completely diastereoselective intramolecular titanium-induced cyclisation to afford the diol (209). This diastereoselectivity can be explained mechanistically as the result of effective, non-chelate reaction through a monocoordinated titanium “Felkin-Anh”-type transition
state,\textsuperscript{129c,145} in which intramolecular arylation occurs exclusively at the \textit{re}-face of the aldehyde, resulting in the 1,2-\textit{anti} addition product (209).

This transition state is further favoured (Scheme 40), since the methyl group at C-3 adopts its preferred stereochemistry, i.e., equatorial. Furthermore, with the C-4 oxygen pseudoequatorial, the distance between the two oxygens is minimised for the required titanium coordination.

Scheme 40

A further example of these conformational changes was shown as follows. Selective protection of the phenolic hydroxyl at C-5 in diol (209) afforded the monomethyl ether (241) in a yield of 88\%. Here the stereochemistry remains unchanged from that observed for the 4,5-diol (209). This was shown in the $^1$H NMR spectrum of compound (241), in which the 3-H proton resonated at $\delta$ 4.09 with a coupling constant of 5.4 Hz between 3-H and 4-H. Acetylation of methyl ether (241) led to the C-4 acetate (242) in a 76\% yield. The $^1$H NMR spectrum of (242) revealed a coupling constant of 1.9 Hz between 3-H and 4-H. This once again supported a conformational change to the alternative half chair promoted by increased C-4/C-5 \textit{peri} interactions, as for the diacetate (240).

The alternative diastereomer (244) was also made using methodology developed by Giles and co-workers.\textsuperscript{119} Treatment of methyl ether (241) with phosphorus pentachloride
in dry ether afforded the 4-chloro derivative (243). Compound (243) in acetonitrile was immediately treated with an excess of silver nitrate in water to give the desired C-4 pseudoaxial hydroxy compound (244).

![Diagram](243.png)

The coupling constant between the 3-H and 4-H proton was 1.9 Hz in the \(^1\)H NMR spectrum thus showing an axial/pseodoequatorial arrangement.

![Diagram](244.png)

**Scheme 41 (244)**

The reversal of C-4 stereochemistry through the transformation of the benzopyran (241) into its C-4 epimer (244) provided a model for the eventual asymmetric synthesis of quinone A’ (17) from the appropriate precursors to quinone A (16).\(^{119}\)

### 2.1.4 Intramolecular Titanium-Mediated Cyclisation of Phenolic Aldehyde (229)

The phenolic aldehyde (229), the benzylic diastereomer of compound (208), was similarly dissolved in dichloromethane and treated with titanium tetraisopropoxide and irradiated in a sonication bath to give the diol (245), the product of anti addition, as a single diastereomer in a 77% yield. \(^1\)H NMR and \(^{13}\)C NMR spectroscopy confirmed this.
The relative stereochemistry at C-3 and C-4 in diol (245) was identified by the large coupling constant of 9.0 Hz between 3-H and 4-H in the $^1$H NMR spectrum, indicating that two protons had an axial/pseudoaxial relationship between them (Scheme 42). In comparison, the C-1 epimer (209) of (245) showed a coupling constant of 7.0 Hz between 3-H and 4-H.

![Scheme 42 (245)](image)

The 3-H proton signal of (245) appeared as a doublet of quartets at $\delta$ 3.54 ($J_{6.1}$ and 9.0 Hz), characteristically upfield of the same signal ($\delta$ 3.93) in compound (209), indicative of a cis-1,3-dimethyl arrangement. The proton 4-H appeared as a doublet of doublets at $\delta$ 4.62 ($J_{6.7}$ and 9.0 Hz) and 1-H resonated as a quartet at $\delta$ 4.72 ($J_{6.5}$ Hz). The C-3 and C-1 methyl doublets appeared at $\delta$ 1.40 ($J_{6.1}$ Hz) and $\delta$ 1.47 ($J_{6.5}$ Hz) respectively. The 8-H and 6-H aromatic protons appeared as two doublets each at $\delta$ 6.61 ($J_{7.9}$ Hz) and $\delta$ 6.71 ($J_{7.9}$ Hz) with the 7-H proton resonating as a triplet at $\delta$ 7.12 ($J_{7.9}$ Hz). The mass spectrum showed the correct molecular ion peak at m/z 194 and the base peak at m/z 177 relating to the loss of an OH radical.
In view of the conformational changes observed on converting the diol (209) into its diacetate (240), and the 5-methoxybenzopyran-4-ol (241) into its acetate (242), it was decided to make the methyl ether (246) to compare with the C-4 epimer (248). Thus diol (245) in dichloromethane was treated with methyl iodide and potassium carbonate to give the methyl ether (246) in 68% yield. The coupling constant between 3-H and 4-H in the $^1$H NMR spectrum remained more or less unchanged at 8.8 Hz.

Compound (246) was similarly treated with phosphorus pentachloride in dry ether to afford the 4-chloro derivative (247), the residue from which was immediately treated with silver nitrate in acetonitrile containing water to give the desired methyl ether (248) with the C-4 hydroxy group pseudoaxial. The C-4 stereochemistry of compound (248) was established from the coupling constant (1.7 Hz) between 3-H at $\delta$ 3.74 and 4-H at $\delta$ 4.59 in the $^1$H NMR spectrum. This value was consistent with their axial/pseudoequatorial relationship.$^{105,131}$

Cyclisation of the aldehyde (229) was completely diastereoselective, giving only compound (245), unlike the cyclisation of the corresponding para-methoxyphenol (194) for which the two C-4 (249a) and (249b) diastereoisomers were observed.$^{128c}$ It was reasoned that this earlier lack of complete diastereoselectivity was as a result of
increased peri interactions between the C-8 methoxy and the pseudoequatorial C-1 methyl groups. This is now supported in the formation of a single stereoisomer, in the case where the C-8 substituent is the much smaller hydrogen atom.

![Chemical structures](image)

### 2.2 The Sequence Using t-Butyldimethylsilyl Protection of the Phenol

#### 2.2.1 Synthesis of Diastereomeric Alcohols (256) and (257).

t-Butyldimethylsilyl was originally examined as a protecting group when difficulties were experienced deprotecting the benzyl ether (227) through hydrogenolysis in the benzyloxy series (Section 2.1). This was as a result of adventitious sulphur from the Swern oxidation poisoning the Pd/C catalyst upon hydrogenation. The use of silyl as protecting group in (250) required the relatively mild reaction conditions of fluoride\textsuperscript{146} to give the target phenolic aldehyde (208) and its benzylic epimer (229) (Scheme 44).
The first part of the synthesis is described in Scheme 45 and follows the related methodology employed in the benzyloxy series (Section 2.1). 3-Hydroxyacetophenone (211) in dimethylformamide was treated with t-butyldimethylsilyl chloride and imidazole to afford the silyloxy ether (251) in 93% yield. Reduction of (251) with lithium aluminium hydride gave the alcohol (252).
Alcohol (252) was then converted into the imidate (253) in a yield of 90%, using sodium hydride and trichloroacetonitrile.

The mass spectrum of (253) gave the correct molecular ion peak at m/z 395 (C_{16}H_{24}O_{2}^{35}Cl_{3}NSi). The infrared spectrum showed the presence of a C≡N stretch at 1664 cm\(^{-1}\). The \(^1\)H NMR spectrum showed a broad singlet at δ 8.32 for the N-H while the \(^{13}\)C NMR spectrum showed the imidate carbon atom (C-1) resonating at δ 162.0. As was found in the benzyl ether series, a downfield shift was observed for the signal of the benzylic carbon (C-1) from δ 70.1 in the alcohol (252) to δ 77.3 (C-α') for the imidate (253).

The imidate (253) was subsequently dissolved in a 2:1 mixture of dichloromethane and hexane after which ethyl (S)-lactate (181) was added and the reaction mixture stirred at room temperature. The addition of a catalytic amount of boron trifluoride diethyl etherate afforded an inseparable mixture of diastereomeric esters (254) and (255) in a combined yield of 88%.

\[
\text{Scheme 45 (contd.)}
\]
The correct molecular ion peak at m/z 352 was observed in the mass spectrum. The infrared spectrum showed a carbonyl stretch at 1750 cm\(^{-1}\) and the carbonyl carbon atoms (C-1) resonated at δ 173.4 and δ 174.1 cm\(^{-1}\) in the \(^{13}\)C NMR spectrum.

The ester mixture (254) and (255) was exposed to lithium aluminium hydride to give the mixture of diastereomeric alcohols (256) and (257) in a combined yield of 87%.

The alcohols (256) and (257) were again separated at this stage through repeated radial chromatography, and obtained in a ratio of 55:45 respectively. Through previous work\(^{127,128b,132}\) it was reasonable to assume that the product of lower \(R_F\) was that shown in structure (256) which would give rise to the trans-1,3-dimethylbenzopyran on cyclisation, while the product of higher \(R_F\) was (257), which would afford the cis-1,3-dimethyl analogue. However, the \(^1\)H NMR spectra of the cyclisation products later in the synthesis would confirm this.

The individual alcohols (256) and (257) each gave a correct molecular ion peak at m/z 310 in the mass spectrum.

The product of lower \(R_F\) (256) showed an OH stretch at 3431 cm\(^{-1}\) relating to the aliphatic hydroxy group. For this diastereomeric alcohol, the signals for the two diastereotopic protons at C-1 and the signal for the 2-H were well resolved in the 300
MHz $^1$H NMR spectrum. The two diastereotopic protons ($\delta$ 3.46 and $\delta$ 3.65) attached to C-1 had a geminal coupling constant of 10.9 Hz, and 1-H to 2-H coupling constants of 5.7 and 3.4 Hz, respectively. These results compare well with the data reported by Joli$^{128b}$ for the analogous alcohol (188) where the geminal coupling constant for the two diastereotopic protons at C-1 ($\delta$ 3.44 and $\delta$ 3.66) was 11.3 Hz, and the 1-H to 2-H coupling constants were 5.9 and 3.6 Hz respectively.

![Chemical Structure](image)

The product of higher R$_F$ (257) showed the OH stretch at 3451 cm$^{-1}$ in the infrared spectrum and the hydroxylic proton as a broadened singlet at $\delta$ 1.97 in the $^1$H NMR spectrum. The two diastereotopic protons attached to the C-1 and the 2-H proton were not well resolved and showed a 3-proton multiplet in the region $\delta$ 3.38-3.53 and the individual coupling constants could therefore not be calculated.

The enantiomeric purities of the two alcohols (256) and (257) were determined to establish the possibility of racemisation occurring at the carbon atom $\alpha$ to the ester group during the formation of the ester mixture (254) and (255) or during their reduction to the alcohols.

The respective enantiomeric alcohols (258) and (259) were synthesised to assist in the interpretation of the $^1$H NMR spectra. This was again achieved by making the diastereomeric esters (260) and (261) by using the (R)-lactate (182). Reduction of the ester mixture and chromatography afforded the individual alcohols (258) and (259).
The optical rotations of the alcohols (256) and (257) were measured and compared well with their enantiomers (258) and (259) as shown in Table 2.

![Chemical Structures](258) ![Chemical Structures](259) ![Chemical Structures](260) ![Chemical Structures](261)

<table>
<thead>
<tr>
<th></th>
<th>256</th>
<th>258</th>
<th>257</th>
<th>259</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D$ (c 1.0, CHCl$_3$)</td>
<td>-40.1°</td>
<td>+37.6°</td>
<td>+79.4°</td>
<td>-76.4°</td>
</tr>
</tbody>
</table>

**Table 2:** Optical Rotations of the Alcohols (256), (258), (257) and (259)

With the four enantiomeric alcohols in hand, the optical purity of alcohols (256) and (257) were determined using Eu(hfc) as the shift reagent. By adding 15 mol% of the shift reagent to a 60:40 mixture of the enantiomers (256) and (258), good separation was achieved in many of the signals in the $^1$H NMR spectrum. The respective signals (258; 256) for 2-CH$_3$ occurred at $\delta$ 2.10 and $\delta$ 2.14, for $\alpha'$-CH$_3$ at 2.23 and 2.25 and for $\alpha'$-H at $\delta$ 5.69 and $\delta$ 5.76. The same procedure was then applied to a pure sample of alcohol (256) to examine it for signals due to the enantiomer (258). However, no signals resulting from that enantiomer were detected.
To obtain any reasonable separation in any signal in the $^1$H NMR spectrum of a 60:40 mixture of (257) and (259), it was necessary to use 25 mol% of shift reagent to achieve separation in three signals; for 2-CH$_3$ at $\delta$ 2.31 and $\delta$ 2.34, for $\alpha'$–CH$_3$ at $\delta$ 2.93 and $\delta$ 2.99 and for 2-H at $\delta$ 8.16 and $\delta$ 8.25. Once again, the spectrum of the enantiomer obtained from (S)-lactate (257) containing 25 mol% of the shift reagent showed no signals due to the enantiomer (259).

We can conclude from the results of this experiment that, as in the case with the benzyl ether alcohols (225) and (226), the diastereomeric alcohols (256) and (257) were found to be optically pure within the limits of $^1$H NMR spectroscopy. No racemisation at the chiral centre of the (S)-lactate during the reduction of the ester mixture to the alcohols could thus be observed.

2.2.2 Deprotection and Intramolecular Cyclisation of Aldehydes (250) and (262)

Swern oxidation$^{130}$ of the enantiomerically pure alcohols (256) and (257) afforded the corresponding aldehydes (250) and (262), both in yields of 87%.

The infrared spectrum of the aldehyde (250) showed a strong signal at 1737 cm$^{-1}$ due to the C=O aldehydic stretch. In the $^1$H NMR spectrum the aldehydic proton resonated as a doublet at $\delta$ 9.68 ($J$ 1.9 Hz) while in the $^{13}$C NMR spectrum the aldehydic carbon signal appeared at $\delta$ 204.0 (C-1). The mass spectrum showed the correct molecular ion peak at m/z 308.

The alternative aldehyde, (262), showed a C=O stretch at virtually the same value, 1735 cm$^{-1}$, in the infrared spectrum, while the aldehyde proton resonated as a doublet slightly
up-field from the benzylic epimer (250) at $\delta$ 9.49 and with a typically smaller coupling constant ($J$ 1.5 Hz). The aldehyde carbon signal (C-1) resonates at $\delta$ 203.2 in the $^{13}$C NMR spectrum with the mass spectrum giving a molecular ion at m/z 308.

Next it was necessary to form the phenolic aldehydes (208) and (229) by removing the silyl protecting groups of (250) and (262), respectively.

Several unsuccessful attempts were made in order to remove these groups. The first attempt, and seemingly the most common method, was to treat the aldehydes in acetonitrile with $t$-butylammonium fluoride at room temperature, which only gave a mixture of compounds with no specific products forming. The second attempt used a 0.25 M methanol in chloroform solvent mixture under ultrasound. This method only gave products of decomposition. Another method involved boiling the aldehyde in a 1% solution of iodine in methanol which gave the dimethyl acetal (263) as the main product.

However, when a mixture of saturated aqueous solutions of sodium fluoride and ammonium chloride (1:1) was added to a solution of the aldehyde (250) in tetrahydrofuran, the complex $^1$H NMR spectrum showed the absence of an aldehydic proton and it was suspected that it may have spontaneously cyclised to a benzopyran upon loss of the protecting group. The residue was therefore acetylated.
This afforded an inseparable mixture of diastereomeric 4,7-diacetates (264) and (265) as the major products, together with the 4,5-diacetate (265a) of the alternative regiochemistry as a minor component. These inseparable compounds were obtained in a combined overall yield of 47% and in a ratio of ∼4.6:4.6:0.8 from the phenolic aldehyde (250), as judged by $^1$H NMR spectroscopy.

The C-4 stereochemistry of the isolated minor 4,5-diacetate (265a) was determined using $^1$H NMR spectroscopy by comparing the chemical shifts of its protons with those of the only other possibility, diacetate (240) isolated earlier from the diol (209) obtained through titanium tetraisopropoxide-mediated ring closure of the phenolic aldehyde (208). Significant differences were observed for the C-1 methyl, 3-H, 1-H, 4-H, 6-H and 8-H protons; those for the latter two signals 6-H and 8-H were observed at δ 7.02 and 7.06 in compound (240), but were conspicuous by their absence in the spectrum of the mixture. Indeed, the signals for the protons 6-H for each of the alternative 4,7-diacetates (264) and (268) in the region δ 6.95 − δ 7.00 integrate for ∼ 2.38 protons, suggesting that these major signals obscure the pair of ortho coupled doublets expected for the protons 6-H and 8-H for the minor isomer (265a).

The absence of the fourth isomer (240), if formed, from the observed mixture may arise through its inadvertently having been removed through chromatography as a minor
component of different R<sub>F</sub>. Since the major isomers (264) and (265) were formed in a ratio of very close to 1:1, it was not possible to assign every signal to each of the individual isomers without significant additional spectroscopy using long-range connectivity techniques.

<table>
<thead>
<tr>
<th></th>
<th>Compound (240)</th>
<th>Compound (265a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.25</td>
<td>1.24</td>
</tr>
<tr>
<td>1-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.60</td>
<td>1.52</td>
</tr>
<tr>
<td>4-OAc</td>
<td>2.09</td>
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</tr>
<tr>
<td>5-OAc</td>
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<td>4-H</td>
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</tr>
<tr>
<td>6-H</td>
<td>7.02</td>
<td>-</td>
</tr>
<tr>
<td>8-H</td>
<td>7.06</td>
<td>-</td>
</tr>
<tr>
<td>7-H</td>
<td>7.37</td>
<td>7.35</td>
</tr>
</tbody>
</table>

Table 3: Comparison of Chemical Shifts of Compound (240) and Compound (265a)

It was anticipated that this spontaneous cyclisation occurred through the formation of the phenoxide ion upon desilylation of the silyl ethers as drawn for the starting aldehyde (250) (Scheme 46).
The oxide ion promotes spontaneous electrophilic substitution predominantly at the para position. This selectivity may arise, at least in part, through greater steric compression being caused by the adjacent substituent at the alternative ortho site, thereby inhibiting such ring closure.

The mass spectrum of the mixture (264) and (265) gave no molecular ion peak but showed a fragment ion at m/z 234 as a result of the loss of acetaldehyde, through a retro Diels-Alder reaction. The infrared spectrum showed a strong signal at 1733 cm$^{-1}$ due to the C-4 and C-7 carbonyl stretches and in the $^{13}$C NMR spectrum the two 4-OAc carbonyl carbons resonated at $\delta$ 169.4 and $\delta$ 169.5 and at $\delta$ 171.1 and $\delta$ 171.2 for those of the 7-OAc groups.

The structures of the products were assigned on the basis of the $^1$H NMR spectrum; for each of the 4,7-diacetates one proton (5-H) appeared as an ortho coupled doublet, the second (8-H) as a meta coupled doublet, and the third (6-H) as a doublet of doublets, both ortho and meta coupled. For the minor 4,5-diacetate (265a), the protons H-6 and
H-8 were obscured by the aromatic signals of the major compounds in the mixture, but the proton H-7 resonated as a clear triplet \((J \, 7.9 \text{ Hz})\) at \(\delta \, 7.35\). Thus \(\sim 92\%\) of the products arise from cyclisation \textit{para} to the phenolic substituent, while only \(\sim 8\%\) occurred through \textit{ortho} cyclisation.

The \(^1\)H NMR spectrum of diacetate (264) showed the coupling constant of the \textit{trans}-diaxial protons 3-H and 4-H to be 4.0 Hz (Scheme 47). The proton 3-H at \(\delta \, 4.18\) appeared as a doublet of quartets \((J \, 4.0 \text{ and } 6.4 \text{ Hz})\) and the 4-H proton appeared as a doublet at \(\delta \, 5.63\) \((J \, 4.0 \text{ Hz})\).

\[
\begin{align*}
\text{Scheme 47 (264)}
\end{align*}
\]

The \(^1\)H NMR spectrum of diacetate (265) showed a smaller coupling constant of 2.0 Hz between the protons 3-H and 4-H. The small coupling constant between the 3-H and 4-H protons supported their axial-pseudoequatorial arrangement (Scheme 48). This is again consistent with results reported for analogous compounds.\(^{105,131}\)

It was impractical to assign the remaining resonances since the mixture of compounds (264) and (265) was inseparable and these components were obtained in approximately equal proportions.

\[
\begin{align*}
\text{Scheme 48 (265)}
\end{align*}
\]
Aldehyde (262), the benzylic epimer of (250), was dissolved in tetrahydrofuran and also treated with a 1:1 mixture of saturated ammonium chloride and sodium fluoride solution to give the two diols (267) and (268) in a 1:1 ratio as the major component observed by TLC. The mixture was chromatographed rapidly to avoid potential decomposition. The component was acetylated and careful chromatography of the products afforded the corresponding diacetates (269) and (270) in a yield of 24% and 27% respectively from the original aldehyde (262). Ring closure again took place at the position para to the phenolic hydroxy group. Chromatography at the diol level may have removed any of the 4,5-regioisomers as minor components.

The arrangement of substituents at C-3 and C-4 in (269) was identified by the large coupling constant of 9.0 Hz between 3-H and 4-H in the $^1$H NMR spectrum, indicating a axial-pseudoaxial relationship$^{105,131}$ as can be seen in the conformation drawn in Scheme 49. The C=O stretch of the C-4 and C-7 acetoxy groups appears at 1741 cm$^{-1}$ in the infrared spectrum and the carbonyl carbons at $\delta$ 168.7 (4-OAc) and $\delta$ 170.3 (7-OAc) in the $^{13}$C NMR spectrum. The mass spectrum gave a fragment ion peak at m/z 234 relating to the loss of acetaldehyde from the molecular ion, through a retro Diels-Alder reaction.
The $^1$H NMR spectrum of diastereomer (270) showed a small coupling constant of 1.9 Hz between the 3-H and the 4-H. This value is consistent$^{105,131}$ with their axial-pseudoequatorial relationship (Scheme 49). The infrared spectrum showed the C=O stretches at 1734 cm$^{-1}$ and the carbonyl carbon signals at $\delta$ 168.7 and $\delta$ 170.5 in the $^{13}$C NMR spectrum. The mass spectrum showed an M$^+$-1 peak at m/z 277 arising from the loss of hydrogen and the base peak at m/z 219 arising from the alternative loss of acetoxy.

An alternative method$^{149}$ was found to afford the diol mixture (267) and (268). This involved the addition of a pH 5 fluoride buffer, prepared by addition of the 0.1 M hydrogen fluoride to 0.1 M sodium fluoride, to the aldehyde (262). This method afforded the same yields but was found to be less reproducible.

2.3 Concluding Remarks

The results described in this chapter answer the question posed at its outset, viz. can the regioselectivity of ring closure of meta hydroxybenzyl-protected lactaldehydes to form benzopyrans be controlled by appropriate choice of conditions? That is, can conditions be found under which ring closure could be achieved selectively at the position either ortho or para to the phenolic substituent? It was shown that use of the reagent titanium tetraisopropoxide led to regio- and diastereoselectivity, affording solely the benzopyran-4,5-diol in which the C-4 alcohol was pseudoequatorial. Reversal of the C-4
stereochemistry was achieved for the 5-O-methyl ether. These results were accomplished irrespective of the stereochemistry of the benzylic methyl substituent in the two lactaldehydes (208) and (229).

The observed complete diastereoselectivity in both these cases was in contrast to the corresponding meta hydroxybenzyl-protected lactaldehydes (191) and (194), in which, for the latter only, the 4,5-diols (271) and (272) were obtained in a ratio of 3:1.

In that earlier work, it was reasoned that this loss in diastereoselectivity was the consequence of the C-1 methyl in the derived benzopyran, which was pseudoequatorial, leading to less favourable peri interactions with the C-8 aromatic methoxy group. This reasoning was borne out by the fact that no such unfavourable peri interactions occur in the transformation of the lactaldehyde (229) into the benzopyran (245), in which methoxy is replaced by the much less sterically demanding hydrogen atom.
The alternative regioselectivity to afford two corresponding 4,7-diols was achieved through generation of the phenoxides of the lactaldehydes (208) and (229). This was achieved through their liberation from the corresponding t-butyldimethylsilyl ethers (250) and (262), whereupon these phenoxides spontaneously cyclised with high regioselectivity. In these cases, as would be anticipated, there was no control over the stereochemistry of the C-4 alcohol.
2.4 Experimental

General

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity PolAAr 2001 polarimeter for chloroform solutions of c 1.0 at 20 °C. Infrared (IR) spectra were recorded as a nujol mull for solids and as thin films between NaCl plates for oils, using a Perkin Elmer 1720-X Fourier Transform Spectrometer. The sonication bath used was a Branson B3200-E4, operating at a frequency of 44 kHz. Mass spectra were obtained on a VG Autospec spectrometer operating in the electron impact mode at 70eV [at the University of Western Australia]. No logical fragmentation pattern for the final quinones (16), (17), (359) and (360) could be determined and were therefore not reported. Only high resolution mass measurements were obtained for the final quinones except for quinone A'. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd.

Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AM-300 spectrometer (1H, 300MHz; 13C, 75.5MHz). The spectra were run at ambient temperature in deuterochloroform (CDCl3) solution, with tetramethylsilane (TMS) (δ 0.00) for 1H NMR spectra and TMS (δ 0.00) and chloroform (δ 77.00) for 13C NMR spectra as internal standards. In the NMR spectra, assignments of signals with the same superscripts are interchangeable.

All solvents were purified by distillation and, if necessary, were dried according to standard methods. The amount of residual water present in solvents was determined using a Metrohm Karl Fischer Calorimeter 684. The hydrocarbon solvent referred to as hexane routinely had a b.p. range of 65-70 °C.

Chromatography refers to dry-packed columns of Merck silica gel 60 (70-230 mesh). Preadsorption was carried out on Merck silica gel 60 (35-70 mesh). The adsorbent for radial chromatography was Merck silica gel 60 PF254. Merck silica gel 60 F254 aluminium backed sheets were used for thin layer chromatography (TLC). Compounds were routinely visualized under short wavelength (245nm) ultraviolet light.
The phrase “residue obtained upon work-up” refers to the residue when the organic layer was separated, dried with anhydrous magnesium sulfate (MgSO₄) and concentrated under reduced pressure.

**3′-Benzylxoyacetophenone (212)**

Potassium carbonate (12.68 g, 91.9 mmol) was added to a stirred solution of benzyl bromide (15.72 g, 91.9 mmol) and 3′-hydroxyacetophenone (211) (5 g, 36.8 mmol) in dry dimethylformamide (50 cm³). The resulting suspension was heated under reflux for 12 h. The reaction mixture was cooled, filtered through a pad of celite and the filtrate concentrated under reduced pressure. The residue was subsequently chromatographed (10–20% ethyl acetate–hexane) to give compound (212) (6.81 g; 82%) as cream coloured plates, m.p. 29.5–30 °C (hexane) (Lit, 150 oil) (Found: M⁺, 226.0988. C₁₅H₁₄O₂ requires M, 226.0993; νₘₐₓ/cm⁻¹ 1676 (C=O) and 1578 and 1484 (C=C); δₜ 2.56 (3H, s, COCH₃), 5.10 (2H, s, OCH₂), 7.16 (1H, ddd, J 2.6, 3.6 and 8.2 Hz, 4′-H), 7.31-7.45 (6H, m, C₆H₅ and 5′H), 7.51-7.55 (1H, m, 6′-H) and 7.57 (1H, m, 2′-H); δc 26.7 (COCH₃), 70.2 (OCH₂), 113.6 (C-4′), 120.3 (C-5′), 121.3 (C-6′), 127.6 (C-2′ and C-6″), 128.1 (C-2′), 128.7 (C-3″ and C-5″), 129.6 (C-4″), 136.5 (C-1″'), 138.6 (C-1″'), 159.0 (C-3′) and 197.8 (COCH₃); m/z 226 (M⁺, 14%), 92 (100), 91 (100) and 65 (8).

**1-(3′-Benzylxoyphenyl)ethanol (213)**

To a stirred slurry of lithium aluminium hydride (336 mg, 8.85 mmol) in dry ether (30 cm³) was added drop-wise a solution of 3′-benzylxoyacetophenone (212) (200 mg, 0.88 mmol) in dry ether (8 cm³) under argon. The mixture was stirred for 1 h under argon after which saturated ammonium chloride solution was added drop-wise, followed by MgSO₄. Filtration through celite and subsequent chromatography (radial, 10-20% ethyl acetate–hexane) yielded the benzyl alcohol (213) as a light yellow oil (200 mg, 99%) (Found: C,
78.45; H, 7.0; M⁺, 228.1144. C₁₅H₁₆O₂ requires C, 78.9; H, 7.05%; M, 228.1150; νmax(film)/cm⁻¹ 3392 (OH) and 1585 and 1488 (C=C); δH 1.44 (3H, d, J 6.5 Hz, 1-CH₃), 2.18 (1H, br. s, OH), 4.80 (1H, q, J 6.5 Hz, 1-H), 5.03 (2H, s, OCH₂), 6.85 (1H, dd, J 2.0 and 7.9 Hz, 6'-H), 6.92 (1H, dd, J 2.0 and 7.9 Hz, 4'-H), 7.00 (1H, t, J 2.0 Hz, 2'-H), 7.23 (1H, t, J 7.9 Hz, 5'-H) and 7.30-7.43 (5H, m, C₆H₅); δC 25.1 (C-2), 69.9 (OCH₂), 70.2 (C-1), 111.9 (C-6'), 113.7 (C-4'), 118.0 (C-2'), 127.5 (C-2'' and C-6''), 127.9 (C-4''), 128.5 (C-3'' and C-5''), 129.5 (C-5'), 137.0 (C-1'), 147.6 (C-1'') and 158.9 (C-3''); m/z 228 (M⁺, 6%), 92 (7), 91 (100), 86 (15), 84 (19), 65 (8) and 51 (9).

3'-Benzyloxy-α'-methylbenzyl-2,2,2-trichloroethanimidate (220)

The benzyl alcohol (213) (1 g, 4.39 mmol) in dry diethyl ether (4 cm³) was added drop-wise to a stirred suspension of sodium hydride (60% dispersion in oil) (70 mg, 2.92 mmol) in diethyl ether (15 cm³). The mixture was stirred for 10 min under argon at -10 °C. Trichloroacetonitrile (1.27 g, 8.79 mmol) was added drop-wise over 10 min, and the reaction mixture stirred for a further 30 min at that temperature, after which it was allowed to reach room temperature. The solution was concentrated and chromatographed (radial, 10% ethyl acetate-hexane) to afford the imidate (220) (1.41 g, 85%) as a white solid m.p. 78-79 °C (hexane) (Found: C, 54.85; H, 4.35; N, 3.7; M⁺, 373.0202. C₁₇H₁₆Cl₃NO₂ requires C, 55.0; H, 4.35; N, 3.75%; M(³⁵Cl₂³⁷Cl), 373.0217); νmax/cm⁻¹ 1 3340 (N-H), 1662 (C=N) and 1597 and 1499 (C=C); δH 1.62 (3H, d, J 6.6 Hz, α'-CH₃), 5.04 (2H, s, OCH₂), 5.95 (1H, q, J 6.6 Hz, α'-H), 6.90 (1H, dd, J 2.0 and 7.9 Hz, 6'-H), 7.00 (1H, dd, J 2.0 and 7.9 Hz, 4'-H), 7.05 (1H, t, J 2.0 Hz, 2'-H), 7.25 (1H, t, J 7.9 Hz, 5'-H), 7.28-7.43 (5H, m, C₆H₅) and 8.30 (1H, s, NH); δC 22.1 (α'-CH₃), 69.9 (OCH₂), 76.9 (C-α'), 91.7 (CCL₃), 112.2 (C-6'), 114.2 (C-4'), 118.3 (C-2') 127.5 (C-2'' and C-6''), 127.9 (C-4''), 128.5 (C-3' and C-5''), 129.5 (C-5'), 137.0 (C-1'), 147.6 (C-1'') and 158.9 (C-3''); m/z 228 (M⁺, 6%), 92 (7), 91 (100), 86 (15), 84 (19), 65 (8) and 51 (9).
Ethyl (α′R, 2S)-2-(3′-benzyloxy-α′-methylbenzyloxy)propanoate (214) and its (α′S) diastereomer (215)

Boron trifluoride diethyl etherate (18 mg, 0.13 mmol) was added dropwise to a solution of imidate (220) (470 mg, 1.27 mmol) and ethyl (S)-lactate (181) (300 mg, 2.54 mmol) in dry hexane:dry dichloromethane (15 cm³, 2:1). The reaction mixture was stirred under nitrogen for 40 min. Solid sodium hydrogen carbonate was added to the mixture and the resulting suspension was filtered through celite. The clear solution was then concentrated and chromatographed (radial, 10% ethyl acetate-hexane) to yield (214) and (215) as an oily, inseparable mixture of diastereomers (310 mg, 75%) in a ratio of 55:45 respectively.

(Found: C, 73.5; H, 7.45; M⁺, 328.1662. C₂₀H₂₄O₄ requires C, 73.15; H, 7.35%; M, 328.1674; υ_max(film)/cm⁻¹ 1746 (C=O) and 1599, and 1487 (C=C); δ_H (major diastereomer) 1.28 (3H, t, J 7.2 Hz, C₆H₃CH₂), 1.32 (3H, d, J 6.9 Hz, 2-CH₃), 1.47 (3H, d, J 6.5 Hz, α′-CH₃), 3.82 (1H, q, J 6.9 Hz, 2-H), 4.15 - 4.25 (2H, m, CH₃C₆H₂), 4.49 (1H, q, J 6.5 Hz, α′-H), 5.06 (2H, s, OCH₂), 6.85-7.30 (4H, m, 2′, 4′, 5′- and 6′-H) and 7.30-7.46 (5H, m, C₆H₅); δ_C (mixture of two diastereomers) 14.1 and 14.3 (CH₃CH₂), 18.3 and 19.0 (C-3), 23.2 and 24.4 (α′-CH₃), 60.7 and 60.7 (CH₃CH₂), 69.9 and 70.0 (OCH₂), 72.0 and 72.8 (C-α′), 77.0 and 77.3 (C-2), 112.6 and 112.9 (C-6′), 114.0 (C-4′), 119.0 and 119.2 (C-2′), 127.6 and 127.5 (C-2′′ and C-6′′), 128.0 and 127.9 (C-4′′), 128.5 and 128.6 (C-3′′ and C-5′′), 129.4 and 129.6 (C-5′), 136.9 and 137.0 (C-1′), 144.7 and 144.0 (C-1′′), 158.9 and 159.1 (C-3′) and 173.1 and 173.7 (C-1); m/z 328 (M⁺, 8%), 237 (7), 227 (25), 212 (9), 211 (36), 120 (5), 92 (18), 91 (100) and 65 (10).
(α′S, 2S)- and (α′R, 2S)-2-(3′-Benzyloxy-α′-methylbenzyloxy)propan-1-ol (225) and (226)

The mixture of diastereomeric esters (214) and (215) (400 mg, 1.22 mmol) was reduced with lithium aluminium hydride as described for the reduction of 3′-benzyloxyacetophenone (212). The pale yellow oil was subjected to chromatography (radial, 5-10% ethyl acetate-hexane) to achieve separation of the two alcohols (225) and (226) as colourless oils.

The product of lower Rf was identified as compound (225) (180 mg, 52%) [α]D −38.1° (c 1.0 in CHCl3); (Found: C, 75.6; H, 7.65; M+, 286.1574. C18H22O3 requires C, 75.5; H, 7.75%; M, 286.1568); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3436 (OH) and 1586 and 1486 (C=C); \( \delta_{\text{H}} \) 1.00 (3H, d, J 6.2 Hz, 2-CH3), 1.43 (3H, d, J 6.4 Hz, α′-CH3), 1.99 (1H, br. s, OH), 3.43-3.69 (3H, m, CH2OH and 2-H), 4.56 (1H, q, J 6.4 Hz, α′-H), 5.07 (2H, s, OCH2), 6.89 (1H, dd, J 2.0 and 8.0 Hz, 6′-H), 6.92 (1H, dd, J 2.0 and 8.0 Hz, 4′-H), 6.99 (1H, t, J 2.0 Hz, 2′-H), 7.25 (1H, t, J 8.0 Hz, 5′-H) and 7.30-7.46 (5H, m, C6H5); \( \delta_{\text{C}} \) 17.9 (C-3), 24.6 (α′-CH3), 66.4 (C-1), 70.6 (OCH2), 74.7 (C-2), 76.9 (C-α′), 113.2 (C-6′), 114.3 (C-4′), 119.4 (C-2′), 128.1 (C-2″ and C-6″), 128.6 (C-4″), 129.1 (C-3″ and C-5″), 130.0 (C-5′), 137.6 (C-1′), 146.8 (C-1″) and 159.5 (C-3′); m/z 286 (M+, 10%), 212 (25), 211 (54), 92 (14) and 91 (100).

The product of higher Rf was identified as compound (226) (140 mg, 40%) [α]D +67.2° (c 1.0 in CHCl3); (Found: M+, 286.1555. C18H22O3 requires M, 286.1568); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3435 (OH) and 1599 and 1486 (C=C); \( \delta_{\text{H}} \) 1.10 (3H, d, J 5.9 Hz, 2-CH3), 1.41 (3H, d, J 6.4 Hz, α′-CH3), 2.24 (1H, br. s, OH), 3.35-3.46 (3H, m, CH2OH and 2-H), 4.51 (1H, q, J 6.4 Hz, α′-H), 5.02 (2H, s, OCH2) and 6.86-7.43 (9H, m, 2′, 4′, 5′, 6′-H and C6H5); \( \delta_{\text{C}} \) 15.6 (C-3), 24.5 (α′-CH3), 66.6 (C-1), 69.9 (OCH2), 72.7 (C-2), 74.9 (C-α′), 112.8 (C-6′), 113.8 (C-4′), 118.8 (C-2′), 127.6 (C-2″ and C-6″), 127.9 (C-4″), 128.5 (C-3″ and C-5″), 129.6 (C-5′), 136.9 (C-1′), 145.5 (C-1″) and 159.0 (C-3′); m/z 286 (M+, 18%), 212 (22), 211 (54), 92 (14) and 91 (100).

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(α′S, 2S)-2-(3′-Benzyl氧-α′-methylbenzyl氧)propanal (227)

To a solution of oxalyl chloride (220 mg, 1.74 mmol) in dry dichloromethane (4 cm³) at -70 °C under an atmosphere of argon was added dropwise a solution of dimethyl sulfoxide (270 mg, 3.5 mmol) in dry dichloromethane (4 cm³), while keeping the temperature below -65 °C. After stirring for 15 min, a solution of the (α′S, 2S) alcohol (225) (100 mg, 0.35 mmol) in dry dichloromethane (4 cm³) was added drop-wise. The temperature was kept below -65 °C and the stirring continued for a further 15 min at that temperature. Dry diisopropylethylamine (540 mg, 4.19 mmol) was added slowly and the reaction stirred for a further 10 min at -70 °C before being allowed too warm to room temperature over 1 h. The reaction mixture was quenched with water and exhaustively extracted with dichloromethane and the residue obtained upon work-up was chromatographed (radial, 10-20% ethyl acetate-hexane) to give the aldehyde (227) as a colourless oil (73 mg, 75%) [α]D -107.4 ° (c 1.0 in CHCl₃); (Found: M⁺, 284.1421. C₁₈H₂₀O₃ requires M⁺, 284.1412); νmax(film)/cm⁻¹ 1733 (C=O) and 1586 and 1486 (C=C); δH 1.17 (3H, d, J₇.₀ Hz, 2-CH₃), 1.49 (3H, d, J 6.4 Hz, α′-CH₃), 3.69 (1H, dq, J 1.8 and 7.0 Hz, 2-H), 4.51 (1H, q, J 6.4 Hz, α′-H), 5.06 (2H, s, OCH₂), 6.86-6.95 (3H, m, 2′-, 4′- and 6′-H), 7.25 (1H, t, J 7.8 Hz, 5′-H), 7.30-7.45 (5H, m, C₆H₅) and 9.66 (1H, d, J 1.8 Hz, CHO); δC 15.2 (C-3), 23.6 (α′-CH₃), 69.3 (OCH₂), 76.8 (C-2), 77.0 (C-α′), 111.9 (C-6′), 113.5 (C-4′), 118.2 (C-2′), 126.8 (C-2′′ and C-6′′), 127.3 (C-4′′), 127.9 (C-3′′ and C-5′′), 129.0 (C-5′), 136.2 (C-1′), 143.9 (C-1′′), 158.4 (C-3′) and 203.1 (C-1); m/z 284 (M⁺, 7%), 212 (12), 211 (55), 92 (11) and 91 (100).

(α′R, 2S)-2-(3′-Benzyl氧-α′-methylbenzyl氧)propanal (228)

According to the method described above for the preparation of the aldehyde (227) from the (α′S, 2S) alcohol (225), the (α′R, 2S) alcohol (226) (200 mg, 0.7 mmol) was converted into the aldehyde (228) as a crude pale orange oil. Chromatography (radial, 10-30% ethyl acetate-hexane) gave a colourless oil (160 mg, 80%) [α]D +51.6 ° (c 1.0 in CHCl₃); (Found: C,
1736 (C=O) and 1586 and 1486 (C=C);
\[ \delta_H \text{ } 1.23 \text{ (3H, d, } J \text{ 6.9 Hz, } 2'-\text{CH}_3) \],
\[ 1.48 \text{ (3H, d, } J \text{ 6.5 Hz, } \alpha'-'\text{-CH}_3) \],
\[ 3.71 \text{ (1H, dq, } J \text{ 1.3 and 6.9 Hz, } 2'-\text{H}) \],
\[ 4.52 \text{ (1H, q, } J \text{ 6.5 Hz, } \alpha'-\text{H}) \],
\[ 5.06 \text{ (2H, s, OCH}_2\text{) } \]
\[ 6.85-7.00 \text{ (3H, m, } 2', 4'-\text{ and } 6'-\text{H}) \],
\[ 7.23 \text{ (1H, t, } J \text{ 7.9 Hz, } 5'-\text{H}) \],
\[ 7.32-7.44 \text{ (5H, m, C}_6\text{H}_5\text{) and } 9.41 \text{ (1H, d, } J \text{ 1.3 Hz, CHO); } \delta_C \text{ 15.9 (C-3),} \]
\[ 24.7 (\alpha'-\text{CH}_3) \],
\[ 70.9 (\text{OCH}_2) \],
\[ 76.3 (\text{C-2}) \],
\[ 78.9 (\text{C-}\alpha') \],
\[ 113.9 (\text{C-6}') \],
\[ 115.2 (\text{C-4}') \],
\[ 120.1 (\text{C-2}') \],
\[ 128.4 (\text{C-2'' and C-6''}) \],
\[ 128.9 (\text{C-4''}) \],
\[ 129.5 (\text{C-3'' and C-5''}) \],
\[ 130.6 (\text{C-5'}) \],
\[ 137.7 (\text{C-1'}) \],
\[ 145.7 (\text{C-1''}) \],
\[ 160.0 (\text{C-3'}) \] and 204.1 (C-1);
\[ m/z \text{ 284 (M}^+\text{, 5%), 212 (16), 211 (65), 92 (13) and 91 (100).} \]

(\text{$\alpha'$S, 2S}-2-(3'-\text{Hydroxy-}$\alpha'$-methylbenzylxylo)$\text{propanal (208)}$

A suspension of the pure benzyl ether (227) (200 mg, 0.7 mmol) and 10% palladium on carbon catalyst (200 mg, 100%) in dry ethyl acetate (10 cm$^3$) was stirred under a hydrogen atmosphere for 1.5 h. The mixture was filtered through filter aid, subjected to another portion of 10% palladium on carbon catalyst (200 mg, 100%) and exposed to a hydrogen atmosphere for a further 1.5 h. The reaction mixture was again filtered through filter aid, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate-hexane) to afford the potentially unstable phenol (208) (98 mg, 72%) as a light pink oil.

(Found: M$^+$, 194.0950. C$\text{11H14O3}$ requires M, 194.0942);
\[ \nu_{\text{max}}\text{(film)/cm}^{-1} \text{ 3389 (OH),} \]
\[ 1730 (\text{C}=\text{O}) \] and 1592 and 1484 (C=C);
\[ \delta_H \text{ 1.23 (3H, d, } J \text{ 7.0 Hz, 2-CH}_3) \],
\[ 1.50 (3H, d, } J \text{ 6.4 Hz, } \alpha'-\text{CH}_3) \],
\[ 3.76 (1H, dq, } J \text{ 1.8 and 7.0 Hz, 2-H}) \],
\[ 4.51 (1H, q, } J \text{ 6.4 Hz, } \alpha'-\text{H}) \],
\[ 6.29 (1H, br. s, OH), \]
\[ 6.73-6.95 (3H, m, 2', 4'-\text{ and } 6'-\text{H}) \],
\[ 7.20 (1H, t, } J \text{ 7.9 Hz, 5'-H) \] and 9.68 (1H, d, J 1.8 Hz, CHO);
\[ \delta_C \text{ 15.8 (C-3), 24.2 (}$\alpha'$-\text{CH}_3) \],
\[ 77.6 (C-2) \],
\[ 77.7 (\text{C-}$\alpha'$) \],
\[ 113.0 (\text{C-6}') \],
\[ 115.0 (\text{C-4'}) \],
\[ 118.5 (\text{C-2'}) \],
\[ 129.9 (\text{C-5'}) \],
\[ 144.6 (\text{C-1'}) \],
\[ 156.2 (\text{C-3'}) \] and 204.3 (C-1);
\[ m/z \text{ 194 (M}^+, 7%), 177 (19), 149 (15), 122 (15) and 121 (100).} \]
(α'R, 2S)-2-(3'-Hydroxy-α'-methylbenzyloxy)propanal (229)

In a similar manner to the hydrogenolysis of benzyl ether (227) described above, the benzyl ether (228) (100 mg, 0.35 mmol) was deprotected to give the potentially unstable phenol (229) which was rapidly chromatographed (radial, 30% ethyl acetate-hexane) to afford a light pink oil (48 mg, 71%) (Found: (M-H)⁺, 193.0853. C₁₁H₁₃O₃ requires M-H, 193.0864); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3378 \text{ (OH)} , 1729 \text{ (C=O)} \) and 1608 and 1589 (C=C); \(\delta_H 1.27 \) (3H, d, \(J 6.8 \text{ Hz, 2-CH₃}\)), 1.48 (3H, d, \(J 6.4 \text{ Hz, } \alpha'\text{-CH₃}\)), 2.06 (1H, br. s, OH), 3.79 (1H, dq, \(J 1.5 \text{ and } 6.8 \text{ Hz, 2-H}\)), 4.52 (1H, q, \(J 6.4 \text{ Hz, } \alpha'\text{-H} \)), 6.73-6.95 (3H, m, 2'\text{-}, 4'\text{-} \text{ and } 6'\text{-H}), 7.17 (1H, t, \(J 7.8 \text{ Hz, } 5'\text{-H} \)) and 9.45 (1H, d, \(J 1.5 \text{ Hz, CHO} \)); \(\delta_C 15.0 \text{ (C-3), 23.7} \text{ (C'-CH₃), 77.1} \text{ (C-2), 78.1} \text{ (C-C' ), 113.4} \text{ (C-6), 115.3} \text{ (C-4'), 118.7} \text{ (C-2'), 129.9} \text{ (C-5'), 144.3} \text{ (C-1')} \text{, 156.4} \text{ (C-3')} \text{ and } 203.8 \text{ (C-1)}\); m/z 193 [M'-H, 9%], 177 (28), 150 (11), 149 (21), 122 (12) and 121 (100).

(1S, 3S, 4R)-4,5-Diacetoxy-3,4-dihydro-1,3-dimethylbenzo[c]pyran (240)

Fresh, neat titanium tetraisopropoxide (120 mg, 0.42 mmol) was added to a solution of the (α'S, 2S) phenolic aldehyde (208) (55 mg, 0.28mmol) in dry dichloromethane (15 cm³) at 0 °C, under argon. After standing for 10 min at 0 °C, the reaction mixture was sonically irradiated at 8-35 °C for 5 h, after which dichloromethane (30 cm³) and a mixture of saturated aqueous solutions of sodium fluoride and ammonium chloride (60 cm³, 1:1) was added and stirred until the yellow colour disappeared. The aqueous layer was extracted with dichloromethane and the residue obtained upon work-up was chromatographed (radial, 50% ethyl acetate-hexane) to give the potentially unstable (1S, 3S, 4R)-3,4-dihydro-1,3-dimethylbenzo[c]pyran-4,5-diol (209) as a light yellow oil (40 mg, 73%) (Found: (M-H)⁺, 193.0852. C₁₁H₁₃O₃ requires M-H, 193.0864); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1} 3319 \text{ (OH) } \) and 1591 and 1464 (C=C); \(\delta_H 1.34 \) (3H, d, \(J 6.3 \text{ Hz, 3-CH₃}\)), 1.49 (3H, d, \(J 6.7 \text{ Hz, 1-CH₃}\)), 3.52 (1H, br. s, 4-OH)³, 3.93 (1H, dq, \(J 6.3 \text{ and } 7.0 \text{ Hz, 3-H} \)), 4.56 (1H, d, \(J 7.0 \text{ Hz, 4-H} \)), 4.90 (1H, q, \(J 6.7 \text{ Hz, 1-H} \)), 6.55 (1H, d, \(J 7.9 \text{ Hz, 6-H} \)), 6.69 (1H, d, \(J 7.9 \text{ Hz, 8-H} \), 1H, d, \(J 7.9 \text{ Hz, 8-H} \)).
7.12 (1H, t, J 7.9 Hz, 7-H) and 7.98 (1H, br. s, 5-OH); δC 17.7 (3-CH3), 21.5 (1-CH3), 69.0 (C-3), 69.8 (C-4), 70.1 (C-1), 114.2 (C-8), 116.8 (C-6), 120.3 (C-7), 128.9 (C-8a), 140.6 (C-4a) and 155.8 (C-5); m/z 194 (M+, 20%), 193 (17), 178 (14), 177 (100), 176 (10), 159 (24), 150 (35) and 149 (11).

The crude diol (209) (40 mg, 0.21 mmol) was immediately dissolved in dry pyridine (2 cm³) and acetic anhydride (2 cm³) and stirred for 24 h at room temperature. The reaction mixture was quenched and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water and saturated sodium chloride solution. The residue obtained upon work-up was chromatographed (radial, 10-20% ethyl acetate-hexane) to afford the diacetate (240) as a colourless oil (42 mg, 74%) [α]D -88.8° (c 1.0 in CHCl₃); (Found: C, 65.05; H, 6.45; (M-CH₃CO₂H)+, 218.0951. C₁₅H₁₈O₅ requires C, 64.7; H, 6.5%; M-CH₃CO₂H, 218.0942); υmax(film)/cm⁻¹ 1770 and 1733 (C=O) and 1612 and 1587 (C=C); δH 1.25 (3H, d, J 6.9 Hz, 3-CH₃), 1.60 (3H, d, J 6.5 Hz, 1-CH₃), 2.09 (3H, s, 4-OCOCH₃), 2.27 (3H, s, 5-OCOCH₃), 4.25 (1H, dq, J 2.0 and 6.9 Hz, 3-H), 4.91 (1H, q, J 6.5 Hz, 1-H), 5.72 (1H, d, J 2.0 Hz, 4-H), 7.02 (1H, d, J 8.0 Hz, 8-H), 7.06 (1H, d, J 8.0 Hz, 6-H) and 7.37 (1H, t, J 8.0 Hz, 7-H); δC 17.6 (3-CH₃), 22.9 (4-OCOCH₃), 23.2 (8-OCOCH₃), 23.9 (1-CH₃), 67.7 (C-3), 67.8 (C-4), 72.9 (C-1), 122.9 (C-8), 124.1 (C-6), 124.3 (C-7), 131.6 (C-8a), 143.8 (C-4a), 152.1 (C-5), 171.5 (4-OCOCH₃) and 172.7 (5-OCOCH₃); m/z 278 (M⁺ 11%), 236 (13), 234 (96), 218 (100), 203 (65) and 192 (72).

(1S, 3S, 4R)-3,4-Dihydro-4-hydroxy-1,3-dimethyl-5-methoxybenzo[c]pyran (241)

A suspension of the diol (209) (900 mg, 4.64 mmol), potassium carbonate (320 mg, 2.32 mmol) and methyl iodide (330 mg, 2.32 mmol) in dry dimethylformamide (8 cm³) was stirred at room temperature for 12 h under nitrogen. The reaction was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The residue obtained upon work-up was then chromatographed (radial, 15%
ethyl acetate-petroleum ether) to give the methyl ether (241) (850 mg, 88%) as white prisms m.p. 78-80 °C (hexane) [α]D +9.6° (c 1.0 in CHCl3) (Found: C, 69.4; H, 7.6; (M-H)+, 207.1019. C12H16O3 requires C, 69.2; H, 7.75%; M-H, 207.1021); υmax/cm⁻¹ 3409 (OH), and 1588 and 1473 (C=C); δH 1.32 (3H, d, J 6.5 Hz, 3-CH₃), 1.56 (3H, d, J 6.7 Hz, 1-CH₃), 3.38 (1H, br. s, OH), 3.88 (3H, s, OCH₃), 4.09 (1H, dq, J 5.4 and 6.5 Hz, 3-H), 4.59 (1H, d, J 5.4 Hz, 4-H), 4.90 (1H, q, J 6.7 Hz, 1-H), 6.68 (1H, d, J 8.0 Hz, 6-H), 6.77 (1H, d, J 8.0 Hz, 8-H) and 7.22 (1H, t, J 8.0 Hz, 7-H); δC 17.5 (3-CH₃), 21.6 (1-CH₃), 66.9 (C-3), 68.7 (C-4), 69.9 (C-1), 108.3 (C-8), 117.4 (C-6), 123.4 (C-8a), 128.4 (C-7), 140.8 (C-4a) and 157.9 (C-5); m/z 207 [M⁺-H, 13%], 192 (15), 191 (100), 173 (25) and 164 (53).

(1S, 3S, 4S)-4-Acetoxy-3,4-dihydro-1,3-dimethyl-5-methoxybenzo[c]pyran (242)

Compound (241) (60 mg, 0.29 mmol) was dissolved in dry pyridine (2 cm³) and acetic anhydride (2 cm³) and stirred for 24 h at room temperature. The reaction mixture was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water and saturated sodium hydrogen carbonate solution to afford a yellow oil which was chromatographed (radial, 15% ethyl acetate-hexane) to afford the monoacetate (242) (55 mg, 76%) as pure white needles, m.p. 96-97 °C (hexane) [α]D -77.5° (c 1.0 in CHCl3); (Found: C, 67.35; H, 7.3; (M-H)+, 249.1149 C₁₄H₁₂O₄ requires C, 67.15; H, 7.25%; M-H, 249.1126); υmax/cm⁻¹ 1718 (C=O) and 1589 and 1474 (C=C); δH 1.25 (3H, d, J 6.9 Hz, 3-CH₃), 1.57 (3H, d, J 6.5 Hz, 1-CH₃), 2.09 (3H, s, OCOCH₃), 3.81 (3H, s, OCH₃), 4.31 (1H, dq, J 1.9 and 6.9 Hz, 3-H), 4.88 (1H, q, J 6.5 Hz, 1-H), 5.79 (1H, d, J 1.9 Hz, 4-H), 6.75 and 6.77 (each 1H, d, J 8.0 Hz, 6- and 8-H) and 7.31 (1H, t, J 8.0 Hz, 7-H); δC 15.6 (3-CH₃), 21.3 (1-CH₃), 21.9 (4-OCOCH₃), 55.6 (OCH₃), 65.7 (C-3), 66.4 (C-4), 70.9 (C-1), 108.3 (C-8), 116.5 (C-6), 117.7 (C-8a), 129.6 (C-7), 141.4 (C-4a), 158.3 (C-5) and 170.9 (4-OCOCH₃); m/z 191 [M⁺-CH₂CO₂⁺, 100%], 190 (20), 175 (11) and 173 (29).
Compound (241) (120 mg, 0.58 mmol) was dissolved in dry diethyl ether (7 cm³) and phosphorus pentachloride (240 mg, 1.15 mmol) was added. The mixture was stirred for 10 min at room temperature, then quenched with water (25 cm³). More diethyl ether (25 cm³) was added and the organic phase was washed exhaustively with deionised water. The residue obtained upon work-up was immediately redissolved in acetonitrile (9 cm³) and then deionised water (2 cm³) containing silver nitrate (540 mg, 3.18 mmol) was added. The mixture was stirred for 4 h at room temperature, during which time a white precipitate formed.

Water was added and the mixture was exhaustively extracted with diethyl ether to afford the crude pseudoaxial C-4 epimeric alcohol (244), which was chromatographed (radial, 15% ethyl acetate-hexane) to afford first, starting material (241) (46 mg, 38%) followed by its C-4 epimeric alcohol (244) (38 mg, 32%, or 51% based on consumed starting material) as white needles m.p. 93-94 °C (hexane) \([\alpha]_D^\text{o} +18.3 ° (c 1.0 \text{ in CHCl}_3); (\text{Found: C, 69.35; H, 7.65; (M-H)}^+, 207.1003. C_{12}H_{16}O_3 \text{ requires C, 69.2; H, 7.75%; M-H, 207.1021)}; \nu_{\text{max/cm}^{-1}} 3522 (\text{OH}) \text{ and } 1587 \text{ and } 1468 (\text{C} = \text{C}); \delta_{\text{H}} 1.39 (3\text{H, d, } J 6.5 \text{ Hz, 3-CH}_3), 1.48 (3\text{H, d, } J 6.8 \text{ Hz, 1-CH}_3), 2.20 (1\text{H, br. s, OH}), 3.89 (3\text{H, s, OCH}_3), 4.03 (1\text{H, dq, } J 1.9 \text{ and } 6.5 \text{ Hz, 3-H}), 4.57 (1\text{H, d, } J 1.9 \text{ Hz, 4-H}), 4.99 (1\text{H, q, } J 6.8 \text{ Hz, 1-H}), 6.63 (1\text{H, d, } J 8.0 \text{ Hz, 8-H}), 6.76 (1\text{H, d, } J 8.0 \text{ Hz, 6-H}) \text{ and } 7.24 (1\text{H, t, } J 8.0 \text{ Hz, 7-H}); \delta_{\text{C}} 16.8 (3\text{-CH}_3), 20.8 (1\text{-CH}_3), 55.6 (\text{OCH}_3), 62.8 (\text{C}-3), 66.8 (\text{C}-4), 71.1 (\text{C}-1), 108.2 (\text{C}-8), 117.6 (\text{C}-6), 124.3 (\text{C}-8a), 128.8 (\text{C}-7), 140.1 (\text{C}-4a) \text{ and } 157.5 (\text{C}-5); m/z 207 [M^-H, 18%], 192 (16), 191 (100), 173 (25), 164 (42), 163 (13), 149 (20), 117 (11), 111 (11), 109 (19), 105 (11), 97 (22), 95 (27), 93 (11), 85 (15), 83 (33), 81 (32), 79 (13) \text{ and } 69 (66).
The phenolic aldehyde (229) (350 mg, 1.79 mmol) was treated with titanium tetraisopropoxide, as described above for the phenolic aldehyde (208), to afford the potentially unstable benzo[c]pyran-4,5-diol (245) (270 mg, 77%) as an pale orange oil. (Found: (M-H)+, 193.0865. \( \text{C}_{11}\text{H}_{14}\text{O}_3 \) requires M-H, 193.0864); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3338 (OH) and 1614 and 1588 (C=C); \( \delta_H \) 1.40 (3H, d, \( J \) 6.1 Hz, 3-CH\(_3\)), 1.47 (3H, d, \( J \) 6.5 Hz, 1-CH\(_3\)), 3.46 (1H, d, \( J \) 6.7 Hz, 4-OH), 3.54 (1H, dq, J 6.1 and 9.0 Hz, 3-H), 4.62 (1H, dd, J 6.7 and 9.0 Hz, 4-H), 4.72 (1H, q, J 6.5 Hz, 1-H), 6.61 (1H, d, J 7.9 Hz, 8-H), 6.71 (1H, d, J 7.9 Hz, 6-H), 7.12 (1H, t, J 7.9 Hz, 7-H) and 8.12 (1H, br. s, 5-OH); \( \delta_C \) 19.9 (3-CH\(_3\)), 23.0 (1-CH\(_3\)), 72.7 (C-3), 74.7 (C-4), 76.5 (C-1), 116.2 (C-8), 117.5 (C-6), 122.8 (C-7), 130.6 (C-8a), 142.8 (C-4a) and 157.0 (C-5); m/z 194 (M\(^+\), 34%), 193 (24), 178 (16), 177 (100), 159 (25), 150 (59), 149 (17) and 91 (28).

A portion of the crude diol (245) (200 mg, 1.03 mmol) was immediately dissolved in dry dimethylformamide (8 cm\(^3\)). Potassium carbonate (710 mg, 5.15 mmol) and methyl iodide (710 mg, 5.15 mmol) were added and the resulting suspension was stirred at room temperature for 12 h under nitrogen. The reaction mixture was quenched with water and exhaustively extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 15% ethyl acetate-hexane) to afford the methyl ether (246) (147 mg, 68%) as a clear oil \( [\alpha]_D \) +132.6 ° (c 1.0 in CHCl\(_3\)); (Found: C, 68.7; H, 7.65; (M-H)+, 207.1010. \( \text{C}_{12}\text{H}_{16}\text{O}_3 \) requires C, 69.2; H, 7.75%; M-H, 207.1021); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3557 (OH) and 1584 and 1476 (C=C); \( \delta_H \) 1.48 (3H, d, J 6.1 Hz, 3-CH\(_3\)), 1.50 (3H, d, J 6.5 Hz, 1-CH\(_3\)), 3.65 (1H, dq, J 6.1 and 8.8 Hz, 3-H), 3.87 (3H, s, OCH\(_3\)), 3.98 (1H, d, J 1.5 Hz, OH), 4.66 (1H, dd, J 1.5 and 8.8 Hz, 4-H), 4.80 (1H, q, J 6.5 Hz, 1-H), 6.75 (1H, d, J 8.1 Hz, 8-H), 6.78 (1H, d, J 8.1 Hz, 6-H) and 7.22 (1H, t, J 8.1 Hz, 7-H); \( \delta_C \) 19.8 (3-CH\(_3\)), 21.4 (1-CH\(_3\)), 55.5 (OCH\(_3\)), 69.3 (C-3), 72.9 (C-4), 75.0 (C-1), 108.7 (C-8), 116.9 (C-6), 125.3 (C-8a), 115.7 (C-7), 148.2 (C-5) and 157.0 (C-5); m/z 194 (M\(^+\), 34%), 193 (24), 178 (16), 177 (100), 159 (25), 150 (59), 149 (17) and 91 (28).
128.3 (C-7), 141.8 (C-4a) and 157.5 (C-5); m/z 207 [M⁺-H, 28%], 192 (14), 191 (100),
173 (31), 164 (68), 163 (15), 161 (12), 97 (11), 95 (15), 83 (16), 81 (18) and 69 (22).

(1R, 3S, 4S)-3,4-Dihydro-4-hydroxy-1,3-dimethyl-5-methoxybenzo[c]pyran-4-ol
(248)

Compound (246) (100 mg, 0.48 mmol) was treated with phosphorus pentachloride (20 mg, 0.96 mmol) and silver nitrate (450 mg, 2.65 mmol) as described for compound (244). This afforded the crude pseudoaxial C-4 epimeric alcohol (248), which was chromatographed (radial, 15% ethyl acetate-hexane) to afford a light yellow oil (55 mg, 55%) [α]D +76.6° (c 1.0 in CHCl₃); (Found: (M-H)⁺, 207.1016.  C₁₂H₁₅O₃ requires M-H, 207.1021);

υmax(film)/cm⁻¹ 3502 (OH) and 1586 and 1462 (C=O); δH 1.42 (3H, d, J 6.5 Hz, 3-CH₃),
1.56 (3H, d, J 6.5 Hz, 1-CH₃), 2.04 (1H, br. s, OH), 3.74 (1H, dq, J 1.7 and 6.5 Hz, 3-H),
3.86 (3H, s, OCH₃), 4.59 (1H, d, J 1.7 Hz, 4-H), 4.78 (1H, q, J 6.5 Hz, 1-H), 6.75 (1H, d, J 8.0 Hz, 8-H), 6.79 (1H, d, J 8.0 Hz, 6-H) and 7.26 (1H, t, J 8.0 Hz, 7-H); δC 16.9 (3-CH₃), 21.8 (1-CH₃), 55.6 (OCH₃), 63.2 (C-3), 73.3 (C-4), 73.7 (C-1), 108.4 (C-8), 116.6 (C-6), 125.0 (C-8a), 129.0 (C-7), 140.7 (C-4a) and 157.5 (C-5); m/z 208 (M⁺, 13%) 207 (43), 192 (16), 191 (100), 173 (23), 164 (50) and 163 (13).

3'-t-Butyldimethylsilyloxyacetophenone (251)

-t-Butyldimethylsilyl chloride (16.6 g, 0.11 mol) and imidazole (7.5 g, 0.11 mol) were added to a solution of 3'-hydroxyacetophenone (211) (10 g, 73.5 mmol) in dry dimethylformamide (150 cm³). The mixture was stirred under argon for 12 h at room temperature, after which water was added and the mixture exhaustively extracted with ethyl acetate and the residue obtained upon work-up was chromatographed (10% ethyl acetate-hexane) to afford (251) (17 g, 93%) as a colourless oil (Found: C, 67.2; H, 8.75; M⁺, 250.1379.  C₁₄H₂₂O₂Si requires C, 67.15;
H, 8.85%; M, 250.1389); υmax(film)/cm⁻¹ 1688 (C=O) and 1582 and 1484 (C=O); δH 0.23 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.00 (9H, s, OSi(CH₃)₂C(CH₃)₃), 2.57 (3H, s, COCH₃),

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7.04 (1H, ddd, J 7.8, 2.0 and 1.0 Hz, 4'-H), 7.32 (1H, t, J 7.8 Hz, 5'-H), 7.42 (1H, t, J 2.0 Hz, 2'-H) and 7.54 (1H, ddd, J 7.8, 2.0 and 1.0 Hz, 6'-H); \( \delta_C -4.4 \) (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 18.2 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 25.7 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 26.7 (COCH\(_3\)), 119.5 (C-4'), 121.6 (C-5'), 124.9 (C-2'), 129.5 (C-6'), 138.6 (C-1'), 156.0 (C-3') and 197.8 (COCH\(_3\)); m/z 250 (M', 13%), 194 (21), 193 (100), 165 (12), 151 (19), 121 (12), 105 (11), 86 (11) and 84 (17).

**1-(3'-t-Butyldimethylsilyloxyphenyl)ethanol (252)**

To a stirred slurry of lithium aluminium hydride (610 mg, 16.1 mmol) in dry diethyl ether (60 cm\(^3\)) was added dropwise a solution of compound (251) (2g, 8 mmol) in dry diethyl ether (10 cm\(^3\)) under argon. The mixture was stirred for 1 h, after which saturated ammonium chloride solution was added drop-wise, followed by MgSO\(_4\). Filtration through filter aid and concentration of the filtrate gave a light yellow oil. Chromatography (radial, 10-30% ethyl acetate-hexane) yielded the alcohol (252) as a colourless oil (1.85 g, 93%) (Found: C, 66.6; H, 9.4; M', 252.1543. C\(_{14}\)H\(_{24}\)O\(_2\)Si requires C, 66.65; H 9.6%; M, 252.1545); \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 3350 (OH) and 1603 and 1587 (C=C); \( \delta_H \) 0.21 (6H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.99 (9H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 1.43 (3H, d, J 6.4Hz, 1-CH\(_3\)), 2.33 (1H, br. s, OH), 4.78 (1H, q, J 6.4 Hz, 1-H), 6.73 (1H, dd, J 2.0 and 7.8 Hz, 6'-H), 6.85 (1H, t, J 2.0 Hz, 2'-H), 6.92 (1H, br. dd, J 2.0 and 7.8 Hz, 4'-H) and 7.18 (1H, t, J 7.8 Hz, 5'-H); \( \delta_C -4.4 \) (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 18.2 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 25.1 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 25.7 (C-2), 70.1 (C-1), 117.1 (C-6'), 118.3 (C-2'), 118.9 (C-4') 129.4 (C-5'), 147.6 (C-1') and 155.7 (C-3'); m/z 252 (M', 20%), 195 (21), 177 (100), 149 (23), 123 (12), 109 (14), 91 (10), 75 (30) and 67 (14).
3′-t-Butyldimethylsilyloxy-α′-methylbenzyl-2,2,2-trichloroethanimidate (253)

The alcohol (252) (1 g, 3.96 mmol) in dry diethyl ether (10 cm³) was added drop-wise to a stirred suspension of sodium hydride (60% dispersion in oil) (64 mg, 2.67 mmol) in dry diethyl ether (7 cm³). The mixture was stirred for 10 min under argon at -10 °C. Trichloroacetonitrile (1.12 g, 7.93 mmol) was added drop-wise over 10 min and the reaction mixture stirred for a further 30 min at that temperature, after which it was allowed to reach room temperature. The solution was concentrated and chromatographed (radial, 5% ethyl acetate-hexane) to yield the imidate (253) (1.41 g, 90%) as a colourless oil (Found: M⁺, 395.0644. C₁₆H₂₄Cl₃NO₂Si requires M⁺(35Cl₃), 395.0641); νmax(film)/cm⁻¹ 3347 (NH), 1664 (C=N) and 1606 and 1486 (C=C); δH 0.20 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.99 (9H, s, OSi(CH₃)₂C(CH₃)₃), 1.64 (3H, d, J 6.5 Hz, α'-CH₃), 5.95 (1H, q, J 6.5 Hz, α'-H), 6.78 (1H, dd, J 2.0 and 7.8 Hz, 6'-H), 6.93 (1H, t, J 2.0 Hz, 2'-H), 7.00 (1H, br. dd, J 2.0 and 7.8 Hz, 4'-H), 7.22 (1H, t, J 7.8 Hz, 5'-H) and 8.32 (1H, s, NH); δC -4.0 (OSi(CH₃)₂C(CH₃)₃), 18.6 (OSi(CH₃)₂C(CH₃)₃), 22.5 (OSi(CH₃)₂C(CH₃)₃), 26.1 (α'-CH₃), 77.3 (C-α'), 92.1 (CCl₃), 117.8(C-6'), 119.1 (C-2'), 119.9 (C-4'), 129.8 (C-5'), 143.3 (C-1'), 156.2 (C-3') and 162.0 (C-1); m/z 338 [M⁺-(CH₃)₃C⁺, 25%], 235 (23), 234 (41), 178 (50), 177 (100), 151 (22) and 149 (12).

Ethyl (α'R or S, 2S)-2-(3′-t-butyldimethylsilyloxy)propanoate (254) and (255)

Boron trifluoride diethyl etherate (37.7 mg, 0.27 mmol) was added drop-wise to a solution of imidate (253) (500 mg, 1.26 mmol) and ethyl (S)-lactate (300 mg, 2.54 mmol) in dry hexane:dry dichloromethane (20 cm³, 2:1). The reaction was stirred under nitrogen for 40 min. Solid sodium hydrogen carbonate was added to the reaction mixture and the resulting suspension was filtered through filter aid. The clear solution was then concentrated and chromatographed (radial, 10-30% ethyl acetate-hexane) to yield (254) and (255) as an oily, inseparable mixture of diasteriomers (390 mg, 88%) in a ratio of 65:35 respectively (Found: C, 64.7; H, 8.65; M⁺, 352.2065. C₁₉H₃₂O₃Si requires C, 64.75; H, 9.15%; M, 352.2069); νmax(film)/cm⁻¹ 1750 (C=O) and 1603 and 1484 (C=C); δH (major
diastereomer) 0.20 (6H, s, OSi(CH3)2C(CH3)3), 0.99 (9H, s, OSi(CH3)2C(CH3)3), 1.28 (3H, t, J 7.1 Hz, CH3CH2), 1.35 (3H, d, J 6.9 Hz, 2-CH3), 1.46 (3H, d, J 6.4 Hz, α ’-CH3), 3.83 (1H, q, J 6.9 Hz, 2-H), 4.20 and 4.22 (each 1H, dq, J 7.1 and 10.8 Hz, CH3CH2), 4.46 (1H, q, J 6.4 Hz, α ’-H), 6.76 (1H, dt, J 2.0 and 7.8 Hz, 4 ’-H), 6.80 (1H, t, J 2.0 Hz, 2 ’-H), 6.86 (1H, br. dd, J 2.0 and 7.8 Hz, 6’-H) and 7.19 (1H, t, J 7.8 Hz, 5 ’-H); δH (minor diastereomer) 0.20 (6H, s, OSi(CH3)2C(CH3)3), 0.99 (9H, s, OSi(CH3)2C(CH3)3), 1.19 (3H, t, J 7.1 Hz, CH3CH2), 1.40 (3H, d, J 6.7 Hz, 2-CH3), 1.46 (3H, d, J 6.4 Hz, α ’-CH3), 4.02 (1H, q, J 6.7 Hz, 2-H), 4.05 (2H, q, J 7.1 Hz, CH3CH2), 4.51 (1H, q, J 6.4 Hz, α ’-H), 6.73 (1H, d, J 7.8 Hz, 4’-H), 6.80 (1H, t, J 2.0 Hz, 2 ’-H), 6.94 (1H, br. dd, J 2.0 and 7.8 Hz, 6’-H) and 7.17 (1H, t, J 7.8 Hz, 5 ’-H); δC (mixture of two diasteriomers) -4.1 (OSi(CH3)2C(CH3)3), 14.5 and 14.6 (CH3CH2), 18.6 and 18.6 (C-3), 19.4 (OSi(CH3)2C(CH3)3), 23.7 and 24.8 (α ’-CH3), 26.1 (OSi(CH3)2C(CH3)3), 61.0 and 61.1 (CH3CH2), 72.3 and 73.0 (C-α’), 77.1 and 77.5 (C-2), 118.1 and 118.5 (C-4’), 119.6 and 119.8 (C-2’), 119.8 and 119.9 (C-6’), 129.6 and 129.8 (C-5’), 145.0 and 145.2 (C-1’), 156.1 and 156.3 (C-3’) and 173.4 and 174.1 (C-1); m/z 352 (M’, 20%), 295 (13), 252 (15), 251 (70), 250 (20), 249 (97), 235 (100), 177 (92) and 151 (22).

(α’S, 2S)- and (α’R, 2S)-2-(3’-t-Butyldimethylsilyloxy-α ’-methylbenzyl oxy)propan-1-ol (256) and (257)

The mixture of diasteriomer esters (254) and (255) (1 g, 2.84 mmol) was reduced with lithium aluminium hydride (220 mg, 5.79 mmol) as described for the reduction of 3’-t-butyldimethylsilyloxyacetophenone (252). The resulting pale yellow oil was subjected to chromatography (radial, 5-15% ethyl acetate-hexane) to achieve separation of the two alcohols (256) and (257) as colourless oils.

The compound of lower Rf was identified as (256) (411 mg, 47%); [α]D -40° (c 1.0 in CHCl3); (Found: C, 66.1; H, 9.55; M+, 310.1964. C17H30O3Si requires C, 65.75; H, 9.75%; M, 310.1964); νmax (film)/cm⁻¹ 3431 (OH) and 1603 and 1483 (C=C); δH 0.20 (6H, s, OSi(CH3)2C(CH3)3), 0.99 (9H, s, OSi(CH3)2C(CH3)3), 1.01 (3H, d, J 6.3 Hz, 2-CH3), 1.43 (3H, d, J 6.5 Hz, α ’-CH3), 2.06 (1H, br. s, OH), 3.45 (1H, dd, J 5.7 and 10.9 Hz, 1-
Hα), 3.57 (1H, ddq, J 3.4, 5.7 and 6.3 Hz, 2-H), 3.65 (1H, dd, J 3.4 and 10.9 Hz, 1-Hβ), 4.53 (1H, q, J 6.5 Hz, α′-H), 6.75 (1H, dd, J 2.0 and 7.8 Hz, 6′-H), 6.84 (1H, t, J 2.0 Hz, 2′-H), 6.91 (1H, d, J 7.8 Hz, 4′-H) and 7.19 (1H, t, J 7.8 Hz, 5′-H); δc -4.4 (OSi(CH3)2C(CH3)3), 17.4 (OSi(CH3)2C(CH3)3), 18.2 (OSi(CH3)2C(CH3)3), 24.1 (C-3), 25.7 (α′-CH3), 65.7 (C-1), 74.0 (C-2), 76.3 (C-α′), 117.8 (C-6′), 119.1 (C-2′), 119.2 (C-4′), 129.3 (C-5′), 145.1 (C-1′) and 155.8 (C-3′); m/z 310 (M+, 7%), 249 (12), 237 (11), 236 (34), 235 (63), 179 (22), 178 (31), 177 (100), 151 (15), 133 (25) and 121 (12).

The compound of higher Rf was identified as (257) (355 mg, 40%); [α]D +79.4° (c 1.0 in CHCl3); (Found: C, 65.7; H, 9.55; M+, 310.1975. C17H30O3Si requires C, 65.75; H, 9.75%; M, 310.1964); υmax(film)/cm−1 3451 (OH) and 1595 and 1479 (C=C);

δH 0.20 (6H, s, OSi(CH3)2C(CH3)3), 0.99 (9H, s, OSi(CH3)2C(CH3)3), 1.13 (3H, d, J 5.8 Hz, 2-CH3), 1.43 (3H, d, J 6.5 Hz, α′-CH3), 1.97 (1H, br. s, OH), 3.38-3.53 (3H, m, CH2OH and 2-H), 4.51 (1H, q, J 6.5 Hz, α′-H), 6.75 (1H, dd, J 2.0 and 7.8 Hz, 6′-H), 6.80 (1H, t, J 2.0 Hz, 2′-H), 6.91 (1H, br. dd, J 2.0 and 7.8 Hz, 4′-H) and 7.20 (1H, t, J 7.8 Hz, 5′-H); δc -4.4 (OSi(CH3)2C(CH3)3), 15.6 (OSi(CH3)2C(CH3)3), 18.2 (OSi(CH3)2C(CH3)3), 24.5 (C-3), 25.7 (α′-CH3), 66.8 (C-1), 72.7 (C-2), 74.9 (C-α′), 117.9 (C-6′), 119.3 (C-2′), 119.3 (C-4′), 128.9 (C-5′), 145.4 (C-1′) and 155.9 (C-3′); m/z 310 (M+, 9%), 236 (29), 235 (100), 177 (14) and 133 (19).

(α′S, 2S)-2-(3′-t-Butyldimethylsilyloxy-α′-methylbenzyloxy)propanal (250)

To a solution of oxalyl chloride (310 mg, 2.44 mmol) in dry dichloromethane (4 cm3) at -70 °C under an atmosphere of argon was added drop-wise a solution of dimethyl sulfoxide (380 mg, 4.86 mmol) in dry dichloromethane (4 cm3) while keeping the temperature below -65 °C. After stirring for 20 min, a solution of the alcohol (256) (150 mg, 0.48 mmol) in dry dichloromethane (4 cm3) was added drop-wise (keeping the temperature below -65 °C) and the stirring continued for a further 15 min. Dry triethylamine (590 mg, 5.83 mmol) was added slowly and the reaction stirred for a further 10 min at -70 °C before being allowed to reach room temperature over 1h. The reaction mixture was
quenched with water and exhaustively extracted with dichloromethane and the residue obtained upon work-up was chromatographed (radial, 10-20% ethyl acetate-hexane) to give the aldehyde (250) (130 mg, 87%) as a colourless oil $[\alpha]_D^{20} -108.8^\circ$ (c 1.0 in CHCl$_3$); (Found: C, 65.9; H, 9.0; M$^+$, 308.1794. C$_{17}$H$_{28}$O$_3$Si requires C, 66.2; H, 9.1%; M, 308.1807); $\nu_{\text{max}}$(film)/cm$^{-1}$ 1737 (C=O) and 1603 and 1484 (C=C); $\delta$H 0.20 (6H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 0.99 (9H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 1.22 (3H, d, $J$ 7.0 Hz, 2-CH$_3$), 1.49 (3H, d, $J$ 6.4 Hz, $\alpha'$-CH$_3$), 3.71 (1H, dq, $J$ 1.9 and 7.0 Hz, 2- H), 4.49 (1H, q, $J$ 6.4 Hz, $\alpha'$-H), 6.76 (1H, dd, $J$ 2.0 and 7.8 Hz, 6'-H), 6.80 (1H, t, $J$ 2.0 Hz, 2'-H), 6.86 (1H, br. dd, $J$ 2.0 and 7.8 Hz, 4'-H), 7.20 (1H, t, $J$ 7.8 Hz, 5'-H) and 9.68 (1H, d, $J$ 1.9 Hz, CHO); $\delta$C -4.3 (OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 16.0 (9H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 18.3 (OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 24.4 (C-3), 25.8 ($\alpha'$-CH$_3$), 77.6 (C-2), 77.7 (C-$\alpha'$) 117.9 (C-6), 119.5 (C-2), 119.7 (C-4), 129.7 (C-5'), 144.6 (C-1'), 156.1 (C-3') and 204.0 (C-1); m/z 308 (M$^+$, 2%), 252 (11), 236 (34), 235 (100), 207 (63), 195 (11), 177 (73), 163 (13), 151 (22), 137 (8), 121 (13), 97 (11) and 85 (15).

$\alpha'$R, 2S)-2-(3'-t-Butyldimethylsilyloxy-$\alpha'$-methylbenzyl oxy)propanal (262)

According to the method described above for the preparation of the aldehyde (250) from the alcohol (256), the alcohol (257) (150 mg, 0.48 mmol) was converted to the aldehyde (262) as a crude pale yellow oil which was chromatographed (radial, 10-20% ethyl acetate-hexane) to give a colourless oil (130 mg, 87%) $[\alpha]_D^{20} +123.2^\circ$ (c 1.0 in CHCl$_3$); (Found: M$^+$, 308.1792. C$_{17}$H$_{28}$O$_3$Si requires M, 308.1807); $\nu_{\text{max}}$(film)/cm$^{-1}$ 1735 (C=O) and 1601 and 1486 (C=C); $\delta$H 0.2 (6H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 0.99 (9H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 1.27 (3H, d, $J$ 6.8 Hz, 2-CH$_3$), 1.49 (3H, d, $J$ 6.4 Hz, $\alpha'$-CH$_3$), 3.75 (1H, dq, $J$ 1.5 and 6.8 Hz, 2-H), 4.53 (1H, q, $J$ 6.4 Hz, $\alpha'$-H), 6.77 (1H, dd, $J$ 2.0 and 7.8 Hz, 6'-H), 6.84 (1H, t, $J$ 2.0 Hz, 2'-H), 6.92 (1H, d, $J$ 7.8 Hz, 4'-H), 7.20 (1H, t, $J$ 7.8 Hz, 5'-H) and 9.49 (1H, d, $J$ 1.5 Hz, CHO); $\delta$C -4.4 (OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 15.1 (9H, s, OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 18.2 (OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 23.8 (C-3), 25.7 ($\alpha'$-CH$_3$), 77.0 (C-2'), 78.0 (C-$\alpha'$) 118.2 (C-6'), 119.7 (C-2'), 119.8 (C-4'), 129.6 (C-5'), 144.3 (C-1'), 156.0 (C-3') and 203.2 (C-1); m/z
308 (M⁺, 2%), 251 (8), 235 (37), 235 (100), 233 (14), 208 (17), 207 (97), 179 (21), 178 (20), 177 (12), 163 (12), 151 (17), 149 (11), 86 (10) and 84 (18).

(1S, 3S, 4R)- and (1S, 3S, 4S)-4,7-Diacetoxy-3,4-dihydro-1,3-dimethyl-benzo[\textit{c}]pyran (264) and (265)

The aldehyde (250) (300 mg, 0.97 mmol) was dissolved in tetrahydrofuran (25 cm³), and a mixture of saturated aqueous solutions of ammonium chloride and sodium fluoride (40 cm³, 1:1) was added. The solution was then stirred for 16 h at room temperature, whereupon it was exhaustively extracted with diethyl ether, dried (MgSO₄) and concentrated to afford a mixture of two crude C-4 epimeric benzo[\textit{c}]pyran-4,7-diols (210) and (266) (91 mg, 50%). This mixture of diols was immediately dissolved in dry pyridine (2 cm³) and acetic anhydride (2 cm³) and stirred for 24 h at room temperature. The reaction mixture was quenched with water and exhaustively extracted with ethyl acetate. The combined organic extracts were washed with dilute hydrochloric acid (5 M), water and saturated sodium hydrogen carbonate solution and the residue obtained upon work-up was chromatographed (radial, 10-30% ethyl acetate-hexane) to give the diastereomeric diacetates (264) and (265) as an inseparable oily mixture [128 mg, 47% overall yield from aldehyde (250)] (Found: C, 65.05; H, 6.45; (M-H)+, 277.1094. C_{15}H_{18}O_{5} requires C, 64.75; H, 6.5%; M-H, 277.1075); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1733 (C=O) and 1615 and 1500 (C=C); \(\delta_{H}\) (mixture of diastereomers) 1.25 (3H, d, J 6.7 Hz, 3-CH₃), 1.27 (3H, d, J 6.4 Hz, 3-CH₃), 1.50 (3H, d, J 6.8 Hz, 1-CH₃), 1.56 (3H, d, J 6.6 Hz, 1-CH₃), 2.10 (3H, s, 4-OCOCH₃), 2.12 (3H, s, 4-OCOCH₃), 2.28 (3H, s, 7-OCOCH₃), 2.29 (3H, s, 7-OCOCH₃), 4.18 (1H, dq, J 4.0 and 6.4 Hz, 3-H), 4.19 (1H, dq, J 2.0 and 6.7 Hz, 3-H), 4.93 (1H, q, J 6.6 Hz, 1-H), 5.11 (1H, q, J 6.8 Hz, 1-H), 5.63 (1H, d, J 4.0 Hz, 4-H), 5.78 (1H, d, J 2.0 Hz, 4-H), 6.81 (1H, d, J 2.3 Hz, 8-H), 6.84 (1H, d, J 2.2 Hz, 8-H), 6.96 (1H, dd, J 2.3 and 8.5 Hz, 6-H) 6.98 (1H, dd, J 2.2 and 8.4 Hz, 6-H), 7.30 (1H, d, J 8.5 Hz, 5-H) and 7.40 (1H, d, J 8.4 Hz, 5-
δC (mixture of diastereomers) 16.65 and 16.73 (3-CH₃), 20.1 and 21.2 (4-OCOCH₃), 21.3 (1-CH₃ for each isomer), 21.5 and 21.8 (7-OCOCH₃), 65.6 and 67.8 (C-3), 68.2 and 69.3 (C-4), 70.8 and 70.9 (C-1), 117.8 and 118.3 (C-8), 120.6 (C-6), 128.4 and 129.2 (C-5), 130.7 and 131.5 (C-8a), 141.4 and 141.4 (C-4a), 150.7 and 150.8 (C-7), 169.4 and 169.5 (4-OCOCH₃) and 171.1 and 171.2 (7-OCOCH₃). m/z 234 [M⁺-CH₃CHO, 24%], 218 (38), 203 (11), 192, (57), 177 (12), 176 (44), 162 (13), 161 (100), 105 (14) and 91 (19).

(1R, 3S, 4R) - and (1R, 3S, 4S)-4,7-Diacetoxy-3,4-dihydro-1,3-dimethylisochromane (269) and (270)

According to the method described above, the aldehyde (262) (290 mg, 0.94 mmol) was deprotected and cyclised to afford a mixture of two crude C-4 epimeric benzo[c]pyran-4,7-diols (1R, 3S, 4R)- and (1R, 3S, 4S)-3,4-dihydro-4,7-dihydroxy-1,3-dimethyl[c]pyran-4,7-diols (267) and (268) (91 mg, 50%). These were immediately acetylated as above to afford the crude diastereomeric diacetates (269) and (270) as a yellow oil, which was carefully chromatographed (radial, 10-30% ethyl acetate-hexane) to give fractions.

The product of higher Rf was (269) (63 mg, 24%), m.p. 50-51 °C (hexane) [α]D -8.3 ° (c 1.0 in CHCl₃); (Found: C, 65.2; H, 6.6; M⁺, 278.1155. C₁₅H₁₈O₅ requires C, 64.75; H, 6.5%; M, 278.1154); υ max(film)cm⁻¹ 1741 (C=O) and 1614 and 1498 (C=C); δH 1.32 (3H, d, J 6.2 Hz, 3-CH₃), 1.52 (3H, d, J 6.5 Hz, 1-CH₃), 2.18 (3H, s, 4-OCOCH₃), 2.30 (3H, s, 7-OCOCH₃), 3.74 (1H, dq, J 6.2 and 9.0 Hz, 3-H), 4.88 (1H, q, J 6.5 Hz, 1-H), 5.85 (1H, d, J 9.0 Hz, 4-H), 6.83 (1H, d, J 2.2 Hz, 8-H), 6.96 (1H, dd, J 2.2 and 8.5 Hz, 6-H) and 7.16 (1H, d, J 8.5 Hz, 5-H); δC: 17.8 (3-CH₃), 20.4 (4-OCOCH₃), 20.4 (7-OCOCH₃), 20.8 (1-CH₃), 70.8 (C-3), 72.2 (C-1), 72.4 (C-4), 116.4 (C-8), 119.5 (C-6), 126.9 (C-5), 130.5 (C-8a), 140.9 (C-4a), 149.2 (C-7), 168.7 (4-OCOCH₃) and 170.3 (7-OCOCH₃); m/z 234 (M⁺-CH₃CHO, 62%), 218 (35), 193 (15), 192 (100), 176 (44), 161 (74), 151 (11.4), 150 (92), 149 (36) and 133 (16).
The compound of lower Rf was identified as \((270)\) (70 mg, 27%), obtained as white needles, m.p. 70-72 °C (hexane) \([\alpha]_D +226.86\) \(^o\)
(c 1.0 in CHCl\(_3\)); (Found: C, 64.85; H, 6.4; (M-H)\(^+\), 277.1097. C\(_{15}H_{18}O_5\) requires C, 64.75; H, 6.5%; M-H, 277.1075); \(\nu_{\max}/cm^{-1}\)
1734 (C=O) and 1612 and 1498 (C=C); \(\delta_H\) 1.32 (3H, d, \(J\) 6.5 Hz, 3-CH\(_3\)), 1.58 (3H, d, \(J\) 6.5 Hz, 1-CH\(_3\)), 2.11 (3H, s, 4-OCOCH\(_3\)), 2.30 (3H, s, 7-OCOCH\(_3\)), 3.90 (1H, dq, \(J\) 1.9 and 6.5 Hz, 3-H), 4.81 (1H, q, \(J\) 6.5 Hz, 1-H), 5.80 (1H, d, \(J\) 1.9 Hz, 4-H), 6.90 (1H, d, \(J\) 2.2 Hz, 8-H), 7.00 (1H, dd, \(J\) 2.2 and 8.2 Hz, 6-H) and 7.42 (1H, d, \(J\) 8.2 Hz, 5-H); \(\delta_C\)
16.2 (3-CH\(_3\)), 20.4 (4-OCOCH\(_3\)), 20.5 (7-OCOCH\(_3\)), 20.6 (1-CH\(_3\)), 67.6 (C-3), 71.5 (C-1), 72.4 (C-4), 116.7 (C-8), 119.8 (C-6), 129.1 (C-8a), 131.0 (C-5), 140.1 (C-4a), 150.2 (C-7), 168.7 (4-OCOCH\(_3\)) and 170.5 (7-OCOCH\(_3\)); \(m/z\) 277 [M\(^+-\)H, 11%], 234 (17), 219 (100), 192 (11) and 159 (11).
3.0 Introduction

Previous model studies directed towards achieving the syntheses of quinone A (16) and quinone A’ (17) involving the metal induced intramolecular ring closure of an (S)-lactate-derived asymmetric meta phenolic aldehyde were undertaken with great success, as was described in Section 1.5. This having been accomplished,\textsuperscript{128c} the correct absolute stereochemistry would be achieved through commencing with the more expensive (R)-lactate. Furthermore, bromine was included to direct the regioselectivity of the reaction of the appropriate diene with the target quinone (199) in the final Diels-Alder reaction. Problems were encountered, however, in the oxidation of the precursor benzopyran-4,5-diol (197) since the required oxidative demethylation did not provide the target quinone (199) under a variety of conditions, whereas it proceeded smoothly, in a yield of 91%, for the non-brominated model (183). Since, aside from chirality, the only difference between the model (183) and the substrate (197) was the presence of the bromine atom in the latter, it was assumed that this reaction did not proceed owing to steric crowding around the C-8 methoxy group, this being between the C-7 bromine and the C-1 methyl group.

\begin{center}
\textbf{Scheme 52}
\end{center}
This chapter describes research directed towards the syntheses of the desired quinones (16) and (17) using an appropriate trialkoxynaphthol, which it was intended to convert (Scheme 53) using its ether (273) into the tethered lactaldehyde (274). This would avoid the regioselective synthesis of halogenated quinones of the type described above.

![Scheme 53](image)

The synthesis of a model naphthalenic compound using the cheaper (S)-lactate would, however, be attempted first, using the more stable methoxy rather than benzyloxy protection to establish our reaction conditions.

### 3.1 The Trimethoxynaphthol Sequence.

There have been a number of different methods used for the synthesis of naphthalenic precursors to dihydronaphthopyranquinones. In 1991 Giles and Sargent\(^{151}\) studied the regioselective Diels-Alder reaction between methoxybenzynes and methoxyfurans. They found that 2-methoxyfuran (277) adds regioselectively to 3,5-dimethoxybenzyne...
(276), derived from the bromotosylate (275) (Scheme 54). This method conveniently provided a short regioselective route to the trimethoxynaphthol (278),\textsuperscript{151b} which was immediately converted into its more stable acetate (279).

Scheme 54

It was planned to convert this acetate (279) into the target intermediate (282) \textit{via} a Fries rearrangement to the phenol (280) using the sequence shown in Scheme 55.
Giles et al.\textsuperscript{152,153} discovered an unexpected meta Fries rearrangement for the acetates (283) and (285), in which the acetyl groups migrated to the more electron rich carbon in the aromatic ring. The products in each case were isolated as their monoacetates (284) and (286) respectively, and the yields are based on consumed starting material (Scheme 56).
The first step proposed in Scheme 55 involves the related rearrangement of (279), the methyl ether of (283). It was recognised that the change from the phenolic substituent in (283) to its methyl ether in (279) might reduce the electron availability at C-3 in the transition state for the conversion of (279) into acetylnaphthol (280), but it was hoped that this would not be critical to the success of the reaction since the Fries rearrangement of (285) to (286) had also been achieved, in which there was only one methoxy group in the alternative ring to activate C-3.†

When the reaction of naphthyl acetate (279) with boron trifluoride was examined, the only product that was isolated was the deacetylated naphthol (278).

This might have arisen either because of the C-4 methoxy group as discussed above, or because the correct conditions had not been established.

† For consistency, the numbering of all naphthalenes will be that shown in structure (286).
This particular line of investigation was discontinued since two other routes were being considered simultaneously, one of which achieved the desired objective, viz. the synthesis of the methoxy analogue (282) of the required naphthalenic alcohol (273).

The second route as a model for the generation of the target alcohol (273) was through reaction of the appropriate aryl lithium with acetaldehyde. Thus, a preliminary target was the 3- bromonaphthalene (287).

\[
\text{(287)}
\]

Giles et al.\textsuperscript{154} have shown (Scheme 57) that the not entirely unrelated 3-bromonaphthalene (290) is available through dibromination of the Stobbe-derived naphthalene (288) to afford the 3,8-dibrominated derivative (289), a process which was shown to involve preliminary bromination at the \( \alpha \)-site, C-8, of the ring more activated to electrophilic substitution. This was followed by the second bromination in the alternative ring at the site, C-3, activated to further bromonium ion attack by all three alkoxy groups.

\[
\begin{align*}
\text{(288)} & \quad \text{2Br}_2 \quad \text{pyridine} \\
\text{(289)} &
\end{align*}
\]

Scheme 57 (contd. over)
The analogous process was therefore examined for the assembly of the alternative substrate (287).

It was envisaged that by brominating the 1-acetoxy-4,5,7-trimethoxy naphthalene (279) at the C-3 position and subsequently treating the resulting bromonaphthalene (287) with butyl lithium and acetaldehyde in tetrahydrofuran, the phenol (292) could be formed. It was, however, anticipated that bromination would occur first at C-8, which was expected to be the more electrophilic site and that it would therefore be necessary to dibrominate compound (279) to give the dibromonaphthalene (291), with bromine substituents at C-3 and C-8, and then remove the C-8 bromine to give the monobrominated naphthalene (287) (Scheme 58).\textsuperscript{154}

Scheme 57 (contd.)

Scheme 58 (contd. over)
Initially only one molar equivalent of bromine was added to the starting material (279) and indeed this afforded the C-8 bromo naphthalene (293) in a 70% yield. The structure of the product was confirmed by studying the aromatic protons in the $^1$H NMR spectrum. This showed a large coupling constant of 8.6 Hz between the ortho coupled protons 3-H ($\delta 6.72$) and 2-H ($\delta 7.07$) protons. The 6-H proton appeared as a singlet at $\delta 6.66$. Thus, bromine had replaced one of the meta coupled protons, and it was reasonably assumed that $\alpha$-substitution had occurred to yield the C-8 bromo derivative (293).

Subsequently, two molar equivalents of bromine were added to naphthalene (279) to form the dibrominated naphthalene (291), with the bromines adding to the desired C-8 and C-3 positions. The $^1$H NMR spectrum showed only two singlets in the aromatic region due to 6-H and 2-H at $\delta 6.69$ and $\delta 7.33$ respectively. Thus the desired dibromination had indeed occurred.

Yields for these bromination reactions varied greatly with complete decomposition sometimes occurring. At first it was thought that the reaction was extremely acid sensitive and a large excess of pyridine was added as acid scavenger to remove any hydrogen bromide forming. These precautions increased the yield only slightly. The
rate of addition of bromine to the reaction mixture was also examined. None of these seemed to increase the yields significantly. The problem, however, was found to be in the dilution factor of the starting material in dichloromethane. The highest yield of dibrominated compound (291) obtained was 92% if the reaction was undertaken in relatively high dilution.

The next challenge involved the debromination of the C-8 bromine of dibromo naphthalene (291). 3,8-Dibromonaphthalene (291) in dichloromethane was treated with trifluoroacetic acid and phenol, the latter added to capture the liberated bromonium ion. The reaction mixture was then stirred at room temperature for two hours to afford the monodebrominated naphthalene (287) in 84% yield. The product, however, contained traces of the brominated phenol and even repeated chromatography could not entirely purify it.

The reaction was repeated using 3,5-dimethoxyphenol (294) as bromine scavenger instead, but the desired product (287) and brominated phenol were difficult to separate.

\[
\text{OMe} \\
\text{MeO} \\
\text{OH}
\]

(294)

Tribenzyloxybenzene (296), obtained from the benzylation of phloroglucinol (295), was used and found it to be the best bromine scavenger, with chromatography yielding a pure product (287), albeit in a moderate yield of 65%.

\[
\text{OH} \\
\text{HO} \\
\text{OH}
\]

(295)

\[
\text{OBn} \\
\text{BnO} \\
\text{OBn}
\]

(296)
The $^1$H NMR spectrum of product (287) showed a coupling constant of 2.3 Hz between the meta coupled aromatic protons 6-H ($\delta$ 6.56) and 8-H ($\delta$ 6.64), with the proton 2-H appearing as a singlet at $\delta$ 7.38.

Having successfully made 1-acetoxy-3-bromo-4,5,7-trimethoxynaphthalene (287), attention was now focused on the synthesis of the alcohol (292). Reaction of the naphthalene (287) to afford the target (292), as proposed in Scheme 58, would require two equivalents of butyl lithium as this would be expected to react with both the acetate and also, as desired, with bromine in a lithium-halogen exchange reaction. Therefore butyl lithium (2 molar equivalents) was added to a solution of bromonaphthalene (287) in tetrahydrofuran at -78°C, followed by acetaldehyde. Work-up of the reaction mixture only afforded a complicated mixture of products, possibly because of the additional reactivity of the acetate group to butyl lithium.

In view of this, it was decided to protect the brominated naphthol as the $t$-butyldimethylsilyl ether (298), as this would be expected to provide protection to all four of the naphthalenic oxygens that would be stable to the reaction conditions. This was undertaken by two methods. First, the acetate (287) was hydrolysed to form the corresponding naphthol (297), followed by conversion to the $t$-butyldimethylsilyl ether (298).

![Diagram of molecule](image)

This was achieved in very good overall yield (83%) for the two steps. Secondly, in order to avoid the two extra steps involved in deacetylation followed by silylation, the silyl ether (298) was prepared directly from the naphthol (278). In order to arrive at the monobrominated derivative (300), the sequence related to that just described for the conversion of the acetate (279) into its mono-brominated derivative (287) would be investigated, bearing in mind the possible loss of the silyl protecting group during the
debromination of the related dibromonaphthalene under acidic conditions. Thus, exactly the same reaction sequence was employed to synthesize the brominated silyloxy naphthalene (300) (Scheme 59).

Scheme 59

Briefly, following the procedure described by Giles, Hughes and Sargent\textsuperscript{151b} for the synthesis of 4,5,7-trimethoxynaphthalene-1-ol (278), the silyl ether (298) was obtained in a yield of 61%. Bromine in dichloromethane was slowly added to a solution of (298), diluted with dichloromethane and pyridine, to afford the dibrominated compound (299) in a yield of 69%. Debromination of the C-8 bromine with trifluoroacetic acid and phenol gave the product (300) in a 52% yield. This crystalline product was fully characterised and the \(^1\)H NMR spectrum was unambiguous. In the \(^1\)H NMR spectrum the presence of the silyl protecting group as well as the three O-methyls was confirmed by appropriate resonances (see Experimental) as were three aromatic protons. Two of these were meta coupled doublets at \(\delta\) 6.57 (6-H) and \(\delta\) 7.08 (8-H) and the third was a
singlet at $\delta$ 6.98. These results were mirrored in the $^{13}$C NMR spectrum. In particular, of the ten aromatic carbon singlets, three were particularly intense, indicating that they were methine carbon signals. The DEPT 90 spectrum confirmed the presence of three methine carbons in the molecule, all of which ($\delta$ 94.9, $\delta$ 100.9 and $\delta$ 118.6) were aromatic.

The reaction also produced a minor naphtholic byproduct (302) in 15%. It is assumed that it is the naphthol (302) since the hydroxyl proton was hydrogen bonded at $\delta$ 10.25, and preferential loss of the methyl on O-4 would occur to relieve steric strain.\textsuperscript{156}

This was an interesting and unexpected result since O-demethylation was preferred to the anticipated electrophilic substitution of the bromonium ion by a proton. This no doubt occurred through protonation of the methoxy oxygen and removal of the attached methyl by the trifluoroacetate anion. This result was unambiguously confirmed by the presence, in the $^1$H NMR spectrum, of only two three-proton O-methyl groups at $\delta$ 3.97 and $\delta$ 4.03, the signals for the silyl protecting group, two aromatic singlets at $\delta$ 6.92 and $\delta$ 7.05, and a hydrogen-bonded phenolic proton at $\delta$ 10.25. A DEPT 90 $^{13}$C NMR experiment showed that only two methine protons were present, both in the aromatic region ($\delta$ 94.4 and $\delta$ 117.8).

It was not possible to convert the bromo compound (300) into the alcohol (301) using butyl lithium followed by acetaldehyde. A number of products as well as starting material were observed in the reaction mixture.
A different approach was envisaged involving the conversion of the 1-acetoxy-4,5,7-trimethoxynaphthalene (279) into the ketonaphthalene (308). By removing the acetyl group with a 1% potassium hydroxide in methanol the phenol (303) was formed, which was immediately oxidised with cerium(IV) ammonium nitrate to afford quinone (304). This was washed with sodium dithionite solution to afford the unstable hydroquinone (305), which was acetylated to give the diacetate (306) (Scheme 60).

Scheme 60 (contd. over)
Using the same reaction conditions as Giles et al.,\textsuperscript{153} the diacetate (306) was treated with boron trifluoride diethyl etherate at 65 °C to undergo a Fries rearrangement involving the C-4 acetoxy to give naphthol (307), which was in turn immediately methylated with methyl iodide to afford the ketone (308) in a overall yield of 40% from the original starting material (279).

The \( t \)-butyldimethylsilyl group was chosen for protection since deprotection can be achieved under neutral conditions using a saturated aqueous solution of sodium fluoride (Section 2.2.2) and also because it would be expected to survive the reaction conditions in the subsequent sequence, whereas acetate would not. Thus ketone (308) was deprotected with a 1% potassium hydroxide in methanol solution to afford naphthol (280), which was immediately treated with \( t \)-butyldimethylsilyl chloride and imidazole to give the naphthalene (281). Lithium aluminium hydride reduction then afforded the target alcohol (282) in a 90% yield (Scheme 61).
The infrared spectrum showed an OH stretch at 3482 cm\(^{-1}\) and its proton signal appeared as a broad singlet at \(\delta 2.34\) in the \(^1\)H NMR spectrum. The two butyldimethylsilyloxy signals appeared at \(\delta 0.27\) and \(\delta 1.10\) with the 4-, 5- and 7- methoxy singlets resonating at \(\delta 3.80, 3.89\) and \(3.97\). The 1-H proton was evident as a quartet at \(\delta 5.41\) (\(J 6.4 \text{ Hz}\)) while the C-1 methyl appeared as the mutually coupled doublet at \(\delta 1.52\). The coupling constant between the aromatic protons 6-H (\(\delta 6.56\)) and 8-H (\(\delta 7.11\)) was 2.4 Hz, confirming meta coupling, while the 2-H proton appeared as a singlet at \(\delta 6.95\).

Following the methodology of Chapter 2 and previous work\textsuperscript{127,128b,132} alcohol (282) and sodium hyride in dry ether at -10 \textdegree C were treated with trichloroacetonitrile in an attempt to make the imidate (309). However, only starting material was recovered on work-up in spite of several attempts at achieving the desired reaction. A possible reason is that the trichloroacetimidate group is prone to loss on aqueous work-up through the combined activation by each of the three methoxy groups of the naphthalenic system. This is shown for one of these in structure (309).
3.2 The Dibenzyloxy Methoxynaphthol Sequence.

While the work on the trimethoxynaphthol sequence described in the preceding Section 3.1 was being undertaken, a parallel sequence was investigated to synthesize corresponding compounds which contained benzyl protection at O-5 and O-7 since, had these earlier experiments proved successful, the intermediate (273) would be required to synthesise quinone A (16) and quinone A’ (17), since hydrogenation would afford easy deprotection to afford the target molecules.\(^{119}\)

Commercially available phloroglucinol (295) in dimethylformamide was treated with an excess of benzyl bromide and potassium carbonate to give 1,3,5 tribenzyloxybenzene (296) in a 66% yield. Following the procedure of Feutrill and Mirrington,\(^{157a}\) the tribenzyloxybenzene (296) was monodebenzylated using sodium thioethoxide in dimethylformamide to afford the phenol (310) in a 64% yield.

![Scheme 62 (contd. over)](image_url)
Exactly the same synthetic route was followed as in Section 3.1 to synthesize naphthalene (314). Dibenzyloxyphenol (310) in dichloromethane was treated with tosyl chloride and triethylamine to give the tosyl ester (311) in a yield of 85%. Compound (311) was then brominated to give the bromobenzene (312) in a yield of 69%. The Diels-Alder methodology of Giles and co-workers\textsuperscript{151b} was repeated and the bromotosylate (312) in dry tetrahydrofuran was treated with \textit{n}-butyl lithium at -78 °C to form the benzyne. This underwent cycloaddition with 2-methoxyfuran (277). Acid work-up of the reaction afforded the unstable naphthol (313), which was immediately acetylated to yield compound (314) in 87% overall yield based on the bromotosylate (312). It is noteworthy that, for the dimethoxybenzyne, both trimethoxynaphthol regioisomers, \textit{i.e.} (279) and its 1,4-regioisomer were formed, in yields of 70% and 7% respectively,\textsuperscript{151b} whereas, in the case of the dibenzyloxybenzyne, only the required regioisomer (314) was obtained in the higher yield of 87%.

Bromination of naphthalene (314) gave a mixture of the di- and tribrominated naphthalenes (315) and (316) even when less than two molar equivalents were used. It should be recalled that the dibromination reaction of the trimethoxy analogue (279) of the dibenzyloxy derivative (314) required some optimisation, and it was anticipated that this would also be true for the conversion of (314) into (315).
At this point in time, however, it was shown that it was not possible to form the trichloroacetimidate (309) related to the desired analogue (317) as described in Section 3.1, and this sequence was therefore discontinued in favour of the research to be described in the next chapter, which ultimately led to the successful asymmetric syntheses of quinone A (16) and quinone A’ (17), and each of their C-1 epimers.

3.3 Concluding Remarks

The purpose of the work described in this chapter was to investigate the feasibility of synthesizing the quinone A and quinone A’ via a route that first assembled the required dibenzyloxynaphthalene (273) regioselectively, and then to form the required tethered lactaldehydes. While the naphthalenes were synthesised regioselectively and in high yield, it was not possible to attach the lactaldehyde via the proposed route since the intermediate model trichloroacetimidate (309), and therefore, presumably, the required analogue (317) could not be isolated. Considerable experience had been obtained in preparing benzylic trichloroacetimidates in Chapter Two, and an ortho benzyloxybenzyltrichloroacetimidate is also assembled in Chapter Four. It is believed
that the trichloroacetimidate (309) could not be isolated owing to its being too highly activated by the electron donating methoxy substituents on the naphthalenic ring system.
3.4 Experimental

**1-Acetoxy-4,5,7-trimethoxynaphthalene (279)**

Following the procedure described by Giles, Hughes and Sargent\(^{151b}\), the acetate (279) was synthesized from the bromotosylate (275) (1 g) as pale orange crystals (640 mg, 66%) m.p. 111-113 \(^\circ\)C (lit.,\(^{153}\)110-112 \(^\circ\)C; (lit.,\(^{151b}\)114-115 \(^\circ\)C) (dichloromethane-hexane) \(\delta_H\) 2.35 (3H, s, COCH\(_3\)), 3.89 (3H, s, OCH\(_3\)), 3.94 (6H, s, 2 x CH\(_3\)), 6.53 (1H, d, \(J\) 2.3 Hz, 6-H), 6.66 (1H, d, \(J\) 2.3 Hz, 8-H), 6.67 (1H, d, \(J\) 8.5 Hz, 3-H) and 7.11 (1H, d, \(J\) 8.5 Hz, 2-H).

**1-Acetoxy-8-bromo-4,5,7-trimethoxynaphthalene (293)**

Bromine (58 mg, 0.36 mmol) in dry dichloromethane (20 cm\(^3\)) was added drop-wise over 1.5 h to a solution of 1-acetoxy-4,5,7-trimethoxynaphthalene (279) (100 mg, 0.36 mmol) in dichloromethane (250 cm\(^3\)) and pyridine (115 mg, 1.45 mmol). The reaction mixture was stirred at 0 \(^\circ\)C for 5 min and then at room temperature for 3 h, after which it was extracted with dichloromethane. The residue obtained upon work-up was chromatographed (15% ethyl acetate-hexane) to afford compound (293) (90 mg, 70%) as light yellow needles m.p. 132-134 \(^\circ\)C (dichloromethane-hexane) (Found: M\(^+\) 354.0124. C\(_{15}\)H\(_{15}\)BrO\(_5\) requires M(\(^{79}\)Br), 354.0102); \(\nu_{max}/cm^{-1}\) 1755 (C=O) and 1460 (C=C); \(\delta_H\) 2.40 (3H, s, OCOCH\(_3\)), 3.92, 3.95 and 3.97 (each 3H, s, 4-, 5- and 7-OCH\(_3\)), 6.66 (1H, s, 6-H), 6.72 (1H, d, \(J\) 8.6 Hz, 3-H) and 7.07 (1H, d, \(J\) 8.6 Hz, 2-H); \(\delta_C\) 22.1 (OCOCH\(_3\)), 56.7 (OCH\(_3\)), 57.0 (2 x OCH\(_3\)), 93.9 (C-8), 96.1 (C-6), 104.4 (C-3), 115.9 (C-4a), 122.9 (C-2), 128.3 (C-8a), 138.7 (C-4), 155.4 (C-5), 155.9 (C-7), 158.8 (C-1) and 170.7 (OCOCH\(_3\)); m/z 356 [M\(^+\) (\(^{81}\)Br), 9%], 354 [M\(^+\) (\(^{79}\)Br), 10%], 314 (42), 312 (40), 275 (21), 234 (74), 233 (19), 149 (94) and 95 (100).
1-Acetoxy-3,8-dibromo-4,5,7-trimethoxynaphthalene (291)

Bromine (440 mg, 2.75 mmol) in dry dichloromethane (50 cm³) was added drop-wise over 1.5 h to a solution of 1-acetoxy-4,5,7-methoxynaphthalene (279) (400 mg, 1.45 mmol) and an excess of pyridine (459 mg, 5.8 mm mol) in dry dichloromethane (300 cm³). The solution was stirred at 0 °C for 5 min and then at room temperature for 3 h. The reaction mixture was extracted with dichloromethane and the residue obtained upon work-up was chromatographed (15% ethyl acetate-hexane) to afford compound (291) (580 mg, 92%) as white needles m.p. 158-159 ºC (dichloromethane-hexane) (Found: C, 41.7; H, 3.15; M⁺ 433.9184. C₁₅H₁₄Br₂O₅ requires C, 41.5; H, 3.25%; M(⁷⁹Br₈¹Br), 433.9187); υmax/cm⁻¹ 1753 (C=O) and 1514 and 1466 (C=C); δH 2.41 (3H, s, OCOCH₃), 3.84, 3.97 and 3.99 (each 3H, s, 4-, 5- and 7-OCH₃), 6.69 (1H, s, 6-H) and 7.33 (1H, s, 2-H); δC 22.0 (OCOCH₃), 56.8, 57.0 and 61.8 (4-, 5- and 7-OCH₃), 94.1 (C-8), 96.4 (C-6), 111.6 (C-4a), 119.3 (C-5), 126.9 (C-2), 127.7 (C-7), 141.4 (C-8a), 152.0 (C-4), 155.4 (C-3), 157.1 (C-1) and 170.1 (OCOCH₃); m/z 314[(M⁺(⁸¹Br⁷⁹Br)+H)-⁷⁹Br-CH₂=C=O], 312 [(M⁺(⁸¹Br⁷⁹Br)+H)-⁸¹Br-CH₂=C=O], 276 (27), 235 (14), 234 (100), 233 (19), 219 (12), 218 (8), 191 (17), 190 (5), 189 (5), 161 (6), 86 (19) and 84 (30).

1-Acetoxy-3-bromo-4,5,7-trimethoxynaphthalene (287)

An excess of trifluoroacetic acid (53 mg, 2.3 mmol) was added to a solution of 1-acetoxy-3,8-dibromo-4,5,7-trimethoxynaphthalene (291) (200 mg, 0.46 mmol) and tribenzyloxybenzene (296) (182 mg, 0.46 mmol) in dry dichloromethane (4 cm³) and the mixture stirred at room temperature for 2 h. The reaction was quenched with water and extracted with dichloromethane. The residue upon work-up was chromatographed (radial, 10% ethyl acetate-hexane) to afford compound (287) (106 mg, 65%) as white needles m.p. 155-156 ºC (hexane) (Found: C, 50.6; H, 4.3; M⁺ 355.0172. C₁₅H₁₅BrO₅ requires C, 50.7; H, 4.25%; M(⁷⁹Br), 355.0181); υmax/cm⁻¹ 1753 (C=O) and 1579 and 1504 (C=C); δH 2.42 (3H, s, OCOCH₃), 3.86 (6H, s, 5-and 7-OCH₃), a 3.93 (3H, s, 4-OCH₃), a 6.56 (1H, d, J 2.3 Hz, 6-H), 6.64 (1H, d, J 2.3 Hz, 8-H) and 7.38 (1H, s, 2-H); δC 21.39

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(OCOCH₃), 55.6 (5-OCH₃), 62.1 (4-OCH₃), 92.8 (C-6), 100.6 (C-8), 111.0 (C-3), 118.0 (C-4a), 124.0 (C-2), 130.7 (C-8a), 142.1 (C-5), 151.9 (C-7), 157.6 (C-4), 159.3 (C-1) and 169.5 (OCOCH₃); m/z 356 [M+ (81Br), 29%], 354 [M+ (79Br)], 314 (100), 312 (99), 298 (10), 296 (12), 190 (24), 189 (11) and 159 (10).

3-Bromo-1-hydroxy-4,5,7-trimethoxynaphthalene (297)

1-Acetoxy-3-bromo-4,5,7-trimethoxynaphthalene (287) (432 mg, 1.22 mmol) was dissolved in methanolic potassium hydroxide (1%, 15 cm³) and stirred for 10 min at room temperature. Thereafter the reaction mixture was quenched with water (200 cm³) and acidified using dilute hydrochloric acid (1 M) (litmus paper). The reaction mixture was exhaustively extracted with dichloromethane and the residue obtained upon work-up was chromatographed (radial, 20% ethyl acetate-hexane) to give the naphthol (297) (380 mg; 99%) as pale brown needles m.p. 123-124 °C (dichloromethane-hexane) (Found: M⁺ 312.0005. C₁₃H₁₃BrO₄ requires M(79Br), 311.9997); υmax/cm⁻¹ 3349 (OH) and 1586 and 1511 (C=C); δH 3.85, 3.89 and 3.95 (each 3H, s, 4-, 5- and 7-OCH₃), 6.57 (2H, d, J 2.3 Hz, 6-H and 1-OH), 6.99 (1H, s, 2-H) and 7.05 (1H, d, J 2.3 Hz, 8-H); δC 55.4, 56.2 and 61.8 (3 x OCH₃), 93.4 (C-2), 100.3 (C-6), 111.0 (C-4a), 113.7 (C-2), 117.1 (C-3), 128.7 (C-8a), 146.3 (C-4), 147.6 (C-5), 156.6 (C-7) and 157.9 (C-1); m/z 313 [M⁺-H (81Br), 100%], 311 [M⁺-H (79Br), 98%], 296 (13), 217 (92) and 155 (10).

1-t-Butyldimethylsilyloxy-4,5,7-trimethoxynaphthalene (298)

The procedure described by Giles, Hughes and Sargent¹⁵¹b was followed for the preparation of 4,5,7-trimethoxynaphthalene-1-ol (278). The naphthol (278) (1.82 g) was immediately dissolved in dimethylformamide and t-butyldimethylsilyl chloride (2.37 g, 15.7 mmol) and imidazole (1.07 g, 15.7 mmol) were added. The reaction mixture was stirred under nitrogen for 12 h after which water was added and the organic layer extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 5%
ethyl acetate-hexane) to afford compound (298) (2.00 g, 61%) as yellow needles m.p. 59-60 °C (dichloromethane-hexane) (Found: C, 65.6; H, 7.95; M+, 348.1766. C₁₉H₂₈O₄Si requires C, 65.5; H, 8.1%; M, 348.1756); νmax/cm⁻¹ 2954 (C-H) and 1516 and 1468 (C=C); δH 0.17 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.03 (9H, s, OSi(CH₃)₂C(CH₃)₃), 3.81, 3.82 and 3.86 (each 3H, s, 4-, 5- and 7-OCH₃), 6.47 (1H, d, J 2.4 Hz, 6-H), 6.50 (1H, d, J 8.4 Hz, 3-H), 6.69 (1H, d, J 8.4 Hz, 2-H) and 7.06 (1H, d, J 2.4 Hz, 8-H); δC - 4.3 (OSi(CH₃)₂C(CH₃)₃), 18.33 (OSi(CH₃)₂C(CH₃)₃), 25.92 (OSi(CH₃)₂C(CH₃)₃), 55.09, 56.3 and 57.0 (3 x OCH₃), 93.8 (C-6), 99.2 (C-3), 104.5 (C-2), 113.5 (C-8), 114.3 (C-4a), 131.7 (C-8a), 144.4 (C-4), 151.6 (C-5), 157.8 (C-7) and 158.3 (C-1); m/z 348 (M⁺ 100%), 333 (11), 291 (36), 276 (10), 261 (20), 260 (20), 233 (7), 218 (10) and 201 (6).

3,8-Dibromo-1-tert-butyldimethylsilyloxy-4,5,7-trimethoxynaphthalene (299)

Bromine (138 mg, 0.86 mmol) in dry dichloromethane (20 cm³) was added drop-wise over 1.5 h to a solution of trimethoxynaphthalene (298) (150 mg, 0.43 mmol) and an excess of pyridine (136 mg, 1.72 mmol) in dry dichloromethane (350 cm³). The solution was stirred at 0 °C for 5 min and then at room temperature for 3 h. The reaction mixture was extracted with dichloromethane, washed with dilute hydrochloric acid (1 M), and the residue obtained upon work-up was chromatographed (15% ethyl acetate-hexane) to afford the unstable compound (299) (150 mg, 69%) m.p. 136 °C (hexane) (Found: M⁺, 503.9928. C₁₉H₂₆Br₂O₄Si requires M(79Br₂), 503.9967); νmax/cm⁻¹ 2926 (C-H) and 1575 and 1464 (C=C); δH 0.31 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.00 (9H, s, OSi(CH₃)₂C(CH₃)₃), 3.80, 3.98 and 3.99 (each 3H, s, 4-, 5- and 7-OCH₃), 6.71 (1H, s, 6-H) and 7.07 (1H, s, 2-H); δC -3.0 (OSi(CH₃)₂C(CH₃)₃), 19.3 (OSi(CH₃)₂C(CH₃)₃), 26.8 (OSi(CH₃)₂C(CH₃)₃), 57.2, 57.6 and 62.1 (3 x OCH₃), 96.5 (C-8), 97.3 (C-2), 112.4 (C-3), 119.8 (C-4a), 121.0 (C-6), 128.2 (C-8a), 147.6 (C-4), 148.4 (C-5), 155.1 (C-7) and 157.0 (C-1); m/z 495 [M⁺ (⁸¹Br₂)+2H-CH₃, 13%], 494 [M⁺ (⁸¹Br₂)+H-CH₃, 52%], 493 [M⁺ (⁸¹Br₇⁹Br)+2H-CH₃, 25%], 492 [M⁺ (⁸¹Br₇⁹Br)+H-CH₃, 100%], 491 [M⁺ (⁷⁹Br₂)+2H-CH₃, 13%] and 490 [M⁺ (⁷⁹Br₂)+H-CH₃, 50%].
3-Bromo-1-t-butyl(dimethyl)silyloxy-4,5,7-trimethoxynaphthalene (300)

Method A:

An excess of trifluoroacetic acid (184 mg, 1.61 mmol) was added to a solution of the dibromonaphthalene (299) (163 mg, 0.32 mmol) and phenol (295) (30 mg, 0.32 mmol) in dry dichloromethane (10 cm³) and the mixture stirred at room temperature for 2 h. The reaction was quenched with water and extracted with dichloromethane. The residue upon work-up was chromatographed (radial, 10% ethyl acetate-hexane) to afford two products. The lower Rf compound was identified as (300) (72 mg, 52%) as fine white needles, m.p. 78-80 °C (methanol) (Found: C, 53.4; H, 6.25; M⁺ 426.0852. C₁₉H₂₇BrO₄Si requires C, 53.4; H, 6.35; M(⁷⁹Br), 426.0862); νmax/cm⁻¹ 2923 (C-H) and 1570 and 1465 (C=C); δH 0.27 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.09 (9H, s, OSi(CH₃)₂C(CH₃)₃), 3.83, 3.88 and 3.96 (each 3H, s, 4-, 5- and 7-OCH₃), 6.57 (1H, d, J 2.4 Hz, 6-H), 6.98 (1H, s, 2-H) and 7.08 (1H, d, J 2.4 Hz, 8-H); δC -3.5 (OSi(CH₃)₂C(CH₃)₃), 19.1 (OSi(CH₃)₂C(CH₃)₃), 26.6 (OSi(CH₃)₂C(CH₃)₃), 56.0, 57.1 and 62.5 (3 x OCH₃) 94.9 (C-2), 100.9 (C-8), 111.8 (C-3), 118.1 (C-4a), 118.6 (C-6), 131.9 (C-8a), 147.8 (C-4), 148.3 (C-5), 157.7 (C-7) and 158.7 (C-1); m/z 428 [M⁺ (⁸¹Br), 100%], 426 [M⁺ (⁷⁹Br), 93%], 413 (16), 411 (15), 332 (11), 290 (40) and 275 (16).

The compound of higher Rf was identified as (302) (20 mg, 15%) (Found: M⁺ 489.9803. C₁₈H₂₄Br₂O₄Si requires M(⁷⁹Br₂), 489.9811); νmax/cm⁻¹ 3351 (OH) and 1589 and 1516 (C=C); δH 0.28 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.09 (9H, s, OSi(CH₃)₂C(CH₃)₃), 3.97 and 4.03 (each 3H, s, 5- and 7-OCH₃), 6.92 (1H, s, 6-H) and 7.05 (1H, s, 2-H) and 10.25 (1H, s, 4-OH); δ¹H -4.3 (OSi(CH₃)₂C(CH₃)₃), 19.1 (OSi(CH₃)₂C(CH₃)₃), 26.6 (OSi(CH₃)₂C(CH₃)₃), 56.2 and 62.8 (2 x OCH₃), 94.4 (C-2), 99.8 (C-8), 108.2 (C-3), 14.3 (C-4a), 117.8 (C-6), 128.6 (C-8a), 145.2 (C-4), 148.1 (C-5), 151.0 (C-7) and 155.1 (C-1); m/z 492 [M⁺ (⁸¹Br), 100%], 490 [M⁺ (⁷⁹Br), 47%], 477 (17), 461 (10), 414 (30), 412 (30), 356 (13), 354 (12), 341 (23), 359 (21), 149 (12) and 115 (19).
Method B:

Naphthol (297) (380 mg, 1.21 mmol) was dissolved in dimethylformamide (15 cm³) and t-butyldimethylsilyl chloride (275 mg, 1.82 mmol) and imidazole (124 mg, 1.82 mmol) were added. The reaction mixture was stirred at room temperature for 3 h under nitrogen. Water was added and the organic layer extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 5% ethyl acetate-hexane) to afford compound (300) (320 mg, 84%) as fine white needles m.p. 78-80 °C (methanol).

1-Acetoxy-3-acetyl-4,5,7-trimethoxynaphthalene (308)

1-Acetoxy-4,5,7-trimethoxynaphthalene (279) (1.1 g, 4 mmol) was dissolved in 1% methanolic potassium hydroxide (15 cm³) and stirred for 10 min at room temperature. Thereafter the reaction mixture was quenched with water (200 cm³) and acidified using dilute hydrochloric acid (lithmus paper). The reaction mixture was exhaustively extracted with dichloromethane and the crude intermediate (303) was immediately dissolved in acetonitrile. Cerium(IV) ammonium nitrate (4.4 g, 8 mmol) in water (5 cm³) was added drop-wise and the reaction stirred at room temperature for 1 h. The mixture was extracted with dichloromethane, dried (MgSO₄), concentrated and chromatographed (radial, 15% ethyl acetate-hexane) to give the crude quinone (304) (870 mg, ~100%) δH 3.75 and 3.77 (each 3H, s, 5- and 7-OCH₃), 6.54 (1H, d, J 2.4 Hz, 6-H), 6.62 (2H, s, 2- and 3-H), 7.01 (1H, d, J 2.4 Hz, 8-H).
Quinone (304) (870 mg) was shaken with a sodium dithionite solution to afford the unstable 1,4-dihydroxy-5,7-dimethoxynaphthalene (305) intermediate which was treated with pyridine (3 cm³) and acetic anhydride (1.5 cm³) and stirred at room temperature overnight. The reaction mixture was diluted with water, extracted with ethyl acetate and the residue obtained upon work-up was chromatographed (radial, 20% ethyl acetate-hexane) to afford the diacetate (306) (950 mg, 78%) \( \delta \text{H} 2.14 \text{ and } 2.22 \text{ (each } 3\text{H, s, } 1-\text{ and } 4-\text{OCOCH}_3\text{), } 3.65 \text{ (6H, s, } 5-\text{ and } 7-\text{OCH}_3\text{), } 6.32 \text{ (1H, d, } J 2.2 \text{ Hz, } 6\text{-H), } 6.50 \text{ (1H, d, } J 2.2 \text{ Hz, } 8\text{-H), } 6.69 \text{ (1H, d, } J 8.2 \text{ Hz, } 3\text{-H) and } 7.00 \text{ (1H, d, } J 8.2 \text{ Hz, } 2\text{-H).}

The diacetate (306) (950 mg) was stirred in boron trifluoride diethyl etherate (2 cm³) at 65 °C for 30 min under nitrogen. The reaction mixture was poured into ice, stirred for 10 min and exhaustively extracted with dichloromethane, dried (MgSO₄) and concentrated to afford the crude phenol (307) which was immediately dissolved in dimethylformamide (15 cm³). Potassium carbonate (1.47 g, 10.7 mmol) and iodomethane (2.42 g, 17 mmol) were added and the mixture stirred under nitrogen for 3 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate and the residue obtained upon work-up was chromatographed (radial, 10% ethyl acetate-hexane) to give product (308) [500 mg, 50%, or 39% overall yield from original starting material (279)] as yellow prisms m.p. 101-102 °C (dichloromethane-hexane) (Found: C, 64.05; H, 5.75; M⁺ 318.1112. C₁₇H₁₈O₆ requires C, 64.15; H, 5.7 %; M, 318.1103; \( \nu_{\text{max}}/\text{cm}^{-1} \) 1765 and 1670 (C=O), \( \delta \text{H} \) 2.44 (3H, s, OCOCH₃), 2.75 (3H, s, CCOCH₃), 3.86, 3.92 and 4.02 (each 3H, s, 4-, 5- and 7-OCH₃), 6.61 (1H, d, \( J 2.3 \text{ Hz, } 6\text{-H), } 6.68 \text{ (1H, d, } J 2.3 \text{ Hz, } 8\text{-H) and } 7.52 \text{ (1H, s, } 2\text{-H); } \delta \text{C} 21.4 \text{ (OCOCH}_3\text{), } 31.6 \text{ (CCOCH}_3\text{), } 55.8, 56.7 \text{ and } 64.4 \text{ (3 x OCH}_3\text{), } 93.1 \text{ (C-6), } 100.3 \text{ (C-8), } 116.8 \text{ (C-4a), } 119.7 \text{ (C-2), } 127.2 \text{ (C-8a), } 134.1 \text{ (C-5), } 142.1 \text{ (C-7), } 157.2 \text{ (C-4), } 159.1 \text{ (C-3), } 161.0 \text{ (C-1), } 169.8 \text{ (COCH}_3\text{) and } 199.6 \text{ (OCOCH}_3\text{); } m/z 318 \text{ (M⁺ } 35\%), 276 \text{ (100) and } 261 \text{ (44).}
3-Acetyl-1-t-butyldimethylsilyloxy-4,5,7-trimethoxynaphthalene (281)

Acetylnaphthalene (308) (1.00 g, 3.14 mmol) was dissolved in 1% methanolic potassium hydroxide (15 cm³) and stirred for 10 min at room temperature. Thereafter the reaction mixture was quenched with water (200 cm³) and acidified using dilute hydrochloric acid (litmus paper). The reaction mixture was exhaustively extracted with dichloromethane and the residue obtained upon work-up gave the crude and potentially unstable intermediate (280) (640 mg).

This crude product (280) was then immediately dissolved in dimethylformamide (15 cm³). t-Butyldimethylsilyl chloride (710 mg, 4.71 mmol) and imidazole (320 mg, 4.71 mmol) were added and the mixture stirred under nitrogen for 3 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 10% ethyl acetate-hexane) to give compound (281) (870 mg, 71%) as light yellow prisms m.p 99-101 °C (dichloromethane-hexane) (Found: C, 64.7; H, 7.95; M, 390.1847. C₂₁H₃₀O₅Si requires C, 64.6; H, 7.75 %; M, 390.1862); νₓ/₁cm⁻¹ 1671 (C=O) and 1577 and 1504 (C=C); δₓ 0.19 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.99 (9H, s, OSi(CH₃)₂C(CH₃)₃), 2.65 (3H, s, COCH₃), 3.72, 3.82 and 3.91 (each 3H, s, 4-, 5- and 7-OCH₃), 6.50 (1H, d, J 2.4 Hz, 6-H), 7.04 (1H, s, 2-H) and 7.06 (1H, d, J 2.4 Hz, 8-H); δₓ -3.9 (OSi(CH₃)₂C(CH₃)₃), 18.7 (OSi(CH₃)₂C(CH₃)₃), 26.2 (OSi(CH₃)₂C(CH₃)₃), 31.8 (COCH₃), 55.6, 55.7 and 64.3 (3 x OCH₃), 94.7 (C-6), 100.1 (C-2), 112.9 (C-8), 116.6 (C-4a), 127.4 (C-8a)), 135.1 (C-7), 147.0 (C-5), 153.4 (C-4), 158.8 (C-1), 160.1 (C-3) and 200.67 (COCH₃); m/z 390 (M, 100%), 375 (16).
1-t-Butyldimethylsilyloxy-3-(hydroxyethyl)-4,5,7-trimethoxynaphthalene (282)

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{OH} \\
\text{MeO} & \quad \text{TBS} & &
\end{align*}
\]

Lithium aluminium hydride (500 mg, 1.38 mmol) was added to a stirred solution of compound (281) in dry diethyl ether (15 cm³). Stirring was continued for 20 min after which the reaction mixture was quenched drop wise with saturated ammonium chloride solution, dried (MgSO₄), filtered and concentrated. Chromatography (radial, 20% ethyl acetate) of the crude product gave compound (282) (450 mg, 90%) as white crystals m.p. 79-80 °C (dichloromethane-hexane) (Found: C, 64.2; H, 8.05; M⁺ 392.05. C₂₁H₃₂O₅Si requires C, 64.25; H, 8.2 %; M 392.2019; \( \nu \text{max/cm}^{-1} \) 3482 (OH) and 1507 and 1460 (C=C); \( \delta_{H} \) 0.27 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.10 (9H, s, OSi(CH₃)₂C(CH₃)₃), 1.52 (3H, d, J 6.4 Hz, Ar-CHOHCH₃), 2.34 (1H, br. s, OH), 3.80, 3.89 and 3.97 (each 3H, s, -5- and 7-OCH₃), 5.41 (1H, q, J 6.4 Hz, Ar-CHOHCH₃), 6.56 (1H, d, J 2.4 Hz, 6-H), 6.95 (1H, s, 2-H) and 7.11 (1H, d, J 2.4 Hz, 8-H); \( \delta_{C} \) -4.2 (OSi(CH₃)₂C(CH₃)₃), 18.4 (OSi(CH₃)₂C(CH₃)₃), 24.1 (OSi(CH₃)₂C(CH₃)₃), 25.9 (Ar-CHOHCH₃), 55.2, 56.1 and 63.0 (3 x OCH₃), 64.5 (Ar-CHOHCH₃), 93.9 (C-6), 99.4 (C-2), 111.5 (C-8), (C-4a), 131.1 (C-3), 132.1 (C-4), 147.0 (C-5), 147.0 (C-7), 157.2 (C-8a) and 157.6 (C-1); m/z 392 (M⁺ 100%), 377 (11) and 334 (20).

1,3,5-Tribenzyloxybenzene (296)

\[
\begin{align*}
\text{OBn} & \quad \text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{BnO} & &
\end{align*}
\]

A mixture of phloroglucinol dihydrate (295) (2 g, 12.3 mmol), benzyl bromide (6.33 g, 37 mmol) and potassium carbonate (10.2 g, 74 mmol) in dry dimethylformamide (50 cm³) was stirred under reflux for 4 h under nitrogen. The reaction mixture was cooled, diluted with water and exhaustively extracted with ethyl acetate after which the residue obtained upon work-up was chromatographed (15% ethyl acetate-hexane) to afford product (296) (3.2 g, 66%) as brilliant white needles m.p. 94-95 °C (diethyl ether-hexane) (Lit., 86-87 °C); \( \delta_{H} \) 4.95 (6H, s, 3 x OCH₂), 6.56 (3H, s, 2- 4- and 6-H), 7.26-7.41 (15H, m, 3 x C₆H₃); \( \delta_{C} \) 68.9 (3 x OCH₂), 93.7 (C-2, C-4 and C-6), 126.8 (3 x C-2’ and C-6’), 127.3 (C-1, C-3 and C-5), 127.4 (3 x C-3’ and C-5’), 135.7 (3 x C-1’) and 159.5 (3 x C-4’).

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3,5-Dibenzyloxyphenol (310)

Following the method used by Feutrill et al.\textsuperscript{157a} ethanethiol (2.35 g, 37.8 mmol) in dry dimethylformamide (20 cm\textsuperscript{3}) was added with stirring under nitrogen to a suspension of NaH (60% dispersion in paraffin oil) (2.42 g, 101 mmol) in dry dimethylformamide (30 cm\textsuperscript{3}) during 20 min. The mixture was then stirred for a further 0.5 h and 1,3,5-tribenzyloxy benzene (296) (3 g, 7.6 mmol) in dry dimethylformamide (20 cm\textsuperscript{3}) was added over 5 min. The reaction mixture was then heated and stirred under reflux for 2 h. The cooled mixture was diluted with water and extracted with diethyl ether, dried (MgSO\textsubscript{4}), concentrated and chromatographed (10-50% ethyl acetate-hexane) to afford the phenol (310) (1.49 g, 64%) as white crystals m.p. 95-96 °C (diethyl ether-hexane) (Lit.,\textsuperscript{157b} 94 °C); $\delta$\textsubscript{H} 4.90 (4H, s, 2 x OCH\textsubscript{2}), 5.54 (1H, br. s, OH), 6.06 (2H, d, $J$ 2.1 Hz, 2- and 6-H), 6.21 (1H, t, $J$ 2.1 Hz, 4-H) and 7.35 (10H, m, 2 x C\textsubscript{6}H\textsubscript{5}).

3,5-Dibenzyloxy-1-tosyloxybenzene (311)

A stirred solution of 3,5-dibenzyloxyphenol (211) (1.33 g, 4.35 mmol) and triethylamine (530 mg, 5.23 mmol) in dry dichloromethane (10 cm\textsuperscript{3}) was treated drop-wise at 0 °C with a solution of p-toluenesulphonyl chloride (1 g, 5.23 mmol) in dry dichloromethane (20 cm\textsuperscript{3}) and stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with dichloromethane and the residue obtained upon work-up was chromatographed (10-50% ethyl acetate-hexane) to give compound (311) (1.7 g, 85%) as pure white crystals m.p. 82-84 °C (dichloromethane-hexane) (Found: C, 70.55; H, 5.25; M,\textsuperscript{+} 460.1362. C\textsubscript{27}H\textsubscript{24}O\textsubscript{5}S requires C, 70.4; H, 5.25%; M, 460.1344); $\nu_{\text{max}}$/cm\textsuperscript{-1} 2926 (C-H) and 1497 and 1453 (C=C); $\delta$\textsubscript{H} 2.41 (3H, s, CH\textsubscript{3}), 4.89 (4H, s, 2 x OCH\textsubscript{2}), 6.27 (2H, d, $J$ 2.2 Hz, 2-and 6-H), 6.48 (1H, t, $J$ 2.2 Hz, 4-H), 7.27 (2H, d, $J$ 8.2 Hz, 3′-and 5′-H), 7.32-7.38 (10H, m, 2 x C\textsubscript{6}H\textsubscript{5}) and 7.69 (2H, d, $J$ 8.2 Hz, 2′- and 6′-H); $\delta$\textsubscript{C} 21.7 (4′-CH\textsubscript{3}), 70.3 (2 x OCH\textsubscript{2}), 101.0 (C-4), 101.9 (C-2 and C-6), 127.5 (C-2′ and C-6′), 128.2 (C-2″ and C-6″), 128.5 (C-3′ and C-5′), 128.6 (C-3‴and C-5‴), 129.7 (C-4‴), 132.4 (C-
1), 136.2 (C-3 and C-5), 145.3 (C-4'), 151.0 (C-1') and 160.1 (C-1''); m/z 306 [(M+H-CH3C6H4SO2), 5%], 305 (4), 181 (13) and 91 (100).

3,5-Dibenzyloxy-2-bromo-1-tosyloxybenzene (312)

Method A

A solution of bromine (194 mg, 1.21 mmol) in acetic acid was added drop-wise to a stirred solution of the tosylate (311) (620 mg, 1.35 mmol) in acetic acid containing anhydrous sodium acetate (166 mg, 2.02 mmol). The reaction mixture was stirred for 1 h at room temperature and then poured into an aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 15% ethyl acetate-hexane) to afford compound (312) (500 mg, 69%) as white needles m.p. 117-118 °C (dichloromethane-hexane) (Found: C, 60.1; H, 4.3; M+, 538.0454. C27H2379BrOS requires C, 60.1; H, 4.3%; M, 538.0450); υmax/cm⁻¹ 1616, 1592 and 1476 (C=C); δH 2.41 (3H, s, 4'-CH3), 4.96 and 5.02 (each 2H, s, OCH2), 6.49 (1H, d, J 2.2 Hz, 4-H), 6.68 (1H, d, J 2.2 Hz, 6-H), 7.27 (2H, d, J 8.1 Hz, 3'-and 5'-H), 7.37 (10H, m, 2 x C6H5) and 7.77 (2H, d, J 8.1 Hz, 2'-and 6'-H); δC 22.2 (4-CH3), 71.0 and 71.4 (2 x OCH2), 99.5 (C-2), 101.1 (C-4), 102.4 (C-6), 127.4 (C-2 and C-6), b 128.1 (C-2 and C-6), c 128.5 (C-3 and C-5), b 128.7 (C-3 and C-5), c 129.0 (C-4), b 129.1 (C-4), c 129.2 (C-2 and C-6), a 131.1 (C-3 and C-5), a 133.1 (C-1), b 136.3 (C-1), c 146.0 (C-1), a 148.6 (C-4), a 152.3 (C-5), 157.0 (C-3) and 159.1 (C-1); m/z 540 [M+ (81Br), 3%], 538 [M+ (79Br), 3%], 459 (2), 383 (2), 293 (1), 181 (25) and 91 (100).

Method B

Bromine (916 mg, 5.73 mmol) in dichloromethane (25 cm³) was added slowly to a solution of 3,5-dibenzylozy-1-toluenesulphonyloxybenzene (311) (2.93 g, 6.37 mmol) and pyridine (504 mg, 6.37 mmol) in dry dichloromethane (50 cm³) at 0 °C. The solution was stirred at 0 °C for 5 min and then at room temperature for 3 h. The mixture was extracted with dichloromethane, washed with dilute hydrochloric acid (1 M) and the
residue obtained upon work-up chromatographed (12% ethyl acetate-hexane) to afford compound (312) (3.72g, 93%).

1-Acetoxy-5,7-dibenzyloxy-4-methoxynaphthalene (314)

Following the procedure described by Giles, Hughes and Sargent\textsuperscript{151b} for the preparation of 4,5,7-trimethoxynaphthalene-1-ol, a solution of butyl lithium (2.5 M) in cyclohexane (18 mg, 0.28 mmol) was added to a stirred solution of the tosylate (312) (150 mg, 0.28 mmol), and 2-methoxyfuran (55 mg, 0.56 mmol) in anhydrous tetrahydrofuran (20 cm\textsuperscript{3}) at \(-78\, ^\circ\text{C}\) under nitrogen. The solution was stirred at that temperature for 50 minutes after which it was allowed to reach room temperature. The mixture was acidified with concentrated hydrochloric acid, stirred for 15 minutes and then poured into water and extracted with ethyl acetate, dried (MgSO\textsubscript{4}) and concentrated. The crude product was immediately dissolved in dry pyridine (3 cm\textsuperscript{3}) and acetic anhydride (3 cm\textsuperscript{3}) and stirred at room temperature for 12 h under nitrogen. Water was added and the organic layer extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (radial, 15% ethyl acetate-hexane) to afford compound (314) (104 mg, 87%) as yellow needles m.p. 148-150 °C (dichloromethane-hexane); (Found: C, 75.45; H, 5.65; M\textsuperscript{+} 428.1612. C\textsubscript{27}H\textsubscript{24}O\textsubscript{5} requires C, 75.7; H, 5.65%; M, 428.1623); \upsilon_{\text{max}}/\text{cm}^{-1} 1753 (C=O) and 1588 and 1517 (C=C); \delta\textsubscript{H} 2.36 (3H, s, OCOCH\textsubscript{3}), 3.89 (3H, s, OCH\textsubscript{3}), 5.12 and 5.14 (each 2H, s, OCH\textsubscript{2}), 6.65 (1H, d, J 8.5 Hz, 3-H), 6.69 (1H, d, J 2.2 Hz, 6-H), 6.75 (1H, d, J 2.2 Hz, 8-H), 7.09 (1H, d, J 8.5Hz, 2-H) and 7.28-7.50 (10H, m, 2 x C\textsubscript{6}H\textsubscript{5}); \delta\textsubscript{C} 21.5 (OCOCH\textsubscript{3}), 56.8 (4-OCH\textsubscript{3}), 70.6 and 71.6 (2 x OCH\textsubscript{2}), 94.6 (C-3), 101.9 (C-8), 103.7 (C-6), 115.0 (C-1),\textsuperscript{a} 119.7 (C-2), 127.4 (C-2’ and C-6’),\textsuperscript{a} 128.1 (C-4’),\textsuperscript{a} 128.2 (C-3’ and C-5’),\textsuperscript{a} 128.7 (C-4’),\textsuperscript{b} 128.9 (C-2’ and C-6’),\textsuperscript{b} 129.2 (C-3’ and C-5’),\textsuperscript{b} 131.3 (C-1’),\textsuperscript{b} 137.2 (C-8a), 137.7 (C-4a), 139.7 (C-1’),\textsuperscript{b} 156.0 (C-7), 158.3 (C-5), 158.4 (C-1) and 170.3 (OCOCH\textsubscript{3}); m/z 428 (M\textsuperscript{+} 11%), 386 (30), 295 (22), 206 (7), 181 (12) and 91 (100).
CHAPTER 4

4.0 Introduction

Owing to the difficulties encountered with the naphthalenic precursors (Chapter 3), another attempt was made to achieve the enantioselective synthesis of quinone A (16) by making the bromoquinone (199) with the correct absolute stereochemistry, from diol (318) and regioselectively adding 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene (200).\textsuperscript{133}

It was imperative that the correct protecting group at the C-8 oxygen be chosen in order to facilitate its easy deprotection and the subsequent oxidation of the derived hydroquinone to afford quinone (199) (Scheme 63).

\begin{center}
\textbf{Scheme 63}
\end{center}
Previous research involved the assembly of the diol (197) with a methoxy group at the C-8 position, which was prevented by the C-7 bromine substituent from undergoing oxidative demethylation (Section 1.5).\(^{132}\)

![Scheme 64](image)

Scheme 64 shows how quinone A’ (17) could then be assembled by reversing the stereochemistry of the C-4 hydroxy group of the methylated diol (319) by using phosphorus pentachloride and silver nitrate, a method well documented by Giles and co-workers,\(^{119}\) (Chapter 2) to afford the alternative stereoisomer (320). Subsequent deprotection of the C-8 benzyl ether followed by oxidative demethylation would then afford the bromoquinone (321) with the correct stereochemistry to undergo Diels-Alder addition of diene (200) to afford the second target, quinone A’ (17).
Halogenated quinones are well known to undergo regioselective Diels-Alder reactions with oxygenated dienes. The mode of addition usually occurs through attachment of the carbon supporting the halogen to C-1 of the diene. Subsequent elimination of hydrogen halide followed by aromatisation and hydrolysis allows the ready assembly of polycyclic quinones. This methodology has been used extensively in the syntheses of anthracyclinones. Competition between conjugate addition and Diels-Alder cycloaddition of the diene to the halogen-substituted quinone has been achieved.

It was necessary to halogenate the quinonoid ring of compound (199) regioselectively in order to achieve the correct regiochemistry for the two phenolic substituents in quinone A (16), as discussed in Chapter 1.

4.1 Choice of Appropriate Protecting Groups for the Hydroquinonoid Oxygens of the Starting Material 2,5-Dihydroxyacetophenone (322).

It was decided that model reactions should first be carried out to optimize certain reaction conditions. Scheme 65 shows the constructions of a simple model compound and the choice of protection at O-2 and O-5. This was in order to determine the relative ease with which these protecting groups could be added and later removed for oxidation to the quinone (332) in the presence of the required bromine atom. There is also the question of whether this bromine substituent would survive the ensuing oxidative dealkylation reaction conditions.

Commercially available 2,5-dihydroxyacetophenone (322) was treated with tert-butyldimethylsilyl chloride and imidazole to give the selectively monoprotected 5-tert-butyldimethylsilyloxy-2-hydroxyacetophenone (323) in a 97% yield. The structure was assigned on the basis of the $^1$H NMR spectrum, which showed the presence of a strongly hydrogen bonded hydroxyl proton at $\delta$ 11.85. A silyl group was chosen because of its easy removal under neutral conditions which would be unaffected by adventitious sulphur residues from the previous Swern oxidation (Section 2.1.2). Regioselective bromination of the compound (323) to afford the ortho-bromophenol (324) was easily achieved in an excellent yield of 96% by addition of bromine to a solution of the phenol
(323) and pyridine in dichloromethane at 0 °C. This complete regioselectivity arose since the phenolic group was solely ortho-directing and the acetyl substituent meta-directing. The combined directing influence of these two substituents would therefore both support bromination at C-3.

Scheme 65 (contd. over)
Benzyl was chosen as the C-2 protecting group, since as in the case of the silyl ether, only mild reaction conditions are necessary for complete deprotection. Different protecting groups at C-2 and C-5 were important to ensure their selective removal.

A suspension of potassium carbonate and bromophenol (324) in dimethylformamide was treated with benzyl bromide and stirred at 100 °C for 3 h. $^1$H NMR spectroscopy revealed two two-proton benzylic singlets at δ 4.93 and δ 5.04 and the absence of the intramolecularly bonded hydroxy group previously at δ 12.49. This evidence suggests that the carbonate is sufficiently nucleophilic in the dipolar aprotic solvent to remove the silyl group and allow dibenzylation to afford the dibenzyl ether (333). The use of methanol as an alternative solvent gave a mixture of the same of dibenzylated product (333) and the phenol (334).

This result was unexpected, in view of the reported$^{146,134b}$ stability of this silyl protecting group to carbonate in methanol. The alternative method, in which silver(I) oxide was added to a stirred solution of benzyl bromide and phenol (324) in dry chloroform, afforded the monobenzylated compound (325) in a 85% yield. $^1$H NMR spectroscopy
showed only one two-proton benzyl methylene signal at $\delta$ 4.95 with the silyl ether still intact, its two signals appearing at $\delta$ 0.24 and $\delta$ 1.01.

Taylor\textsuperscript{132} found that by reducing the bromoketone (335) with lithium aluminium hydride the bromine was removed to afford the debrominated alcohol (336).

![Diagram of compounds](image)

Using the milder reducing agent, sodium borohydride, the brominated alcohol (326) was obtained in a 91\% yield from the ketone (325).

![Diagram of compound](image)

The next step involved the formation of the imidate (327). Trichloroacetanilide was added to a stirred suspension of the alcohol (326) and a catalytic amount of sodium hydride in ether at -10 °C to afford the imidate (327) in 88\% yield.

![Diagram of compound](image)

The infrared spectrum showed the N-H stretch at 3337 cm\textsuperscript{-1} and the C=N stretch at 1661 cm\textsuperscript{-1}. The imidate carbon atom (C-1) resonated at $\delta$ 161.2 in the $^{13}$C NMR spectrum and this also showed a downfield shift for the benzylic carbon (C-1) from $\delta$ 65.1 in the
alcohol (326) to $\delta$ 72.7 in the imidate (C-$\alpha'$). The $^1$H NMR spectrum also showed a marked deshielding of the $\alpha'$-H signal from $\delta$ 5.03 to $\delta$ 6.25 and was the result of the greater polarisation of the C-O bond owing to the presence of the imidate moiety. The N-H proton appeared as a broad singlet at $\delta$ 8.35.

The next step was the substitution of the trichloroacetimidate group with methoxy, since the product (328) was deemed a reasonable model for the isochromane ring system. This would allow an examination of the possibility of removing the benzyl protection where it had previously proved impossible to remove methyl from compound (197). This would then allow for the oxidation of the hydroquinone derived from compound (318) by silver(I) oxide to give the required quinone (199), whereas oxidative demethylation using the more vigorous silver(II) oxide with concentrated nitric acid failed in the crowded environment in (197).

The imidate (327) in methanol was therefore treated with a catalytic amount of boron trifluoride diethyl etherate to afford the methyl ether (328) in 82% yield. The infrared spectrum confirmed the loss of the N-H and C=N groups, while a methyl ether group appeared as a three proton singlet at $\delta$ 3.15 in the $^1$H NMR spectrum.

\[
\begin{align*}
\text{OMe} & \quad \text{Br} \\
\text{OMe} & \quad \text{OMe} \\
\text{OTBS} & \quad \text{(328)}
\end{align*}
\]

A final modification to the model structure was to convert the silyl protection into acetyl since, for the real molecule leading to benzopyran (318), the silyl group is removed prior to cyclisation to the benzopyran-4,5-diol (318). Previously, also, such diols had been purified by their immediate conversion into the more stable 4,5-diacetates.\(^{128c}\)

The $t$-butyldimethylsilyl group was easily removed using $t$-butylammonium fluoride\(^{146}\) to afford the unstable phenol (329). Immediate acetylation with pyridine and acetic anhydride gave the monoacetate (330).
Treatment of compound (330) with 10% Pd/C catalyst and subsequent oxidation of the product with cerium(IV) ammonium nitrate produced the quinone (332) in a 64% overall yield from compound (330).

These results therefore supported the view that the choice of benzyl and t-butyldimethylsilyl protecting groups was appropriate, as shown in Scheme 65, for the formation of the trichloroacetimidate (327), from which it was hoped to obtain the targets, quinone A (16) and quinone A’ (17).

### 4.2 Syntheses of the Two Diastereomeric Phenolic Aldehydes (347) and (348)

Following the general method of Iversen and Bundle, the imidate (327) was treated with methyl (R)-lactate (182) together with a catalytic amount of boron trifluoride diethyl etherate. This produced an inseparable mixture of esters (337) and (338) in a 91% yield and in a ratio of 1.3:1, as judged by $^1$H NMR spectroscopy. The diastereomer (337) required for the synthesis of quinone A (16) and quinone A’ (17) was slightly favoured (vide infra).
The mass spectrum of the mixture of diastereoisomers (337) and (338) gave molecular ion peaks at m/z 524 (^{81}\text{Br}) and 522 (^{79}\text{Br}). The infrared spectrum showed the C=O stretch at 1754 cm\(^{-1}\) with the carbonyl carbon atoms resonating at \(\delta\) 173.0 and \(\delta\) 173.9 in the \(^{13}\text{C}\) NMR spectrum. The esters (337) and (338) were obtained from commercially available 2,5-dihydroacetophenone (322) in six high yielding steps in an overall yield of 58%.

The next step was the reduction of the ester mixture to the corresponding alcohols (339) and (340). It was already known that lithium aluminium hydride removed the bromine atom when ketone (335) was reduced to the alcohol (336).\(^{132}\) Thus an alternative reducing agent was sought for obtaining the alcohols from the mixture of esters. Reduction of these diastereomeric esters (337) and (338) with sodium borohydride, however, gave only a complicated mixture of products. Although lithium borohydride is a relatively mild reducing agent which is commonly used for the reduction of esters\(^{161}\) and, indeed, was used by Giles and Taylor\(^{132}\) to successfully reduce ketone (335) to the corresponding alcohol in high yield, it was decided to investigate the use of lithium aluminium hydride by adding the reagent portion-wise to a solution of esters in dry ether and carefully monitoring the completion of the reaction by TLC. In doing so it was possible to synthesize the corresponding diastereomeric alcohols (339) and (340) which could be separated through repeated radial chromatography to produce the individual alcohols in a ratio of 1.3:1 respectively (combined yield of 91%).
Confirmation of their relative stereochemistry will again be confirmed subsequently through examination of the $^1$H NMR spectra of the resulting benzo[c]pyrans.

The mass spectrum of the lower R_F alcohol (339) showed the correct molecular ion peaks at m/z 496 ($^{81}$Br) and m/z 494 ($^{79}$Br) with the base peak appearing at m/z 91. The infrared spectrum revealed an aliphatic OH stretch at 3447 cm$^{-1}$ and the presence of this group was confirmed by a broad singlet at $\delta$ 1.90 in the $^1$H NMR spectrum. The signals for the two diastereotopic protons attached to C-1 and the 2-H signal were not well resolved and appeared as a three proton multiplet in the region $\delta$ 3.36 - 3.62. It was therefore not possible to determine the individual coupling constants for these three protons.

The product of higher R_F (340) gave exactly the same mass spectrum. The presence of the OH group was confirmed by an absorption at 3466 cm$^{-1}$ in the infrared spectrum and a resonance at $\delta$ 1.85 as a broad doublet in the $^1$H NMR spectrum. The C-1 diastereotopic protons and the 2-H proton were once more not well resolved and again appeared as a three proton multiplet in the region $\delta$ 3.34-3.48.

The enantiomeric purity of the alcohols (339) and (340) needed to be determined in order to establish whether any racemisation had occurred at the carbon atom $\alpha$ to the ester group during the formation of the mixture of diastereomeric esters (337) and (338), or during their reduction to these alcohols.
Eu(hfc)$_3$ was again used as the chiral lanthanide shift reagent for the determination of the optical purity of the individual alcohols (339) and (340). For this purpose it was necessary to synthesize their respective enantiomeric alcohols (341) and (342).

The diastereoisomeric esters (343) and (344) were prepared from the imidate (327) using ethyl (S)-lactate (181) and a catalytic amount of boron trifluoride diethyl etherate.

Controlled reduction of the mixture of esters (343) and (344) with lithium aluminium hydride furnished the alcohols (341) and (342) in a similar ratio to their respective enantiomers (339) and (340).
The optical rotations of the alcohols (339) and (340) were also measured and these compared well with those of their respective enantiomers (341) and (342) (Table 4).

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<td>(341)</td>
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<tr>
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Table 4: Optical Rotations of the Alcohols (339), (341), (340) and (342)

With the four alcohols (339), (340), (341) and (342) available, the enantiomeric excesses of the alcohols (339) and (340) could be determined using the chiral shift reagent. Separation of some of the signals in the ¹H NMR spectrum (500 MHz) was achieved by adding 15 mol % of the shift reagent to a 60:40 mixture of the enantiomeric alcohol (339) and (341). The respective signals (339; 341) for OSi(CH₃)₂C(CH₃)₃ resonated at δ 0.38 and δ 0.39, for 2-CH₃ at δ 2.28 and δ 2.38, for OH at δ 6.07 and 6.20 and for 6'-H at δ 7.22 and δ 7.24.

From this information, when the same procedure was applied to a sample of pure (339), the appropriate regions of the spectrum could be examined for signals due to the enantiomer (341). However, no signals were detected for the latter.

It was necessary to add 25 mol % of the shift reagent to a 60:40 mixture of (340) and (342) in order to observe reasonable separation of any signals in the ¹H NMR spectrum. Separation was only achieved in two signals: for the benzylic signals at δ 5.32 and δ 5.34 and for a pair of aromatic signals at δ 7.99 and δ 8.03. No signals arising from the enantiomer (342) were observed when the same procedure was applied to (340) alone.

The enantiomeric excesses were also determined through HPLC using a Daicel OD chiral column. The mobile phase was 1% 2-propanol in hexane. Separation could only be achieved, however for the alcohols (339) and (341) (a 35:65 mixture) which
confirmed high enantiomeric excesses for each alcohol. **Figure 1** shows the mixture in which the $\alpha'S$, $2S$ enantiomer (341) had a retention time (under the conditions used) of 10.8 min while the $\alpha'R$, $2R$ enantiomer (339) was observed at 14.71 min. The results for (339), the precursor to quinones A and A', was found to have an e.e. value of at least 97.8% (**Figure 3**) while the value for the enantiomeric (341) was found to be 99.6% (**Figure 2**). Unfortunately, although a variety of solvent systems were examined, HPLC conditions were not found to separate the pair of enantiomers (340) and (342) and therefore the enantiomeric excesses were not determined. It was reasonably assumed, however, that similar values would be achieved.
Figure 2

Figure 3
Two methods of oxidation were used to convert the individual alcohols (339) and (340) into their respective aldehydes (345) and (346). The first method involved Swern oxidation.\textsuperscript{130} Alcohol (339) was treated with a mixture of oxalyl chloride and dimethyl sulphoxide at -70 °C. After the addition of N,N-diisopropylamine, work-up afforded the aldehyde (345) in a 88% yield.

The second method used pyridinium chlorochromate (PCC)\textsuperscript{163} as the oxidizing agent. Alcohol (339) in dry dichloromethane was added to a stirred slurry of PCC and basic alumina in dichloromethane at 0 °C. The reaction was stirred for a further 14 h at room temperature and filtered through a short silica column to afford aldehyde (345) in a 76% yield. Although a lower yield was obtained, this method was preferred since it had the advantage of not being contaminated by adventitious sulphur residues, which are hard to remove and poison the catalyst upon hydrogenolysis of the benzyl ether.

\[ \text{Alcohol (340) was treated in the same way with PCC to afford the aldehyde (346) in a 75% yield.} \]

The C=O stretch of the aldehyde moiety was present at 1735 cm\(^{-1}\) in the infrared spectrum. The aldehydic proton resonated as a doublet \((J 1.7 \text{ Hz})\) at \(\delta 9.60\) in the \(^1\text{H}\) NMR spectrum, while the aldehydic carbon atom (C-1) appeared downfield at \(\delta 203.3\) in the \(^{13}\text{C}\) NMR spectrum.

Alcohol (340) was treated in the same way with PCC to afford the aldehyde (346) in a 75% yield. The carbonyl stretch in the infrared spectrum remained virtually unchanged at 1739 cm\(^{-1}\) with the aldehydic proton appearing at \(\delta 9.49\) \((J 1.2 \text{ Hz})\) in the \(^1\text{H}\) NMR spectrum. The \(^{13}\text{C}\) NMR spectrum showed the carbonyl carbon atom (C-1) at 202.6.

Having made both aldehydes (345) and (346) the key phenolic aldehydes (347) and (348) were assembled. Aldehyde (345) in tetrahydrofuran was treated with a mixture of equal volumes of saturated aqueous solutions of sodium fluoride and ammonium
chloride to afford the phenolic aldehyde (347) in 73% yield. The product was rapidly chromatographed and submitted for a high resolution mass spectrum which gave the correct molecular formula and a low resolution spectrum afforded molecular ions at m/z 362 (\(^{81}\)Br) and m/z 360 (\(^{79}\)Br). The \(^1\)H NMR spectrum lacked the silyl signals of ether (345) and the aldehydic proton of (347) appeared as a doublet at 9.58 (\(J \ 1.5\) Hz). The phenolic hydroxyl appeared as a broad singlet at \(\delta 6.40\). The infrared spectrum showed the OH and C=O stretches at 3383 cm\(^{-1}\) and 1730 cm\(^{-1}\) respectively.

The aldehyde (346), after treatment with the sodium fluoride:ammonium chloride solution, similarly yielded the phenolic aldehyde (348) in 76% yield. The OH stretch of the phenol was present at 3386 cm\(^{-1}\) and the C=O stretch at 1732 cm\(^{-1}\). The coupling constant between the 1-H and 2-H protons in the \(^1\)H NMR spectrum was 0.9 Hz.

The individual phenolic aldehydes (347) and (348) were regarded as potentially unstable and were therefore treated immediately as their titanium phenolates to achieve ring closure to afford diols as discussed in the following sections.

4.3 The Synthesis of Quinone A (16) from the Phenolic Aldehyde (347)

The potentially unstable enantiopure phenolic aldehyde (347) was treated with titanium(IV) tetraisopropoxide and the mixture sonically irradiated for 5 h, after which a 1:1 mixture of saturated aqueous solutions of sodium fluoride:ammonium chloride were added. The mixture was stirred until the yellow colour had discharged to afford the diol (318).
Using the methodology of Casirighi and co-workers,\textsuperscript{129,135} as well as the results from the Giles group,\textsuperscript{127,128,132} cyclisation of the enantiopure phenolic aldehyde (347) as the titanium phenolate was achieved successfully to afford the diol (318) in a yield of 69\%. The method was that used for simpler substrates as discussed in Chapter 2.

The reaction was completely diastereoselective, yielding only the one isomer. It was found that the diol (318) was stable enough for chromatography, and this product and its diastereoisomers discussed below were fully characterized. The mass spectrum showed the correct molecular ion peaks at m/z 380 (\textsuperscript{81}Br) and m/z 378 (\textsuperscript{79}Br), in addition to the confirmation of the molecular formula through high resolution mass spectrometry. The infrared spectrum showed two signals at 3450 cm\textsuperscript{-1} and 3292 cm\textsuperscript{-1} relating to the two OH stretches. No carbonyl stretch, previously seen in the phenolic aldehyde (347), was visible. The 4- and 5-OH signals appeared together as a broad singlet at $\delta$ 4.20 – 5.20 in

\[ \text{Scheme 66} \]
the $^1$H NMR spectrum. The large coupling constant of 8.7 Hz between 3-H ($\delta$ 3.86) and 4-H ($\delta$ 4.51) confirmed a near trans-diaxial arrangement between these two protons. This is the preferred conformation since the C-3 methyl group is in the favoured equatorial configuration and the C-1 methyl is pseudoaxial. The chemical shift ($\delta$ 3.86) of 3-H, the signal appearing as a doublet of quartets ($J$ 6.1 and 8.7 Hz), was consistent for compounds having a trans 1,3-dimethyl arrangement.$^{105,131}$ The proton 4-H resonated as a doublet ($J$ 8.7 Hz) with 1-H appearing as a quartet at $\delta$ 4.96 ($J$ 6.7 Hz). The two methyl doublets at C-3 and C-1 were observed at $\delta$ 1.36 ($J$ 6.1 Hz) and $\delta$ 1.54 ($J$ 6.7 Hz), respectively. The benzylic methylene protons resonated as two doublets ($J$ 10.7 Hz) at $\delta$ 4.71 and $\delta$ 5.12.

The benzylic ether protection was then removed from the diol (318) through hydrogenolysis using ethyl acetate as the solvent and 10% palladium on carbon as the catalyst.

The crude unstable hydroquinone (349) was immediately treated with cerium(IV) ammonium nitrate to afford the chromatographically separable products (199) and (350).

Scheme 67

The crude unstable hydroquinone (349) was immediately treated with cerium(IV) ammonium nitrate to afford the chromatographically separable...
bromobenzopyranquinone (199) and the debrominated analogue (350) in an approximate ratio of 2.4:1 respectively. Thus partial debromination had occurred during hydrogenolysis to give a mixture of the hydroquinones (349) and (351). The enantiomer (183) of debrominated quinone (350) was previously made in these laboratories in the model studies discussed in Chapter 1. The spectral data for the enantiomers (350) and (183) were identical [except for an additional 0.5 Hz coupling between 1-H and 3-H observed for the ^1H NMR spectrum of the latter, which was determined at 500 MHz, as opposed to 300MHz for the new enantiomer (350)].

The quinonoid racemate (350) and (183) has also previously been synthesized as a minor product in a reaction involving cerium(IV) ammonium nitrate induced cyclisation, followed by oxidative demethylation. Giles and Joll were the first to synthesize (183) in enantiopure form. The optical rotation of the enantiomers (350) and (183) compared well, being measured -307.7 ° and +313.1 ° respectively.

In addition to the correct combustion data, the molecular formula of the bromobenzopyranquinone (199) was confirmed by an accurate mass measurement through high resolution mass spectrometry. The corresponding low resolution spectrum
showed fragmentations corresponding to loss of water ($M^+ - 18$) and base peaks at $m/z$ 244 and 242 corresponding to a retro Diels-Alder reaction.

The infrared spectrum showed the OH stretch at 3505 cm$^{-1}$ and the C=O stretches at 1677 and 1652 cm$^{-1}$. The $^1$H NMR spectrum showed the 4-OH as a doublet at $\delta$ 3.43 ($J$ 2.6 Hz) coupled to proton 4-H. The signal for 3-H at $\delta$ 3.84 was a doublet of quartets ($J$ 7.7 and 6.2 Hz). The proton 4-H appeared as a doublet of doublet of doublets ($J$ 1.4, 2.6 and 7.7 Hz) at $\delta$ 4.35. The proton assigned to 1-H appeared as a doublet of quartets ($J$ 1.4 and 6.8 Hz) at $\delta$ 4.80. The pseudoequatorial proton 1-H showed long range homoallylic coupling ($J$ 1.4 Hz) to the pseudoaxial 4-H, which is characteristic of a pseudoaxial-pseudoequatorial relationship between 4-H and 1-H.$^{105,131}$ Cameron$^{105}$ has used the findings of Karplus$^{165}$ to show for naphthopyranquinones that the extent of coupling between homoallylic protons 1-H and 4-H is greatest when the protons involved are both pseudoaxial ($J \sim 2.9$ Hz),$^{105}$ smaller when one of the protons is pseudoaxial and the other pseudoequatorial ($J \sim 1.5$ Hz), and negligible when both protons are pseudoequatorial. This long-range coupling constant ($J$ 1.4 Hz) found in quinone (350) therefore confirms the stereochemical assignment. A single one proton signal appeared at $\delta$ 7.27 (6-H), for the quinonoid proton, deshielded by the adjacent bromine.

The $^1$H NMR spectrum of the debrominated benzopyran (350) also showed the 4-OH resonating as a sharp doublet ($J$ 2.5 Hz) at $\delta$ 3.52, coupled to 4-H. The proton 4-H appeared as a doublet of doublet of doublets ($J$ 1.6, 2.5 and 7.8 Hz) at $\delta$ 4.35. The pseudoequatorial 1-H proton showed long-range homoallylic coupling ($J$ 1.6 Hz) to the pseudoaxial proton 4-H and is, once again, characteristic of a pseudoaxial-
pseudoequatorial relationship between 4-H and 1-H.\textsuperscript{105,131} The large coupling constant of 7.8 Hz between 3-H and 4-H is indicative of a \textit{trans}-dialxial arrangement.

The next challenge was the all important Diels-Alder addition of the diene (200) to the bromoquinone (199) to form quinone A (16).

Diene (200)\textsuperscript{133} was prepared according to Scheme 68. Ketone (352) was converted into its silyl enol ether, the ester (353).\textsuperscript{133,166}

![Scheme 68](attachment:image.png)

Ester (353) was added drop-wise to a previously prepared LDA solution, after which the addition of trimethylsilyl chloride gave the 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene (200).\textsuperscript{133}

A simple model compound (356) was assembled in order to test the Diels-Alder addition reaction with the diene (200).

2-Methylphenol (354) was dibrominated at C-4 and C-6 to afford compound (355), which was then immediately oxidized with cerium(IV) ammonium nitrate to afford the 2-bromo-5-methyl-1,4-quinone (356) in an overall yield of 81% from starting material.
The method of Cameron\textsuperscript{167} for the addition of dienes to naphthoquinones was adapted to the reaction of the diene (200) with quinone (356). The resulting dark green reaction mixture was stirred at room temperature for a further 40 min after which concentrated sulphuric acid was added and stirring continued for a further 2 h. This was done to remove the trimethylsilyl group (Scheme 70).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme69.png}
\caption{Scheme 69}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme70.png}
\caption{Scheme 70}
\end{figure}

\textsuperscript{1}H NMR spectroscopy still showed, however, that a mixture was present even through TLC showed only one product. Recrystallisation afforded the quinone (357) as bright orange needles.
The use of concentrated acid in our reactions was of concern lest racemisation and/or dehydration of our target molecules (16) and (17) occurred. It was found, however, that it was unnecessary to add this acid in the cases studied in this research since when the diene (200) and quinone (356) were stirred together for the much longer time of 24 h, a colour change was observed from dark green to bright yellow. The naphthoquinone (357) was produced in a yield of 73% after recrystallisation in a reaction which involved the elimination of hydrogen bromide and methanol, and desilylation.

This method was then attempted using the bromoquinone (199) and diene (200). The reaction mixture was stirred for 24 h after which the initial dark green colour had changed to bright yellow. Work-up afforded the target compound quinone A (16) in a yield of 30% after recrystallisation from benzene.

The sample was submitted for a high resolution spectrum which gave the correct molecular ion at m/z 289 (-H⁺). The infrared spectrum showed the OH stretch at 3402 cm⁻¹ and the C=O stretch at 1641 cm⁻¹. An accurate microanalysis was also obtained.

The ¹H NMR spectra of quinone A and quinone A’ have not been reported in the literature. These were obtained from our synthetic samples in both methanol-d₄ and acetone-d₆ (see following pages), in view of their poor solubility in deuterochloroform. The ¹H NMR spectrum of quinone A in acetone-d₆ is shown on the following pages. In subsequent discussions with Professor Cameron, the ¹H NMR spectral data for quinone A were provided, having previously been obtained in dimethyl sulfoxide-d₆. The data obtained in each of these solvents are reported in Table 5.
Table 5: Comparison of Chemical Shifts of Quinone A (16) in Dimethyl Sulfoxide-d₆, Methanol-d₄ and Acetone-d₆.

The large coupling constant of 7.2 Hz between 3-H and 4-H confirmed their near trans-diaxial arrangement. The small coupling constant between 1-H and 4-H indicated long-range coupling between the pseudoequatorial 1-H and pseudoaxial 4-H proton.¹⁰⁵,¹⁶⁵

Unfortunately, when it was ultimately determined that ¹H NMR spectra had been obtained from the natural material in dimethyl sulphoxide-d₆, insufficient synthetic material remained for the same purpose. Prior to having this information this solvent had not been chosen for determining the spectrum in view of the relative difficulty of recovering the scarce synthetic material from it. This all not withstanding, the data obtained in the other two solvents were entirely consistent with the assigned structure.
These data, when combined with those described in the experimental, confirmed the first successful synthesis of the enantiopure target quinone A (16). The specific rotation for the quinone A has not been reported hitherto, but has been measured as +41 ° in Professor Cameron’s group, as a solution in methanol containing 1% acetic acid. Under these conditions our synthetic material gave a value of +37.1 °, which compared well with the naturally derived material.

4.4 The Syntheses of the C-1 Epimers (358) and (359) from Phenolic Aldehyde (348).

There are three asymmetric centres about the pyran ring in quinone A (16), and, therefore, eight possible diastereoisomers, of which four belong to the C-3 (R) series and four enantiomers belong to the corresponding C-3 (S) series. Of the first four in the C-3 (R) series, quinone A (16) and quinone A’ (17) are two, while their two C-1 epimers (358) and (359) complete this group of four diastereomers based on (R)-lactate. The remaining four would be available from (S)-lactate. Previous model studies in this laboratory suggest that the diastereomers (358) and (359) would both be available from the benzylic epimer of (347), the latter having been used above for the assembly of quinone A (16).

Since the benzylic epimer (348) was in hand, the syntheses of the quinones (358) and (359) were investigated. Once the syntheses of all four diastereoisomers (including quinones A and A’) were successfully achieved, the information was conveyed to Professor Cameron at which point it was learned that he had, in fact, isolated two further, hitherto unreported, diastereoisomers of the quinones A and A’ as derivatives from alternative natural sources. These two additional compounds (360) and (361) were the enantiomers of our synthetic compounds (358) and (359), the syntheses of which are described in this section.
Cyclisation of the phenolic aldehyde (348) with titanium tetraisopropoxide did not proceed with complete diastereoselectivity but produced the two diastereomeric diols (362) and (363). The product of anti addition (362) was the major product in a yield of 51% with the minor product of syn addition (363) being formed in 30% yield (Scheme 71).

![Scheme 71](image)

In model studies this loss of diastereoselectivity in the formation of the cis-1,3-dimethyl compounds was ascribed to peri interactions in the Felkin-Anh transition state\(^{129c,145a}\) between the C-8 alkoxy and C-1 methyl substituents in the derived benzopyran\(^{128c}\) (Scheme 72). This was strongly supported (Chapter 2) by complete diastereoselectivity in the formation of the corresponding benzopyran (245) carrying only hydrogen at C-8,
when none of the pseudoaxial alcohol of syn addition was obtained. When C-8 was substituted with methoxy the ratio of pseudoequatorial to pseudoaxial alcohols was 3:1,\textsuperscript{128c} while in the present study with the more sterically demanding C-8 benzyloxy group this ratio drops to $\sim$ 5:3. This trend therefore vindicates the original hypothesis.\textsuperscript{128c}

Scheme 72

The higher R\textsubscript{F} compound was assigned structure (362). The mass spectrum showed a loss of water to give signals at m/z 362 (\textsuperscript{81}Br) and 360 (\textsuperscript{79}Br). The infrared spectrum showed two hydroxy (C-4 and C-5) stretches at 3450 cm\textsuperscript{-1} and 3292 cm\textsuperscript{-1}. The carbonyl signal, which previously appeared at 1732 cm\textsuperscript{-1}, was absent. These two hydroxy groups appeared together as a broad singlet in the \textsuperscript{1}H NMR spectrum at $\delta$ 3.90 – 4.30. As with diol (318), the large coupling constant of 8.8 Hz between 3-H ($\delta$ 3.39) and 4-H ($\delta$ 4.55) indicated a axial-pseudoaxial relationship\textsuperscript{105,131} between these two protons (Scheme 73). The proton 4-H resonated as a doublet ($J$ 8.8 Hz) with 3-H appearing as a doublet of quartets ($J$ 8.8 and 6.1 Hz). The chemical shift of 3-H ($\delta$ 3.39) appeared well upfield from that at $\delta$ 3.84 for the diastereoisomer (318) and was indicative of a cis dimethyl arrangement.\textsuperscript{35b,36e,126} The 1-H proton appeared at $\delta$ 4.76 as a doublet of quartets ($J$ 0.7 and 6.3 Hz) with the CH\textsubscript{2} benzylic protons resonating as two doublets ($J$ 10.7 Hz) at $\delta$ 4.69 and 4.99. Additional long-range coupling ($J$ 0.7 Hz) between the homoallylic protons 1-H and 4-H confirmed the pseudoaxial orientation of each, which provided further confirmation of the assigned stereochemistry.
The lower Rf compound was identified as (363). The mass spectrum of this compound showed a loss of OH to give m/z 363 (81Br) and m/z 361 (79Br). The infrared spectrum showed the C-4 and C-5 hydroxy stretches at 3495 and 3265 cm\(^{-1}\) and these OH protons appeared as a broad singlet at \(\delta\) 3.80 – 4.30 in the \(^1\)H NMR spectrum.

The stereochemistry was confirmed, first, by the chemical shift of the proton 3-H as a doublet of quartets (\(J\) 1.6 and 6.5 Hz) at \(\delta\) 3.59, which is consistent with a cis-arrangement of the 1,3-dimethyl substituents (Scheme 74).

The coupling constant (\(J\) 1.6 Hz) between 3-H and 4-H confirmed that, with the C-3 methyl equatorial, the proton 3-H was axial and 4-H was pseudoequatorial. Thus the C-4 hydroxyl group was pseudoaxial. The pair of diastereotopic benzylic protons appeared as two doublets at \(\delta\) 4.71 and \(\delta\) 4.97, while the pseudoaxial proton 1-H appeared as a quartet (\(J\) 6.3 Hz) at \(\delta\) 4.63. Here, the absence of long-range homoallylic coupling between 1-H and 4-H seen in the C-4 epimer (362) supported the pseudoaxial-pseudoequatorial orientation of these protons in isomer (363).
The major diastereomer (362) in ethyl acetate was then hydrogenated to afford the unstable mixture of 4,5,8-triols (364) and (365), which was subsequently treated with cerium(IV) ammonium nitrate. Work-up and chromatography yielded the individual bromobenzo[c]pyranquinone (366) and debrominated pyranquinone (367) in equal proportions.

Scheme 75†

The mass spectrum of (366) showed two molecular ion peaks at m/z 288 ($^{81}\text{Br}$) and m/z 286 ($^{79}\text{Br}$). The infrared spectrum showed carbonyl stretches at 1666 cm$^{-1}$ and 1652 cm$^{-1}$ and the OH stretch at 3226 cm$^{-1}$. In the $^1$H NMR spectrum the proton 4-H appeared as a doublet of doublet of doublets ($J$ 2.2, 2.9 and 8.3 Hz) at $\delta$ 4.38. The coupling ($J$ 8.3 Hz) of 4-H to 3-H confirmed their near anti relationship, while the chemical shift ($\delta$ 3.41) of 3-H once again confirmed a 1,3-cis dimethyl arrangement. The proton 1-H appeared as

† Insufficient (367) was available to determine the specific rotation, but the literature value for the enantiomer is recorded$^{128c}$ as $+241.9^\circ$. 

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a doublet of quartets ($J$ 2.9 and 6.7 Hz) at $\delta$ 4.70, in which the mutual long-range coupling constant of 2.9 Hz between the 1-H and 4-H protons confirmed a pseudoaxial orientation for each of them.\textsuperscript{105,131} The spectrum also showed the aromatic proton 6-H as a singlet at $\delta$ 7.25. The hydroxyl proton 4-OH appeared as a doublet ($J$ 2.2 Hz) coupled to 4-H.

The $^1$H NMR spectrum of the debrominated analogue (367) was virtually identical to that for quinone (366), except that the quinonoid protons 6- and 7-H appeared as a two-proton singlet at $\delta$ 6.72.

The quinone (366) was treated in tetrahydrofuran at 0 $^\circ$C with the diene (200) as for quinone A (16). After 24 h the initial green colour had turned bright yellow when the reaction was worked-up and the naphtho[2,3-c]pyranquinone (358) was obtained in a yield of 23%.

![Figure 358](image)

The optical rotation was measured for our quinone (358) as $-459$ $^\circ$ under the same conditions as for quinone A (16). Very little synthetic material was available, however, and there was some doubt as to the accuracy of this value. This was compared with the value determined by the Cameron group under the same conditions as $+568$ $^\circ$ for the naturally derived enantiomer.\textsuperscript{168} Professor Cameron, however, also expressed some doubt about his value, since he also had had very little material.

Table 6 compares the chemical shifts in the $^1$H NMR spectra of the synthesized quinone (358) in both methanol-d$_4$ and acetone-d$_6$ to those of its enantiomer (360) in dimethyl sulphoxide-d$_6$, previously isolated as the natural derivative by Cameron.\textsuperscript{168} The large coupling constant of 8.2 Hz between the protons 3-H and 4-H indicated their near trans-
diaxial relationship. The relatively large long-range coupling constant \((J = 2.5 \text{ Hz})\) between 1-H and 4-H indicated that both protons were pseudoaxial.105

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<th>Acetone-d\textsubscript{6} (358)</th>
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<td>(J) (1H-4H)</td>
<td>3 Hz</td>
<td>2.6 Hz</td>
<td>2.5 Hz</td>
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*partially obscured by solvent

Table 6: Comparison of Chemical Shifts of Naturally Derived (360) in Dimethyl Sulfoxide-d\textsubscript{6} and the Synthesized Enantiomer (358) in Methanol-d\textsubscript{4} and Acetone-d\textsubscript{6}.

The third diasteriomer (359) was assembled using the same methodology.
Diol (363) was debenzylated through hydrogenolysis using the same catalyst (palladium on carbon). A unstable mixture of brominated triol (368) and debrominated triol (369) was obtained which was immediately oxidised with cerium(IV) amonium nitrate to afford the separate quinones (370) and (371).

Scheme 76

The mass spectrum of (370) gave fragment ion peaks at m/z 270 ($^{81}$Br) and m/z 268 ($^{79}$Br), which indicated a loss of water from the molecular ions. The infrared spectrum showed the hydroxy stretch at 3470 cm$^{-1}$ and the quinonoid carbonyl stretches at 1672 cm$^{-1}$ and 1653 cm$^{-1}$. In the $^1$H NMR spectrum the OH signal appeared as a doublet ($J$ 8.1 Hz) at $\delta$ 2.13 through coupling with the proton 4-H at $\delta$ 4.37, which appeared as a doublet of doublet of doublets ($J$ 1.4, 1.6 and 8.1 Hz). The proton 1-H appeared as a doublet of quartets ($J$ 1.4 and 6.6 Hz) at $\delta$ 4.67. The mutual long-range coupling ($J$ 1.4 Hz) between 1-H and 4-H confirmed a pseudoaxial-pseudoequatorial relationship of quinone (350). The proton 3-H appeared at $\delta$ 3.59 as a doublet of quartets coupled to

197
4-H ($J$ 1.6 Hz) and 3-CH$_3$ ($J$ 6.4 Hz). In the quinonoid region the proton 6-H appeared as a one proton singlet at $\delta$ 7.32. The small coupling constant ($J$ 1.6 Hz) between 3-H and 4-H confirms that, with the C-3 methyl equatorial, 3-H is axial and 4-H is pseudoequatorial.

The mass spectrum of the debrominated quinone (371) showed no molecular ion peak but the base peak at m/z 164 corresponding to a loss of acetaldehyde through a retro Diels-Alder fragmentation. The quinonoid region in the $^1$H NMR spectrum showed both protons 6- and 7-H as doublets ($J$ 10.2 Hz) at $\delta$ 6.73 and 6.80. This compound has been reported previously as its racemate.$^{124c}$

The bromoquinone (370) was treated with the diene (200) as for the previous quinones (350) and (366). The quinone (359) was obtained in a yield of 23% after recrystallisation.

A comparison of $^1$H NMR spectral data of synthetic (359) in methanol-d$_4$ and acetone-d$_6$ with those of its enantiomer (361), which was isolated from natural sources by Cameron,$^{168}$ shows the expected similarities (Table 7). The small coupling constant of 1.2 Hz between 3-H and 4-H confirms that, with the C-3 methyl equatorial, 3-H is axial and 4-H is therefore pseudoequatorial. The C-4 hydroxy group is therefore pseudoaxial. The long-range coupling constant between the pseudoaxial proton 1-H and the pseudoequatorial proton 4-H was found to be 1.2 Hz, which confirms the stereochemical assignment.$^{105,165}$
<table>
<thead>
<tr>
<th></th>
<th>DMSO-d$_6$ (361)</th>
<th>Methanol-d$_4$ (359)</th>
<th>Acetone-d$_6$ (359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-CH$_3$</td>
<td>-</td>
<td>1.31</td>
<td>1.31</td>
</tr>
<tr>
<td>1-CH$_3$</td>
<td>-</td>
<td>1.59</td>
<td>1.56</td>
</tr>
<tr>
<td>3-H</td>
<td>3.60</td>
<td>3.58</td>
<td>3.64</td>
</tr>
<tr>
<td>4-H</td>
<td>4.38</td>
<td>4.42</td>
<td>4.44</td>
</tr>
<tr>
<td>1-H</td>
<td>4.72</td>
<td>4.74</td>
<td>4.76</td>
</tr>
<tr>
<td>8-H</td>
<td>-</td>
<td>6.51</td>
<td>6.62</td>
</tr>
<tr>
<td>6-H</td>
<td>-</td>
<td>7.03</td>
<td>7.10</td>
</tr>
<tr>
<td>7-OH</td>
<td>-</td>
<td>-</td>
<td>3.20 – 3.60</td>
</tr>
<tr>
<td>9-OH</td>
<td>-</td>
<td>-</td>
<td>12.16</td>
</tr>
<tr>
<td>$J$ (3H-4H)</td>
<td>1.5 Hz</td>
<td>1.2 Hz</td>
<td>1.2 Hz</td>
</tr>
<tr>
<td>$J$ (1H-4H)</td>
<td>1.5 Hz</td>
<td>1.2 Hz</td>
<td>1.2 Hz</td>
</tr>
</tbody>
</table>

Table 7: Comparison of Chemical Shifts of Naturally Derived (361) in Dimethyl Sulfoxide-d$_6$ and the Synthesized Enantiomer (359) in Methanol-d$_4$ and Acetone-d$_6$. 
The optical rotation of the synthesized compound (360) was measured as \(-134^\circ\), whereas that for the naturally derived enantiomer (362) was \(+278^\circ\).\(^{168}\) Once again, owing to very limited quantities of both (360) and (362), both Professor Cameron and we had some doubts about our values.

### 4.5 The Synthesis of Quinone A’ (17) from Diol (318).

As discussed in **Section 4.3**, the completely diastereoselective ring closure of the titanium phenolate of the phenolic aldehyde (347) afforded the desired benzopyran-4,5-diol (318) as a single diastereoisomer.

![Chemical structure of (347) and (318)](image)

In order to synthesize quinone A’ (17) it was necessary to reverse the stereochemistry of the C-4 hydroxyl group of the benzopyran. This was undertaken by using methodology developed by Giles and co-workers\(^{119}\) (**Section 2.1.3**).

To achieve this the C-5 hydroxy group had to be selectively methylated. This was done by dissolving the diol (318) in dry dimethylformamide and adding an excess of potassium carbonate and iodomethane to afford the methyl ether (319) in 96% yield.

![Chemical structure of (319)](image)
The mass spectrum showed the correct molecular ion peaks at m/z 394 ($^{81}$Br) and 392 ($^{79}$Br). The 5-OCH$_3$ appeared as a singlet at δ 3.86 in the $^1$H NMR spectrum.

Compound (319) in dry diethyl ether was treated with phosphorus pentachloride and stirred briefly to give the crude, unstable chlorinated product (372). This was immediately dissolved in acetonitrile and then treated with aqueous silver nitrate to afford some starting material (22%) and also the C-4 epimeric alcohol (320) in a yield of 72%, or 94% based on consumed starting material.

The mass spectrum of the pseudoaxial alcohol (320) showed two molecular ion peaks at m/z 394 ($^{81}$Br) and 392 ($^{79}$Br), and the infrared spectrum showed an OH stretch at 3466 cm$^{-1}$. The proton 4-H (δ 4.49) appeared as a doublet ($J$ 1.9 Hz) mutually coupled with the proton 3-H at δ 4.03. The small coupling constant observed between these two protons confirmed that, with the C-3 methyl equatorial, the protons 3-H and 4-H are axial and pseudoequatorial respectively. The chemical shift of the proton 3-H at δ 4.03 confirmed the $trans$ arrangement of the methyl groups at C-1 and C-3, and also, that the C-1 methyl remains pseudoaxial. The C-4 hydroxyl proton appeared as a broad singlet at δ 2.13.

Alcohol (320) was treated with the catalyst palladium on carbon in the presence of hydrogen to form a mixture of the brominated and debrominated hydroquinones (373) and (374). This mixture was immediately oxidised with cerium(IV) ammonium nitrate to afford the brominated quinone (321) and debrominated quinone (375) in yields of 51% and 22% (Scheme 77).
It was worth noting that the hydroquinone monomethyl ether (373) underwent smooth oxidative demethylation to form the quinone (321) with ceric ammonium nitrate, whereas the regioisomer (197) did not. Since the only difference between these two isomers is the site of bromination (as well as the stereochemistry of the alcohol, which would be immaterial for the oxidation), the hypothesis was vindicated that the oxidation with ceric ammonium nitrate or silver(II) oxide did not work on account of steric crowding around the methoxy group.

![Scheme 77](image)

The mass spectrum of bromoquinone (321) showed no molecular ions, but fragment ions at m/z 270 ($^{81}$Br) and m/z 268 ($^{79}$Br) arose through loss of water. The infrared spectrum showed the hydroxy stretch at 3506 cm$^{-1}$ and C=O stretches at 1677 and 1652 cm$^{-1}$. In the $^1$H NMR spectrum, the proton 4-H at $\delta$ 4.35 resonated as a doublet of doublets ($J$ 2.2 and 7.3 Hz) which showed coupling ($J$ 7.3 Hz) to the hydroxy ($J$ 7.3 Hz) and coupling ($J$ 2.2 Hz) to 3-H at $\delta$ 3.96. The small coupling constant of 2.2 Hz between 3-H and 4-H confirmed, once again, that the C-4 hydroxyl group was pseudoaxial. No long-range
coupling was observed between the protons 1-H and 4-H, which confirmed that both these protons were pseudoequatorial.\textsuperscript{105} The hydroxy proton appeared as a doublet ($J$ 7.3 Hz) at $\delta$ 2.25.

The quinone (321) was treated with diene (200) as for the three previous bromoquinones. After the expected colour change had occurred (approximately 24 h) the product was chromatographed and recrystallised to afford bright orange crystals of quinone $A'$ (17) in a yield of 20%.

The $^1$H NMR spectral data for this synthetic compound, obtained in both methanol-d$_4$ and acetone-d$_6$, were compared to those of the enantiomer in dimethyl sulphoxide-d$_6$ derived naturally by Cameron.\textsuperscript{168} These are listed in Table 8 below.

<table>
<thead>
<tr>
<th>CHEMICAL SHIFTS</th>
<th>DMSO-d$_6$ (17)</th>
<th>MeOH-d$_6$ (17)</th>
<th>Acetone-d$_6$ (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-CH$_3$</td>
<td>1.29</td>
<td>1.30</td>
<td>1.11</td>
</tr>
<tr>
<td>1-CH$_3$</td>
<td>1.51</td>
<td>1.51</td>
<td>1.35</td>
</tr>
<tr>
<td>3-H</td>
<td>3.97</td>
<td>3.97</td>
<td>3.84</td>
</tr>
<tr>
<td>4-H</td>
<td>4.35</td>
<td>4.38</td>
<td>4.41</td>
</tr>
<tr>
<td>1-H</td>
<td>4.83</td>
<td>4.91*</td>
<td>4.75</td>
</tr>
<tr>
<td>8-H</td>
<td>6.51</td>
<td>6.51</td>
<td>6.48</td>
</tr>
<tr>
<td>6-H</td>
<td>6.96</td>
<td>7.04</td>
<td>6.98</td>
</tr>
<tr>
<td>7-OH</td>
<td>-</td>
<td>-</td>
<td>2.64 – 2.80</td>
</tr>
<tr>
<td>9-OH</td>
<td>-</td>
<td>-</td>
<td>12.05</td>
</tr>
<tr>
<td>$J$(3H-4H)</td>
<td>2</td>
<td>1.90</td>
<td>1.90</td>
</tr>
<tr>
<td>$J$(1H-4H)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*partially obscured by solvent

Table 8: Comparison of Chemical Shifts for synthesized quinone $A'$ (17) in Methanol-d$_4$ and Acetone-d$_6$ with those of the Naturally Derived Material in Dimethyl Sulfoxide-d$_6$. 

203
The small coupling constant of 1.9 Hz between the protons 3-H and 4-H confirmed once again that, with the C-3 methyl equatorial and the proton 3-H axial, the proton 4-H is pseudoequatorial. The methyls at C-1 and C-3 are trans, since the chemical shifts of the proton 3-H in each of the three solvents (δ 3.84 - 3.97) are at lower field than those for the cis 1,3-dimethyl compounds (358)-(361), for which the related range is δ 3.25 – 3.64. Thus, related comparisons can be made in the deuterated solvents methanol, acetone and dimethyl sulphoxide which have previously been made for ¹H NMR spectra run in deuterochloroform, viz. for the latter solvent the proton 3-H is deshielded (usually δ 3.9 - 4.3) for the trans compounds compared to the range for the cis compounds (usually δ 3.5 – 3.9). This generalisation can also be made for all the benzopyrans and their quinones reported in this chapter.

4.6 Concluding Remarks

This chapter describes the first asymmetric syntheses from commercially available 2,5-dihydroxyacetophenone of quinone A (16) and quinone A’ (17), as well as those of their C-1 epimers (358) and (359). These comprise all four diastereoisomers based on 3R stereochemistry, and the remaining four would be available similarly from (S)-lactate. While quinone A (16) and quinone A’ (17) have been reported,¹⁰⁴ it transpired after completion of this research that quinones (358) and (359) are the enantiomers of two hitherto unreported aphid insect pigment derivatives (360) and (361).¹⁶⁸ The yields for all but two of the steps were high. Those that were not were, first, the final Diels-Alder reactions. Although the yields for the model compound (357) was 73% after recrystallisation, those for the four naphthopyranquinones were in the range 20 – 30%. These yields are not low compared to those for many such cyclisations, which involve a number of processes in the formation of this additional aromatic ring; dehydrobromination, loss of methanol and two desilylations. Furthermore, nucleophilic addition of the electron-rich diene to the quinonoid ring, adjacent to the halogen atom, would be a possible competing reaction. In addition, the product (357) in the model reaction is less sensitive than the benzo- and naphthopyranquinones to the reaction conditions. Secondly, the yields of the debenzylations of the benzopyrans were lowered.
by unavoidable partial debromination. A study of this reaction to achieve optimisation was not undertaken through a lack of time.

5.7 Future Work

Although the syntheses of these naphthopyranoquinones were in general efficient, there are a few issues that need to be resolved. First, while the specific rotation for the naturally and synthetically derived quinone A and quinone A’ agree very well, those for the remaining two diastereoisomers do not, and this situation needs to be resolved, particularly as the natural materials have not been reported in the literature.

Secondly, the debromination reaction needs to be optimized further through using an alternative protecting group such as 4-methoxybenzyl, which may be removed more readily, or through varying the conditions of catalyst, solvent, temperature and/or pressure. This would require a more detailed study of this particular reaction.

Furthermore, if more of the cis-1,3-dimethylnaphthopyranoquinones are to be made to resolve the issues above, now that it is known that the natural derivatives are the (1R, 3S, 4R) and (1R, 3S, 4S) diastereoisomers (360) and (361), it would be more appropriate to assemble these natural 3S derivatives themselves from ethyl (S)-lactate, rather than their enantiomers from (R)-lactate.

Finally, as a minor point, the formation of the benzyl ether (325) as an oil was accompanied by traces of inseparable impurities (see Experimental, p. 207). Even though the yield was high, these prevented an accurate microanalysis and this reaction requires optimisation leading to a pure product.
4.7 Experimental

5′-t-Butyldimethylsilyloxy-2′-hydroxyacetophenone (323)

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{OTBS} & \quad (323)
\end{align*}
\]

\(t\)-Butyldimethylsilyl chloride (5.94 g, 39 mmol) and imidazole (2.68 g, 39 mmol) were added to a solution of 2,5-dihydroxyacetophenone (322) (5 g, 33 mmol) in dry dimethylformamide (80 cm\(^3\)). The mixture was stirred under argon for 12 h at room temperature after which water was added and the mixture exhaustively extracted with ethyl acetate. The residue obtained upon work-up was chromatographed (10% ethyl acetate-hexane) to give product (323) as a yellow oil (8.5 g, 97%) (Found: C, 62.9; H, 8.4; M\(^+\), 266.1336. C\(_{14}\)H\(_{22}\)O\(_3\)Si requires C, 63.1; H, 8.3 %; M, 266.1338; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1648 (C=O) and 1616, 1588 and 1481 (C=C); \(\delta_H\) 0.21 (6H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 0.99 (9H, s, OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 2.59 (3H, s, COCH\(_3\)), 6.86 (1H, d, \(J\) 8.9 Hz, 3′-H), 7.02 (1H, dd, \(J\) 2.9 and 8.9 Hz, 4′-H), 7.16 (1H, d, \(J\) 2.9 Hz, 6′-H) and 11.85 (1H, s, OH); \(\delta_C\) -4.6 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 17.1 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 24.7 (OSi(CH\(_3\))\(_2\)C(CH\(_3\))\(_3\)), 25.6 (COCH\(_3\)), 118.0 (C-1′), 118.4 (C-6′), 119.1 (C-3′) 128.3 (C-4′), 146.2 (C-2′), 155.7 (C-5′) and 202.9 (COCH\(_3\)); m/z 266 (M\(^+\), 60%), 209 (100), 181 (20), 167 (10), 86 (11) and 84 (17).

3′-Bromo-5′-t-butyldimethylsilyloxy-2′-hydroxyacetophenone (324)

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
\text{OTBS} & \quad (324)
\end{align*}
\]

Bromine (2.40 g, 15 mmol) was added to a solution of 5′-t-butyldimethylsilyloxy-2′-hydroxyacetophenone (323) (4 g, 15 mmol) and pyridine (4.75 g, 60 mmol) in dry dichloromethane (150 cm\(^3\)) at 0 °C. The solution was stirred at this temperature for 5 min and then at room temperature for 3 h. The reaction was then quenched with hydrochloric acid (1 M) and the mixture was exhaustively extracted with dichloromethane. The organic extracts were washed further with hydrochloric acid (1 M) and saturated sodium chloride, after which the residue obtained upon work-up was chromatographed (10% ethyl acetate-hexane) to give product (324) (5 g, 96%) as light yellow prisms m.p. 66-67 °C (hexane).
(Found: C, 49.0; H, 6.2; M+, 344.0443. C₁₄H₂₁BrO₃Si requires C, 48.7; H, 6.15%; M(⁷⁹Br), 344.0443; υmax/cm⁻¹ 1654 (C=O) and 1447 (C=C); δH 0.21 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.99 (9H, s, OSi(CH₃)₂C(CH₃)₃), 2.61 (3H, s, COCH₃), 7.15 (1H, d, J 2.8 Hz, 4'-H), 7.30 (1H, d, J 2.8 Hz, 6'-H) and 12.49 (1H, s, OH); δC -4.5 (OSi(CH₃)₂C(CH₃)₃), 18.2 (OSi(CH₃)₂C(CH₃)₃), 25.6 (OSi(CH₃)₂C(CH₃)₃), 26.7 (COCH₃), 111.8 (C-1'), 119.7 (C-3'), 119.9 (C-4'), 132.2 (C-6'), 147.3 (C-2'), 153.7 (C-5') and 203.7 (COCH₃); m/z 346 [M+ (⁸¹Br), 24%], 344 [M+ (⁷⁹Br), 22%], 289 (39), 287 (37), 97 (15), 95 (11), 84 (100), 83 (18), 81 (12) and 71 (18).

2'-Benzylxy-3'-bromo-5'-t-butyldimethylsilyloxyacetophenone (325)

Silver(I) oxide (795 mg, 3.4 mmol) was added to a stirred solution of benzyl bromide (704 mg, 4.1 mmol) and 3'-bromo-5'-t-butyldimethylsiloxo-2'-hydroxyacetophenone (324) (474 mg, 1.4 mmol) in dry chloroform (50 cm³). The resulting suspension was stirred at room temperature overnight under an atmosphere of argon. The reaction mixture was subsequently filtered through a pad of celite and the filtrate concentrated under reduced pressure. The residue was chromatographed (10% ethyl acetate-hexane) to give the benzyl ether (325) (505 mg, 85%) as a light yellow oil containing traces of inseparable impurities. Found: M⁺, 434.0923. C₂₁H₂₇BrO₃Si requires M(⁷⁹Br), 434.0912; υmax(film)/cm⁻¹ 1677 (C=O) and 1591 and 1495 (C=C); δH 0.24 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.01 (9H, s, OSi(CH₃)₂C(CH₃)₃), 2.55 (3H, s, COCH₃), 4.95 (2H, s, OCH₂), 7.01 (1H, d, J 3.0 Hz, 4'-H), 7.24 (1H, d, J 3.0 Hz, 6'-H) and 7.38-7.51 (5H, m, C₆H₅); δC -4.1 (OSi(CH₃)₂C(CH₃)₃), 18.5 (OSi(CH₃)₂C(CH₃)₃), 26.0 (OSi(CH₃)₂C(CH₃)₃), 31.0 (COCH₃), 70.1 (OCH₂), 119.1 (C-1'), 120.0 (C-3'), 128.6 (C-6'), 128.7 (C-4''), 128.9 (C-2'' and C-6''), 129.0 (C-3'' and C-5''), 136.3 (C-4''), 136.5 (C-1''), 148.9 (C-5'), 152.8 (C-2') and 199.9 (COCH₃); m/z 436 [M⁺ (⁸¹Br), 5%], 434 [M⁺ (⁷⁹Br), 5%], 394 (9), 392 (9), 345 (6), 343 (5), 289 (8), 287 (8), 115 (11), 91 (100) and 73 (52).
**1-(2'-Benzyloxy-3'-bromo-5'-t-butyldimethylsilyloxyphenyl)ethanol (326)**

To a stirred slurry of sodium borohydride (570 mg, 1.5 mmol) in dry ethanol (30 cm³) was added drop-wise a solution of the compound (325) in dry ethanol (10 cm³). The mixture was stirred at room temperature for 1 h, after which a saturated ammonium chloride solution was added drop-wise, followed by anhydrous magnesium sulphate. Filtration through celite and concentration of the filtrate followed by chromatography (radial, 10-20% ethyl acetate-hexane) yielded alcohol (326) (525 mg, 91%) as a light yellow oil. (Found: C, 57.8; H, 6.6; M⁺, 436.1082. C₂₁H₂₉BrO₃Si requires C, 57.65; H, 6.7%; M(⁷⁹Br), 436.1069); ν_max(film)/cm⁻¹: 3409 (OH), and 1599 and 1496 (C=C); δ_H: 0.21 (6H, s, OSi(C₃H₇)₂C(CH₃)₃), 0.98 (9H, s, OSi(CH₃)₂C(C₃H₇)₃), 1.38 (3H, d, J 6.4 Hz, 1-CH₃), 1.94 (1H, d, J 2.9 Hz, OH), 4.99 (2H, s, OCH₂), 5.03 (1H, dq, J 2.9 and 6.4 Hz, 1-H), 6.88 (1H, d, J 2.9 Hz, 6’-H), 7.00 (1H, d, J 2.9 Hz, 4’-H) and 7.34-7.48 (5H, m, C₆H₅); δ_C: -4.5 (OSi(CH₃)₂C(CH₃)₃), 18.2 (OSi(CH₃)₂C(CH₃)₃), 23.9 (C-2), 25.6, (OSi(CH₃)₂C(CH₃)₃), 65.1 (C-1), 75.6 (OCH₂), 117.0 (C-6’), 117.1 (C-3’), 123.8 (C-2’’ and C-6’’), 125.9 (C-4’’), 128.4 (C-4’), 128.6 (C-3’’ and C-5’’), 136.5 (C-1’’), 141.1 (C-1’), 146.6 (C-2’ and 152.7 (C-5’); m/z: 438 [M⁺ (⁸¹Br), 6%], 436 [M⁺ (⁷⁹Br), 6%], 347 (10), 345 (10), 330 (57), 328 (55), 273 (30), 271 (26), 115 (28), 91 (84) and 73 (100).

**2'-Benzyloxy-3'-bromo-5'-t-butyldimethylsilyloxy-α'-methylbenzyl-2,2,2-trichloroethanimidate (327)**

The benzyl alcohol (326) (3 g, 6.9 mmol) in dry diethyl ether (10 cm³) was added drop-wise to a stirred suspension of sodium hydride (60% dispersion in mineral oil) (110 mg, 4.6 mmol) in diethyl ether (15 cm³). The mixture was stirred for 10 min under argon at -10 °C. Trichloroacetonitrile (1.94 g, 13.7 mmol) was added drop-wise over 10 min and the reaction mixture stirred for a further 30 min at that temperature, after which it was allowed to reach room temperature. The solution was concentrated and chromatographed (radial, 5% ethyl acetate-hexane) to afford the imidate (327) (3.5 g,
88%) as a light yellow oil. (Found: C, 47.9; H, 5.1; N, 2.3; M⁺, 579.0165. C₂₃H₂₉BrCl₃NO₅Si requires C, 47.5; H, 5.05; N, 2.4%; M⁺(⁷⁹Br and ³⁵Cl), 579.0165); ν max(film)/cm⁻¹ 3337 (N-H), 1661 (C=N) and 1600, 1562 and 1464 (C=C); δH 0.18 (6H, s, OSi(C₃H₃)₂C(CH₃)₃), 0.96 (9H, s, OSi(CH₃)₂C(C₃H₃)₃), 1.54 (3H, d, J 6.5 Hz, α'-CH₃), 5.10 and 5.14 (each 1H, d, J 10.6 Hz, OCH₂), 6.25 (1H, q, J 6.5 Hz, α'-H), 6.94 (1H, d, J 2.9 Hz, 6'-H), 7.02 (1H, d, J 2.9 Hz, 4'-H), 7.32-7.44 (5H, m, C₆H₅) and 8.35 (1H, br. s, NH); δC -4.5 (OSi(C₃H₃)₂C(CH₃)₃), 18.1 (OSi(CH₃)₂C(C₃H₃)₃), 22.1 (OSi(CH₃)₂C(CH₃)₃), 25.6 (α'-CH₃), 72.7 (C-α’), 74.8 (OCH₂), 91.6 (CCl₃), 116.4 (C-6’), 117.3 (C-3’), 124.1 (C-4’), 127.8 (C-4”), 128.2 (C-2” and C-6”), 128.5 (C-3” and C-5”), 137.1 (C-1”), 137.6 (C-1’), 146.5 (C-2’), 152.7 (C-5’) and 161.2 (C-1); m/z 581 [M⁺ (⁸¹Br³⁵Cl), 4%], 579 [M⁺ (⁷⁹Br³⁷Cl), 2%], 420 (34), 418 (31), 363 (17), 361 (16), 329 (38), 327 (34), 272 (11), 270 (13), 248 (18), 191 (100) and 91 (77).

**Methyl (α'S and R, 2R)-2-(2'-benzyloxy-3'-bromo-5'-t-butyldimethylsilyloxy-α'-methylbenzyloxy)propanoate (337) and (338)**

Methyl (α'S and R, 2R)-2-(2'-benzyloxy-3'-bromo-5'-t-butyldimethylsilyloxy-α'-methylbenzyloxy)propanoate (337) and (338)

Boron trifluoride diethyl etherate (79 mg, 0.56 mmol) was added dropwise to a solution of imidate (327) (1.61g, 2.8mmol) and methyl (R)-lactate (182) (577 mg, 5.5 mmol) in dry hexane:dichloromethane (20 cm³, 2:1). The reaction was stirred under nitrogen for 40 min. Solid sodium hydrogen carbonate was added to the reaction and the resulting suspension was filtered through celite. The clear solution was then concentrated and chromatographed (radial, 10% ethyl acetate-hexane) to afford (337) and (338) as a yellow, oily inseparable mixture of diastereomers (1.33 g, 91%) (Found: M⁺, 522.1426. C₂₃H₃₅BrO₂Si requires M⁺(⁷⁹Br), 522.1437); ν max(film)/cm⁻¹ 1754 (C=O) and 1598 and 1498 (C=C); δH (mixture of two diasteriomers) 0.21 (12H, s, OSi(CH₃)₂C(CH₃)₃), 0.98 and 0.99 (each 9H, s, OSi(CH₃)₂C(CH₃)₃), 1.33 and 1.35 (each 3H, d, J 6.8 Hz, 2-CH₃), 1.36 and 1.40 (each 3H, d, J 6.5 Hz, α'-CH₃), 3.61 and 3.65 (each 3H, s, CO₂CH₃), 3.80 and 3.88 (each 1H, q, J 6.8 Hz, 2-H), 4.70-5.11 (6H, m, α'-H and OCH₂), 6.88, 6.93, 6.99 and 7.02 (each 1H, d, J 2.9 Hz, 4' and 6'-H) and 7.33-7.51 (10H, m, 2 x C₆H₅); δC (mixture of two
diasteriomers) -4.6 and -4.5 (OSi(CH₃)₂C(CH₃)₃), 18.1 and 19.0 (C-3), 18.1 and 18.2 , (OSi(CH₃)₂C(CH₃)₃), 23.2 and 23.6 , (OSi(CH₃)₂C(CH₃)₃), 25.6 (α’-CH₃), 51.8 and 51.7 (CO₂CH₃), 70.9 and 71.4 (C-2), 72.2 and 72.5 (C-α’), 75.5 (OCH₂), 127.6 and 127.8 (C-4’), 128.1 and 128.3 (C-2’” and C-6’”), 128.5 and 128.6 (C-3’” and C-5’”), 136.7 and 137.0 (C-1’’), 138.9 and 139.0 (C-1’), 147.1 and 147.6 (C-2’), 152.8 and 152.9 (C-5’) and 173.0 and 173.9 (C-1); m/z 524 [M + (81Br), 5%], 522 [M + (79Br), 5%], 433 (46), 431 (43), 330 (41), 328 (38), 272 (16), 270 (16), 191 (29) and 91 (100).

(α’R, 2R)-2-(2’-Benzyloxy-3’-bromo-5’-t-butyldimethylsilyloxy-α’-methylbenzyloxy)propanol (339) and (α’S, 2R)-2-(2’-Benzyloxy-3’-bromo-5’-t-butyldimethylsilyloxy-α’-methylbenzyloxy)propanol (340)

Lithium aluminium hydride was added portion-wise to a solution of the methyl ester (337) and (338) (600 mg, 1.15mmol) in dry diethyl ether (25 cm³) until TLC indicated no starting material remained. A saturated ammonium chloride solution was added drop-wise to the reaction mixture followed by anhydrous magnesium sulphate. Filtration through celite and concentration of the filtrate gave crude product, which was chromatographed (radial, 5-50% ethyl acetate-hexane) to afford two products as colourless oils.
136.8 (C-1′′), 140.4 (C-1′), 146.9 (C-2′) and 152.7 (C-5′); m/z 496 [M+ (^81Br), 4%], 494 [M+ (^79Br), 4%], 421 (7), 419 (6), 330 (80), 328 (76%), 274 (15), 272 (15), 191 (18) and 91 (100).

The product of higher Rf was identified as compound (340) (224 mg, 39%); [α]D -58.0° (c 1.0 in CHCl3) (Found: C, 58.55; H, 7.0; M+, 494.1474. C24H35BrO4Si requires C, 58.3; H, 7.15%; M(^79Br), 494.1487); ν(max(film)/cm⁻¹ 3466 (OH), 1598 and 1495 (C=C); δH 0.21 (6H, s, OSi(CH3)2C(CH3)3), 0.98 (9H, s, OSi(CH3)2C(CH3)3), 1.08 (3H, d, J 5.7 Hz, 2-CH3), 1.33 (3H, d, J 6.4 Hz, α′-CH3), 1.85 (1H, br. s, OH), 3.34-3.48 (3H, m, CH2OH and 2-H), 4.90 (1H, q, J 6.4 Hz, α′-H), 4.93 and 4.96 (each 1H, d, J 11.0 Hz, OCH2), 6.86 (1H, d, J 2.9 Hz, 6′-H), 7.01 (1H, d, J 2.9 Hz, 4′-H) and 7.35-7.51 (5H, m, C6H5); δC -4.5, (OSi(CH3)2C(CH3)3), 15.8, (C-3), 18.2, (OSi(CH3)2C(CH3)3), 23.8 (α′-CH3), 25.6 (OSi(CH3)2C(CH3)3), 67.1 (C-1), 67.7 (C-2), 73.1 (C-α′), 75.9 (OCH2), 117.2 (C-6′), 124.0 (C-4′), 125.9 (C-3′), 128.0 (C-2′′ and C-6′′), 128.3 (C-4′′), 128.6 (C-3′′ and C-5′′), 136.8 (C-1′′), 139.6 (C-1′), 147.3 (C-2′) and 152.9 (C-5′); m/z [M+ 496 (^81Br), 5%], 494 [M+ (^79Br), 5%], 421 (7), 419 (7), 330 (87), 328 (84), 273 (41), 271 (36), 192 (18) and 91 (100).

((α′R, 2R)-2-(2′-Benzyloxy-3′-bromo-5′-t-butyldimethylsilyloxy-α′-methybenzyloxy)-propanal (345)

Method A

Alcohol (339) (150 mg, 0.3mmol) in dry dichloromethane (5 cm³) was added to a stirred slurry of PCC (260 mg, 1.21 mmol) and basic alumina (4 g) in dry dichloromethane (15 cm³) at 0 °C under an atmosphere of argon. The reaction was allowed to reach room temperature and stirred for a further 14 h. The reaction mixture was then filtered through a short silica column (50% ethyl acetate-hexane), concentrated and chromatographed (radial, 5% ethyl acetate-hexane) to give aldehyde (345) (115 mg, 76%) as a colourless oil. [α]D +46.6° (c 1.0 in CHCl3); (Found: M+, 492.1333.

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C₂₄H₃₃BrO₄Si requires M(⁷⁹Br), 492.1331;  ν_{max}(film)/cm⁻¹ 1735 (C=O) and 1596 and 1496 (C=C); δ_H 0.21 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.99 (9H, s, OSi(CH₃)₂C(CH₃)₃), 1.18 (3H, d, J 7.0 Hz, 2-CH₃), 1.39 (3H, d, J 6.4 Hz, α'-CH₃), 3.59 (1H, dq, J 1.7 and 7.0 Hz, 2-H), 4.80 (1H, q, J 6.4 Hz, α'-H), 4.84 and 4.95 (each 1H, d, J 10.9 Hz, OCH₂), 6.88 (1H, d, J 2.9 Hz, 6'-H), 7.03 (1H, d, J 2.9 Hz, 4'-H), 7.32-7.48 (5H, m, C₆H₅) and 9.60 (1H, d, J 1.7 Hz, CHO); δ_C -4.5, (OSi(CH₃)₂C(CH₃)₃), 15.8 (C-3), 18.2 (OSi(CH₃)₂C(CH₃)₃), 23.6 (α'-CH₃), 25.6 (OSi(CH₃)₂C(CH₃)₃), 71.8 (C-2), 75.6 (OCH₂), 77.9 (C-α'), 117.0 (C-6'), 117.2 (C-3'), 124.3 (C-4'), 128.2 (C-2'' and C-6''), 128.4 (C-4''), 128.6 (C-3'' and C-5''), 136.6 (C-1''), 138.7 (C-1'), 147.3 (C-2'), 152.8 (C-5') and 203.3 (C-1'); m/z 494 [M⁺ (⁸¹Br), 1%], 492 [M⁺ (⁷⁹Br), 1%], 420 (15), 418 (14), 359 (13), 357 (13), 329 (32), 248 (11), 191 (66), 149 (21), 91 (88) and 73 (100).

**Method B**

To a solution of oxalyl chloride (453 mg, 3.57 mmol) in dry dichloromethane (10 cm³) at 70 °C under an atmosphere of argon was added dropwise a solution of dimethyl sulfoxide (558 mg, 7.14 mmol) in dry dichloromethane (2 cm³) keeping the temperature below -65 °C. After stirring for 15 min, a solution of the (α'R, 2R) alcohol (339) (354 mg, 0.71 mmol) in dry dichloromethane (2 cm³) was added drop-wise keeping the temperature below -65 °C and the stirring continued for a further 15 min at that temperature. Dry diisopropylamine (1.11 g, 8.59 mmol) was added slowly and the reaction stirred for a further 10 min at -70 °C before being allowed to warm to room temperature over 1 h. The reaction mixture was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 10-20% ethyl acetate-hexane) to give aldehyde (345) (312 mg, 88%).
According to method A described above for the preparation of the aldehyde (345) from the alcohol (339), the (α′S, 2R) alcohol (340) (200 mg, 0.4 mmol) was converted, after chromatography (radial, 5% ethyl acetate-hexane), into the aldehyde (346) as a colourless oil (150 mg, 75%) \([\alpha\]D = -21.3 ° (c 1.0 in CHCl3); (Found: C, 59.2; H, 6.95; M+, 492.1337. C24H33BrO4Si requires C, 58.5; H, 6.75; M(79Br), 492.1331); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1739 (C=O) and 1596 and 1495 (C=C); \(\delta\)H 0.20 (6H, s, OSi(CH3)2C(CH3)3), 0.98 (9H, s, OSi(CH3)2C(CH3)3), 1.21 (3H, d, J 6.8 Hz, 2-CH3), 1.37 (3H, d, J 6.4 Hz, α′-CH3), 3.61 (1H, d, J 1.2 and 6.8 Hz, 2-H), 4.87 (1H, q, J 6.4 Hz, α′-H), 4.94 (2H, s, OCH2), 6.90 (1H, d, J 2.9 Hz, 6′-H), 7.02 (1H, d, J 2.9 Hz, 4′-H) and 7.34-7.49 (5H, m, C6H5), 9.49 (1H, d, J 1.2 Hz, CHO); \(\delta\)C -4.5, (OSi(CH3)2C(CH3)3), 15.0 (C-3), 18.2 (OSi(CH3)2C(CH3)3), 23.4 (α′-CH3), 25.6 (OSi(CH3)2C(CH3)3), 70.6 (C-2), 75.8 (OCH2), 78.1 (C-α′), 117.2 (C-3′), 117.4 (C-6′), 124.4 (C-4′), 128.1 (C-2′ and C-6′), 128.3 (C-4′), 128.6 (C-3′ and C-5′), 136.6 (C-1′), 138.7 (C-1′), 147.3 (C-2′), 152.9 (C-5′) and 202.6 (C-1); m/z 494 [M+ (81Br), 1%], 492 [M+ (79Br), 1%], 359 (19), 357 (20), 329 (32), 191 (45), 91 (86) and 73 (100).

A mixture of the aldehyde (345) (300 mg, 0.61 mmol), tetrahydrofuran (20 cm\(^3\)) and saturated solutions of aqueous ammonium chloride and sodium fluoride (40 cm\(^3\), 1:1) was stirred for 16 h at room temperature. The reaction mixture was exhaustively extracted with diethyl ether and the residue obtained upon work-up was rapidly chromatographed (radial, 35% ethyl acetate-hexane) to afford the potentially unstable phenolic aldehyde (347) (168 mg, 73%) as a colourless oil. (Found: (M-H2O)+, 360.0353. C18H17BrO3 requires M(79Br), 360.0361); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3383 (OH), 1730 (C=O) and 1603 and 1497 (C=C); \(\delta\)H 1.19 (3H, d, J 7.0 Hz, 2-CH3), 1.39 (3H, d, J 6.4 Hz, 1′-H) and 7.34-7.49 (5H, m, C6H5), 9.49 (1H, d, J 1.2 Hz, CHO); \(\delta\)C -4.5, (OSi(CH3)2C(CH3)3), 15.0 (C-3), 18.2 (OSi(CH3)2C(CH3)3), 23.4 (α′-CH3), 25.6 (OSi(CH3)2C(CH3)3), 70.6 (C-2), 75.8 (OCH2), 78.1 (C-α′), 117.2 (C-3′), 117.4 (C-6′), 124.4 (C-4′), 128.1 (C-2′ and C-6′), 128.3 (C-4′), 128.6 (C-3′ and C-5′), 136.6 (C-1′), 138.7 (C-1′), 147.3 (C-2′), 152.9 (C-5′) and 202.6 (C-1); m/z 494 [M+ (81Br), 1%], 492 [M+ (79Br), 1%], 359 (19), 357 (20), 329 (32), 191 (45), 91 (86) and 73 (100).
Hz, $\alpha'$-CH$_3$), 3.64 (1H, dq, $J$ 1.5 and 7.0 Hz, 2-H), 4.80 (1H, $J$ 6.4 Hz, $\alpha'$-H), 4.85 and 4.93 (each 1H, d, $J$ 10.8 Hz, OCH$_2$), 6.40 (1H, br. s, OH), 6.90 (1H, d, $J$ 2.9 Hz, 6'-H), 7.03 (1H, d, $J$ 2.9 Hz, 4'-H), 7.35-7.48 (5H, m, C$_6$H$_5$) and 9.58 (1H, d, $J$ 1.5 Hz, CHO);
$\delta$C 16.1 (C-3), 23.8 ($\alpha'$-CH$_3$), 74.4 (C-2), 76.2 (OCH$_2$), 78.4 (C-$\alpha'$), 113.0 (C-6'), 118.0 (C-3'), 120.2 (C-4'), 128.7 (C-2'' and C-6''), 128.8 (C-4''), 129.0 (C-3'' and C-5''), 136.9 (C-1''), 139.4 (C-1'), 146.9 (C-2''), 153.7 (C-5'') and 203.8 (C-1); m/z 362 [(M-H$_2$O)$^+$ ($^{81}$Br), 4%], 360 [(M-H$_2$O)$^+$ ($^{79}$Br), 4%], 167 (8) 149 (27) and 91 (100).

According to the method described above for the preparation of the phenolic aldehyde (347) from the ($\alpha'$R, 2R) aldehyde (345), the ($\alpha'S$, 2R) aldehyde (346) (130 mg, 0.26 mmol) was converted, after chromatography (radial, 5% ethyl acetate-hexane), into the phenolic aldehyde (348) as a colourless oil (115 mg, 76%); (Found: (M-H$_2$O)$^+$, 360.0352. C$_{18}$H$_{17}$BrO$_3$ requires M($^{79}$Br), 360.0361); $\nu_{max}$(film)/cm$^{-1}$ 3386 (OH), 1732 (C=O) and 1602, 1575 and 1498 (C=C); $\delta$H 1.23 (3H, d, $J$ 6.9 Hz, 2-CH$_3$), 1.36 (3H, d, $J$ 6.4 Hz, $\alpha'$-CH$_3$), 3.68 (1H, dq, $J$ 0.9 and 6.9 Hz, 2-H), 4.87 (1H, q, $J$ 6.4 Hz, $\alpha'$-H), 4.90 and 4.95 (each 1H, d, $J$ 11.1 Hz, OCH$_2$), 4.85-4.97 (1H, br. s, OH), 6.96 (1H, d, $J$ 2.9 Hz, 6'-H), 7.04 (1H, d, $J$ 2.9 Hz, 4'-H), 7.35-7.49 (5H, m, C$_6$H$_5$) and 9.45 (1H, d, $J$ 0.9 Hz, CHO); $\delta$C 14.9 (C-3), 23.3 ($\alpha'$-CH$_3$), 70.8 (C-2), 75.9 (OCH$_2$), 78.1 (C-$\alpha'$), 112.8 (C-6'), 117.6 (C-3'), 120.0 (C-4'), 128.2 (C-2'' and C-6''), 128.4 (C-4''), 128.6 (C-3'' and C-5''), 136.6 (C-1''), 138.7 (C-1'), 146.4 (C-2''), 153.4 (C-5'') and 202.8 (C-1); m/z 362 [(M-H$_2$O)$^+$ ($^{81}$Br), 4%], 360 [(M-H$_2$O)$^+$ ($^{79}$Br), 4%], 167 (6), 149 (22) and 91 (100).
(1R, 3R, 4S)-8-Benzylxy-7-bromo-3,4-dihydro-4,5-dihydroxy-1,3-dimethyl-
benzo[c]pyran (318)

Fresh neat titanium tetraisopropoxide (253 mg, 0.89 mmol) was
added to a solution of the (α’R, 2R) phenolic aldehyde (347) (240
mg, 0.63 mmol) in dry dichloromethane (15 cm$^3$) at 0 °C, under an
atmosphere of argon. After standing for 10 min at 0 °C, the reaction
mixture was sonically irradiated at 8-35 °C for 5 h, after which dichloromethane (30
cm$^3$) and saturated solutions of aqueous sodium fluoride and ammonium chloride (60
cm$^3$, 1:1) were added. The mixture was stirred until the yellow colour had discharged.
The aqueous layer was extracted with dichloromethane and the residue obtained upon
work-up was rapidly chromatographed (radial, 30-50% ethyl acetate-hexane) to give the
potentially unstable cyclised product (318) (165 mg, 69%) as white prisms m.p. 149-150
°C (dichloromethane-hexane) [α]$_D$ -46.5 ° (c 1.0 in CHCl$_3$); (Found: M$^+$, 378.0472.
C$_{18}$H$_{19}$BrO$_4$ requires M(+$^{81}$Br), 378.0466); $\nu_{\text{max}}$/cm$^{-1}$ 3450 and 3292 (OH) and 1581 and
1496 (C=C); $\delta$$_H$ 1.36 (3H, d, J 6.1 Hz, 3-CH$_3$), 1.54 (3H, d, J 6.7 Hz, 1-CH$_3$), 3.86 (1H,
dq, J 6.1 and 8.7 Hz, 3-H), 4.20-5.20 (2H, br. s, 4- and 5-OH), 4.51 (1H, d, J 8.7 Hz, 4-
H), 4.71 and 5.12 (each 1H, d, J 10.7 Hz, OCH$_2$), 4.96 (1H, q, J 6.7 Hz, 1-H), 6.99 (1H,
s, 6-H) and 7.34-7.48 (5H, m, C$_6$H$_5$); $\delta$$_C$ 18.3 (3-CH$_3$), 19.8 (1-CH$_3$), 67.3 (C-3), 69.0
(C-4), 70.7 (C-1), 75.0 (OCH$_2$), 117.0 (C-8), 119.4 (C-6), 120.6 (C-7), 128.4 (C-2’’ and
C-6’’), 128.7 (C-4’’), 129.0 (C-3’’ and C-5’’), 135.5 (C-1’’), 136.7 (C-8a), 144.4 (C-4a)
and 152.9 (C-5); m/z 380 [M$^+$ ($^{81}$Br), 22%], 378 [M$^+$ ($^{79}$Br), 22%], 363 (17), 361 (20),
299 (42), 287 (17), 282 (14), 270 (77), 253 (30), 227 (96) and 148 (100).
(1R, 3R, 4S)-7-Bromo-3,4-dihydro-4-hydroxy-1,3-dimethylbenzo[c]pyran-5,8-quinone (199) and (1R, 3R, 4S)-3,4-dihydro-4-hydroxy-1,3-dimethylbenzo[c]pyran-5,8-quinone (350)

A solution of the diol (318) (165 mg, 0.44 mmol) in dry ethyl acetate (15 cm³) was stirred with 10% palladium on carbon catalyst (165 mg) under a hydrogen atmosphere until one molar equivalent had been consumed (1.5 h). The mixture was filtered through celite, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate-hexane) to afford unstable compounds (349) and (351) as an oily mixture (126 mg, 0.44 mmol). This was immediately dissolved in acetonitrile (15 cm³) and cerium(IV) ammonium nitrate (342 mg, 0.62 mmol) in water (3 cm³) was added drop-wise to the solution. After stirring for 20 min the reaction was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 15-25% ethyl acetate-hexane) to give a mixture of the brominated quinone (199) and the debrominated quinone (350), each as bright yellow crystals.

The product of higher R_f was identified as (199) (51 mg, 41%) m.p. 140-142 °C (dichloromethane-hexane) [α]D -156 ° (c in 1.0 CHCl₃);
(Found: C, 46.4; H, 3.95; M⁺, 285.9843. C₁₁H₁₁BrO₄ requires C, 46.15; H, 3.9%; M(⁷⁹Br), 285.9843); v_max/cm⁻¹ 3505 (OH), 1677 and 1652 (C=O) and 1590 (C=C); δ_H 1.37 (3H, d, J 6.2 Hz, 3-CH₃), 1.54 (3H, d, J 6.8 Hz, 1-CH₃), 3.43 (1H, d, J 2.6 Hz, OH), 3.84 (1H, dq, J 6.2 and 7.7 Hz, 3-H), 4.35 (1H, ddd, J 1.4, 2.6 and 7.7 Hz, 4-H), 4.80 (1H, dq, J 1.4 and 6.8 Hz, 1-H) and 7.27 (1H, s, 6-H); δ_C 18.8 (3-CH₃), 19.2 (1-CH₃), 67.5 (C-3), 67.6 (C-4), 67.8 (C-1), 138.1 (C-7), 138.3 (C-6), 139.7 (C-8a), 145.7 (C-4a), 178.7 (C-8) and 186.0 (C-5); m/z 270 [M⁺-H₂O (⁸¹Br), 20%], 268 [M⁺-H₂O (⁷⁹Br), 13%], 244 (100), 242 (98), 216 (40), 214 (41), 163 (12), 134 (23) and 107 (34).
The product of lower R F was identified as (350) (15 mg, 17%) m.p. 95-97 °C (dichloromethane-hexane) (Lit., 128b,c for enantiomer 96.5 - 99.5 °C) [α]D -307.7 ° (c in 1.0 CHCl3) (Lit., 128b,c for enantiomer +313.1 °); (Found: C, 63.7; H, 6.2; (M+2)+, 210.0879. C11H12O4 requires C, 63.45; H, 5.8%; M, 210.0892); υmax/cm-1 3492 (OH) and 1650 (C=O); δH 1.37 (3H, d, J 6.2 Hz, 3-CH3), 1.52 (3H, d, J 6.8 Hz, 1-CH3), 3.52 (1H, d, J 2.5 Hz, OH), 3.84 (1H, dq, J 7.8 and 6.2 Hz, 3-H), 4.35 (1H, ddd, J 1.6, 2.5 and 7.8 Hz, 4-H), 4.75 (1H, dq, J 1.6 and 6.8 Hz, 1-H) and 6.73 (2H, s, 6- and 7-H); δC 18.8 (3-CH3), 19.3 (1-CH3), 67.2 (C-3), 67.3 (C-4), 67.6 (C-1), 136.8 (C-6), 137.3 (C-7), 138.3 (C-8a), 146.5 (C-4a), 186.3 (C-8) and 188.8 (C-5); m/z 210 [(M+2)+, 100%], 208 (12), 193 (74), 191 (20), 175 (32), 165 (11) and 147 (11).

6,8-Dihydroxy-2-methyl-1,4-naphthoquinone (357)

To a stirred solution of 2-bromo-6-methyl-1,4-benzoquinone (356) (150 mg, 0.75 mmol) in dry tetrahydrofuran (10 cm3) at 0 °C was added drop-wise a solution of the diene (200) (1.29 g, 4.96 mmol) in tetrahydrofuran (5 cm3). The green coloured mixture was stirred for 24 h during which time a bright yellow solution was obtained. The reaction mixture was diluted with dichloromethane (100 cm3) and the mixture poured into water (150 cm3) and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 30% ethyl acetate-hexane) and recrystallised (dichloromethane-hexane) to give the diol (357) (110 mg, 73%) as bright orange plates, m.p. 190° C (decomp.) (hexane). (Found: C, 64.15; H, 3.9; M, 204.0415. C11H8O4 requires C, 64.7; H, 3.9%; M, 204.0422); υmax/cm-1 3405 (OH), 1637 and 1616 (C=O) and 1490 (C=C); δH (acetone-d6) 2.09 (3H, d, J 1.5 Hz, 2-CH3), 6.54 (1H, d, J 2.4 Hz, 7-H), 6.74 (1H, q, J 1.5 Hz, 3-H), 6.96 (1H, d, J 2.4 Hz, 5-H), 9.86 (1H, br. s, 6-OH) and 12.21 (1H, br. s, 8-OH); δC 18.1 (2-CH3), 107.8 (C-8), 110.3 (C-5), 110.6 (C-3), 112.3 (C-8a), 138.6 (C-4a), 137.6 (C-7), 151.7 (C-2), 167.6 (C-6), 186.8 (C-1) and 192.0 (C-4); m/z 204 (M+, 64%), 149 (40), 91 (16) and 57 (100).
To a stirred solution of bromoquinone (199) (100 mg, 0.35 mmol) in dry tetrahydrofuran (10 cm³) at 0 °C was added drop-wise a solution of the diene (200) (181 mg, 0.70 mmol) in tetrahydrofuran (5 cm³). The green coloured mixture was stirred for 24 h during which time a bright yellow solution was obtained. The reaction mixture was diluted with dichloromethane (100 cm³) and the mixture poured into water (150 cm³) and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 30% ethyl acetate-hexane) and recrystallised to give quinone A (16) (30 mg, 30%) as bright orange plates, m.p. 200 °C (decomp.) (benzene) (Lit., 104 200 °C) [α]D +37.1 ° (c 1.0 in 1% CH₃CO₂H/CH₃OH) (Lit. 168 +41 °) (Found: C, 61.75; H, 4.4; (M-H)⁺, 289.0702. C₁₅H₁₄O₆ requires C, 62.05; H, 4.85%; (M-H), 289.0712); νmax/cm⁻¹ 3402 (OH), 1641 (C=O) and 1552 (C=C); δH (acetone-d₆) 1.09 (3H, d, J 6.3 Hz, 3-CH₃), 1.36 (3H, d, J 6.8 Hz, 1-CH₃), 2.60-2.70 (1H, br. s, 4-OH), 3.66 (1H, dq, J 6.3 and 7.2 Hz, 3-H), 4.00-4.10 (1H, br. s, 7-OH), 4.15 (1H, dd, J 1.2 and 7.2 Hz, 4-H), 4.61 (1H, dq, J 1.2 and 6.8 Hz, 1-H), 6.40 (1H, d, J 2.4 Hz, 8-H), 6.85 (1H, d, J 2.4 Hz, 6-H) and 11.89 (1H, s, 9-OH); δC 18.5 (3-CH₃), 19.5 (1-CH₃), 66.9 (C-3), 67.2 (C-1), 69.0 (C-4), 108.4 (C-8), 108.9 (C-6), 126.8 (C-4a), 135.0 (C-10a), 142.5 (C-5a), 148.5 (C-9a), 165.3 (C-7), 165.7 (C-9), 185.0 (C-5) and 188.0 (C-10).

The (α′S, 2R) phenolic aldehyde (348) (200 mg, 0.53 mmol) was treated with titanium tetraisopropoxide (225 mg, 0.79 mmol) as described above for the phenolic aldehyde (347), to afford the potentially unstable diols (362) and (363) as colourless oils in a ratio of 5:3 respectively.
The product of higher R_F was identified as (362) (101 mg, 51%) [α]D -45.9 ° (c 1.0 in CHCl3); (Found: M+, 378.0465. C_{18}H_{19}BrO_{4} requires M(^{79}Br), 378.0466); ν_{max}(film)/cm^{-1} 3450 and 3292 (OH) and 1597 and 1461 (C=C); δ_{H} 1.39 (3H, d, J 6.1 Hz, 3-CH_{3}), 1.53 (3H, d, J 6.3 Hz, 1-CH_{3}), 3.39 (1H, dq, J 8.8 and 6.1 Hz, 3-H), 3.90-4.30 (2H, br. s, 4- and 5-OH), 4.55 (1H, dd, J 0.7 and 8.8 Hz, 4-H), 4.69 and 4.99 (each 1H, d, J 10.7 Hz, OCH_{2}), 4.76 (1H, dq, J 0.7 and 6.3 Hz, 1-H), 7.04 (1H, s, 6-H) and 7.34-7.49 (5H, m, C_{6}H_{5}); δ_{C} 17.9 (3-CH_{3}), 22.0 (1-CH_{3}), 71.0 (C-3), 71.9 (C-4), 73.5 (C-1), 75.0 (OCH_{2}), 117.5 (C-8), 119.6 (C-6), 122.5 (C-7), 128.4 (C-4”), 128.4 (C-2” and C-6”), 128.5 (C-3” and C-5”), 135.5 (C-1”), 136.6 (C-8a), 144.9 (C-4a) and 171.7 (C-5); m/z 362 [M^-H_{2}O (^{81}Br), 8%], 360 [M^-H_{2}O (^{79}Br), 8%], 255 (11), 149 (15), 91 (100) and 65 (16).

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\begin{align*}
&\text{Br} &\text{O} &\text{Bn} &\text{O} &\text{H} &\text{OH} \\
&\text{O} &\text{Br} &\text{OH}
\end{align*}
\]

(362)

The product of lower R_F was identified as (363) (60 mg, 30%) [α]D -54.9 ° (c 1.0 in CHCl3); (Found: C, 57.0; H, 5.2; M+, 378.0465. C_{18}H_{19}BrO_{4} requires C, 57.0; H, 5.05%; M(^{79}Br), 378.0466); ν_{max}(film)/cm^{-1} 3495 and 3265 (OH) and 1588 and 1495 (C=C); δ_{H} 1.34 (3H, d, J 6.5 Hz, 3-CH_{3}), 1.57 (3H, d, J 6.3 Hz, 1-CH_{3}), 3.59 (1H, dq, J 1.6 and 6.5 Hz, 3-H), 4.39 (1H, d, J 1.6 Hz, 4-H), 4.63 (1H, q, J 6.3 Hz, 1-H), 3.80-4.30 (2H, br. s, 4- and 5-OH), 4.71 and 4.97 (each 1H, d, J 10.7 Hz, OCH_{2}), 7.06 (1H, s, 6-H), 7.34-7.45 (5H, m, C_{6}H_{5}); δ_{C} 16.8 (3-CH_{3}), 21.9 (1-CH_{3}), 65.2 (C-3), 72.7 (C-4), 73.0 (C-1), 75.4 (OCH_{2}), 118.5 (C-8), 119.6 (C-6), 124.0 (C-7), 128.8 (C-4”), 128.9 (C-2” and C-6”), 129.0 (C-3” and C-5”), 136.0 (C-1”), 136.9 (C-8a), 146.0 (C-4a) and 152.3 (C-5); m/z 363 [M^-OH (^{81}Br), 16%], 361 [M^-OH (^{79}Br), 16%], 255 (12), 253 (12), 205 (8), 149 (42), 84 (100) and 65 (10).

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\begin{align*}
&\text{Br} &\text{O} &\text{Bn} &\text{O} &\text{H} &\text{OH} \\
&\text{O} &\text{OH} &\text{Br}
\end{align*}
\]

(363)
A solution of the diol (362) (55 mg, 0.15 mmol) in dry ethyl acetate (15 cm³) was stirred with 10% palladium on carbon catalyst (55 mg) under a hydrogen atmosphere for 1.5 h. The mixture was filtered through celite, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate-hexane) to afford the diols (364) and (365) as an unstable, oily mixture (42 mg, 0.15 mmol). This was immediately dissolved in acetonitrile (15 cm³) and cerium(IV) ammonium nitrate (159 mg, 0.29 mmol) in water (3 cm³) was added dropwise to the solution. After 20 min the reaction was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 15-25% ethyl acetate-hexane) to give the brominated quinone (366) and the debrominated quinone (367) as bright yellow crystals.

The product of higher Rf was identified as (366) (18 mg, 43%), m.p. 116-118 °C (dichloromethane-hexane) [α]D -349.4° (c in 1.0 CHCl₃); (Found: C, 46.45; H, 3.9; (M-H₂O)⁺, 267.9724. C₁₁H₁₁BrO₄ requires C, 46.15; H, 3.9%; (M-H₂O)(⁷⁹Br), 267.9735); ʋmax/cm⁻¹ 3226 (OH) and 1666 and 1652 (C=O); δH 1.41 (3H, d, J 6.2 Hz, 3-CH₃), 1.46 (3H, d, J 6.7 Hz, 1-CH₃), 3.41 (1H, dq, J 8.3 and 6.2 Hz, 3-H), 3.57 (1H, d, J 2.2 Hz, OH), 4.38 (1H, ddd, J 2.2, 2.9 and 8.3 Hz, 4-H), 4.70 (1H, dq, J 2.9 and 6.7 Hz, 1-H) and 7.25 (1H, s, 6-H); δC 18.2 (3-CH₃), 20.5 (1-CH₃), 67.6 (C-3), 70.5 (C-4), 73.0 (C-1), 137.8 (C-6), 138.0 (C-7), 140.8 (C-8a), 145.5 (C-4a), 178.8 (C-8) and 185.6 (C-5); m/z 288 [M⁺ (⁸¹Br), 100%], 286 [M⁺ (⁷⁹Br), 98%], 215 (41), 213 (41), 164 (70), 136 (41), 107 (63), 77 (44) and 65 (20).

The lower Rf product was identified as (367) (12 mg, 40%) and was obtained as an oil; (Found: (M+2H)⁺, 210.0890. C₁₁H₁₂O₄ requires (M+2H), 210.0894). ʋmax/cm⁻¹ 3230 (OH) and 1672 and 1654 (C=O);
\( \delta_H \) 1.41 (3H, d, \( J \) 6.1 Hz, 3-CH\(_3\)), 1.45 (3H, d, \( J \) 6.7 Hz, 1-CH\(_3\)), 3.42 (1H, dq, \( J \) 8.3 and 6.1 Hz, 3-H), 3.69 (1H, d, \( J \) 2.0 Hz, OH), 4.38 (1H, ddd, \( J \) 2.0, 2.9 and 8.3 Hz, 4-H), 4.67 (1H, dq, \( J \) 2.9 and 6.7 Hz, 1-H) and 6.72 (2H, s, 6- and 7-H); \( \delta_C \) 19.1 (3-CH\(_3\)), 21.4 (1-CH\(_3\)), 68.5 (C-3), 70.8 (C-4), 73.8 (C-1), 126.7 (C-8a), 136.9 (C-6), 138.0 (C-7, 141.0 (C-4a), 141.9 (C-8) and 186.3 (C-5); m/z 164 [M\(^+\)-CH\(_3\)CHO, 100%], 147 (12), 136 (51), 108 (51) and 91 (22).

(1S, 3R, 4S)-3,4-Dihydro-4,7,9-trihydroxy-1,3-dimethylnaptho[2,3-c]pyran-5,10-quinone (358)

Bromoquinone (366) (84 mg, 0.29 mmol) was treated with the diene (200) (152 mg, 0.58 mmol), as described above for the conversion of (199) to the quinone A (16), to give the pyran quinone (358) (20 mg, 23%) as bright orange plates, m.p. 196-198 °C (decomp.) (benzene) \([\alpha]_D\) -459 ° (c 1.0 in 1% CH\(_3\)CO\(_2\)H/CH\(_3\)OH) (Lit.,\(^{168}\) of enantiomer +568 °) Found: M\(^+\), 290.0815. C\(_{15}\)H\(_{14}\)O\(_6\) requires M\(^+\), 290.0790; \( \nu_{\text{max}}/\text{cm}^{-1} \) 3492 and 3222 (OH), 1631 (C=O) and 1497 (C=C); \( \delta_H \) (acetone-d\(_6\)) 1.15 (3H, d, \( J \) 6.2 Hz, 3-CH\(_3\)), 1.31 (3H, d, \( J \) 6.6 Hz, 1-CH\(_3\)), 2.60-2.80 (1H, br. s, 4-OH), 3.23 (1H, dq, \( J \) 6.2 and 8.2 Hz, 3-H), 4.15-4.30 (1H, br. s, 7-OH), 4.18 (1H, dd, \( J \) 2.5 and 8.2 Hz, 4-H), 4.60 (1H, dq, \( J \) 2.5 and 6.6 Hz, 1-H), 6.42 (1H, d, \( J \) 2.3 Hz, 8-H), 6.87 (1H, d, \( J \) 2.3 Hz, 6-H) and 11.92 (1H, br. s, 9-OH); \( \delta_C \) 21.1 (3-CH\(_3\)), 23.8 (1-CH\(_3\)), 68.6 (C-3), 71.1 (C-1), 74.3 (C-4), 111.0 (C-8), 111.3 (C-6), 127.3 (C-4a), 137.4 (C-10a), 147.5 (C-5a), 150.7 (C-9a), 167.7 (C-7), 168.1 (C-9), 187.6 (C-5) and 191.1 (C-10).
(1S, 3R, 4R)-7-Bromo-4-hydroxy-3,4-dihydro-1,3-dimethylbenzo[c]pyran-5,8-quinone (370) and (1S, 3R, 4R)-3,4-dihydro-4-hydroxy-1,3-dimethylbenzo[c]pyran-5,8-quinone (371).

A solution of the diol (363) (110 mg, 0.29 mmol) in dry ethyl acetate (15 cm³) was stirred with 10% palladium on carbon catalyst (110 mg) under a hydrogen atmosphere for 1.5 h. The mixture was filtered through celite, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate-hexane) to afford an unstable oily mixture (368) and (369) (80 mg, 0.28 mmol). This was immediately dissolved in acetonitrile (15 cm³) and cerium(IV) ammonium nitrate (303 mg, 0.55 mmol) in water (3 cm³) was added drop-wise to the solution. After 20 min the reaction was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 15-25% ethyl acetate-hexane) to give the brominated quinone (370) and the debrominated quinone (371) as bright yellow crystals.

The product of higher R_f was identified as (370) (35 mg, 42%) m.p. 143-145 °C (dichloromethane-hexane) [α]_D -107° (c in 1.0 CHCl₃); (Found: C, 46.2; H, 3.8; (M-H₂O)⁺, 267.9724. C₁₁H₁₁BrO₄ requires C, 46.15; H, 3.9%; (M-H₂O) (⁷⁹Br), 267.9735); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3470 (OH) and 1672 and 1653 (C=O); \( \delta_{\text{H}} \) 1.37 (3H, d, J 6.4 Hz, 3-CH₃), 1.54 (3H, d, J 6.6 Hz, 1-CH₃), 2.13 (1H, J 8.1 Hz, OH), 3.59 (1H, dq, J 1.6 and 6.4 Hz, 3-H), 4.37 (1H, ddd, J 1.4, 1.6 and 8.1 Hz, 4-H), 4.67 (1H, dq, J 1.4 and 6.6 Hz, 1-H) and 7.32 (1H, s, 6-H); \( \delta_{\text{C}} \) 16.1 (3-CH₃), 20.6 (1-CH₃), 61.6 (C-3), 70.4 (C-4), 72.2 (C-1), 137.6 (C-6), 137.8 (C-7), 140.2 (C-8a), 145.4 (C-4a), 179.1 (C-8) and 183.3 (C-5); m/z 270 [M⁺-H₂O (⁸¹Br), 27%], 268 [M⁺-H₂O (⁷⁹Br), 16%], 255 (100), 253 (71) and 149 (17).

The product of lower R_f was identified as (371) (20 mg, 33%) as an orange oil; [α]_D +55.9° (c in 1.0 CHCl₃); (Found: C, 63.8; H, 5.6; (M+2H)⁺, 210.0890. C₁₁H₁₂O₄ requires C, 63.45; H, 5.8%; (M+2H), 210.0892); \( \nu_{\text{max}}/\text{cm}^{-1} \) 3569 (OH), 1655 (C=O) and 1602 (C=C); \( \delta_{\text{H}} \) 1.37 (3H, d, J 6.4 Hz, 3-CH₃), 1.53 (3H, d, J 6.6 Hz, 1-CH₃), 2.08 (1H, br. s, OH), 3.59 (1H,
dq, J 1.6 and 6.4 Hz, 3-H), 4.37 (1H, dd, J 1.4 and 1.6 Hz, 4-H), 4.64 (1H, dq, J 1.4 and 6.6 Hz, 1-H) and 6.73 and 6.80 (each 1H, d, J 10.2 Hz, 6- and 7-H): δC 16.1, (3-CH₃), 20.6 (1-CH₃), 61.6 (C-3), 69.9 (C-4), 73.3 (C-1), 136.0 (C-6), 137.1 (C-7), 139.7 (C-8a), 145.1 (C-4a), 185.9 (C-8) and 186.9 (C-5); m/z 164 [M’-CH₃CHO, 100%], 147 (12), 136 (51), 108 (51) and 91 (22).

**15. 3R, 4R)-3,4-Dihydro-4,7,9-trihydroxy-1,3-dimethylnaphtho[2,3-c]pyran-5,10-quinone (359)**

Bromoquinone (370) (60 mg, 0.21 mmol) was treated with the diene (200) (108 mg, 0.42 mmol), as described above for the conversion of the benzoquinone (366) to the naphthopyranquinone (358), to give the product (359) (14 mg, 23%) as bright orange plates, m.p. 102-103 °C (decomp.) (benzene) [α]D -134 ° (c 1.0 in 1% CH₃CO₂H/CH₃OH) (Lit., 168° of enantiomer +278 °) (Found: (M-H)+, 289.0711. C₁₅H₁₄O₆ requires (M-H), 289.0712); νmax/cm⁻¹ 3444 (OH), 1639 (C=O) and 1463 (C=C); δH (acetone-d₆) 1.31 (3H, d, J 6.3 Hz, 3-CH₃), 1.56 (3H, d, J 6.5 Hz, 1-CH₃), 3.20-3.60 (2H, br. s, 4- and 7-OH), 3.64 (1H, dq, J 1.2 and 6.3 Hz, 3-H), 4.44 (1H, t, J 1.2 Hz, 4-H), 4.76 (1H, dq, J 1.2 and 6.5 Hz, 1-H), 6.62 (1H, d, J 2.3 Hz, 8-H), 7.10 (1H, d, J 2.3 Hz, 6-H) and 12.16 (1H, br. s, 9-OH); δC 17.0 (3-CH₃), 21.8 (1-CH₃), 62.4 (C-3), 70.6 (C-1), 73.1 (C-4), 108.7 (C-8), 109.2 (C-6), 110.1 (C-4a), 135.3 (C-10a), 143.9 (C-5a), 148.6 (C-9a), 165.7 (C-7), 166.3 (C-9), 183.5 (C-5) and 189.5 (C-10).
Diol (318) (450 mg, 1.19 mmol) in dry dimethylformamide (15 cm³) was treated with an excess of potassium carbonate (819 mg, 5.93 mmol) and iodomethane (843 mg, 5.93 mmol) and the mixture refluxed under an atmosphere of argon for 1 h. The reaction mixture was then cooled, filtered, concentrated and chromatographed (radial, 15% ethyl acetate-hexane) to give the methylated product (319) as a light yellow oil (450 mg, 96%) \([\alpha]_D -47.7 \degree \text{ (c 1.0 in CHCl}_3)\); (Found: C, 58.6; H, 5.45; M⁺, 392.0636. C\(_{19}H_{21}BrO_4\) requires C, 58.15%; H, 5.4%; M \(^{(79}Br\), 392.0623); \(\nu_{\text{max}}\text{(film)/cm}^{-1}\) 3569 (OH) and 1580 and 1498 (C= C); \(\delta_H\) 1.35 (3H, d, \(J 6.2 \text{ Hz, 3-CH}_3\)), 1.59 (3H, d, \(J 6.6 \text{ Hz, 1-CH}_3\)), 3.64 (1H, d, \(J 2.5 \text{ Hz, OH}\)), 3.86 (3H, s, OCH\(_3\)), 3.96 (1H, dq, \(J 7.5 \text{ and } 6.2 \text{ Hz, 3-H}\)), 4.50 (1H, dd, \(J 2.5 \text{ and } 7.5 \text{ Hz, 4-H}\)), 4.75 and 5.12 (each 1H, d, \(J 10.8 \text{ Hz, OCH}_2\)), 4.96 (1H, q, \(J 6.6 \text{ Hz, 1-H}\)), 7.01 (1H, s, 6-H) and 7.32-7.49 (5H, m, C\(_6\)H\(_5\)); \(\delta_C\) 19.6 (3-CH\(_3\)), 20.6 (1-CH\(_3\)), 56.9 (OCH\(_3\)), 68.4 (C-3), 68.7 (C-4), 69.1 (C-1), 75.7 (OCH\(_2\)), 114.6 (C-6), 116.9 (C-8), 125.8 (C-7), 128.8 (C-4”), 129.1 (C-2” and C-6”’), 129.4 (C-3”’ and C-5”’), 137.2 (C-1”’), 137.6 (C-8a), 146.3 (C-4a) and 155.4 (C-5); m/z 394 [M⁺ \(^{(81}Br\), 2%], 392 [M⁺ \(^{(79}Br\), 2%], 302 (10), 300 (10), 286 (8), 284 (8), 149 (19) and 91 (100).

Phosphorus pentachloride (100 mg, 0.48 mmol) was added to a stirred solution of compound (319) (94 mg, 0.24 mg), in dry diethyl ether (10 cm³). The mixture was stirred for 10 min at room temperature under an atmosphere of argon, then quenched with water (20 cm³), extracted with diethyl ether and concentrated. The residue obtained was immediately redissolved in acetonitrile (10 cm³) and then deionised water (1 cm³) containing silver nitrate (222 mg, 1.31 mmol) was added. The mixture was stirred for a further 3.5 h at room temperature during which time a white precipitate
formed. The reaction mixture was extracted with diethyl ether, dried, concentrated and chromatographed (radial, 15% ethyl acetate-hexane) to afford, first, starting material (319) (20 mg, 22%) followed by its C-4 epimeric alcohol (320) (67 mg, 72%) as white plates m.p. 81.5-82 °C (hexane/dichloromethane) [α]D -50 ° (c 1.0 in CHCl3); (Found: C, 58.4; H, 5.1; M+, 392.0637. C19H21BrO4 requires C, 58.15; H, 5.4%; M(79Br), 392.0623); υmax(film)/cm⁻¹ 3466 (OH) and 1577 and 1498 (C=C); δH 1.38 (3H, d, J 6.4 Hz, 3-CH₃), 1.51 (3H, d, J 6.7 Hz, 1-CH₃), 2.13 (1H, br. s, OH), 3.85 (3H, s, OCH₃), 4.03 (1H, q, J 1.9 and 6.4 Hz, 3-H), 4.49 (1H, d, J 1.9 Hz, 4-H), 4.71 and 5.13 (each 1H, d, J 10.7 Hz, OCH₂), 5.06 (1H, q, J 6.7 Hz, 1-H), 7.01 (1H, s, 6-H) and 7.32-7.49 (5H, m, C₆H₅); δC 18.7 (3-CH₃), 20.8 (1-CH₃), 58.0 (OCH₃), 64.1 (C-3), 68.0 (C-4), 71.1 (C-1), 76.9 (OCH₂), 115.6 (C-6), 118.9 (C-7), 127.1 (C-8), 129. 9 (C-4″), 130.2 (C-2″ and C-6″), 130.5 (C-3″ and C-5″), 137.2 (C-1″), 138.7 (C-8a), 147.3 (C-4a) and 156.3 (C-5); m/z 394 [M⁺ (£¹Br), 1%], 392 [M⁺ (£⁷⁹Br), 1%], 376 (3), 374 (3), 302 (8), 300 (8), 286 (17), 284 (17), 149 (36), 91 (100) and 65 (11).

(1R, 3R, 4R)-7-Bromo-3,4-dihydro-4-hydroxy-1,3-dimethylbenzo[c]pyran-5-8-quinone (321) and (1R, 3R, 4R)-3,4-dihydro-4-hydroxy-1,3-dimethylbenzo[c]pyran-5-8-quinone (375)

A solution of compound (320) (168 mg, 0.43 mmol) in dry ethyl acetate (15 cm³) was stirred with 10% palladium on carbon catalyst (100 mg,) under a hydrogen atmosphere for 1.5 h. The mixture was filtered through celite, concentrated and purified through rapid chromatography (radial, 35% ethyl acetate-hexane) to afford a oily unstable mixture (373) and (374) (130 mg, 0.43 mmol). This was immediately dissolved in acetonitrile (15 cm³) and cerium(IV) ammonium nitrate (470 mg, 0.86 mmol) in water (3 cm³) was added drop-wise to the solution. After 20 min the reaction was quenched with water and exhaustively extracted with dichloromethane. The residue obtained upon work-up was chromatographed (radial, 15-25% ethyl acetate-hexane) to give both the brominated quinone (321) and the debrominated quinone (375) as bright yellow crystals.
The product of higher R_F was identified as (321) (63 mg, 51%) m.p. 144-145 °C (dichloromethane-hexane) [α]D +94 ° (c in 1.0 CHCl₃); (Found: C, 46.25; H, 4.0; (M-H₂O)⁺, 267.9723. C₁₁H₁₁BrO₄ requires C, 46.15; H, 3.9%; (M-H₂O) (¹⁷⁹Br), 267.9735); νₘₐₓ/cm⁻¹ 3506 (OH), 1677 and 1652 (C=O) and 1589 and 1480 (C=C); δH 1.37 (3H, d, J 6.4 Hz, 3-CH₃), 1.47 (3H, d, J 6.9 Hz, 1-CH₃), 2.25 (1H, d, J 7.3 Hz, OH), 3.96 (1H, dq, J 2.2 and 6.4 Hz, 3-H), 4.35 (1H, dd, J 2.2 and 7.3 Hz, 4-H), 4.89 (1H, q, J 6.9 Hz, 1-H) and 7.32 (1H, s, 6-H); δC 16.1 (3-CH₃), 17.9 (1-CH₃), 61.1 (C-3), 66.4 (C-4), 67.6 (C-1), 137.6 (C-7), 137.8 (C-6), 139.2 (C-8a), 144.7 (C-4a), 178.6 (C-8), 183.7 (C-5); m/z 270 [M⁺-H₂O (¹⁷⁹Br), 25%], 268 [M⁺-H₂O (¹⁷⁹Br), 17%], 255 (100), 253 (80) and 149 (84).

The product of lower R_F was identified as (375) (20 mg, 22%) m.p. 126-127 °C (hexane-dichloromethane) [α]D +45.8 ° (c in 1.0 CHCl₃); (Found: C, 63.45; H, 5.8; M⁺, 208.0734. C₁₁H₁₂O₄ requires C, 63.45; H, 5.8%; M, 208.0735); νₘₐₓ/cm⁻¹ 3495 (OH) and 1655 (C=O); δH 1.37 (3H, d, J 6.4 Hz, 3-CH₃), 1.45 (3H, d, J 6.9 Hz, 1-CH₃), 2.22 (1H, br. s, OH), 3.97 (1H, dq, J 2.2 and 6.4 Hz, 3-H), 4.36 (1H, br. s, 4-H), 4.85 (1H, q, J 6.9 Hz, 1-H) and 6.75 and 6.80 (each 1H, d, J 10.8 Hz, 6- and 7-H); δC 16.1 (3-CH₃), 17.9 (1-CH₃), 61.1 (C-3), 66.5 (C-4), 67.0 (C-1), 136.3 (C-6), 136.8 (C-7), 138.6 (C-8a), 144.5 (C-4a), 186.3 (C-8) and 187.1 (C-5); m/z 190 [M⁺-H₂O, 26%], 177 (19), 164 (100), 147 (21), 136 (56) and 119 (17).

(1R, 3R, 4R)-3,4-Dihydro-4,7,9-trihydroxy-1,3-dimethylnaphtho[2,3-c]pyran-5,10-quinone [Quinone A'] (17)

Bromoquinone (321) (100 mg, 0.35 mmol) was treated with the diene (200) (181 mg, 0.70 mmol), as described above for the conversion of (370) to the naphthoquinone (359), to give quinone A' (17) (20 mg, 20%) as bright orange plates, m.p. 234 °C (decomp.) (benzene) (Lit.¹⁰⁴ 236 °C) [α]D +262 ° (c 1.0 in 1% CH₃CO₂H/CH₃OH) (Lit.,¹⁶⁸ +258 °) (Found: C, 62.4; H, 5.05; (M-H)⁺, 289.0724. 226
C_{15}H_{14}O_{6} requires C, 62.05; H, 4.85%; (M-H), 289.0712; \nu_{\text{max}}/\text{cm}^{-1} 3438 \text{ (OH) and 1643 (C=O)}; \delta_{\text{H}} \text{ (acetone-d}_{6} \text{)} 1.11 \text{ (3H, d, } J \text{ 6.3 Hz, 3-CH}_{3} \text{), 1.35 \text{ (3H, d, } J \text{ 6.8 Hz, 1-CH}_{3} \text{), 2.64-2.80 (2H, br. s, 4- and 7-OH), 3.84 (1H, dq, } J \text{ 1.9 and 6.3 Hz, 3-H), 4.41 (1H, d, } J \text{ 1.9 Hz, 4-H), 4.75 (1H, q, } J \text{ 6.8 Hz, 1-H), 6.48 (1H, d, } J \text{ 2.4 Hz, 8-H), 6.98 (1H, d, } J \text{ 2.4 Hz, 6-H) and 12.05 (1H, br. s, 9-OH)}; \delta_{\text{C}} 16.7 \text{ (3-CH}_{3} \text{), 18.5 (1-CH}_{3} \text{), 61.6 (C-3), 68.0 (C-1), 68.3 (C-4), 108.4 (C-8), 109.5 (C-6), 110.1 (C-4a), 135.2 (C-10a), 142.53 (C-5a), 148.2 (C-9a), 165.8 (C-7), 166.7 (C-9), 183.8 (C-5) and 188.6 (C-10); m/z 290 (M,^{+} 20\%), 275 (13), 183 (100) and 90 (22).
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