APPROACHES TO NATURAL ISOCHROMANS BY ISOMERISATION OF ARYLDIOXOLANES

A thesis submitted for the Degree of Doctor of Philosophy

at

The Australian National University

by

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September 1992
The work described herein is the candidate’s own work, unless otherwise stated, and was carried out in the Research School of Chemistry, The Australian National University under the supervision of Professor R. W. Rickards (A.N.U.) and Professor R. G. F. Giles (Murdoch University). None of the material has been submitted in support for any other degree.

Badra Sriyani Senanayake
ACKNOWLEDGMENTS

Many people and institutions helped me during the four years in which I carried out research and wrote this thesis.

I am indebted to the Department of Employment, Education and Training for a postgraduate research award which enabled me to begin this work.

The roots of this work are in Murdoch University where Professor Robin Giles suggested I continue a project from where he had left off. I wish to express my appreciation and thanks to Professor Giles for his continued advice and encouragement throughout this work.

Most of the research took place at the Australian National University where I was extremely fortunate to work under the supervision of Professor Rod Rickards. Because his ideas and enthusiasm for the project enlivened my interest in the project, it is a pleasure for me to say he was highly important to me as a teacher and scholar.

My grateful thanks go to Dr Richard Thomas who, with great patience, read the first draft of this thesis. Grateful thanks also go to Dr Micheal O’Shea, Dr Gerald Haaima, Dr Frances Roden and Dr. Jennifer Thorn for proof-reading. Technical support provided by Ms Jennifer Rothschild, Mr Tony Herlt and the staff at the ANU’s UNMRC were invaluable for the success of my work. I benefited greatly from my association with laboratory colleagues, especially Peter Moeller, Shaun Tennant, Annemarie Ward, Joanne Jamie, Cleofe Calanasan, John Churchill, Roger Waring, Kathryn Morris and the late Jonathan Foreman. My sincere thanks to our close family friend Abey for helping me in many ways.

Members of my family have had to live for a long time with this project. Their practical and emotional support helped me to ease my domestic responsibilities. I wish to express unending gratitude to my husband Willie with whom I had many useful discussions, and to my children Bathiya and Narmadha for their patience during the many hours I spent in the laboratory.
ABSTRACT

The text begins with a review of the naturally occurring kalafungin and related antibiotics and aphid pigments, focusing on their structural elucidation, chemistry, biological activity and synthesis. The synthetic work described in subsequent chapters is concerned with approaches to these compounds by the isomerisation of aryl dioxolanes to isochromans, an intramolecular version of the Mukaiyama reaction.

In Chapter 2, the titanium tetrachloride catalysed stereoselective isomerisation of cis- and trans-4,5-disubstituted(3',5'-symmetrically substituted phenyl)dioxolanes to their corresponding isochromans is dealt with. A study of temperature dependency on the isomerisation reaction established that the formation of isochroman products was favoured only at low temperatures. At higher temperatures, the formation of dihydroisobenzofuran products was observed, which is unexpected since it is a disfavoured (endo-5-trig) process. Other experiments showed that further isomerisation of 6,8-dimethoxyisochromans to dihydroisobenzofuran isomers was possible. The stereochemistry of isochroman formation is controlled by the stereochemistry of the dioxolane precursor and by control of the reaction conditions.

The isomerisation of cis- and trans-4,5-disubstituted-(2',5'-unsymmetrically substituted phenyl)dioxolanes to isochromans is discussed in Chapter 3, together with a study of the diastereoselectivity of this reaction. It was discovered that the yield of isochroman products improved markedly when the C-2' methoxy substituent was replaced with a less electronegative chloro substituent. Efforts were also made to study the diastereoselectivity of the isomerisation reaction, with results indicating that the isomerisation probably proceeds via the more stable E-oxonium ion at -78 °C or above.

Chapter 4 deals with the application of the isomerisation reaction of phenyldioxolanes to a successful synthesis of pyrano-γ-lactones related to kalafungin antibiotics. These investigations established that 4,5-trans-5-carbomethoxymethyl-4-
(3',5'-dimethoxy phenyl)dioxolanes readily isomerise and lactonise to their pyrano-\(\gamma\)-lactones under proton acid catalysis. However, 4,5-\textit{trans}-5-carbomethoxymethyl-4-(2'-chloro-5'-methoxy phenyl)dioxolanes isomerise only with Lewis acid (titanium tetrachloride) to give hydroxy isochromans. More importantly it was found that the 4,5-\textit{trans}-5-carbomethoxymethyl-4-(2',5'-dimethoxy phenyl)dioxolanes and also their hydroxy \(\gamma\)-lactone precursor can be converted to pyrano-\(\gamma\)-lactones under proton acid catalysis. These compounds are more closely resemble the naturally occurring kalafungin. This work illustrates the synthetic viability of the isomerisation of phenyldioxolanes in the synthesis of naturally occurring isochromans.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIBN</td>
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<td>CAN</td>
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</tr>
<tr>
<td>CAS</td>
<td>camphorsulphonic acid</td>
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<td>DBN</td>
<td>diazabicyclo[4,3,0]non-5-ene</td>
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<td>DDQ</td>
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<td>n.m.r.</td>
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</tr>
<tr>
<td>n.O.e.</td>
<td>nuclear Overhauser enhancement</td>
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<td>noesy</td>
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<tr>
<td>t</td>
<td>tert-</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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I do not know what I may appear to the world, but to myself I seem to have been only like a child playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.

ISAAC NEWTON
Chapter 1

Protoaphins, kalafungin and related antibiotics

A large number of naphthoquinones are known to date and they constitute the largest group of naturally occurring quinones.11 Benzophenanthroquinones, which form a substantial sub-group of naphthoquinones, have been isolated in increasing numbers in recent years.11,12 They are found in plants, animals and among microbial metabolites.3 The benzophenanthroquinones isolated so far share several common structural features:

a) a pyran ring with mono- (or larger) side chain at C-1 and/or modified methyl substituents at C-3, either cis or trans; and

b) a naphtho[2,3-a]pyran ring system as represented by skeleton I.1
Chapter 1

Introduction

Protoaphins and nanaomycins, naturally occurring benzoisochromanquinones, are a group of closely related compounds, representatives of which have been shown to be active against a variety of pathogenic fungi, yeasts, protozoa, and Gram-positive and Gram-negative bacteria.\(^1\) Their potent biological activity has encouraged extensive research into their biochemistry, chemistry and synthesis.\(^1,2\)

During the past three decades, many new natural benzoisochromanquinones have been isolated and characterised including several aphid pigments and a number of nanaomycin antibiotics.\(^1,2\) Since the aim of this project is to investigate an efficient synthetic route to benzoisochromans and their quinones, it is appropriate in this chapter to present an overview of their occurrence and synthesis.

1.1 Benzoisochromanquinones

A large number of naphthoquinones are known to date and they constitute the largest group of naturally occurring quinones.\(^1\) Benzoisochromanquinones, which form a substantial sub-group of naphthoquinones, have been isolated in increasing numbers in recent years.\(^1,2,3\) They are found in plants, insects and among microbial metabolites.\(^3\) The benzoisochromanquinones isolated so far share several common structural features:

a) a pyran ring with methyl (or larger) side chain at C-1 and methyl or modified methyl substituent at C-3, either cis or trans; and

b) a naphtho[2,3-c]pyran ring system as represented by skeleton (1).
Some of the benzoisochromanquinones this thesis will be concerned with are the naturally occurring eleutherins, kalafungin and related antibiotics, and protoaphins. It was hoped that a synthesis of the benzoisochroman ring system could be found that would allow control of the stereochemistry in the pyran ring and that this could be extended to syntheses of some of the naturally occurring compounds.

1.2 Eleutherin and isoeleutherin

Eleutherin (2) and isoeleutherin (3) are diastereomers. They are the simplest naturally occurring members of the family of benzoisochromanquinones and are found in tubers of *Eleutherin bulbosa*. It has been found that compound (2) gave alloeleutherin, the enantiomer of isoeleutherin (3), in phosphoric acid. Under similar conditions, alloisoeleutherin, the enantiomer of eleutherin (2), could be obtained from isoeleutherin (3).

The epimerisation of eleutherin and isoeleutherin at C-1 was supported by the observation that on Clemmensen reduction, both eleutherin (2) and the enantiomer of
isoeleutherin (3) afforded the same enantiomer of dihydrofuran (4).\textsuperscript{5} Schmid and his co-workers degraded eleutherin (2) and isoeleutherin (3) and compared the fragments that were obtained with compounds of known stereochemistry and this enabled the configuration at C-3 and C-1 to be established.\textsuperscript{6}

![Chemical structure of dihydrofuran (4)](image)

The \textsuperscript{1}H-n.m.r. spectra of eleutherin (2) and isoeleutherin (3), which became available much later, display considerable fine structure\textsuperscript{7} arising from spin-spin interaction of the methylene protons:

a) with the adjacent axial proton at C-3. This proton is axial in both cases because of the different conformational structure in the pyran ring adopted by eleutherin (2) and isoeleutherin (3); and

b) through homoallylic coupling (HC–C=CH) with the proton at C-1.

The above spectral data were in agreement with the previously established stereochemistry,\textsuperscript{6} and in turn were used to elucidate the stereochemistry of related compounds.

1.3 Kalafungin and related compounds

Kalafungin\textsuperscript{8} and nanaomycins A\textsuperscript{9}, B\textsuperscript{10}, C\textsuperscript{11} and D\textsuperscript{12} are closely related to the eleutherin type benzoisochromanquinones. These compounds are well known antibiotics of the benzoisochromanquinone family and they exhibit significant antimicrobial activity.\textsuperscript{1}
In 1968, Bergy isolated kalafungin (5) from the fermentation broth of *Streptomyces tanashiensis* strain kala. Subsequently, Duchamp described the molecular structure and relative configuration of its three chiral centres. A few years later Hoeksema and Krueger established the absolute configuration of kalafungin by comparison of the optical rotatory dispersion (o.r.d.) curves of 7-O-methyl kalafungin (6) with that of isoeleutherin (3) of known configuration and conformation. They made the following observations relating to the chemical transformation of kalafungin:

\[(5) \quad R = H \]
\[(6) \quad R = Me \]

- a) in aqueous sodium hydroxide, the lactone ring was opened to form kalafunginic acid (7);
- b) treatment of kalafungin with ethanolic hydrogen chloride yielded the corresponding ester (8), the chloro derivative (9) and the elimination product (10); and
- c) kalafungin with methyl iodide-silver oxide afforded the methyl ether (6), but with diazomethane gave the oxirane (11).
Omura et al. isolated the enantiomer of kalafungin (5), nanaomycin D (12), from Streptomyces rosa var. notoensis. The physical properties such as m.p., UV, IR and elemental analysis of nanaomycin D coincided with those of kalafungin, except that the o.r.d. curve of nanaomycin D showed the exact reverse to that of kalafungin. For instance, the o.r.d. curve of nanaomycin D has a trough at 355 nm and a peak at 292 nm, while the curve of kalafungin is enantiomeric with a peak at 355 nm and a trough at 292 nm. Interestingly, kalafungin and its enantiomer, nanaomycin D, are endowed with almost the same antibacterial activities.

Omura et al. isolated two other antibiotics, i.e. nanaomycins A (13) and B (14), from Streptomyces rosa var. notoensis. Nanaomycin A (13) was soluble in aqueous bicarbonate, and formed a methyl ester. The spectral data (UV, $^1$H-n.m.r.) of its methyl ester-methyl ether showed a close resemblance to those of the eleutherins of established configuration. Nanaomycin A was found to be structurally analogous to kalafunginic acid (7) derived from kalafungin. Nanaomycin A (13) can be converted into nanaomycin D (12) by air oxidation in methanolic solution.
Nanaomycin B (14) was found to be a 4a, 10a-hydrated derivative of nanaomycin A (13).\textsuperscript{9,10} When nanaomycin B was treated with cold dilute sodium hydroxide, it was converted into nanaomycin A (13) with the elimination of water. The UV spectrum and the chemical shift of the C-10a and C-4a carbons in the $^{13}$C-n.m.r spectrum clearly demonstrated that the C-10a-C-4a bond in nanaomycin B (14) was saturated.

It was found that \textit{Streptomyces rosa} var. \textit{notoensis} also produced nanaomycin C (15).\textsuperscript{11} The spectral data of nanaomycin C showed a striking resemblance to those of nanaomycin A (13). From the observation that nanaomycin C (15) was neutral and contained a nitrogen atom it was suggested that nanaomycin C (15) was an amide of nanaomycin A. It exerted strong activity against Gram-positive bacteria, as does nanaomycin A, but weaker activity against fungi and mycoplasmas.

Nanaomycin E (16) was obtained from the same strain \textit{S. notoensis}.\textsuperscript{16} It was an epoxy derivative of nanaomycin A and could be converted into nanaomycin A (13) with sodium hydrosulphite in aqueous sodium hydroxide. Similarly reaction of nanaomycin E (16) with sodium hydrosulphite in hydrochloric acid gave a mixture of 4a-\textit{epi-
nanaomycin B (14-1) (63%) and nanaomycin A (13) (35%). The antimicrobial activity of nanaomycin E was weaker than that of nanaomycin A.

Analysis by Tanaka et al. of the biosynthetic origin of nanaomycins using $^{13}$C-labelled compounds and $^{13}$C-n.m.r. spectroscopy established that the carbon skeletons of nanaomycins were derived from eight acetate units (Fig 1.1).17 Thus, kalafungin (5) could be biosynthesised in a similar manner. Omura et al. studied the biosynthetic relationship of the nanaomycins to each other by means of a bioconversion method using the antibiotic cerulenin, a specific inhibitor of fatty acid and polyketide biosyntheses.18 They found that nanaomycin D was the precursor for nanaomycins A, E, and B in sequence. The biosynthesis of nanaomycin C was unclear, but it appeared to be derived from nanaomycin A.

Fig 1.1  Biosynthetic Origin of Nanaomycins
A different strain of *Streptomyces* produced five other antibiotics which were structurally related to the nanaomycins. These compounds were designated as nanaomycin $\alpha\text{A}$ (17), $\beta\text{A}$ (18), $\alpha\text{E}$ (19), $\beta\text{E}$ (20) and $\alpha\text{B}$ (21).19

Nanaomycin $\alpha\text{A}$ (17) was identified by Tanaka *et al.* as nanaomycin A methyl ester, whilst the $\beta\text{A}$ (18) was an analogue of nanaomycin A (13) in which the carboxylic group of nanaomycin A (13) was reduced to the corresponding alcohol. The components $\alpha\text{E}$ (19) and $\beta\text{E}$ (20) were the related ester and alcohol corresponding to nanaomycin E (16), and $\alpha\text{B}$ (21) was the methyl ester of nanaomycin B (14).19

Takano *et al.* isolated an antibiotic related to kalafungin from *Streptomyces* K 73, a strain of *S. tanashiensis*.20 This antibiotic named medermycin (22) was found to be a C-glucoside of kalafungin (5). Medermycin (22) showed a higher order of activity against Gram-positive bacteria.20
A number of workers have described several synthetic routes to nanaomycins and related compounds. The following is a summary of some of the significant work in this field.

1.4 Previous syntheses of kalafungin-type quinones

Li and Ellison were the first to report the total synthesis of kalafungin (5) and nanaomycins A (13) and D (12). Their approach (Fig 1.2) was based on a method originally proposed by Schmid for the synthesis of the eleutherins. The key step of this approach was the condensation of the γ-naphthyl-β-hydroxy ester (23) with acetaldehyde to afford the isochroman (24) which was oxidized quantitatively with silver(I) oxide and then O-demethylated with aluminium trichloride to afford quinone (25). The cis stereochemistry of the C-1 and C-3 substituents of quinone (25) was assigned on the basis of 1H-n.m.r. studies. The methyl group at the C-1 centre of the
quinone (25) was isomerised to give a 2:1 mixture of the trans and cis isomers (26) by treatment with concentrated sulphuric acid. From this mixture, the pure trans isomer (i.e. nanaomycin A ethyl ester) was isolated by fractional recrystallisation. Racemic nanaomycin A (13) was obtained by hydrolysis of the ethyl ester with concentrated hydrochloric acid. Kalafungin (5) and nanaomycin D (12) were then obtained from nanaomycin A by exposing it to air in methanolic solution.21

![Chemical structures](image)

A second approach (Fig 1.3) was made by Kraus, which featured the Michael addition of a butenolide anion equivalent 2-t-butoxyfuran with the acetylnaphthoquinone (27).23,24 The product (28) of addition and subsequent methylation was reduced with lithium aluminium hydride and then treated with trifluoroacetic acid to afford an intermediate butenolide (28-1). This compound (28-1) was cyclised with diazabicyclononane (DBN), oxidized with silver(II) oxide and then demethylated to afford γ-lactonopyrans (29), from which nanaomycin D (12) was separated.
In a third synthesis, Kometani et al. employed the benzindanone derivative (30) as a precursor to the desired nanaomycin heterocyclic ring system (Fig 1.4).\textsuperscript{25,26}Compound (30) was subjected to a Grignard reaction with methylmagnesium iodide and then dehydrated to obtain the indene (31). The double bond of the indene (31) was cleaved with osmium tetroxide followed by sodium periodate oxidation to give the unstable ketoaldehyde (32) which was then subjected to a Wittig reaction with methoxycarbonylmethylene triphenylphosphorane to afford the conjugated ester (33). The reductive cyclisation of conjugated ester (33) using sodium borohydride afforded the cis- and trans-isomers of nanaomycin A derivatives in a ratio of 1:2 in 81\% yield. These two isomers were then separated by chromatography. The trans-isomer was oxidized with ceric ammonium nitrate to the corresponding quinone and finally this was demethylated and hydrolysed to afford (±) nanaomycin A (13).\textsuperscript{25,26}
The same workers described (Fig 1.5) an alternative method for the regioselective introduction of the 2-butenoate side chain to the reduced and protected juglone (34). Juglone (34) was transformed to α-(naphthyloxy)-γ-butyrolactone (35) in 74% yield by reacting it with α-bromo-γ-butyrolactone. Lactone (35) was then subjected to nucleophilic alkyl-oxygen bond cleavage with sodium phenyl selenolate followed by esterification with diazomethane to produce the methyl ester (36). Oxidative elimination of the phenylseleno group from (36) occurred to give the unstable ester (37) which on treatment with methanolic sodium carbonate cyclised to yield the key dihydrofuran intermediate (38). The oxidative removal of the acetonide group of (38) with silver(II) oxide generated a 2-hydroxybutyrate side chain (39). Formation of the methyl ester of nanaomycin A was then achieved according to the method of Li and Ellison (see Fig 1.2).
Uno reported (Fig 1.6) another regioselective allylation of acyl quinones with allylsilanes and allylstannanes. Reaction of the acetyl juglone derivative (40) with butenoate (41) using stannic chloride as a catalyst afforded the conjugate adduct (42). Once compound (42) aromatised to the corresponding hydroquinone, it was converted to the monosilyl ether (43). The successive reduction and cyclisation of monosilyl ether (43) furnished an equimolar mixture of two diastereomers (44). Formation of nanaomycin A was then achieved by desilylative oxidation of diastereomers (44) with ceric ammonium nitrate followed by demethylation with aluminium trichloride, and final separation of the derived diastereomers.
Semmelhack *et al.* used an interesting approach (see Fig 1.7) to the synthesis of nanaomycin antibiotics. This involved the conjugate addition of a carbonyl anion equivalent to the appropriate naphthoquinone monoketal and successive trapping of the generated enolate anion with an allylic halide. This provided a naphthoquinone nucleus with two side chains, which were suitable for the palladium promoted cyclisation to the pyranoquinone ring system. The cyclisation of compound (45) afforded the *trans* and *cis* isomers (46) in ratio of 3:1.
Tatsuta et al. carried out the first enantioselective synthesis of kalafungin (5) and nanaomycin D (12) using a chiral compound (48) derived from a carbohydrate source (Fig 1.8). The requisite naphthopyran structure was constructed by a tandem cyclisation between phthalide (47) and the optically active α,β-unsaturated ketone (48). The intermediates (49 and 50) were converted to enantiomerically pure nanaomycin D (12) and kalafungin (5) respectively.
Brimble et al. have recently reported the synthesis of 5-epi-7-deoxykalafungin and 5-epi-7-O-methylkalafungin (55) (Fig 1.9).\textsuperscript{32,33} For the latter, the furo(3,2-b)naptho(2,1-d)furan (53) was prepared by the uncatalysed 1,4-addition of 2-trimethylsilyloxyfuran (52) to the 2-acetyl-1,4-naphthaquinone (51). Addition of an aqueous solution of cerium ammonium nitrate to a solution of the adduct (53) in acetonitrile at room temperature afforded the isochromanquinone (54) in 76% yield. This was reduced using triethylsilane and trifluoroacetic acid to the kalafungin derivative (55) with a cis relationship between the groups at C-5 and C-3a.\textsuperscript{33}
1.5 Biological activities of kalafungin and related compounds

Johnson and Dietz were able to demonstrate that kalafungin (5) was inhibitory in vitro against a variety of pathogenic fungi (0.5 to 20 µg/ml), yeasts, protozoa, Gram-positive bacteria (1.0 to 16.0 µg/ml) and to a lesser extent Gram-negative bacteria. The biological properties of nanaomycin D (12), the enantiomer of kalafungin, were found to be almost the same as those of kalafungin (5). Tanaka et al. studied the mode of action of nanaomycin A on Gram-positive bacteria and found that it inhibits biosynthesis of protein, DNA, RNA and cell-wall peptidoglycan. As reported by Omura et al., nanaomycins A and D can readily be reduced by the respiratory chain-linked flavin dehydrogenases of a Gram-negative marine bacterium, Vibrio alginolyticus. Nanaomycin D was observed to have a higher growth inhibitory effect than nanaomycin A against this Gram-negative bacterium.

Kalafungin (5) and nanaomycin D (12) contain a pyrano-γ-lactone moiety fused to a quinone nucleus. As a result of this moiety, these compounds were listed in a review by Moore as having the potential to behave as dialkylating agents by a bioreductive mechanism (Fig 1.10). This process involved the reduction of the molecular species in...
vivo and ring opening of the derived hydroquinone by the expulsion of both good leaving groups which are benzylic to the phenolic system. The resulting quinone methide could be readily alkylated by nucleophiles. Thus bioreductive alkylating agents such as kalafungin and nanaomycin D could possibly possess significant antineoplastic activity.\textsuperscript{37} By the same mechanism of quinone methide formation, it is also possible that the protoaphins (56) and (57) might also act as bioreductive alkylating agents.

1.6 The protoaphins

Our knowledge of these compounds is entirely due to the extensive investigations by Lord Todd and D. W. Cameron and their co-workers.\textsuperscript{38,39} Protoaphins are yellow water soluble substances which occur in at least twenty species of aphids. Three protoaphins so far reported are protoaphin-\textit{fb} (56), protoaphin-\textit{sl} (57) and deoxyprotoaphin (58), the suffixes in (56) and (57) indicating the species from which the protoaphin was first isolated; i.e. \textit{Aphis fabae} Scop. and \textit{Tuberolachnus salignus} Gemlin

\begin{align*}
\text{(56)} & \quad R_1 = \text{OH}, \quad R_2 = \text{H} \\
\text{(57)} & \quad R_1 = \text{H}, \quad R_2 = \text{OH} \\
\text{(58)} & \quad R_1 = R_2 = \text{H}
\end{align*}
respectively. Deoxypyprotoaphin (58) was isolated from the aphid *Dactynotus cirsii* L. It is different from the compounds (56) and (57) in that it lacks the hydroxy group at C-4 of the naphthopyranquinone moiety.

Protoaphins are present in the haemolymph of living insects and are accompanied by an enzyme. After the death of the insects, this enzyme rapidly converts the protoaphins into unstable fluorescent yellow compounds called xanthoaphins. Thus protoaphin (56) is converted into xanthoaphin (59). This gradually changes into a slightly more stable orange chrysoaphin (60) and finally into a fluorescent, stable red erythroaphin (61). The same changes can be initiated by the pigment-free enzyme extract prepared from fresh insects. Both *in vitro* and *in vivo* this enzymatic reaction gives the erythroaphin as the stable end product. Therefore in order to isolate protoaphins, this enzyme system must be carefully deactivated without damaging the protoaphin. 40,41 This can be achieved either by using organic solvents or by heating.
Mild acid hydrolysis of protoaphins affords D-glucose and an aglucone which can only be isolated under nitrogen. This aglucone is converted into the corresponding erythroaphin by further treatment with acid. Cameron and his co-workers reported that prolonged reduction of protoaphins with sodium dithionite (or by catalytic hydrogenation), in aqueous buffer at pH 6.6 followed by aerial oxidation yielded an acidic quinone and a naphthalenic glucoside. 41

From these investigations they established that protoaphin-fb (56) and protoaphin-sl (57) give the same glucosidic component, glucoside B (62), but two different quinones, quinone A (63) and quinone A' (64). These two quinones are epimeric at C-4. Deoxyprotoaphin (58) similarly gives glucoside B (62) and deoxyquinone A (65) with sodium dithionite. This systematic simplification brought about by the cleavage of the binaphthyl linkage greatly assisted structural elucidation of these protoaphins.
Glucoside B (62) was also found in the bright orange *Aphis nerri* along with a related compound, neriaphin (66).\textsuperscript{42} The facile hydrolysis with almond emulsion of glucoside B to D-glucose and an unstable aglucone confirmed its β configuration.\textsuperscript{43} Glucoside B was very susceptible to aerial oxidation, even in the solid state. The structure however, was confirmed by oxidation with Femy's salt to naphthoquinone (67), and this was easily hydrolysed to quinone A (63).

Quinone A is a 7,9-dihydroxy-5,10-naphthopyranquinone (63); its structure and absolute stereochemistry were confirmed by mild chromic acid oxidation \textsuperscript{41} which yielded D, D-(+)-dilactic acid of known absolute stereochemistry \textsuperscript{44} and by a detailed analysis of the \textsuperscript{1}H-n.m.r. spectrum.\textsuperscript{45}
The coupling constant \( J \) 8.0 Hz) of the 4-H and 3-H protons determined their trans diaxial relationship at the adjacent pyran carbons of quinone A (63). The C-4 hydroxy group of quinone A (63) could be removed by reduction with sodium stannite to give a compound having the same dihydropyran structure as isoeleutherin (3) which had, in fact, the same stereochemistry as quinone A (63) for the methyl groups at C-1 and C-3. Quinone A was thus formulated as structure (63).

Reductive fission of protoaphin-sl (57) gave glucoside B together with another quinone (A'), isomeric with quinone A. Quinone A' also gave D,D-(+)-dilactic acid on oxidative degradation. Thus these two quinones differ only in their configuration at the C-4 centre.

It is likely that the formation of the protoaphins in vivo involves a coupling reaction between the two halves of the molecule at some stage. The in vitro linkage of the two halves of the protoaphins was achieved by Cameron et al. when quinone A and glucoside B were left at 80 °C in aqueous solution at pH 6.6. The yield of protoaphin-fb is about 18%. They also noted that a similar coupling of quinone A' and glucoside B effected a partial synthesis of protoaphin-sl (57). Thus syntheses of quinones A (63), A' (64) and glucoside B (62) would constitute a formal synthesis of protoaphin-fb (56) and -sl (57).

1.7 Previous syntheses of protoaphin-type quinones

Syntheses of derivatives of quinones A and A' were first achieved by Professor Giles and his co-workers. Their first attempt was to synthesise the racemates of 7,9-
dideoxyquinones A and A'. The allylation and benzopyran ring formation were established as key steps of this synthesis (Fig 1.11).

The acylquinone (68) was propylated and reductively methylated to afford the dimethoxynaphthalene (69) which was brominated with N-bromosuccinimide to afford the benzylic bromide (70). This was dehydrobrominated with 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) and the products then reduced to the corresponding alcohol (71) with sodium borohydride. The oxidative cyclisation of alcohol (71) to the benzoisochromans (72) and (73) was achieved by the use of ceric ammonium nitrate. However, they observed that the oxidative cyclisation of tetra-alkoxy alcohol (74) to the corresponding isochromanquinone with ceric ammonium nitrate was not successful (Fig 1.12). It was assumed that the additional two alkoxy substituents increased the electron availability on the naphthalene ring, which promoted alternative oxidative pathways and these led to consumption of starting material without isolation of any identifiable product.47
The stereoselective cyclisation of tetra-oxygenated alcohol (74) to the \textit{trans} 1,3-dimethyl pyran (75) was, however, achieved in high yields by the alternative use of potassium \textit{t}-butoxide in dimethylformamide under nitrogen (Fig 1.12).\textsuperscript{48} These naphthopyrans could then be converted into the epimeric pair of C-4 alcohols (76) and (77) by reaction with potassium \textit{t}-butoxide in air. Moderate yields were obtained in dimethylformamide as solvent, but the alternative use of dimethyl sulfoxide gave C-4 alcohols (76) in 62\% and (77) in 23\% yield in a reaction in which a considerable degree of stereoselectivity was observed in favour of the \textit{pseudo}-equatorial alcohol.\textsuperscript{49} This base-induced cyclisation and oxygenation reaction sequence led to the syntheses of the racemates of quinones A and A' as well as deoxyquinone A.\textsuperscript{49}

Recently Professor Giles and his co-workers have extended their work towards the synthesis of a 7,9-dideoxy derivative of the aglucone of glucoside B. First, a series of reactions involving base-catalysed cyclisation to a naphthopyran, followed by selective aryl-oxygen cleavage and finally benzylic hydroxylation afforded the 7,9-dideoxy analogue (89) of the aglucone of glucoside B. The sequence of reactions is that shown in (Fig 1.13).
Treatment of the methyl ether of naphthalene (79) with 1% methanolic potassium hydroxide solution cleaved the acetoxy group to yield the naphthol (80). This was allylated with allyl bromide in dry acetone and potassium carbonate to give allyl ether (81).
which underwent Claisen rearrangement to afford the unstable naphthol (82) which was converted into the benzyl ether (83) with benzyl bromide. The compound (83) was then reduced with lithium aluminium hydride to afford the alcohol (84). This alcohol was treated with potassium \( t \)-butoxide in dry dimethylformamide under nitrogen to afford naphthopyran (85) with complete stereoselectivity. Removal of the benzyl group was achieved by treatment of compound (85) with boron trichloride at \(-78^\circ\text{C}\). The resultant naphthol (86) was converted directly into the methanesulphonate ester (87), which was heated to reflux with an excess of Raney nickel in aqueous ethanol to afford the trans-dimethyl-naphtho[2,3-c] pyran (88). This compound was treated with potassium \( t \)-butoxide in oxygenated dry dimethyl sulphoxide to obtained the target molecule (89) with complete stereoselectivity.\(^{50}\)

In view of the successful synthesis of the 7,9-dideoxy glucoside B analogue (89) using base promoted cyclisation and oxygenation reactions Giles et al. attempted to synthesise a glucoside B derivative with the correct oxygenation pattern, using the same methodology for the construction of the substituted pyran ring.\(^{50}\) However, in this case the naphthalene ring system was constructed without a C-5 oxygen substituent (Fig 1.14). A Wittig reaction between aldehyde (90) and ethyltriphenylphosphonium bromide afforded a mixture of Z-and E-olefins (91). Treatment of this mixture with a palladium catalyst yielded the pure E-olefin (92). This was converted to naphthylcarbinol (93) by treatment with butyllithium and acetaldehyde which was then subjected to base-induced ring closure to afford exclusively the trans-dimethylpyran (94) in 83% yield (Fig 1.14). However, treatment of pyran (94) with potassium \( t \)-butoxide in the presence of oxygen afforded the desired product (95) in only 33% yield together with lactone (96).
The difference in behaviour of naphthopyran (88) to that of naphthopyran (94), may be due to a number of factors. Pyran (94) is more electron rich because of the additional two oxygen substituents on the terminal aromatic ring and this factor might well promote the over-oxidation of the alcohol product (95) compared to compound (89). The greater bulk of the isopropoxy protecting group in pyran (94) may also lead to the destabilisation of the pyran ring due to the peri-interaction between it and the C-1 methyl group. However, there might well be additional factors responsible for the observed difference. 50

Most recently Giles et al. have developed a novel approach towards the construction of the pyran ring systems similar to those of quinones A and A' and
glucoside B systems related to aphid pigments. 51* This approach involved the isomerisation of aryldioxolanes to pyrans with titanium tetrachloride. The key step of the procedure was the use of an intramolecular version of the Mukaiyama reaction. Since present work develops this approach in detail, it is apposite here to describe the background of the Mukaiyama reaction.

1.8 The Mukaiyama reaction

Carbon-carbon bond formation α to the carbonyl group of aldehydes and ketones and the formation of one or two new centres of chirality at the α- and/or β-positions are among the most important synthetic operations in organic chemistry. 52 Aldol condensation has long been recognised as one of the most versatile synthetic tools in carbon-carbon bond forming reactions. The reaction is usually carried out under basic conditions, and dimers, polymers, self-condensation products or α,β-unsaturated carbonyl compounds are invariably formed as by-products. These undesirable side reactions frequently limit the utility of this otherwise efficient reaction. In order to alleviate these difficulties, useful synthetic procedures have been developed, especially under basic conditions, by Wittig et al. 53 using lithio derivatives of imines and by Corey et al. 54 using lithio derivatives of hydrazones. In addition, Stork et al. 55 and House et al. 56 reported the selective formation of lithium enolates which in the presence of metal salts led to cross aldol products under almost neutral conditions. Although clean reactions occur, this method is of limited scope since the preparation of one regioisomer of a trimethylsilyl enol ether, the precursor of the lithium enolates, directly from an unsymmetrical ketone remains a difficult problem and requires tedious separation in some cases. The detour via a metalated hydrazone is often recommended, but has the disadvantage that in the case of unsymmetrical ketones only the less substituted α-position can be alkylated.52

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51* Some of the author's work in this paper is described in chapters 2 and 3.
The above problems have been solved to a certain extent by using complementary methodology such as Lewis acid induced C-C bond formation using enol ethers. Ethereal-boron trifluoride, ferric chloride, tin(IV) chloride and titanium tetrachloride can be used as promoters. Mukaiyama replaced alkyl enol ethers by silyl analogues since the silicon-oxygen bond is more readily cleaved than a carbon oxygen bond leading to a faster reaction. He carried out an impressive series of aldol additions with acetals, aldehydes and ketones. When the silyl enol ether (97) was treated with stoichiometric amounts of ketone or aldehyde and titanium tetrachloride in dichloromethane, the aldol-type product (99) was selectively obtained in excellent yield (95%) without accompanying self-condensation products.

\[
\begin{align*}
\text{(97)} & \quad \text{(98)} & \quad \text{(99)} \\
\end{align*}
\]

Fig 1.15

Powerful activation of carbonyl groups by titanium tetrachloride led to the assumption that silyl enol ethers of type (97) could readily attack carbonyl compounds to form trimethylsilyl chloride and the titanium salt of the aldol-type product (Fig 1.15). In this case, undesirable dissociation of the adduct was inhibited by the formation of a stable titanium chelate (98) hydrolysis of which would yield the desired \(\beta\)-hydroxy ketone (99).
With aldehydes, the reaction proceeded even at -78° C, whereas in the case of ketones, a reaction temperature of 0° C or room temperature is required.

Later, Mukaiyama proved the regioselectivity of this reaction using two structurally isomeric silyl enol ethers (100) and (102). The reaction of enol ether (100) with benzaldehyde afforded two diastereomers (101), whereas enol ether (102) reacted with benzaldehyde to give four diastereomers (103). Accordingly, the addition reaction appears to take place regioselectively at the double bond of the silyl enol ether (Fig 1.16).

$$\begin{align*}
\text{SiMe}_3\text{O} & + \text{PhCHO} \\
\text{(100)} & \xrightarrow{1) \text{TiCl}_4 \quad 2) \text{H}_2\text{O}} \text{HO} \\
& \quad \text{Ph} \\
& \text{(101)}
\end{align*}$$

$$\begin{align*}
\text{SiMe}_3\text{O} & + \text{PhCHO} \\
\text{(102)} & \xrightarrow{1) \text{TiCl}_4 \quad 2) \text{H}_2\text{O}} \text{HO} \\
& \quad \text{Ph} \\
& \text{(103)}
\end{align*}$$

Fig 1.16

Similarly Mukaiyama observed that, in the presence of Lewis acids, enolacetates react with various acetals to afford the corresponding aldol-type products in good yield. The actual carbon-carbon bond formation (Fig 1.17) is accomplished by using a suitable acetal (105) in the presence of Lewis acids such as titanium tetrachloride and stannic chloride. This reaction was explained by assuming the initial formation of a titanium tetrachloride complex, which in turn was immediately trapped, for example with isopropenyl acetate (104) to give the addition product (106). This initial addition product (106) was rapidly deacetylated making oligomerization impossible. This postulate is depicted in Fig 1.17.
The reaction of acetals with silicon-containing nucleophiles (allylsilanes, enol silanes, silyl acetylenes) has proved to be a powerful method for carbon-carbon bond forming reactions. Remarkable levels of stereoselection in the Lewis acid promoted nucleophilic addition reactions of chiral dioxolane and dioxane acetals were observed by Kishi \(^61\) and also by Johnson and Bartlett.\(^62\) For example, reaction of chiral dioxane acetals (107) proceeded stereoselectively to give coupling products (108) and (109) in which the former was predominant (Fig 1.18).\(^63\)

Considerable interest has been directed towards the intramolecular variant of the titanium tetrachloride-mediated carbon-carbon bond forming reactions, using acetals, as a valuable annulation method. Posner \textit{et al.} reported the titanium tetrachloride-mediated condensation of acetal silyl enol ether (110) to afford hydroazulenone (111) \(^64\); see Fig 1.19.
In the period 1982-1985, Kocienski et al. showed that an intramolecular Mukaiyama reaction could be used to construct six, seven and eight membered rings easily. A key fragment of pederin having a six membered ring was readily formed by the cyclisation of model dioxolanes (112) and (114) (Fig 1.20). Treatment of cis-dioxolane (112) with 1 to 2 equivalents of titanium tetrachloride in dichloromethane at -78° C afforded the cis-tetrahydropyran-4-one (113) exclusively, whereas similar reactions with the trans-dioxolane (114) afforded a 1:1 mixture of (113) and (115).
They also reported that the 1:1 mixture of dioxopanes (116) reacted with titanium tetrachloride to give the oxepanones (117) and (118) and the oxocanone (119) (88% combined yield) 66, 67; see Fig 1.21. It is particularly noteworthy that eight-membered rings, the most difficult medium-size rings to form, were easily constructed, without the need for high dilution techniques.

Overman reported (Fig 1.22) an interesting reaction for the synthesis of tetrahydrofuran (122) by means of a Lewis acid promoted reaction of the vinyl dioxolane (120). 68 He proposed that this reaction occurred through initial formation of a six membered ring (121) which was contracted to a five membered ring (122) by a pinacol rearrangement.
The Mukaiyama reaction was developed systematically in order to make this type of carbon-carbon bond formation possible, which was not feasible using classical enolate chemistry. Despite the fact that most of the Lewis acid promoted reactions occur under mild conditions, generally show regiospecificity, and do not afford polyalkylated products, some problems remain unexplored. Mechanistic aspects are currently unclear, in particular with respect to the Lewis acid. Also, the possible influence of the nature of the Lewis acid on diastereoselectivity during bond formation has not been studied systematically.

This thesis examines various aspects of the application of the intramolecular version of the Mukaiyama reaction for the synthesis of isochromans related to the protoaphin-type and kalafungin-type natural products. Therefore it would be useful here to describe work previously done in this field.

1.8.1 Intramolecular Mukaiyama reactions relevant to the benzoisochroman synthesis.

Recently Professor Giles' group demonstrated the regioselective isomerisation of aryldioxolanes to afford angular pyrans.\(^51^*\) This procedure (Fig 1.23) involved the titanium tetrachloride promoted ring opening of aryldioxolanes (124) and (125) to their corresponding oxonium ion(s) (126) which were trapped intramolecularly by the naphthalene ring carbon para to the electron rich isopropyl ether group.

\(^{51^*}\) Some of the author's work in this paper is described in chapters 2 and 3.
In the initially formed cation (126), the oxonium ion moiety acted as the electrophile in the intramolecular electrophilic substitution reaction to form the naphthopyrans (127) and (128). It is important to stress that the relative stereochemistry at C-3 and C-4 of the pyran ring was determined by the stereochemistry of the dioxolane precursor. Although titanium tetrachloride did promote ring opening at the C-2 to O-3 bond of the dioxolanes (124) and (125) to give the desired oxonium ion (126), this intermediate ring closed to C-4' of the naphthalene ring to give an angular naphtho[3,4-
Clearly, for a synthesis of the target molecules, ring closure must take place at C-2' to give rise to the linear naphtho[2,3-c]pyran (129).

The naphthyldioxolanes (124) and (125) used in this study by Professor Giles' group were prepared by acetalation of diol (123), a single diastereomer, with 1,1-dimethoxyethane and (±)-camphorsulphonic acid in boiling dichloromethane. Under these conditions a 1:1 diastereomeric mixture of the dioxolanes (124) and (125) was obtained and treatment of this mixture with ten molar equivalents of titanium tetrachloride in dichloromethane at -78 °C resulted in the formation of angular pyrans (127) (13%), (128) (39%) and diol (123) (13%).

Structures (127) and (128) were distinguished from the alternative naphthofuran isomers (130) on the basis of a comparison of their $^1$H-n.m.r. spectra and those of their respective acetates (131) and (132). The shift to lower field of the doublet due to the 4-H proton in acetates (131) and (132) provided evidence that compounds (127) and (128) were pyrans and not furans. If the latter had been acetylated a deshielding of the doublet of quartets would have occurred. The relative configuration at C-3 and C-4 for
compounds (127) and (128) was confirmed by the coupling constant (J 1.5 Hz) observed between the 3-H and 4-H protons. The configuration of the C-1 methyl group relative to the substituents at C-3 and C-4, and the angular ring system in each case was established by X-ray crystallography, which also confirmed the spectral assignments.

A second example (Fig 1.24) supported the generality of the method. In view of the fact that the diastereomeric mixture of dioxolanes (124) and (125) had afforded angular naphthopyrans (127) and (128), the 5'-bromo naphthalene (134) was then investigated to establish whether the bromine would have sufficient steric bulk to prevent angular ring closure, thereby giving rise to the desired linear naphthopyran (133) instead.

Thus the bromodiol (134) afforded the dioxolane (135) as a single diastereomer. Its treatment with titanium tetrachloride as above afforded debrominated pyran (136) (45%) as a single diastereomer, together with the derivative (137) (18%) arising from migration of bromine, and the diol precursor (134) (14%). The stereochemical relationship between the two pyrans (136) and (137) was confirmed by treatment of the latter with butyllithium followed by water, which gave the former (81%).
The coupling constant \( J = 8.3 \text{ Hz} \) between the 3-H and 4-H protons determined the \textit{trans} relative stereochemistry at the adjacent pyran carbons of pyran (136). Moreover, the \textit{trans} relationship between the two pyran methyls (i.e. 1-CH\(_3\) and 3-CH\(_3\) groups) and the nature of the ring system were confirmed by the conversion of pyran (136) into the desoxy \textit{trans}-dimethyl pyran (138) (using phosphorus tribromide followed by Raney nickel), identical with material similarly obtained from pyran (127) (Fig 1.23), and different from the \textit{cis}-dimethyl isomer (139) derived from (128).
It had already been shown that blocking the naphthalene at C-5' did not lead to linear naphthopyrans, and it needed to be established whether halogenation at C-4' (ortho- to the dioxolane ring) would lead to the desired result. Secondly, the bulky isopropoxy group at C-1' could have prevented the formation of the required linear naphthopyran.

The isopropoxy group was used in this earlier sequence for several reasons. First, had the isomerisation reaction of the naphthylidioxolane (135) given rise to the desired linear naphthopyran (133), rather than pyrans (136) and (137), this on debromination would have provided the naphthopyran (95) prepared earlier, which would have confirmed the stereochemistry about the pyran ring. Secondly, the bulk of the isopropoxy substituent was expected to favour the pseudo-axial configuration for the C-1 methyl, as found in the protoaphins. Thirdly, isopropyl can be removed selectively from oxygen in the presence of methoxy groups using boron trichloride. Thus compound (95) obtained by this route would provide the naphthol (140), oxidation of which with Fremy’s salt would have provided quinone A dimethyl ether (141)\textsuperscript{41,48b}, thereby again confirming the stereochemistry of the product. This Mukaiyama route might therefore have provided access to both the protoaphin quinones and glucoside B.

![Chemical structures](images/140.png) ![Chemical structures](images/141.png)

The work to be described in this thesis demonstrates that the use of a large excess of titanium tetrachloride is not necessary, as fewer equivalents can be used, provided the reaction is allowed to go to completion. Premature quenching of the reaction mixture leads to diol formation by acid catalysed hydrolysis of the starting acetal.
1.9 Present project

The present project describes the use of an intramolecular version of the Mukaiyama reaction for the synthesis of isochromans related to the protoaphins and the kalafungin antibiotics. It focuses mainly on the factors governing the relative stereochemistry of the substituents about the pyran ring and the limitations of the procedures described above. Rather than working with naphthalene derivatives, it is proposed to use phenyl dioxolanes as simpler models. These have the advantage of ease of preparation of a variety of substitution patterns in the aromatic ring which would allow a systematic study of the isomerisation. An attempt is made to find a suitable substitution pattern that will give rise to isochromans in high yield. In order to minimise any steric effects, a methoxy group is used in place of the bulky isopropoxy group used in the previous study. The generality of the isomerisation reaction is examined. Most importantly, the mechanistic aspects of the isomerisation of phenylidioxolanes to isochromans is studied.
References:


Chapter 2

Isomerisation of 4,5-disubstituted
(3',5'-symmetrically substituted phenyl)dioxolanes to isochromans
Chapter 2

Isomerisation of 4,5-disubstituted (3',5'-symmetrically substituted phenyl)dioxolanes to isochromans

The stereochemical outcome of the C2A value of the resulting isochromans was calculated to be derived from the partial stereochemistry of cyclisation of the oxonium ion intermediates. The inversion and retention factors for oxonium ions calculated to be small, and cyclisation should proceed via the atropisomeric oxonium ion intermediates. It was mentioned in the preceding Chapter that the invariable retention on the first ring...
2.1 Introduction

Considerable attention has been directed towards the intramolecular version of the Mukaiyama reaction as a valuable annulation method.\(^1\) As discussed in Chapter 1, the present work deals with the synthetically useful carbon-carbon bond forming cyclisation (isomerisation) reaction of methoxy substituted phenyldioxolanes, and the application of this reaction to the novel synthesis of isochromans.

This Chapter describes the stereoselective isomerisation of symmetrically substituted phenyldioxolanes to the corresponding isochromans with titanium tetrachloride. The use of phenyldioxolanes, rather than naphthyldioxolanes as in the previous work, means that the question of linear versus angular ring closure does not arise, facilitating study of the isomerisation reaction itself. Furthermore, symmetrical substitution of the phenyl ring avoids the possibility of the formation of regioisomeric isochroman isomers through ring closure at non-equivalent ortho-positions. The overall sequence is illustrated in Fig. 2.1.

The stereochemical outcome at the C-1 centre of the resulting isochroman was anticipated to be derived from the preferred stereochemistry of cyclisation of the oxonium ion intermediates. The inversion and rotation barriers for oxonium ions are calculated to be small, and cyclisation should proceed via the more stable oxonium ion intermediate.\(^2\) It was mentioned in the preceding Chapter that the isopropoxy substituent on the aryl ring
might have disfavoured ring closure ortho to itself on account of its steric bulk. It was hoped that the less bulky methoxy substituent would not preclude adjacent ring closure, but would still have sufficient steric demand to require that the C-1 methyl adopt a pseudo-axial configuration, to minimise peri-type interactions.

The stereochemistry of the C-3 and C-4 positions of the isochroman products would be determined by the stereochemistry at the C-5 and C-4 positions respectively of the dioxolane precursors. Therefore, the present work concentrates particularly on the stereoselective syntheses of cis-4,5-disubstituted phenyldioxolanes and trans-4,5-disubstituted phenyldioxolanes and their isomerisation.

2.2 Possible isomerisation sequences

The possible isomerisation sequences for the cis-4,5-disubstituted phenyldioxolane system (148) are shown in Fig. 2.2. The dioxolane (148) has two different oxygens and carbon oxygen bonds, namely C-2 to O-1 and C-2 to O-3. The Lewis acid promoted ring opening of this dioxolane was expected to give two different oxonium ion intermediates (149) and (150). A recent study by Overman revealed (see Fig. 2.3) that a carbon-carbon bond forming cyclisation of the intermediate (X), which is similar to intermediate (149), was a disfavoured (endo-5-trig) process because of the poor overlap between the p-orbitals on the alkene and the electron deficient carbon. Thus, a disfavoured cyclisation process would be expected for the intermediate (149) due to poor overlap between the π-electrons on the aromatic ring and the electron deficient carbon in intermediate (149). Therefore, the most likely reaction pathway open to intermediate (149) would be reversion to the starting dioxolane (148). More details of this process will be given in Chapter 3.
It was assumed that intermediate (150) could readily undergo a carbon-carbon bond forming reaction, since it is a favoured \((\text{endo-6-trig})\) process, to yield the desired isochromans (151) and (152). It was anticipated that the stereochemistry at positions C-3 and C-4 of the pyran products would be determined by the stereochemistry of the dioxolane precursor; \(i.e\). isomerisation of \(\text{cis}-4,5\)-phenyldioxolanes (148) would give \(\text{trans}-3,4\)-isochromans. As can be seen from the mechanism outlined in Fig. 2.2, the relative stereochemistry at the C-3 and C-4 positions in the pyran products is determined by the phenyldioxolanes which already have the correct relative stereochemistry. Thus the \(\text{trans}\) substituents at the C-3 and C-4 centres of isochromans (151) and (152) can be generated as would be required for a synthesis of quinone A and glucoside B analogues.
The reaction mechanism for the isomerisation of the \textit{trans}-4,5-phenyldioxolanes (154) is given in Fig 2.4. Of the two oxonium ions (155) and (156), the former was expected to undergo a carbon-carbon bond forming reaction to give isochromans (157) and (158). The relative stereochemistry of the substituents at the C-3 and C-4 positions of isochromans (157) and (158) would be \textit{cis}, since the corresponding substituents at the C-5 and C-4 positions of the starting dioxolanes (154) have a \textit{trans} relative configuration. Thus, as shown in Fig 2.4, \textit{cis} stereochemistry for the C-3 and C-4 centres of isochromans (157) and (158) can be generated as would be needed for the synthesis of quinone A'. Furthermore, oxonium ion (156) was not expected to undergo isomerisation to dihydroisobenzofurans for reasons similar to those given above for oxonium ion (X).
2.2.1 Diastereoselectivity of the isomerisation reaction

It was expected that the oxonium ions (150) and (155) generated by titanium tetrachloride would show diastereofacial selectivity in their cyclisation to the aromatic ring. The idea was to use the steric bulk of the neighbouring methoxy substituent of the resulting isochroman to influence the stereochemistry at the C-1 centre of the pyran products. This peri-interaction of the developing C-1 methyl group with the neighbouring methoxy group might favour the pseudo-axial configuration for the resultant C-1 methyl group. However, if the carbon-carbon bond forming cyclisation reaction occurred via intermediate species (150) and (155) still co-ordinated to titanium, the steric bulk of the titanium species rather than the influence of the methoxy group might then be responsible for determining the stereochemistry at the C-1 centre.3
The next step was to plan carefully the reaction sequence in order to obtain the phenyldioxolanes with the appropriate stereochemistry, as shown in structures (148) and (154). The precursors of these phenyldioxolanes would have to be formed stereoselectively. The synthetic strategy for obtaining the dioxolanes with correct stereochemistry will be discussed in detail in the next section.

2.3 Retrosynthetic analysis of phenyldioxolanes

Fig. 2.5 illustrates a retrosynthetic analysis of dioxolanes (148) and (154). Disconnection of the two acetal bonds of dioxolanes (148) yields the erythro diol (147) as an intermediate. *Erythro* diol (147) could be obtained either *via* *cis* hydroxylation of the *Z*-olefin (143b) or *via* *SN2* cleavage of the *trans*-epoxide (144) formed from the *E*-olefin (143a), since the ring opening of the epoxide (144) would result in inversion of stereochemistry at the C-1 centre. Similarly, a retroanalysis of the dioxolanes (154) afforded the *threo* diol (153) as a precursor. Further analysis of this *threo* diol gave the *E*-olefin (143a) as a key intermediate (Fig. 2.5).

Thus, it could be identified from the retrosynthetic analysis that the first step in the synthesis of the dioxolanes was the preparation of either the stereochemically pure *E*-1-(3',5'-dimethoxyphenyl)-1-propene (143a) or alternatively the stereochemically pure *Z*-olefin (143b). Both the *E*- and *Z*-olefins should be accessible from the corresponding aldehyde (142).
2.4 Synthesis of phenyldioxolanes (148) and (154)

To perform the synthesis of either the cis-phenyldioxolane (148) or the trans-phenyldioxolanes (154) successfully required the preparation of the stereochemically pure E-olefin (143a) or the Z-olefin (143b). The E-olefin was chosen...
for both preparations because of the difficulty of obtaining stereochemically pure Z-olefin (143b). The Wittig olefin synthesis generally gives good yields of predominantly one isomer (E or Z), but lacks full stereochemical control. Furthermore, it is difficult to separate alkenes from each other chromatographically.

2.4.1 Routes for the synthesis of the stereochemically pure E-olefin (143a)

Two methods have recently been reported for obtaining pure E-olefins. The first method was based on the conversion of isomeric alkenes into a single stereoisomer. In this method, the transition metal catalyst, palladium bisacetonitrile dichloride, was used to isomerise the Z-component of a mixture of Z- and E-olefins to afford solely the E-olefin in very good yield. According to the second method by Schlosser and Christmann, the ylides (160) and (161) were formed if the Wittig intermediate (159) was treated with phenyllithium or n-butyllithium in ether and tetrahydrofuran at -30 °C. The interconversion of the diastereomeric ylides (160) and (161) was extremely rapid. The equilibrium between the diastereomeric ylides strongly favoured the form (161). With proton donors such as ethereal hydrogen chloride or t-butyl alcohol the ylides regenerated the betaine-lithium bromide adduct. Subsequent treatment with potassium t-butoxide then liberated almost pure trans olefin (Fig 2.6).
With a view to utilising the first method mentioned above to make the stereochemically pure E-olefin (143), the Wittig reaction between the aldehyde (142) and ethyltriphenylphosphonium bromide was examined in dry tetrahydrofuran and ether. The g.c.-analysis of the reaction mixture indicated a 1:2 ratio of two compounds. The $^1$H-n.m.r. spectrum of the mixture showed a doublet of quartets at $\delta$ 6.40 (J 15.0 and 1.6 Hz) coupled to a doublet of quartets at $\delta$ 6.27 (J 15.0 and 4.6 Hz), supporting the presence of the E-isomer. The Z-isomer was indicated by a doublet of quartets at $\delta$ 5.78 (J 11.5 and 1.5 Hz) coupled to a doublet of quartets at $\delta$ 5.80 (11.5 and 4.6 Hz). The accepted coupling constants for a pair of Z- and E-olefins are in the ranges 7 to 12 Hz and 13 to 18 Hz respectively.\(^7\) By comparison of the integrals of the doublet of doublets at $\delta$ 1.92 (J 4.6 and 1.6 Hz) for the methyl group of the E-olefin and at $\delta$ 1.89 (J 4.6 and 1.5 Hz) for the methyl group of the Z-olefin, it was found that the ratio of Z- to E-olefins was approximately 1:2 respectively.

Since the synthesis of the cis-4,5-disubstituted phenylidioxolane (148) required stereochemically pure E-olefin (143a), it was decided to examine the effect of palladium bisacetonitrile dichloride on the Z/E olefin mixture. The 1:2 Z/E olefin mixture was treated with the palladium bisacetonitrile dichloride in chloroform and then the reaction was monitored by means of g.c.- and $^1$H-n.m.r. spectral analyses. After two hours, the g.c. and $^1$H-n.m.r. data of the reaction product showed predominantly the E-isomer, which was obtained pure on recrystallisation. Thus the transition metal catalyst could be used effectively to isomerise the Z-component of the mixture of Z- and E-isomers to yield the E-isomer.

In order to examine the aforementioned second procedure (the Schlosser and Christmann method) for the synthesis of the E-olefin, ethyltriphenylphosphonium bromide was treated with phenyllithium in tetrahydrofuran and ether, followed by aldehyde (142).\(^6\) The Wittig intermediate obtained from the above reaction was treated with more phenyllithium. The reaction mixture was stirred for five minutes at -30°C and then t-butyl alcohol was added. A few minutes later potassium t-butoxide was also
added to the mixture. The $^1$H-n.m.r spectrum of the crude reaction product showed the presence of only one isomer. The coupling constants and chemical shifts of this isomer were identical with those of $E$-isomer (143a) obtained by the first method.

2.4.2 Preparation of cis-4,5-disubstituted phenyldioxolane (148)

Having obtained the stereochemically pure $E$-olefin (143a), the next step was to examine the epoxidation reaction. Olefin (143a) was treated with meta-chloroperbenzoic acid in cold chloroform. A number of products were formed and three of them were identified by $^1$H-n.m.r. and mass spectroscopy as the compounds (144), (145) and (146). After purification of the product mixture, the epoxide (144) was isolated in 37% yield. Compounds (145) and (146) were isolated in 5% and 17% yields respectively. When the epoxidation reaction was performed in the presence of solid sodium bicarbonate, the yield of epoxide (144) was almost doubled and none of the epoxide ring opened product was detected. The $^1$H-n.m.r. spectrum of epoxide (144) showed a doublet at $\delta$ 3.55 (J 2.0 Hz) corresponding to a benzylic proton adjacent to the epoxy linkage and no sign of duplication of the signals due to a diastereomeric mixture.

It was found that the compound (145) was derived by oxidation of the aromatic ring bearing the two methoxy substituents by the peracid (Fig. 2.7). The $^1$H-n.m.r. spectrum of compound (145) contained a doublet of quartets at $\delta$ 6.28 (J 15.0 and 4.6 Hz) and a doublet of quartets at $\delta$ 6.73 (J 15.0 and 1.6 Hz) analogous to $E$-olefin (143a). In addition, the spectrum showed two doublets at $\delta$ 6.37 (J 2.3 Hz) and $\delta$ 6.51 (J 2.3 Hz).
Hz) for the two aromatic protons, and two singlets at \( \delta 3.79 \) and \( \delta 3.88 \) corresponding to asymmetrically located aromatic methoxy groups. The mass spectrum of compound (145) showed an appropriate molecular ion \((m/z 194)\) as the base peak.

![Figure 2.8](image_url)

The diastereomeric mixture of compounds (146) resulted from ring opening of the epoxide (144) by \emph{meta}-chlorobenzoic acid (Fig 2.8). The \(^1\)H-n.m.r. data showed two doublets at \( \delta 6.21 \) (J 6.0 Hz) and \( \delta 6.25 \) (J 4.0 Hz) for each benzylic proton attached to the ester group, and a multiplet around \( \delta 8.0 \) corresponding to \emph{meta}-chlorobenzoic acid. The mass spectrum of compound (146) showed an appropriate molecular ion at \( m/z 350/352 \).

![Figure 2.9](image_url)

The \emph{trans}-epoxide (144) was treated with 15% potassium hydroxide in dimethyl sulphoxide.\(^{10} \) Under these conditions the epoxide was ring opened with inversion of stereochemistry at the C-1 position to afford \emph{erythro} diol (147) in 79% yield (Fig 2.9). The \(^1\)H-n.m.r. spectrum of this compound showed no sign of duplication of the signals
due to a diastereomeric mixture. The benzylic proton resonated as a doublet at $\delta$ 4.60 (J 4.4 Hz).

The *erythro* diol (147) was then treated with 1,1-dimethoxyethane in the presence of camphorsulphonic acid. After heating under reflux for two hours, a single product was obtained. Elemental analysis and the mass spectrum of the compound confirmed its molecular formula as $\text{C}_{13}\text{H}_{18}\text{O}_4$. The $^1\text{H}$-n.m.r. spectrum of this product showed three single protons as a quartet at $\delta$ 5.17 (J 4.9 Hz), a doublet at $\delta$ 4.94 (J 7.0 Hz) and a doublet of quartets at $\delta$ 4.33 (J 7.0 and 6.4 Hz) corresponding to the 2-H, 4-H and 5-H protons respectively. In addition, the spectrum showed two three-proton doublets at $\delta$ 1.55 (J 4.9 Hz) and at $\delta$ 0.99 (J 6.4 Hz) for 2-CH$_3$ and 5-CH$_3$ groups respectively. It was clear from the $^1\text{H}$-n.m.r. spectrum that only one diastereomer of the dioxolane (148) was formed. A detailed nuclear Overhauser effect (n.O.e.) study was conducted to determine the stereochemistry of the dioxolane (148). The n.O.e. spectrum obtained by irradiation at $\delta$ 4.33 (i.e. the signal for 5-H) showed a 9% enhancement for the 2-H proton and a 7% enhancement for the 4-H proton. Complementary n.O.e. spectra were obtained upon irradiation of the other two dioxolane ring protons. These data (see Fig. 2.10) clearly indicate the close proximity of the 5-H, 4-H and 2-H protons of the compound and support the assigned relative configuration of dioxolane (148) as all-cis.

![Diagram](148)

Positive n.O.e

- 5-H to 2-H = 9%
- 2-H to 5-H = 8%
- 5-H to 4-H = 7%

no n.O.e

- 2-Me to 4-H or 5-H

Fig 2.10
**2.4.3 trans-4,5-Disubstituted phenyldioxolanes (154)**

It was mentioned in section 2.3 that the trans-4,5-dioxolanes (154) could be obtained via the threo diol (153). The E-olefin was treated with a catalytic amount of osmium tetroxide and 4-methylmorpholine-N-oxide in aqueous acetone to afford the threo diol (153) with high stereoselectivity. Analysis of the $^1$H-n.m.r. spectrum of diol (153) indicated the presence of only one isomer. For example, the benzylic proton at $\delta$ 4.33 (J 7.1 Hz) appeared as a doublet with no corresponding doublet for the other isomer.

![Diagram](image)

The dioxolanes (154) were obtained by treatment of threo diol (153) with 1,1-dimethoxyethane. Unlike the dioxolane (148), the dioxolanes (154) were formed as a diastereomeric mixture differing in configuration at the C-2 centre (Fig 2.11). The $^1$H-n.m.r. spectrum showed four three-proton doublets at $\delta$ 1.35 (J 6.3 Hz), 1.42 (J 6.1 Hz), 1.48 (J 4.7 Hz) and 1.52 (J 4.8 Hz) corresponding to the two methyl groups of each diastereomer and a two proton multiplet at $\delta$ 3.88, a pair of doublets at $\delta$ 4.40 (J 5.8 Hz) and $\delta$ 4.43 (J 5.1 Hz), and a pair of quartets at $\delta$ 5.39 (J 4.7), and $\delta$ 5.45 (J 4.8 Hz) for the 5-H, 4-H and 2-H protons respectively for each diastereomer. This duplication of signals confirmed the presence of a mixture of dioxolanes epimeric at the C-2 centre. By comparison of the integrals of the one proton quartets at $\delta$ 5.39 and $\delta$ 5.45 it was determined that a 1:1 ratio of diastereomeric dioxolanes was obtained by acetalation of the diol (153), which was a single stereoisomer. Since the subsequent
isomerisation reaction was expected to proceed (see Fig. 2.4) via an oxonium ion (155), it was expected that the stereochemistry at the C-2 centre of the dioxolanes (154) would be irrelevant.

2.5 Isomerisation of cis-4,5-disubstituted phenyldioxolane (148)

Having obtained the dioxolanes (148) and (154) with the correct stereochemistry at the C-4 and C-5 positions, the isomerisation of the cis dioxolane (148) was first examined. The preliminary work on the isomerisation of naphthyldioxolane (135) with titanium tetrachloride had revealed that the angular naphthopyrans (136), (137) and their diol precursor were formed at 0 °C (see section 1.8.1). We decided to examine the isomerisation of dioxolane (148) in detail using similar temperature conditions to those employed for isomerisation of naphthyldioxolane (135).

2.5.1 Results at 0 °C

The dioxolane (148) in dry dichloromethane was first treated with two equivalents of titanium tetrachloride at -78 °C and the reaction mixture was immediately moved into an ice bath maintained at 0 °C. The reaction was monitored by thin layer chromatography (t.l.c.). After about ten minutes, the reaction was tested chromatographically. The results indicated a complete conversion of starting material to products of lower Rf.
The g.c.-mass spectral analysis of the crude product showed two components having the same molecular ions at m/z 238, and the same base peaks at m/z 193 due to the loss of 45 mass units from their molecular ions. These spectra indicated the presence of isomeric dihydroisobenzofurans (162), which would be expected to fragment as observed (Fig. 2.13).

Furthermore, the ¹H-n.m.r. spectrum of the crude product showed a 4:1 mixture of isomers, with, for the major isomer, a doublet of quartets at δ 5.42 (J 3.1 and 6.2 Hz), a doublet of doublets at δ 5.25 (J 3.3 and 3.1 Hz) and a multiplet at δ 3.95 for the 1-H and 3-H ring protons and the side chain methine proton respectively. The long range coupling constants between the 1-H and 3-H protons are known for the dihydroisobenzofuran (163) in the literature. These are 2.8 Hz for the trans 1-H, 3-H protons, but only 1.6 Hz for the cis 1-H, 3-H protons (Fig 2.14). Thus the long range coupling constant of 3.1 Hz between the 1-H and 3-H protons in the present case is in agreement with a trans-1,3 arrangement of substituents in the major stereoisomer (162-1) of the pair of dihydroisobenzofurans. The minor isomer therefore has the cis-1,3 stereochemistry, and this was supported by a coupling constant of 1.6 Hz of the 1-H and 3-H protons.
Thus the isomerisation of dioxolane (148) gave the dihydroisobenzofurans (162) when the temperature of the reaction mixture was increased from -78 °C to 0 °C. This was quite unexpected because the proposed mechanism shown in Fig 2.2 predicted that only intermediate (150) could readily undergo a carbon-carbon bond forming reaction. However, ring opening at the C-1 to O-2 bond of the isochroman products (151) and/or (152) could occur due to the electron donating effect of the methoxy substituents. If the ring opening occurred in this manner, the dihydroisobenzofurans could be derived from the first formed pyran products as shown in Fig 2.15. In an attempt to prevent this second rearrangement, it was decided to investigate the isomerisation reaction at -78 °C.
The phenylidoxolane (148) in dichloromethane was treated with two equivalents titanium tetrachloride at -78 °C and the reaction mixture was then maintained at this temperature for half an hour. Preliminary examination of the reaction mixture by thin layer chromatography indicated a complete conversion of starting material to a product of lower Rf, which was different to that observed for the dihydroisobenzofurans (162). The g.c.-mass spectral analysis of the crude product showed two components having the same molecular ions at m/z 238 and the same major fragment ions at m/z 223 and 205. The fragment ions at m/z 223 could be attributed to the loss of methyl groups from the molecular ions. The fragment ion probably underwent further degradation (loss of water) to give a more stable isochromanyl ring system corresponding to the base peaks at m/z 205 (see Fig 2.16). These mass spectral data were consistent with the presence of isochroman ring systems, and the similar fragmentation pattern for both compounds indicated that they were isomeric. It should be noted that no dihydroisobenzofurans of type (162) was detected.

The 1H-n.m.r. spectrum of the crude product indicated conversion of the starting dioxolane to a mixture of only two pyran products. The ratio of the two isomeric isochromans was found to be approximately 4:1 by comparison of the integrals of the methyl doublets at δ 1.56 and δ 1.48 of the 1H-n.m.r. spectrum of the crude product. The separation of the two isomers on a silica gel column afforded the isochromans (151) and (152) in 70% and 17% yields respectively (Fig 2.17).
The \( ^1H \)-n.m.r. spectra of these two isomers closely resembled each other. The aromatic region of isochroman (151) showed a pair of \textit{meta} coupled protons at \( \delta 6.69 \) and \( \delta 6.35 \) for the 5-H and 7-H protons respectively, whilst these two protons of isochroman (152) appeared at \( \delta 6.76 \) and \( \delta 6.38 \). Moreover, for each compound, three signals due to the 1-H, 4-H and 3-H protons were observed. For isochroman (151) these were quartets at \( \delta 4.96 \) (\( J 6.5 \) Hz), a doublet at \( \delta 4.23 \) (\( J 8.0 \) Hz) and a doublet of quartets at \( \delta 3.85 \) (\( J 8.0 \) and 6.3 Hz) respectively. The corresponding signals for isomer (152) were a doublet of quartets at \( \delta 4.92 \) (\( J 1.5 \) and 6.3 Hz), a doublet of doublets at \( \delta 4.31 \) (\( J 9.0 \) and 1.5 Hz) and a doublet of quartets at \( \delta 3.34 \) (\( J 9.0 \) and 6.2 Hz). These data establish the structures (151) and (152), without regard to the configuration at C-1 in each case. These aspects of stereochemistry will be considered in detail in section 2.5.4.

Treatment of dioxolane (148) with additional titanium tetrachloride (ten equivalents) in dichloromethane at -78 °C was found to give isochromans (151) and (152) in 71% yield. The \( ^1H \)-n.m.r. spectrum of the crude product showed a 3:1 mixture of isochromans (151) to (152). Only a small amount of the unreacted dioxolane (148) and its diol precursor were detected in this experiment. The contrast with the chemistry leading to phthalans at 0 °C and pyrans at -78 °C implied the extreme sensitivity of the pyran products (151) and (152) to the reaction temperature. But to make a proper assessment of the temperature dependence of the isomerisation reaction, it was necessary to consider a few more examples.
2.5.3 Results at -30 °C

It was decided to examine the isomerisation reaction at an intermediate temperature, -30 °C. The dioxolane (148) was first treated with titanium tetrachloride at -78 °C and then the temperature was raised rapidly to -30 °C. The crude product was analysed by g.c., g.c.-mass and \textsuperscript{1}H-n.m.r. spectroscopy. These data confirmed the presence of the same isochromans (151) and (152) as at -78 °C. However, comparison of the g.c. data and the integrals of the methyl doublets at δ 1.56 and δ 1.48 for each isomer indicated a reversed product ratio of approximately 1:7 for the two isochromans (151) to (152). This indicated that at -30 °C the isochroman (152) was formed as the major product. When the reaction was performed at -78 °C, as described in section 2.5.2, the major product was observed to be isochroman (151). This clearly suggested that the isochroman (151) was the kinetic product whilst isochroman (152) was the product of a further isomerisation process.

In order to further demonstrate the temperature sensitivity of the pyran products, the isomerisation of 4:1 mixture of isochromans (151) and (152) with titanium tetrachloride was attempted under various conditions. Comparison of the g.c.-mass and \textsuperscript{1}H-n.m.r. spectra of the crude products showed no change in ratio of isochromans (151) to (152) at -78 °C, whereas when the isomerisation was allowed to proceed at higher temperatures (-30 °C and 0 °C), more isochroman (152) was formed together with the dihydroisobenzofurans (162). This suggests that whilst it is possible to isomerise isochromans to dihydroisobenzofurans, the low conversion indicates that different factors may be operating when the presumed intermediates are subjected to the reaction. For example, in the conversion of dioxolane (148) to compounds (162), the intermediate isochromans are presumably present co-ordinated to titanium, whereas these complexes have first to be formed when the isochromans are added as starting material. Alternatively, temperature variations on a small reaction scale are difficult to control, and these differences may lead to differences in isomerisation rates. It appears that the reaction path is extremely sensitive to temperature, and the formation of isobenzofurans
(162) is owing to the opening of the C-1 to O-2 bond by the effect of the 6- and 8-methoxy substituents of the pyran products at higher temperatures. The experimental conditions and results of the aforementioned reactions are summarised in Table 2.1.

Table 2.1
The ratios of the products (151) to (152) at different temperatures

<table>
<thead>
<tr>
<th>Entry</th>
<th>starting material</th>
<th>Conditions</th>
<th>Yields</th>
<th>Products</th>
<th>products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 equivs. TiCl₄</td>
<td>(151)+(152)</td>
<td>(151):(152)</td>
<td>(162)</td>
</tr>
<tr>
<td>1</td>
<td>(148)</td>
<td>-78 °C, 30 min</td>
<td>87</td>
<td>4:1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(148)</td>
<td>-78 ° to -30 °C, 30 min</td>
<td>81</td>
<td>1:7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(148)</td>
<td>-78 ° to 0 °C, 10 min</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>(148)</td>
<td>-78 °C, 30 min</td>
<td>71</td>
<td>3:1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>(151), (152)</td>
<td>-78 °C, 60 min</td>
<td>80</td>
<td>4:1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>(151), (152)</td>
<td>-78 ° -30 °C, 20 min</td>
<td>75</td>
<td>1.8:1</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>(151), (152)</td>
<td>-78 °C to 0 °C, 10 min</td>
<td>65</td>
<td>1.2:1</td>
<td>15</td>
</tr>
</tbody>
</table>

a (148) in entries 1-4 and (151), (152) in entries 5-7 refer to stereochemically pure cis-4,5-phenyldioxolane and a 4:1 ratio of isochromans (151) to (152) respectively in dichloromethane.

b Temperature at which reaction was quenched with methanol.

c 10 equivs. TiCl₄ were used.

d Isolated yield of isochromans (151) + (152).

e Ratios were determined by g.c. and ¹H-n.m.r. spectroscopy.

f As determined by g.c. analysis.

g Dioxolanes and diol (%) quoted were estimated from ¹H-n.m.r. analysis. (147) = diol precursor of dioxolane (148).
2.5.4 Relative stereochemistry of the isochromans (151) and (152)

The $^1$H-n.m.r. spectrum of isomer (151) showed a vicinal coupling constant of $J = 8.0$ Hz between the 3-H and 4-H protons. The chemical shifts of the 1-H, 4-H and 3-H protons of the isomer (151) were at $\delta = 4.96, 4.23$ and 3.85 respectively. For the isochroman (152), a vicinal coupling constant of 9.0 Hz between the 3-H and 4-H protons and a long-range coupling constant of 1.5 Hz between the 1-H and 4-H protons were observed. The chemical shifts of the 1-H, 4-H and 3-H protons appeared at $\delta = 4.92, 4.31$ and 3.34 respectively.

\[
\text{(151)} \quad \text{(152)}
\]

In order to assign the relative stereochemistry at C-1, C-3 and C-4 of isochromans (151) and (152), it was decided to compare their $^1$H-n.m.r. data with those of known benzoisochromans. A pyran ring system similar to compounds (151) and (152) is present in eleutherin (2), isoeleutherin (3) and dimethyl ether of quinone A (141). The value reported for the vicinal coupling of the axial (3-H) and pseudo-axial (4-H) protons was 8 to 9 Hz for all three compounds. By comparison of this vicinal coupling constant value with that of isochromans (151) and (152), it is possible to evaluate the relative stereochemistry at the C-4 and C-3 positions. Thus, it can be concluded that the 4-H and 3-H protons of isochromans (151) and (152) have pseudo-axial and axial configurations respectively. The observed chemical shifts of the 1-H, 4-H and 3-H protons of the isochroman (151) were in good agreement with those of the dimethyl ether of quinone A (141) ($\delta = 4.92, 4.43$ and 3.84). This suggests that the 1-H proton of isochroman (151) adopts a pseudo-equatorial configuration.
However, to establish the stereochemistry at the C-1 centre of the isochromans (151) and (152), it is necessary to consider the long-range coupling of known benzoisochromans. Cameron et al. have studied in detail the magnitude of the long range-coupling between the 1-H and 4-H protons of eleutherin (2), isoeleutherin (3) and the dimethyl ether of quinone A (141). It has been known for some time that a measurable proton-proton long range coupling of the type H-C-C=C-C-H can occur by the operation of a mechanism involving hyperconjugation and a π configuration interaction.

Compounds such as the eleutherins (2) and (3) and the quinones A and A' provided particularly interesting examples of this because of the different conformations assumed by the C-H bonds with respect to the plane of the C=C bond of the naphthoquinone. Karplus showed that the long range couplings of this type would be a maximum between C-H bonds which are perpendicular to the plane defined by the double bond, and a minimum between C-H bonds in the plane of the bond. Long range-coupling constants of 3.5 Hz and 2.9 Hz were reported for the pseudo-axial-pseudo-axial and pseudo-axial-pseudo-equatorial configurations respectively of the 1-H and 4-H
protons of eleutherin (2). The values reported for the long-range $J_{1,4}$ for the pseudo-equatorial-pseudo-axial protons for isoeleutherin (3) and the dimethyl ether of quinone A (141) were 2.0 Hz and 1.5 Hz respectively.

The models (2), (3) and (141) allow useful comparisons with isochromans (151) and (152) for the purposes of determining the relative stereochemistry at C-1 for the latter pair. However these models are perhaps not the closest since the dihydropyran ring is fused in each case to the quinonoid ring of a 1,4-naphthoquinone. Closer models are perhaps the naphthopyran (76) and its 7-isopropoxy-(164a)\(^{17}\) and 7,10-dibenzyloxy-analogues (164b),\(^{17}\) all of which have an aromatic rather than a quinonoid ring fused to the pyran. Compounds (76) and its analogues differ from isochromans (151) and (152) in two respects; the former are all naphthopyrans and they all possess a methoxy substituent at C-5. Naphthalenic models lacking the C-5 methoxy, which would therefore be the most useful analogues available, are the naphthopyrans (89) and (95).\(^9\) Table 2.2 compares the chemical shifts and coupling constants for the pyran ring protons.
for compounds (76), (164a), (164b), (89), (95), (151) and (152) - the only coupling constants shown are those observed between ring protons.

Table 2.2

Comparison of the chemical shifts and coupling constants for the pyran ring protons

<table>
<thead>
<tr>
<th>Structure</th>
<th>1-H</th>
<th>3-H</th>
<th>4-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>(76)</td>
<td>5.21</td>
<td>3.97 (J 9.0 Hz)</td>
<td>4.74 (J 9.0 Hz)</td>
</tr>
<tr>
<td>(164a)</td>
<td>5.18</td>
<td>4.02 (J 9.0 Hz)</td>
<td>4.70 (J 9.0 Hz)</td>
</tr>
<tr>
<td>(164b)</td>
<td>5.20</td>
<td>4.03 (J 8.0 Hz)</td>
<td>4.74 (J 8.0 Hz)</td>
</tr>
<tr>
<td>(89)</td>
<td>5.28</td>
<td>3.97 (J 8.0 Hz)</td>
<td>4.40 (J 8.0 Hz)</td>
</tr>
<tr>
<td>(95)</td>
<td>5.27</td>
<td>3.90 (J 7.8 Hz)</td>
<td>4.45 (J 7.8 Hz)</td>
</tr>
<tr>
<td>(151)</td>
<td>4.96</td>
<td>3.85 (J 8.0 Hz)</td>
<td>4.23 (J 8.0 Hz)</td>
</tr>
<tr>
<td>(152)</td>
<td>4.92 (J 1.5 Hz)</td>
<td>3.34 (J 9.0 Hz)</td>
<td>4.31 (J 9.0 and 1.5 Hz)</td>
</tr>
</tbody>
</table>

This Table provides data which show differences between compound (152) and the rest of the series in two major respects. The first is that only compound (152) exhibits long-range coupling between 1-H and 4-H protons. Secondly, all the other compounds show the axial 3-H proton in the range $\delta 3.85-4.03$, whereas for isochroman (152) this same axial proton resonates at $\delta 3.34$. The fact that H-3 protons for cis-1,3-dimethylnaphthopyrans appear at higher field than for the corresponding trans isomers has been noted previously.$^{18,19}$

The configurations of isochromans (151) and (152) are depicted by partial formulae (C) and (D) respectively. Formula (C) has 1-H pseudo-equatorial and 4-H pseudo-axial, whereas formula (D) differs only in that 1-H is pseudo-axial. When both
1-H and 4-H protons are *pseudo*-axial, both angles subtended by these C-H bonds and the plane defined by the ring will be greater than when one is *pseudo*-equatorial. As discussed above, the relative magnitude for $J_{14}$ would be expected to be $J'a'a' > J'a'e'$. No long range coupling was observed between the *pseudo*-equatorial 1-H and *pseudo*-axial 4-H protons in isomer (151) (see Formula C). Thus, the observed long range coupling of 1.5 Hz in isochroman (152) would be due to the *pseudo*-axial configuration of the proton at C-1. This evidence confirms the structures assigned for isochromans (151) and (152).

The magnitude of this 1.5 Hz is much less than that observed for the eleutherin (2), (3.5 Hz). This is, however, to be expected since long range-coupling through the benzene ring of isochromans is less favourable than through the quinone π-system. The important point is that the relative magnitude will stay the same *i.e.* $J'a'a' > J'a'e'$.

Further evidence for the C-1 stereochemistry of isochroman (151) was obtained by n.O.e experiments. The n.O.e. spectra of the isochroman (151) obtained upon irradiation at δ 1.56 (*i.e.* the signal for the C-1 methyl group) showed a 14% enhancement of the signal due to the 3-H proton (Fig 2.18). Furthermore, the n.O.e. spectral data indicated the proximity of the C-3 methyl group to the 4-H proton. Thus, it follows from this experiment that the 1-H proton of isochroman (151) should be *pseudo*-equatorial. This strongly supported configuration (C) for the isochroman (151).
Having established the formation of isochromans (151) and (152) from isomerisation of cis-4,5-disubstituted phenyldioxolane (148), the isomerisation of trans-4,5-disubstituted phenyldioxolanes (154) was next investigated at different temperatures. The conditions and the results of these experiments are summarised in Table 2.3 and Fig 2.19.

Treatment of dioxolanes (154) with titanium tetrachloride at -78 °C for 30 minutes gave the isochromans (157) and (158) in good yield (Entry 1). This reaction was repeated in order to establish the reproducibility of this result (Entry 2). The g.c. and $^1$H-n.m.r. data of the crude product showed an ratio of approximately 1:7 for compound (157) to compound (158) by comparing the integrals of the two methyl proton doublets at $\delta$ 1.45 for isochroman (157) and $\delta$ 1.54 for (158). The g.c.-mass spectral data of the crude product indicated two stereoisomers, with molecular ions at $m/z$ 238. The fragmentation pattern was common to both isomers. The mass spectral data of each isomer showed a strong ion at $m/z$ 223, corresponding to $M^+\cdot$CH$_3$, and another strong
ion at \( m/z \) 205, corresponding to loss of H\(_2\)O from the fragment ion at \( m/z \) 223. This fragmentation pattern clearly indicated that the two isomers were isochromans, and it was the same pattern observed for the pair of C-4 epimers (151) and (152) (Fig 2.16).

**Table 2.3**

The ratios of products (157) to (158) and (166) at different temperatures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions(^a)</th>
<th>products ( (157):(158))(^c)</th>
<th>Yields (%)(^e)</th>
<th>products (153),(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78 °C(^b), 30 min</td>
<td>1:7</td>
<td>100:0</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>-78 °C(^b), 30 min</td>
<td>1:7</td>
<td>100:0</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>-78 ° to -30 °C(^b), 30 min</td>
<td>1:7</td>
<td>1.7:1</td>
<td>66(^d)</td>
</tr>
<tr>
<td>4</td>
<td>-78 ° to 0 °C(^b), 10 min</td>
<td>0</td>
<td>0:100 (6:1)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>-78 ° to 0 °C(^b), 10 min</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) (1:1) Mixture of dioxolanes (154) in dichloromethane, except entry 5 which is pure isochroman (158).

\(^b\) Temperature at which reaction was quenched with methanol.

\(^c\) Isomer ratios of isochromans (157) to (158) were determined by g.c. and \(^1\)H-n.m.r. analysis.

\(^d\) As determined by g.c.

\(^e\) Isolated yields.

\(^f\) Dioxolanes and diol (%) quoted were estimated from \(^1\)H-n.m.r. analysis.

Chromatographic separation of the crude product afforded isochromans (157) and (158) in 8% and 70% yields respectively. The \(^1\)H-n.m.r. spectrum of the isochroman (157) showed a multiplet at \( \delta \) 4.10 due to the 3-H and 4-H protons, and a
quartet at $\delta$ 5.03 (J 6.5 Hz) due to the 1-H proton. The overlapping of the resonances due to the 3-H and 4-H protons in the isochroman (157) made the measurement of the vicinal coupling constant more difficult. Therefore, it was decided to make the acetate derivative (165) of compound (157). The $^1$H-n.m.r. spectrum of the acetate (165) showed a doublet of quartets at $\delta$ 4.22 (J 2.1 and 6.3 Hz) for the 3-H proton, a quartet at $\delta$ 5.12 (J 6.5 Hz) for the 1-H proton and a doublet at $\delta$ 5.74 (J 2.1 Hz) for the 4-H proton. The shift to lower field ($\delta$ 4.10 to $\delta$ 5.74) of the doublet due to the 4-H proton in acetate (165) provided further evidence that compound (157) was an isochroman, and not a dihydroisobenzofuran. If the latter had been acetylated, a deshielding of the doublet of quartets would have occurred. This was not observed in the $^1$H-n.m.r. spectrum of acetate (165). The vicinal coupling constant of 2.1 Hz between the 3-H and 4-H protons suggests a cis relative stereochemistry between them, as expected from the stereochemistry of the precursor dioxolanes. The configuration at C-1 will be discussed in detail in section 2.5.6.

The $^1$H-n.m.r. spectrum of the major isochroman (158) showed a doublet of quartets at $\delta$ 3.72 (J 1.6 and 6.6 Hz), a doublet at $\delta$ 4.12 (1.6 Hz) and quartet at $\delta$ 4.87 (J 6.3 Hz) for the 3-H, 4-H and 1-H protons. It is interesting to note that the $^1$H-n.m.r. spectrum of isochroman (157) was relatively similar to that of isochroman (158), apart from the deshielding of 3-H proton. Based on the $^1$H-n.m.r. spectral analysis, the all-cis-isochroman structure (158) was tentatively assigned for this compound and a detailed analysis of the stereochemistry will be discussed in section 2.5.6. However, it was clear that the isomerisation at -78 °C of the trans-4,5-disubstituted phenyldioxolanes (154) favoured the all-cis-isochroman.
Next, the isomerisation of dioxolanes (154) was studied at -30 °C (Entry 3, Table 2.3). Even under these conditions isochroman (158) was formed as the major product. Compared to the results at -78 °C there was no observable change in ratio of isochromans (157) to (158). However, dihydroisobenzofurans (166) were now observed as minor products. Moreover, when the dioxolanes (154) were allowed to stand with titanium tetrachloride at 0 °C for 10 minutes, the rapid formation of dihydroisobenzofurans (166) was observed in good yield (Entry 4) (Fig 2.20). The g.c. analysis of the crude product now indicated a 6:1 mixture of two compounds. The g.c.-mass spectral analysis of this mixture showed two components having the same molecular ions at m/z 238 and the same base peak at m/z 193. From this fragmentation pattern, the two components in the crude product were identified as the dihydroisobenzofurans (166) and the same pattern was observed as for the dihydroisobenzofuran isomers (162) (Fig. 2.13).

![Diagram](image)

The 1H-n.m.r. spectrum of the major component (166-1) showed a multiplet at δ 3.88, a doublet of doublets at δ 5.03 (J 2.9 and 7.3 Hz) and a doublet of quartets at δ 5.39 (J 2.9 and 6.3 Hz) due to the side chain methine proton, 3-H and 1-H ring protons respectively. The trans-1,3 stereochemistry of the compound (166-1) was supported by a coupling constant of 2.9 Hz of the 1-H and 3-H protons. It should be emphasised that the isochroman (158) could itself be fully converted, in turn, into the
dihydroisobenzofurans (166) under similar conditions (Entry 5, Table 2.3) (Fig 2.20). The formation of such dihydroisobenzofurans (166) from isochromans was explained in detail in section 2.5.1.

2.5.6 Relative stereochemistry of isochromans (157) and (158)

The \(^1\)H-n.m.r. spectra of isochroman (165) and isochroman (158) showed a similar coupling constant value (~ J 2 Hz) between the 3-H and 4-H protons. The vicinal coupling constant \(J_{3,4} = 2\) Hz was consistent with the C-H bond at position 3 in either the axial or the equatorial configuration and these configurations are depicted by partial formulae E and F respectively (Fig 2.21). Therefore, the value of the vicinal coupling constant could not be used to confirm the conformation of isochromans (157) and (158), although it seemed very reasonable to assume that the partial formula E would be expected to be the preferred conformation rather than alternative half-chair conformation F since this is the conformation adopted by quinone A'.

As expected, there was no observable coupling between the 1-H and 4-H protons of isochroman (157). The chemical shift values of the 1-H, 4-H and 3-H protons of isochroman (157) (δ 5.03, 4.10) were in good agreement with the values reported for
dimethyl ether of quinone A' (δ 5.0, 4.48 and 4.0) suggesting the same relative stereochemistry at C-1. The n.O.e. spectrum of isochroman (165) obtained upon irradiation at δ 1.46 (i.e. the signal for the C-1 methyl group) showed a 10% enhancement of the signal due to the 3-H proton. This indicated the proximity of the C-1 methyl group to the 3-H proton. This strongly supports the conformation E and the trans-1,3-dimethyl configuration for the isochroman (157), and together with the chemical shift evidence, confirms the stereochemical assignment.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
H & \quad H \\
7 & \quad 1 \\
5 & \quad 4 \\
& \quad \text{CH}_3 \\
\text{MeO} & \quad \text{CH}_3 \\
OAc & \quad OAc
\end{align*}
\]

To obtain evidence for the stereochemistry at the C-1 centre of isochroman (158), it was decided to remove the benzylic hydroxy group at C-4. This would result in the formation of the cis-1,3-dimethylbenzopyran (167) similar to the cis-1,3-dimethylbenzopyran (168) reported by Kometani. Therefore, a comparison of the \( ^1\text{H}-\text{n.m.r.} \) spectra of the two dimethylpyrans would confirm the C-1 stereochemistry.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
1 & \quad 3 \\
4 & \quad 3 \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

Compound (158) was thus treated with phosphorus tribromide. After thirty minutes, two products of higher \( R_f \) were obtained which were shown by \( ^1\text{H}-\text{n.m.r.} \) spectroscopy to be the bromopyrans (169) and (170). The C-4 bromine of compound (169) was pseudo-equatorial, as indicated by the large coupling constant of 8.2 Hz.
between the 3-H and 4-H protons in the $^{1}$H-n.m.r. spectrum. The corresponding vicinal coupling constant between 3-H and 4-H protons of the compound (170) was 1.9 Hz, implying that the C-4 bromine was pseudo-axial. However, the $^{1}$H-n.m.r. spectra of both bromopyrans (169) and (170) showed approximately 2:1 mixture of epimers at the C-1 centre. Treatment of the mixture of compounds (169) and (170) with an aqueous ethanolic solution of Raney nickel catalyst yielded the cis-1,3-dimethylpyran (167) in 40% yield together with dehydrobrominated product (171). The signals due to trans-1,3-dimethylpyran was not detected in the $^{1}$H-n.m.r. spectrum.

The $^{1}$H-n.m.r. spectrum of isochroman (167) showed the pseudo-equatorial 4-H proton as a broad doublet at $\delta$ 2.52 (J 17.1 Hz) and the pseudo-axial 4-H proton as a doublet of doublet of doublets $\delta$ 2.66 (J 17.1, 10.5 and 1.5 Hz). A multiplet and a doublet of a quartets appeared at $\delta$ 3.66 and $\delta$ 4.93 (J 1.5 and 6.3 Hz) for the 3-H and 1-H protons respectively, in the regions reported for cis-1,3-dimethylbenzopyran (168)\textsuperscript{18}. The trans-isomer of compound (168) as well as the trans- and cis-stereoisomers of 8-methoxy-1,3-dimethylicochroman (168a and 168b)\textsuperscript{20} are also known and the $^{1}$H-n.m.r. spectrum reported for the cis-8-methoxy compound shows an even stronger correspondence of the pyran ring protons with those observed for compound (167). These data show, first, that only the cis-compounds in the literature \textsuperscript{18,20} exhibit long-range coupling between the 1-H and 4-H protons. Secondly, once again, the cis-compounds show 3-H proton at higher field [$\delta$ 3.66 (167), $\delta$ 3.65 (168) and $\delta$ 3.66 (168b)] than for the trans compounds [$\delta$ 4.05 (trans-168) and $\delta$ 4.11 (168a)].
Thus, there is no doubt that the major deoxygenated product obtained by reaction of isochroman (158) with phosphorus tribromide followed by Raney nickel possessed the cis-stereochemistry assigned in structure (167). However, owing to the significant loss of stereochemistry at the C-1 centre of isochroman (158) during the bromination reaction, this experiment was not useful in establishing the stereochemistry at C-1.

In order to establish the stereochemistry of the three chiral centres of isochroman (158), one-dimensional n.O.e. spectra were obtained. The spectrum obtained upon irradiation at $\delta$ 4.87, i.e. the signal for the 1-H proton of isochroman (158), showed a 9% enhancement for the signal due to the 3-H proton. A confirmatory n.O.e. spectrum obtained upon irradiation of the 3-H proton showed a similar enhancement for the 1-H proton. Furthermore, the noesy spectrum of the compound (158) showed a close relationship between the 1-H and 3-H protons. Thus, it follows from these experiments that the 1-H proton is pseudo-axial. This supported the conformation E and excluded the alternate F for the isochroman (158). These n.O.e. data confirm the all-cis configuration for isochroman (158).
2.6 Conclusions

The following conclusions can be drawn for the Lewis acid promoted isomerisation of phenyldioxolanes (148) and (154):

• the cis-4,5-disubstituted phenyldioxolane (148) isomerises to trans-3,4-disubstituted isochromans (151) and (152), whilst the trans-4,5-disubstituted phenyldioxolanes (154) isomerise to cis-3,4-disubstituted isochromans (157) and (158);

• isomerisation of cis-4,5-disubstituted phenyldioxolane (148) can be controlled to favour either isochroman (151) or (152), whereas isomerisation of trans-4,5-disubstituted phenyldioxolanes (154) afforded all-cis-isochroman (158) selectively;

• the diastereoselectivity of the isomerisation of phenyldioxolanes to isochromans depends on the stereochemistry of the dioxolane and the temperature of the reaction.

• unless the temperature of the isomerisation reaction is carefully controlled, dihydroisobenzofurans and not isochromans result;

• isochromans isomerise to dihydroisobenzofurans due to the electron donating effect of the 6- and 8-methoxy substituents on the phenyl ring.
References


   
   

   


   
   
   


Chapter 3

Isomerisation of 4,5-disubstituted (2',5'-unsymmetrically substituted phenyl)dioxolanes to isochromans
Chapter 3

3.1 Introduction

The successful synthesis of 6,8-dimethoxyisochromans from cis- and trans-4-(3',5'-dimethoxyphenyl)-5-methyldioxolanes (148) and (154) clearly indicated that the isomerisation of methoxy substituted phenyldioxolanes to isochromans was possible (see Chapter 2). This chapter describes the isomerisation of cis-4-(2',5'-dimethoxyphenyl)-5-methyldioxolane (175) and trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes (181) and (182) to the corresponding 5,8-dimethoxyisochromans (see Fig 3.1). These are considered to be the closest model compounds for an eventual synthesis of the naturally occurring quinones A (63) and A' (64), as substitution of the aromatic ring with two para methoxy substituents would permit subsequent oxidative demethylation to afford quinonoid products. Therefore, it is appropriate to discuss the stereoselective synthesis of the cis-4-(2',5'-dimethoxyphenyl)-5-methyldioxolane (175) and trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes (181) and (182) in the next section.

![Fig 3.1](image-url)
3.2 Synthesis of cis-4-(2',5'-dimethoxyphenyl)-5-methyldioxolane (175) and trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes (181) and (182)

In Chapter 2, it was pointed out that the key step in the synthesis of either the cis- or trans-4,5-disubstituted phenyldioxolane was the preparation of stereochemically pure E- or Z-olefin precursors. In this section, the synthesis of phenyldioxolane (175) and phenyldioxolanes (181) and (182) will be explored using similar intermediates to those discussed in Section 2.3.

3.2.1 Synthesis of phenyldioxolane (175)

![Wittig reaction between 2,5-dimethoxybenzaldehyde (172) and ethyltriphenylphosphonium bromide in dry tetrahydrofuran containing dimethyl sulphoxide](image)

The Wittig reaction between 2,5-dimethoxybenzaldehyde (172) and ethyltriphenylphosphonium bromide in dry tetrahydrofuran containing dimethyl sulphoxide gave the olefinic mixture (173) in 84% yield (Fig 3.2). The g.c. analysis of the olefins (173) showed a 4:1 ratio of two components. The 1H-n.m.r. spectrum contained one major pair of doublets of quartets at $\delta$ 6.47 (J 11.4 and 1.2 Hz) and $\delta$ 5.88 (J 11.4 and 7.1 Hz) having a cis-olefinic coupling and another minor pair of doublets of quartets at $\delta$ 6.68 (J 16.0 and 1.2 Hz) and $\delta$ 6.24 (J 16.0 and 6.6 Hz) having a trans-olefinic coupling. The ratio of Z- to E- olefin was found to be approximately 4:1 by comparing the integrals of the methyl resonances at $\delta$ 1.85 and $\delta$ 1.91. The molecular formula of C$_{11}$H$_{14}$O$_2$ for the components of the olefin mixture was confirmed by its
elemental analysis and mass spectrum. The attempted chromatographic separation of the major Z-olefin from the olefin mixture was unsuccessful and the attempted conversion of this mixture into a single stereoisomer using a palladium catalyst merely gave a 1:3 equilibrium mixture of the Z- and E-olefins. Therefore, it was decided to hydroxylate the 4:1 mixture of Z- and E-olefins in the hope of separating the resultant diols.

\[
\text{cis:trans} = 4:1
\]

(173)  
(174)  
(180)

Fig 3.3

Treatment of the olefin mixture (173) with a catalytic amount of osmium tetroxide and 4-methylmorpholine-N-oxide gave the diols (174) and (180) in 69% yield (Fig 3.3). Based on \(^1\)H-n.m.r. spectral analysis, the ratio of diol (174) to diol (180) was found to be approximately 4:1 as was expected from the ratio of olefins (173). Attempted chromatographic separation of the mixture of diols was partially successful. This improved the ratio of erythro diol to threo diol to approximately 7:1 as shown by examination of the \(^1\)H-n.m.r. spectrum. The \(^1\)H-n.m.r. spectrum of the major component (174) showed a doublet at \(\delta 4.89\) (7.2 Hz) and a doublet of quartets at \(\delta 4.12\) (J 7.2 and 6.4 Hz) corresponding to the two adjacent methine protons. Since the reaction with osmium tetroxide gives rise to cis hydroxylation, the major product (174) was identified as the erythro diol. In addition the spectrum showed weak signals at \(\delta 4.53\) and \(\delta 3.95\) corresponding to the threo diol (180) arising from the minor E-olefin. It was decided to use this 7:1 mixture of diols for the next reaction.

Treatment of the mixture containing predominantly diol (174) with 1,1-dimethoxyethane and (±)-camphorsulphonic acid in boiling dichloromethane afforded a
crude product which on chromatographic separation gave the pure phenyldioxolane (175) as a single stereoisomer in 70% yield (Fig 3.4). The mass spectrum showed an appropriate molecular ion \((m/z \ 238)\) and elemental analysis confirmed its molecular formula as \(C_{13}H_{18}O_4\). The \(^1\)H-n.m.r. spectrum was qualitatively similar to dioxolane (148) (see Section 2.4.3) apart from the ortho coupling in the aromatic region and deshielding of the 4-H proton in the heterocyclic ring. Although the stereochemistry at the C-2 centre of dioxolane was believed not to be important for the isomerisation reaction, it was clear from the spectrum that only one diastereomer had been formed. By analogy with dioxolane (148), it was most likely to be the all-cis-dioxolane (175) although this was not proved. Thus a successful synthesis of phenyldioxolane (175) had been completed.

![Chemical structures](image)

**Fig 3.4**

### 3.2.2 Synthesis of phenyldioxolanes (181) and (182)

As a first step towards the synthesis of phenyldioxolanes (181) and (182), the epoxidation reaction of the 4:1 mixture of Z- and E-olefins (173) was investigated. The olefin mixture was treated with meta-chloroperbenzoic acid and sodium bicarbonate in cold chloroform. After separation of the crude product mixture, stereochemically pure cis-epoxide (178) and an epoxide ring opened product (179) were isolated in 66% and 7% yield respectively (Fig 3.5). Elemental analysis and the mass spectrum of the epoxide (178) confirmed its molecular formula as \(C_{11}H_{14}O_3\). The \(^1\)H-n.m.r. spectrum of epoxide (178) showed a doublet at \(\delta \ 4.16\) (J 4.9 Hz) for the benzylic proton adjacent to
the ether linkage. The $^1$H-n.m.r. and $^{13}$C-n.m.r. data indicated that it was the sole stereoisomer; no signals attributed to the possible presence of the corresponding trans-epoxide were observed.

![Chemical reaction](image)

Fig 3.5

Presumably, compound (179) was derived by acid catalysed ring opening of the epoxide and was found to be the hydroxy ester of meta-chlorobenzoic acid. The $^1$H-n.m.r. spectrum of the compound (179) indicated that it was a 1:1 diastereomeric mixture and was not further investigated.

![Chemical reaction](image)

Fig 3.6

With the epoxide (178) in hand, basic conditions (15% KOH in DMSO) were employed to hydrolyse it to the diol (180). The epoxide ring opening occurred with inversion of stereochemistry at the C-1 centre to produce a threo diol (180) in 76% yield (Fig 3.6). The diol (180) gave a satisfactory elemental analysis for the molecular formula C$_{11}$H$_{16}$O$_4$. The $^1$H-n.m.r. spectrum of diol (180) showed a doublet at $\delta$ 4.53 ($J$ 7.1 Hz)
and a doublet of quartets at $\delta$ 3.95 (J 7.1 and 6.3 Hz) corresponding to the adjacent methine proton.

![Chemical structures](image)

Fig 3.7

Treatnten of diol (180) with 1,1-dimethoxyethane and (±)-camphorsulphonic acid in dichloromethane gave the dioxolanes (181) and (182) in a yield of 77%. A 2:1 ratio of dioxolane diastereomers, differing in configuration at C-2, was determined from the $^1$H-n.m.r. spectrum, by comparing the integrals of the methyl doublets at $\delta$ 1.36 (J 6.4 Hz) and at $\delta$ 1.42 (J 4.8 Hz) (Fig 3.7). The g.c.-mass spectra of epimeric dioxolanes (181) and (182) showed the same molecular ions ($m/z$ 238) and identical fragmentation patterns.

3.3 Isomerisation of cis-4,5-disubstituted phenyldioxolane (175)

The isomerisation reaction of phenyldioxolane (175) to the corresponding isochromans was investigated at various temperatures and reaction times. Treatment of dioxolane (175) with titanium tetrachloride at -78 °C for 30 minutes resulted in the formation of a number of products. The g.c.-mass spectral analysis of the crude product showed:

(a) two compounds having the same molecular ions at $m/z$ 230 with $^{37}$Cl isotope peaks at 232 corresponding to the diastereomeric chlorohydrins (177) with retention times of 13.4 and 13.5 minutes;
(b) two compounds having the same molecular ions at $m/z$ 238 corresponding to dioxolane (175) and isochroman (176) with retention times 13.1 and 14.7 minutes respectively; and

(c) four compounds having the same molecular ions at $m/z$ 194 corresponding to two epoxides (178 and its diastereomer) with retention times 11.4 and 11.6 minutes, and two rearrangement products of these epoxides (178-1 and 178-2) with retention times of 11.5 and 11.8 minutes.

\[ \text{Fig 3.8} \]

The $^1$H-n.m.r. spectrum of the crude product however, showed signals due to starting dioxolane (175), isochroman (176) and chlorohydrins (177), and no signals due to any epoxides or their rearrangement products (Fig 3.8). The chromatographic separation of the crude reaction product afforded the unreacted dioxolane (175), isochroman (176) and the diastereomeric mixture of chlorohydrins (177) in 20%, 18% and 45% yield respectively. Each of these compounds was analysed by g.c.-mass spectroscopy. The dioxolane (175) and isochroman (176) showed their expected molecular ions and characteristic fragmentation patterns. The diastereomeric mixture of chlorohydrins (177) exhibited a mixture of epoxides (178 and its diastereomer), their rearrangement products (178-1 and 178-2) and chlorohydrins. The $^1$H-n.m.r. spectrum of the diastereomeric mixture of chlorohydrins (177) indicated significant resonances at $\delta$ 5.43 for the overlapping 1-H protons of each diastereomer, and similarly at $\delta$ 4.15 for the 2-H protons of each diastereomer, as well as methyl group signals at $\delta$ 1.25 and $\delta$ 1.14 for each isomer. The ratio of chlorohydrin diastereomers was determined as approximately 1:1 by comparing the integrals of the methyl groups at $\delta$ 1.25 and at $\delta$
1.14. The strong electron donating effect of the 2'-methoxy substituent ortho to the dioxolane ring promoted alternative benzylic cleavage to give chlorohydrins (177) and not their regioisomers.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{Cl} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

(177)

\[
\begin{align*}
\Delta & \quad -\text{HCl} \\
\text{m/z} & \quad 188/186
\end{align*}
\]

The question now arises as to why the g.c.-mass spectrum of chlorohydrins (177) showed additional products (Fig 3.9). The most plausible explanation is that chlorohydrins (177) eliminate hydrogen chloride thermally at the g.c. injector, where higher temperatures (~ 250 °C) are used, to give their corresponding epoxides. It was assumed that under these conditions the epoxides rearrange to form ketones (178-1) and (178-2).
In order to clarify these observations, it was decided to synthesise chlorohydrins (177) by treatment of epoxide (178) with titanium tetrachloride in dichloromethane at -78 °C for 45 minutes. This gave a diastereomeric mixture of chlorohydrins (177) in 56% yield together with unreacted epoxide (178) (25%). As before, the g.c.-mass spectrum of chlorohydrins (177) showed four compounds having the same molecular ions ($m/z$ 194) corresponding to the epoxides and their ketone rearrangement products, together with two compounds having the same molecular ions ($m/z$ 230/232) corresponding to the diastereomeric chlorohydrins.

To confirm the identity of the epoxides (178 and its diastereomer), an authentic sample of them was injected into the g.c.-mass spectrometer under conditions identical to those used for the chlorohydrins mixture. The observed retention times (11.4, 11.5, 11.6 and 11.8 minutes) and the fragmentation patterns were similar to those of compounds observed in the chlorohydrins mixture (177). From the g.c.-mass spectral data, two components having retention times 11.4 and 11.6 minutes and major ions at $m/z$ 194, 179, 165 and 151 were identified as epoxides (178 and its diastereomer). Furthermore, components having retention times of 11.5 and 11.8 minutes and base peaks at $m/z$ 165 and 151 were identified as the two ketones (178-1) and (178-2) (Fig 3.9).

![Fig 3.10](image)

The mass spectrum of isochroman (176) showed an appropriate molecular ion at $m/z$ 238, a fragment ion at $m/z$ 223 and the base peak at $m/z$ 205. This indicates the presence of an isochromanyl ring system which would be expected to fragment as
observed (Fig 3.10) and precludes the alternative dihydroisobenzofuran isomer (183). Difficulties in purification of isochroman (176) prevented a satisfactory elemental analysis from being obtained.

\[
\text{MeO} \text{MeO} \text{MeO}
\]

(183)

The \(^1\text{H-n.m.r.}\) spectrum of isochroman (176) contained three distinct proton signals at \(\delta\) 5.01 (q, J 6.6 Hz), \(\delta\) 4.55 (d, J 7.9 Hz) and \(\delta\) 3.98 (dq, J 7.9 and 6.2 Hz) due to the 1-H, 4-H and 3-H protons respectively. A vicinal coupling constant of 7.9 Hz between the 4-H and 3-H protons suggested pseudo-axial and axial configurations for those two protons respectively. The observed values for the 3-H and 4-H coupling constant and the chemical shifts of the 1-H, 4-H and 3-H protons of isochroman (176) were similar to those of the dimethyl ether of quinone A (141) (\(\delta\) 4.92, 4.43 and 3.84) and isochroman (151) (\(\delta\) 4.96, 4.23 and 3.85); see Section 2.4. Furthermore, although the C-1 epimer of isochroman (176) is not available for comparison, the chemical shift (\(\delta\) 3.98) for the 3-H proton is in the vicinity previously experienced for the \(trans\)-1,3-dimethyl stereoisomers closely related in structure to compound (176) (see Table 2.2). This evidence supports the structure and stereochemistry of isochroman (176).

\[
\text{MeO} \text{MeO} \text{MeO}
\]

(175)

\[
\text{MeO} \text{MeO}
\]

(177)

\[
\text{MeO} \text{MeO}
\]

(185)

Fig 3.11a

When the dioxolane (175) was allowed to stand briefly in the presence of titanium tetrachloride at 0 °C or -30 °C, this resulted in rapid conversion to a mixture containing
diastereomers of chlorohydrins (177) and the dehydrated pyran product (185) (Fig 3.11a). This is in contrast to the result at -78 °C where the products formed were the isochroman (176) and chlorohydrins (177). It appears that at higher temperatures, isochroman (176) undergoes ready elimination of water to give the dehydrated pyran product (185). The greater ease with which isochroman (176) eliminates water to form the isochromene (185) relative to the stability of the isochromans (151) and (152) under similar conditions (say -30 °C) is almost certainly the result of the peri-methoxy group assisting the departure of the hydroxy group (presumably co-ordinated to titanium), and this process is followed by loss of a proton to form isochromene (185) (Fig 3.11b).

Isomerisation of phenyldioxolane (175) was examined using other Lewis acids such as boron trifluoride-diethyl etherate, diisopropoxytitanium dichloride, triisopropoxy titanium chloride and stannic chloride in the temperature range -78 °C to 0 °C for 30 minutes. It was observed that boron trifluoride-diethyl etherate and triisopropoxy titanium chloride were not effective for the isomerisation of phenyldioxolane (175) to the corresponding isochroman (176). Starting dioxolane (175) remained unchanged even after a longer reaction time (5 h). However, similar reaction of dioxolane (175) with stannic chloride and diisopropoxytitanium dichloride afforded a mixture of chlorohydrins (177).
3.3.1 Isomerisation of trans-4,5-disubstituted phenyldioxolanes (181) and (182)

In an isomerisation reaction similar to that described in the preceding Section, treatment of the 2:1 mixture of dioxolanes (181) and (182) with titanium tetrachloride at 
-78 °C for 30 minutes gave the same chlorohydrins (177) and the isochroman (184) as the reaction products (Fig 3.12).

![Diagram of chemical reactions]

The products (184) and (177) were isolated in yields of 45% and 40% respectively. The g.c.-mass spectrum of the chlorohydrins (177) was similar to that described in Section 3.3. The g.c.-mass spectrum of isochroman (184) showed an appropriate molecular ion (m/z 238) and fragment ions at m/z 223 and m/z 205 corresponding to loss of a methyl radical and then a water molecule respectively from the molecular ion, indicating the presence of an isochroman ring system. A satisfactory elemental analysis confirming its molecular formula as \( \text{C}_{13}\text{H}_{18}\text{O}_{4} \) was also obtained. The \(^1\text{H}-\text{n.m.r.} \) spectrum of isochroman (184) indicated a quartet at \( \delta \) 4.93 (J 6.3 Hz), a doublet at \( \delta \) 4.58 (J 1.6 Hz) and doublet of quartets at \( \delta \) 3.56 (J 1.6 and 6.3 Hz) due to the 1-H, 4-H and 3-H protons respectively. Based on mass and \(^1\text{H}-\text{n.m.r.} \) data, the structure of isochroman (184) was established (the stereochemistry to be discussed in section 3.3.2) and the alternative dihydroisobenzofuran isomers (186) were ruled out as possibilities.
The use of higher reaction temperatures such as -30 °C or 0 °C led to the formation of a 3:1 mixture of chlorohydrins (177) in 38% yield and the dehydrated pyran product (185) in 36% yield. This result is similar to that observed for the cis-4,5-disubstituted phenyldioxolane (175).

### 3.3.2 Relative stereochemistry of isochroman (184)

In the $^1$H-n.m.r. spectrum of isochroman (184), a vicinal coupling constant of 1.6 Hz was observed between the adjacent methine protons, 3-H and 4-H. This suggested the cis relative stereochemistry between them, as expected from the stereochemistry of the parent dioxolanes. In order to establish the conformation of the pyran ring and the configuration at the C-1 position relative to the C-3 and C-4 positions, n.O.e and noesy experiments were carried out for the compound (184). Irradiation at $\delta$ 3.56, the signal for the 3-H proton, showed an 8% enhancement of the signal for the 1-H proton. From the reciprocal n.O.e. spectrum, a similar enhancement was observed for the 3-H proton upon irradiation at $\delta$ 4.93, the signal for the 1-H proton (Fig 3.13). The noesy spectrum of isochroman (184) also indicated a close relationship between the 1-H and the 3-H protons (Fig 3.14). There was no observable relaxation between the 1-CH$_3$ group at $\delta$ 1.58 and the 3-H proton in either the n.O.e. or noesy spectra. This strongly supported the all-cis configuration for the isochroman (184), in the conformation shown in Fig. 3.13. Once again, even though the C-1 epimer of isochroman (184) is not available for comparison purposes, the chemical shift ($\delta$ 3.56) for 3-H proton falls in the region previously observed for cis-1,3-dimethyl stereoisomers [see Table 2.2, compound (152), once again allowing for some deshielding in compound (184), owing to the neighbouring C-5 methoxy group].
The noesy spectrum of isochroman (184)

Further evidence for the structure of isochroman (184) was obtained by its oxidative demethylation with silver(II) oxide to afford the quinone (187) (Fig 3.15). The
\(^1\)H-n.m.r. spectrum of quinone (187) showed a doublet of quartets at \(\delta 4.64\) (J 1.5 and 6.0 Hz) and a doublet of doublets at \(\delta 4.38\) (J 1.5 and 1.6 Hz) corresponding to the 1-H and 4-H protons respectively. In addition, the third ring proton, 3-H, appeared as a doublet of quartets at \(\delta 3.57\) (J 1.6 and 6.3 Hz). The chemical shift of this latter signal once again fell in the range associated with cis-1,3-dimethyl stereoisomers.

The long range coupling constant of 1.5 Hz between the 1-H and 4-H protons for quinone (187) is in good agreement with the long range coupling constant value of 1.5 Hz reported for quinone A derivative (141),\(^4\) which has a pseudo-axial configuration for the 4-H proton and pseudo-equatorial configuration for the 1-H proton. In the present case, the substituent orientation at each centre is reversed with respect to that of dimethyl ether of quinone A (141), and a similar long range coupling constant would be expected and indeed this is found to be the case. This evidence confirms the structure assigned to quinone (187) and hence to isochroman (184). Had the stereochemistry at C-1 been reversed in structure (187) [and therefore (184)], with the methyl group pseudo-axial and the proton pseudo-equatorial, no coupling would be expected between the two pseudo-equatorial protons 1-H and 4-H. This configuration is known to occur in quinone A', for which no homoallylic coupling was observed.\(^4\)

\[\text{MeO} \quad \text{MeO} \]
\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{1} & \quad \text{3} \\
\text{4} & \quad \text{O} \\
\text{O} \\
\end{align*}
\]
\[\text{AgO} \]  
\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\text{1} & \quad \text{3} \\
\text{4} & \quad \text{O} \\
\text{O} \\
\end{align*}
\]

\(\text{Fig 3.15}\)

### 3.4 Conclusions and outlook

It can be concluded from the above analysis that the isomerisation of cis- and trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes to isochromans is sensitive to the
presence of the methoxy substituent at the C-2' position, to the stereochemistry of the
dioxolane ring system, and to the reaction temperature.

It appears that synthetic routes to isochromans of the type (176) and (184)
described in Sections 3.3 and 3.3.1, are feasible, despite the low yield of the pyran
products. The observed low yield was probably due to the influence of the 2'-methoxy
substituent ortho to the dioxolane ring. The apparent problem was that the strong
electron donating effect of the methoxy group promoted alternative benzylic cleavage to
give chlorohydrins (177). One possible solution was to replace the methoxy substituent
with a group less able to donate its electrons to the ortho-dioxolanyl substituent. Thus, it
was decided to use a 2'-chloro substituent instead of a methoxy substituent for the
following reasons:

a) a chloro substituent is mesomeric but less able to donate electrons
to the aromatic ring compared to a methoxy group;
b) it can be readily removed by reductive dechlorination; and
c) the 1,4- arrangement of chlorine and methoxy groups can permit oxidation
to the corresponding 1,4- quinone.

Points (b) and (c) would be extremely useful in the conversion of appropriately
derived naphthalenic systems into quinones A and A', as well as glucoside B.

3.5 Preparation of 2-chloro-5-methoxybenzaldehyde (191)

It was decided to use 2-chloro-5-methoxybenzaldehyde (191) as the starting
material for the preparation of stereochemically pure Z- or E-olefins, which were the key
intermediates in the synthesis of the phenyldioxolanes. This aldehyde was not readily
available and it was necessary to prepare it using commercially available 4-chloro-3-
methylphenol (188). This can be methylated and converted into benzyl bromide (190)
utilising known literature procedures.5,6
The preparation of aromatic aldehydes from benzyl halides has been reported in the literature. This method was initially developed by Sommelet using benzyl halide (192). The essential step of this method was the heating under reflux of benzyl halide (192) with hexamine in chloroform to afford the hexaminium salt (193) (Fig 3.17). This salt was readily isolated when the reaction was conducted in non-hydroxylic solvents and subsequently hydrolysed at pH 3-6.6 to give compound (194) in good yield.

As a first step towards the synthesis of 2-chloro-5-methoxybenzaldehyde, compound (188) was treated with dimethyl sulphate in acetone and potassium carbonate to afford methyl ether (189) in high yield (94%). Irradiation of compound (189) using a 250 W lamp with N-bromosuccinimide and azoisobisbutyronitrile (AIBN), resulted in formation of benzyl bromide (190). The $^1$H-n.m.r. spectrum of bromide (190) showed the presence both of the benzyl protons ($\delta$ 4.51) and of the aromatic methoxy group ($\delta$ 3.76).

The Sommelet method was then applied to the conversion of benzyl bromide (190) into 2-chloro-5-methoxybenzaldehyde (191). Treatment of bromide (190) with hexamine in chloroform gave the hexamine salt, hydrolysis of which with 50% acetic acid
gave the desired aldehyde (191) in 70% yield (Fig 3.16). The $^1$H-n.m.r. spectrum of aldehyde (191) contained a singlet at $\delta$ 10.38 for the aldehyde proton and the mass spectrum showed an appropriate molecular ion at ($m/z$ 170/172) as the base peak, thus affirming the structure of aldehyde (191).

### 3.6 Preparation of cis-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolane (199)

It was hoped to use a similar strategy to that discussed in Chapter 2, to generate the cis-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolane (199). Consequently, the same synthetic steps discussed in Section 2.4 were used for the synthesis of dioxolane (199) from aldehyde (191). It has been shown that a plausible method of synthesising a stereochemically pure $E$-olefin was via the use of palladium bisacetonitrile dichloride to preferentially isomerise the $Z$-olefin of an olefinic mixture. The Wittig reaction between aldehyde (191) and ethyltriphenylphosphonium bromide was first examined. The g.c. analysis of the reaction product showed a 1:1 mixture of two components. The $^1$H-n.m.r. spectrum of the crude product indicated the presence of both trans coupled protons at $\delta$ 6.77 (dq, J 16.0 and 1.8 Hz) and $\delta$ 6.27 (dq, J 16.0 and 6.6 Hz) and the cis coupled protons at $\delta$ 6.55 (dq, J 11.5 and 1.8 Hz) and $\delta$ 5.96 (dq, J 11.5 and 7.1 Hz), the integration of which confirmed the presence of an approximately 1:1 mixture of olefinic isomers (195) (Fig 3.18).
Treatment of this mixture with the palladium catalyst in boiling chloroform was found to give the E-olefin (196) as the major product (Fig 3.18). After heating under reflux for longer periods of time with the catalyst, an equilibrium mixture containing approximately 7% of Z-olefin, was observed from g.c. analysis and the $^1$H-n.m.r. spectrum. At this stage, it was decided to perform the epoxidation reaction on the 13:1 mixture of E- and Z-olefins and separate the corresponding products due to the Z-isomer at a later stage.

Treatment of the 13:1 olefinic mixture (196) with meta-chloroperbenzoic acid and solid sodium bicarbonate in chloroform at 0 °C gave the trans-epoxide (197) as the major product in high yield (90%) (Fig 3.19). This is to be expected since peracid epoxidation is known to occur without isomerisation of the alkene double bond. The $^1$H-n.m.r. spectrum of epoxide (197) showed a benzylic proton as a doublet at $\delta$ 3.88 (J 2.0 Hz) coupled to a doublet of quartets (methine proton) at $\delta$ 2.87 (J 2.0 and 5.1 Hz). Furthermore, the spectrum showed only a weak doublet at $\delta$ 4.12 (J 4.9 Hz) indicating approximately 7% of cis-epoxide.

As described for a related compound in Section 2.4.2, the mixture containing predominantly trans-epoxide (197) was converted to diol (198), using potassium hydroxide and dimethyl sulphoxide, in 86% yield (Fig 3.19). The $^1$H-n.m.r. spectrum of the mixture containing mainly diol (198) indicated a pair of adjacent methine protons as a doublet of quartets at $\delta$ 4.26 (J 3.2 and 6.5 Hz) and a doublet at $\delta$ 5.22 (J 3.2 Hz). In addition, the spectrum showed a minor signal at $\delta$ 1.19 corresponding to the methyl
protons of the *threo* diol (200) which had arisen from the small amount of *cis* epoxide present in the starting material. Comparison of the integrals of the two methyl groups at $\delta$ 1.10 and $\delta$ 1.19 indicated the 14:1 ratio of *erythro* to *threo* diols. This is to be expected since under the given conditions the epoxides are ring opened with the inversion of stereochemistry at the C-1 position.

Treatment of the mixture containing predominantly *erythro* diol (198) with 1,1-dimethoxyethane and (+)-camphorsulphonic acid in boiling dichloromethane afforded a mixture of dioxolanes in 92% yield (Fig 3.20). Chromatographic separation of the dioxolanes afforded 98% of dioxolane (199) and 2% of another pair of dioxolanes with alternative stereochemistry as shown by g.c. and $^1$H-n.m.r. spectral analysis. The $^1$H-n.m.r. spectrum of dioxolane (199) showed a pair of methyl doublets at $\delta$ 0.95 (J 6.4 Hz) and 1.64 (J 4.7 Hz). The three dioxolane ring protons, 2-H, 4-H and 5-H, were observed as a quartet at $\delta$ 5.26 (J 4.7 Hz), a doublet at $\delta$ 5.48 (J 7.2 Hz) and a doublet of quartets at $\delta$ 4.60 (J 7.2 and 6.4 Hz) respectively. These chemical shift and coupling constant values are compatible with a all- *cis*-dioxolane (199) by analogy with dioxolane (148) (Section 2.4.2.).

![Diagram](image)

**Fig 3.20**

### 3.6.1 Preparation of *trans*-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolanes (201) and (202)

Treatment of the 14:1 mixture of *E* - and *Z*-olefins with osmium tetroxide gave a mixture of *threo*- and *erythro*- diols in quantitative yield (Fig 3.21). This was expected
since the osmium tetroxide hydroxylation of olefins occurs via cis addition to the olefinic double bond. Chromatographic separation of the mixture of diols afforded the threo-diol (200) in 80% yield. The high resolution mass spectrum confirmed its molecular formula as C_{10}H_{13}ClO_{3}.

\[ \text{(196) trans:cis} = 13:1 \]

\[ \text{(200)} \quad \text{(201)} \quad \text{2:1 (202)} \]

Fig 3.21

The trans-4-(2'-chloro-5'-methoxyphenyl)-5-methylidioxolanes (201) and (202) were prepared in 85% yield by acetalation of diol (200) with 1,1-dimethoxyethane as described in Section 2.4.4. The $^1$H-n.m.r. spectrum of the product indicated a 2:1 diastereomeric mixture of dioxolanes by comparing the integrals of the two methyl doublets of each diastereomer. On another occasion, a 2.6:1 ratio of dioxolanes was obtained, using similar conditions. The major diastereomer was separated chromatographically. This compound gave a satisfactory elemental analysis and the mass spectrum showed a molecular ion ($m/z$ 242/244). Its $^1$H-n.m.r. spectrum showed a pair of methyl doublets ($\delta$ 1.46 and $\delta$ 1.49) and the dioxolane ring protons ($\delta$ 3.91, 4.97 and $\delta$ 5.49). The signals corresponding to the other diastereomer were not observed in this spectrum. Moreover, g.c. analysis of this dioxolane indicated the presence of a single compound. The n.O.e. spectral data for this dioxolane are given in Fig 3.22 and based on these results the relative stereochemistry at the C-2 centre and the ring conformation were confirmed as depicted in Fig 3.22 and structure (201).
The \( ^1 \)H-n.m.r. spectrum of the minor dioxolane (202) was similar to dioxolane (201) and showed two methyl doublets (\( \delta \) 1.43 and \( \delta \) 1.54) and three dioxolane ring protons (\( \delta \) 4.03, 5.02 and \( \delta \) 5.42). The g.c. analysis of this compound showed a purity of 95\% with 5\% contamination by isomer (199). This could have been formed from traces of the erythro diol present in the threo diol though none of this compound could be detected in the \( ^1 \)H-n.m.r. spectrum of the threo diol. To establish the ring conformation and the stereochemistry of this isomer, the n.O.e. spectral data were obtained. Irradiation at \( \delta \) 1.43, the signal for the 5-CH\(_3\) group, showed 7 and 9\% enhancements for the 2-H and 4-H protons respectively. There was no observable enhancement between 2-CH\(_3\) group and 5-H proton. These data suggest the conformation and C-2 stereochemistry for the dioxolane (202) as shown in Fig 3.22. Having obtained the \textit{trans}-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolanes (201) and (202), their isomerisation to their corresponding isochromans was next investigated.

### 3.7 Isomerisation of mixed \textit{trans}-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolanes (201) and (202)

The diastereomeric mixture of dioxolanes (201) and (202) was first chosen for the isomerisation reaction. The reaction conditions and isochroman product ratios are summarised in Table 3.1 (also see Fig. 3.23). Analysis of the g.c. and \( ^1 \)H-n.m.r. spectra of the crude products from each experiment showed that the isochromans (203) and (204) (the relative stereochemistry of these compounds will be discussed in section
3.7.5) were formed in high yield (~90%). The ratio of isochromans (203) to (204) at -95 °C was 1.7:1 (Entry 1). However, when the reaction temperature was raised to -78 °C, the ratio of the products was 1:1.7 (Entry 2), with isochroman (204) as the major product. Variation of the product ratio was insignificant for the further temperature rise from -78 °C to 0 °C (Entries 3 and 4).

These results suggest that the change in ratio of isochromans (203) to (204) at -78 °C compared to -95 °C could be due to isomerisation of the products at temperatures of -78 °C or above, or to the higher concentration of reagents employed in the experiment at -95 °C.

**Table 3.1**

The effect of reaction conditions on isomerisation of the isomeric mixture of dioxolanes (201) and (202)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditionsa</th>
<th>Ratio of starting dioxolanes 201 : 202c</th>
<th>Ratio of pyran products 203:204d</th>
<th>Dioxolane products % 201+202e</th>
<th>Pyran products % 203+204e</th>
<th>Diol 200e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-95 °Cb, 60 min</td>
<td>2.6 :1</td>
<td>1.7:1</td>
<td>8</td>
<td>92</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>-78 °Cb, 30 min</td>
<td>2 :1</td>
<td>1:1.7</td>
<td>6</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>-78 ° to -30 °Cb, 30 min</td>
<td>2 :1</td>
<td>1:1.7</td>
<td>2</td>
<td>91</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>-78 ° to 0 °Cb, 30 min</td>
<td>2 :1</td>
<td>1:1.7</td>
<td>2</td>
<td>87</td>
<td>11</td>
</tr>
</tbody>
</table>

(a) Diastereomeric mixture of dioxolanes (201) and (202) in dichloromethane, at a concentration of 3x10^{-3} mol l^{-1} except entry 1 which is 6x10^{-3} mol l^{-1}.

(b) Temperature at which reaction was quenched with methanol.

(c) Ratios were determined by $^1$H-n.m.r. spectral analysis.

(d) The product ratios were determined by g.c. analysis.

(e) Products and dioxolanes (%) quoted were estimated from g.c. analysis. (200) = diol precursor of 201 and 202.
At this stage it was decided to investigate further the isomerisation reaction using each of the diastereomers separately. As stated previously, chromatographic separation of the 2:1 diastereomeric mixture of dioxolanes on a silica gel column afforded pure diastereomer (201) (100% by g.c. and $^1$H-n.m.r. spectroscopy) and diastereomer (202) (95% by g.c.).

3.7.1 Isomerisation of diastereomer (201)

Isomerisation of dioxolane (201) was explored under various conditions (i.e. reaction temperatures and time intervals). The results are summarised in Table 3.2 and Fig 3.24. Dioxolane (201) was treated with titanium tetrachloride at -95 °C and after 2 minutes (Entry 1) and 12 minutes (Entry 2), 5 ml aliquots of the reaction mixture were syringed out and quenched immediately. The temperature of the aliquot was expected to change during this process. The remainder of the reaction mixture was then quickly moved into a dry ice acetone bath at -78 °C and kept at that temperature for 30 minutes (entry 3).

The $^1$H-n.m.r. spectral analysis of the crude product mixture at -95 °C clearly demonstrated that the unreacted dioxolane was now a mixture of diastereomers (201) and (202) (Entries 1 and 2). The amount of unreacted dioxolanes (201) and (202) decreased and the amount of pyran products increased, as the reaction was allowed to proceed for a
longer time or raised to -78 °C (Entry 3). The isochroman (203) was found to be the major product, whereas the isochroman (204) was the minor product. It appeared from Entries 1-3 that there was a gradual decrease in the ratio of isochroman (203) relation to (204) and an increase in their total yield (%) as the reaction time progressed. However, when the isomerisation was performed at -95 °C for 60 minutes almost entirely isochroman (203) was obtained (Entry 4).

### Table 3.2

The effect of reaction conditions on isomerisation of dioxolane (201)

| Entry | Conditions\(^a\) 2 equivs. TiCl\(_4\) | Ratio of dioxolane products 201 : 202\(^c\) | Ratio of pyran products 203 : 204\(^d\) | Ratio (%\(^e\) of products 201 and 202) | Ratio (%\(^e\) of products 203 and 204)
|-------|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 1     | -95 °C, 2 min.                        | 2:1                             | 5.8 : 1                         | 63                             | 37                             | 0
| 2     | -95 °C, 12 min.                       | 1:1                             | 4.6 : 1                         | 21                             | 79                             | 0
| 3     | -95 °C, 12 min. -78 °Cb, 30 min.      | -                               | 3.8 : 1                         | 3                              | 97                             | 0
| 4     | -95 °Cb, 60 min.                      | -                               | 28 : 1                          | 0                              | 100                            | 0
| 5     | -78 °Cb, 2 min.                       | -                               | 1 : 3.2                         | 0                              | 100                            | 0
| 6     | -78 °Cb, 30 min.                      | -                               | 1 : 3.1                         | 0                              | 100                            | 0
| 7     | -78 °C, 30 min. 0 °Cb, 30 min.        | -                               | 1 : 3.1                         | 0                              | 94                             | 6
| 8     | -78 °C, 30 min. 0 °C, 30 min. r.t.    | -                               | 1 : 2.9                         | 0                              | 66                             | 34
| 9     | -78 °C, 2 min.                        | -                               | 1 : 1                           | 3                              | 97                             | 0
| 10    | -78 °Cb, 30 min.                      | -                               | 1 : 1                           | 3                              | 97                             | 0

\(a) \) Stereochemically pure trans-4,5-disubstituted phenyldioxolane (201) in dichloromethane, at a concentration of 6\(x10^{-3}\) mol l\(^{-1}\) except entries 9 and 10 which are 3\(x10^{-3}\) mol l\(^{-1}\).

\(b) \) Temperature at which reaction was quenched with methanol.

\(c) \) Ratios were determined by \(^1\)H-n.m.r spectral analysis.

\(d) \) The product ratio was determined by g.c. analysis.

\(e) \) Products and acetals (%) quoted were estimated from the g.c. analysis.
Hence the results from Entries 1 and 2 are probably misleading, and probably reflect an increase in reaction temperature in the sampling process. They will not be taken into account in further discussion. When the reaction was performed entirely at -78 °C, the ratio of isochromans (203) to (204) changed dramatically so that isochroman (204) became the major product (Entries 5 and 6). It was further observed from the g.c. and ¹H-n.m.r. spectral analyses, that reaction of diastereomer (201) at -78 °C for 2 minutes gave products (203) and (204) in essentially quantitative yield. Even if the reaction was kept at -78 °C 30 minutes, the product ratio and yield remained unchanged. For the temperature range -78 °C to room temperature, there was no significant change in the pyran product ratio (Entries 5-8). However, the dehydrated pyran (205) was observed at higher reaction temperatures (Entries 7-8). Entries 9 and 10 show the variation of product ratio with the concentration of the reactants and the loss of stereoselectivity when the reaction was performed at lower concentration.

In order to confirm that there was no isomerisation of isochromans (203) to (204) isochroman (203) was treated with titanium tetrachloride at -78 °C and the reaction mixture was warmed to 0 °C and then stirred for 30 minutes. From the ¹H-n.m.r.
spectrum and g.c. analyses, the starting isochroman (203) was observed unchanged. Thus it can be concluded that the isomerisation of isochroman (203) to isochroman (204) does not occur under the reaction conditions.

3.7.2 Isomerisation of diastereomer (202)

The isomerisation of dioxolane (202) was performed using the same conditions as described in Section 3.7.1. As before, the crude reaction mixture was analysed by g.c. and $^1$H-n.m.r. spectroscopy. Table 3.3 and Fig 3.25 summarise the results at -95 °C and -78 °C for different reaction times. When the reaction was performed at -95 °C, isochroman (203) was formed as the major isochroman. As the reaction time was increased from 12 minutes to 60 minutes (Entries 1 and 3), a decrease in dioxolane products and an increase in pyran products (203) and (204) were observed.

At -78 °C, isochroman (204) became the major product. No significant change occurred in the ratio of the pyran products as the reaction time was increased from 5 minutes to 30 minutes (see Entries 4 and 5). When the reaction was allowed to proceed for a shorter time (e.g. 5 minutes), the isochromans (203) and (204) were obtained in 89% yield together with unreacted dioxolanes and their diol precursor (200). For longer reaction times (30 minutes), the products (203) and (204) were obtained in nearly quantitative yield (95%). When the concentration of the reaction mixture was reduced by half, the ratio of (203) to (204) was also reduced from about 1:3.4 to 1:1.7 (Entry 7). It should be noted that a small amount of unreacted dioxolanes and their diol precursor (200) were detected in most of these experiments as analysed by $^1$H-n.m.r. spectroscopy. One possible way of generating the diol precursor would be by hydrolysis of the starting dioxolanes under the acidic conditions employed during work up. This could be overcome by neutralising the reaction mixture immediately after quenching the reaction.
Table 3.3
The effect of reaction conditions on isomerisation of dioxolane (202)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions a</th>
<th>Ratio of dioxolane products 201 : 202c</th>
<th>Ratio of pyran products 203: 204d</th>
<th>% of dioxolane products 201+202e</th>
<th>% of pyran products 203+204e</th>
<th>Diol e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-95 °Cb, 12 min</td>
<td>1:5</td>
<td>11.6:1</td>
<td>90</td>
<td>7</td>
<td>~3</td>
</tr>
<tr>
<td>2</td>
<td>-95 °Cb, 60 min</td>
<td>1:5</td>
<td>9.8:1</td>
<td>69</td>
<td>30</td>
<td>-1</td>
</tr>
<tr>
<td>3</td>
<td>-95 °Cb, 60 min</td>
<td>1:5</td>
<td>9.0:1</td>
<td>64</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-78 °Cb, 5 min</td>
<td>-</td>
<td>1:3.3</td>
<td>6</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>-78 °Cb, 30 min</td>
<td>-</td>
<td>1:3.4</td>
<td>~1</td>
<td>95</td>
<td>~4</td>
</tr>
<tr>
<td>6</td>
<td>-78 °Cb, 5 min</td>
<td>-</td>
<td>1:1.7</td>
<td>0</td>
<td>94</td>
<td>~6</td>
</tr>
<tr>
<td>7</td>
<td>-78 °Cb, 30 min</td>
<td>-</td>
<td>1:1.6</td>
<td>0</td>
<td>91</td>
<td>~9</td>
</tr>
</tbody>
</table>

(a) Dioxolane (202) (95%) and dioxolane (199) (5%) in dichloromethane, at a concentration of 6x10⁻³ mol l⁻¹ except entries 5 and 6 which are 3x10⁻³ mol l⁻¹.
(b) Temperature at which reaction was quenched with methanol.
(c) The ratio of dioxolane products determined by ¹H-n.m.r spectral analysis.
(d) The ratio of isochroman products determined by g.c. analysis.
(e) Yields (%) quoted were estimated from the g.c. analysis.
(f) Diol precursor of dioxolanes (201) and (202).
3.7.3 Analysis of the results of isomerisation of dioxolanes (201) and (202)

From Tables 3.2 and 3.3, it is apparent that both reactions at -95 °C formed isochroman (203) as the major product and showed different product ratios. In contrast both dioxolanes gave isochroman (204) as the major product and showed almost similar product ratios at -78 °C and above. At lower reaction concentration at -78 °C the diastereoselectivity observed in the products was reduced in each case. The behaviour of these two diastereomers differed with regard to the reaction rate at -95 °C. Diastereomer (202) appeared to isomerise more slowly to the pyran products at -95 °C than does diastereomer (201). The investigation of the reaction of isochroman (203) with titanium tetrachloride clearly ruled out the possibility of further isomerisation of isochromans at -78 °C or above. It is possible that the increase in reaction temperature from -95 °C to -78 °C could change the course of the reaction to give the higher percentage of isochroman (204).

3.7.4 Possible course for the isomerisation of phenyldioxolanes (201) and (202)

Recent investigations on the mechanism of the intramolecular version of the Mukaiyama reaction have shown that different mechanisms operate depending upon the structure of the acetal. Kocienski has proposed that the electrophilic cleavage of dioxolanes (112) and (114) (Section 1.8) could occur with stereoelectronic control to give the corresponding E- and Z-oxonium ions (A) and (B) respectively, which cyclise directly to products (113) and (115) (Fig 3.26). However, results of those experiments have shown that dioxolane (112) cyclises selectively to pyran (113) and the dioxolane (114) cyclises to a 1:1 mixture of pyrans (113) and (115). Therefore, it was suggested that a meaningful speculation on the course of the reaction of acetals was difficult, owing to the uncertainty of geometry of the intermediate oxonium ions and the problems of relative rates of cyclisation and equilibration.
Even in the present study, it is difficult to explain the results of isomerisation of dioxolanes (201) and (202) due to the uncertainties such as:

* conformation of the reacting dioxolanes;
* the geometry of the oxonium ions;
* relative rates of equilibration and cyclisation of oxonium ions; and
* face of cyclisation.

However, some trends are immediately apparent from the data given in Tables 3.2 and 3.3. First, the isomerisation reaction is not stereoselective at -78 °C, as both dioxolanes examined give a mixture of products. Furthermore, the diastereomeric ratio of products is nearly the same for both dioxolanes at -78 °C. This suggests a common intermediate is accessible from both isomers and may involve an oxonium ion. The dioxolane (201) and its ring flipped conformer can give rise to both the E-oxonium ion (C) and Z-oxonium ion (D) respectively (Fig 3.27). Conversely, dioxolane (202) and its ring flipped conformer can give rise to the Z-oxonium ion (E) which is the rotamer of (D) and E-oxonium ion (F) which is the rotamer of (C).
Clearly, a better explanation of the observed product's stereochemistry is needed. The oxonium ion (C) would be expected to preferentially undergo cyclisation since the transition state would be sterically less crowded (from Dreiding model studies), lacking the unfavourable interaction between the 6'-H proton and the methyl group of oxonium ions (E) and (F) (Fig 3.28). One possible explanation is that after formation of the oxonium ion (C), the face of the subsequent attack by the aromatic π system defines the product's stereochemistry.

As shown in Fig 3.29 attack by the aromatic ring onto the two diastereotopic faces of the oxonium ion (C) gives rise to the different products. Thus, attack from the
re-diastereoface would give the all-cis-isochroman (203), whilst attack from the si-
diastereoface would give isochroman (204). Possibly, the preferential si-face attack at
-78 °C and higher concentrations is favoured.

![Diagram](image)

Fig 3.29

However, the dioxolanes (201) and (202) also showed interconversion and
different product ratios at -95 °C. The dioxolane (201) cyclised and equilibrated
significantly faster than dioxolane (202). The selective formation of isochroman (203) at
-95 °C may be explained in terms of preferential re-face attack of the oxonium ion (C).

However, the different product ratios observed for the isomeric dioxolanes (201) and
(202) at -95 °C leads to the conclusion that mechanisms other than the oxonium ion
mechanism also be possible. A complex mechanistic scheme for the titanium tetrachloride
promoted reaction of dioxane and dioxolane acetals has been proposed involving three
distinct types of ion-pair intermediates.\textsuperscript{12c}

3.7.5 Relative stereochemistry of isochromans (203) and (204)

Compounds (203) and (204) were isomeric from their mass spectra and showed
molecular ions at \textit{m/z} 242/244 and fragment ions at \textit{m/z} 227/229 and \textit{m/z} 209/211
(Fig 3.30). These fragment ions correspond to loss of a methyl radical and then a water molecule respectively from the molecular ion and are indicative of the isochroman ring system, rather than the alternative dihydroisobenzofuran isomers. The mass spectra of the latter would show fragment ions due to \((M^+ - \text{CHOHCH}_3)\). Our previous investigation of related isochromans (see Section 3.3, Fig 3.10) showed a similar fragmentation pattern to that in Fig. 3.30.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[m/z \ 244/242\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[m/z \ 229/227\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[m/z \ 211/209\]

Fig 3.30

The \(^1\text{H}-\text{n.m.r. spectra indicated three one proton signals due to the 1-H, 4-H and 3-H protons for each of the isochromans (203) and (204). The signals for (203) were a quartet at } \delta 4.93 \ (J 6.2 \text{ Hz}), \text{ a doublet at } \delta 4.56 \ (J 1.2 \text{ Hz}) \text{ and a doublet of quartets at } \delta 3.68 \ (J 1.2 \text{ and } 6.3 \text{ Hz}). \text{ The corresponding signals for isochroman (204) were a quartet at } \delta 5.09 \ (J 6.6 \text{ Hz}), \text{ a doublet at } \delta 4.50 \ (J 1.7 \text{ Hz}) \text{ and a doublet of quartets at } \delta 4.11 \ (J 1.7 \text{ and } 6.5 \text{ Hz}).

\[
\begin{align*}
\text{He}^1 & \quad \text{He}^1 \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{Ha}^1 & \quad \text{Ha}^1 \\
\text{O} & \quad \text{O}
\end{align*}
\]

(G)

(H)

Coupling constants of < 2 Hz between the 3-H and 4-H protons in both isochromans (203) and (204) indicated their relative stereochemistry to be cis as expected from the stereochemistry of the parent dioxolanes. The 4-H proton in either the equatorial (formula G) or axial configuration (formula H) would give a coupling constant of < 2 Hz,
although the comparison of coupling constant and chemical shifts with compound (184) (see Section 3.3.2) would favour the former.

As noted earlier in this thesis in several instances, the chemical shift of the proton 3-H arises at higher field for cis-1,3-dimethylpyrans than for the isomeric trans-compounds. A similar difference is observed again for the C-1 epimers (203) and (204); epimer (203) with 3-H proton at δ 3.68 is assigned as cis, epimer (204) with 3-H proton at δ 4.11 as trans. These two values are entirely consistent with those reported earlier for other C-1 epimeric pairs.

Furthermore, to confirm the stereochromistry of the three stereogenic centres of isochromans (203) and (204), n.O.e. and noesy spectra were obtained (Fig 3.31, 3.32 and 3.33). The n.O.e. spectrum of isochroman (203) obtained upon irradiation at δ 4.93, (the signal for the 1-H proton), showed a 7% positive enhancement for the 3-H proton signal. The n.O.e. spectrum of isochroman (204) obtained upon irradiation at δ 1.48, (the signal for the 1-CH₃ group), showed a 10% positive enhancement for the 3-H proton signal (Fig. 3.31). The noesy spectrum of isochroman (204) confirmed this configuration (Fig 3.33).
Both isochromans (203) and (204) showed a relationship between the 3-H and the 4-H protons in both 1-D and 2-D spectra. However, n.O.e. and noesy spectrum of isochroman (203) (Fig 3.32) showed relationship between the 3-H and 1-H protons, whereas isochroman (204) (Fig 3.33) showed relationship between the 3-H and 1-CH$_3$ group. From the above spectral data, the relative stereochemistry at the C-1, C-3 and C-4 centres of isochromans(203) and (204) was assigned as in the structures depicted in Fig. 3.31. These data confirm the all-cis-stereochemistry for the isochroman (203) and trans-1,3-dimethyl stereochemistry for the isochroman (204)
The noesy spectrum of isochroman (204)

3.7.6 Isomerisation of cis-4,5-disubstituted phenyldioxolane (199)

So far the isomerisation of the trans-4,5-disubstituted phenyldioxolanes (201) and (202) has been discussed in detail. Next, an attempt was made to isomerise the cis-4,5-disubstituted phenyldioxolane (199). The isomerisation reaction of dioxolane (199) with titanium tetrachloride was examined under various conditions. Table 3.4 and Fig 3.34 summarise reaction conditions and the results obtained from the g.c. and $^1$H-n.m.r. spectral analysis of each of the experiments.
Table 3.4
The effect of reaction conditions on isomerisation of dioxolane (199)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions$^a$</th>
<th>Conc$^a$ 2equivs. TiCl$_4$ mol l$^{-1}$x10$^{-3}$</th>
<th>Yields (%) of products $^{199c}$ $^{207c}$ $^{198d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-95 °C$^b$, 15 min</td>
<td>6</td>
<td>67 17 2</td>
</tr>
<tr>
<td>2</td>
<td>-95 °C$^b$, 60 min</td>
<td>6</td>
<td>34 47 9</td>
</tr>
<tr>
<td>3</td>
<td>-78 °C$^b$, 30 min</td>
<td>6</td>
<td>5 85 ~2</td>
</tr>
<tr>
<td>4</td>
<td>-78 °C$^b$, 30 min</td>
<td>6</td>
<td>4 84 4</td>
</tr>
<tr>
<td>5</td>
<td>-78 °C to 0 °C, 30 min</td>
<td>3</td>
<td>2 78 4</td>
</tr>
</tbody>
</table>

(a) Phenylidioxolane (199) (98%) and dioxolanes (201) and (202) (2%) in dichloromethane.
(b) Temperature at which reaction was quenched with methanol.
(c) Products and starting acetals (%) quoted were estimated from g.c. analysis.
(d) Diol (%) quoted was estimated from $^1$H-n.m.r spectral analysis.

Experiments 1 to 5 clearly indicate the formation of only one isochroman product (207). The isomerisation reaction of dioxolane (199) was found to be quite slow at -95 °C. The amount of unreacted dioxolane decreased and the yield of isochroman (207) increased when the reaction temperature was raised from -95 °C to -78 °C. A small
amount of diol precursor (198) was also observed. Unlike the dioxolanes (201) and (202) described in previous sections, the dioxolane (199) was isomerised exclusively to isochroman (207).

3.7.7 Relative stereochemistry of isochroman (207)

The $^1$H-n.m.r. spectrum of isochroman (207) indicated three one proton signals due to the 1-H, 4-H and 3-H protons. These signals were a quartet at $\delta$ 4.96 (J 6.3 Hz), a doublet at $\delta$ 4.57 (J 6.0 Hz) and a doublet of quartets at $\delta$ 4.16 (J 6.0 and 6.5 Hz). The vicinal coupling constant of 6.0 Hz between the 4-H and 3-H protons indicated the pseudo-axial and axial configuration of those two protons. Thus the methyl group at the C-3 position occupied the less crowded equatorial configuration and the hydroxy group occupies the pseudo-equatorial configuration. In order to confirm the stereochemistry at the C-1, C-3 and C-4 positions, n.O.e. and noesy spectra were obtained for compound (207) (Figs 3.35 and 3.36). Irradiation at $\delta$ 1.56 (the signal for the 1-CH$_3$) showed an 11% enhancement for the signal due to the 3-H proton signal. No n.O.e. was observed for the 3-H proton by irradiation of the 1-H proton.

Fig 3.35

The positive n.O.e.
1-Me, 3-H = 11%
OMe, 7-H = 25%
The noesy spectrum of isochroman (207) indicates a close relationship between the 1-CH$_3$ group and the 3-H proton. In addition, the noesy spectrum shows a close relationship between the 3-CH$_3$ group and the 4-H proton. These data confirmed the relative stereochemistry at the C-1, C-3 and C-4 positions of isochroman (207).

3.8 Reductive dehalogenation of isochroman (204)

The critical step next explored was the homolytic reductive dechlorination of isochroman (204). Beckwith et al. reported a photochemical procedure which enables the rapid reduction of aromatic halides in good yields.$^{16}$ Irradiation of $p$-iodoanisole or $o$-bromoanisole with di-$t$-butyl peroxide (DTBP) and lithium aluminium hydride in
tetrahydrofuran with a 250 W high-pressure Hg lamp for 2.2 h resulted in reductive
dehalogenation, leading efficiently to the anisole (86-100% yield).

Treatment of isochroman (204) under identical conditions gave a mixture of
starting material and the dehalogenated product (208) (Fig 3.37). The g.c.-mass spectral
analysis and $^1$H-n.m.r. spectrum showed a 1.5:1 mixture of isochromans (204) to (208).
However, increasing the irradiation time to 5 h, eventually gave the desired dechlorinated
product (208) in 58% yield. Its g.c.-mass spectrum had an appropriate molecular ion at
$m/z$ 208, with fragment ions at $m/z$ 193 and $m/z$ 175 corresponding to loss of a methyl
radical from the molecular ion, and then a water molecule, as in previous cases. The $^1$H-
n.m.r. spectrum of isochroman (208) showed three proton signals in the aromatic region
due to the 7-H, 6-H and 5-H protons. These were a doublet at $\delta$ 6.80 (J 8.8 Hz), a
doublet of doublets at $\delta$ 7.25 and a doublet at $\delta$ 7.0 (J 8.8 Hz). In addition, there were
signals corresponding to the 1-H, 4-H and 3-H protons at $\delta$ 5.09 (J 6.6 Hz), 4.18 (1.7
Hz) and $\delta$ 4.11 (1.7 and 6.5 Hz) respectively. These data confirmed that the chloro
substituent of the isochroman (204) can be removed without affecting the pyran ring
system.

3.9 Conclusions

Isomerisation of cis-4-(2',5'-dimethoxyphenyl)-5-methyldioxolane (175) with a
Lewis acid afforded the isochroman (176) selectively in low yield. Isomerisation of
trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes (181) and (182) afforded the all-
cis-isochroman (184) selectively in moderate yield. Both cis- and trans-4-(2',5'-dimethoxyphenyl)-5-methyldioxolanes gave chlorohydrins (177) as the biproduct due to the alternative benzylic cleavage.

Isomerisation of cis-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolanes with a Lewis acid afforded the isochroman product (207) in excellent yield and excellent selectivity. Isomerisation of trans-4-(2'-chloro-5'-methoxyphenyl)-5-methyldioxolanes (201) and (202) can be controlled to afford the isochroman (203) selectively in excellent yield and the isochroman (204) in good yield. The selectivity of the cyclisation of phenyldioxolanes (201) and (202) to isochromans (203) and (204) depends on the reaction conditions such as temperature and concentration. Dihydroisobenzofurans were not observed in the isomerisation of either the 2'-chloro-5'-methoxyphenyldioxolanes or the 2',5'-dimethoxyphenyldioxolanes.

### 3.10 General conclusions and outlook

Lewis acid catalysed stereoselective isomerisation of 4,5-disubstituted phenyldioxolanes, which is an intramolecular version of the Mukaiyama reaction, is a viable synthetic tool for the formation of the isochroman ring system. During our exploration of these reactions it was found that:

* in all cases, the stereochemistry at the C-4 and C-5 positions of the dioxolanes determines the stereochemistry at the C-4 and C-3 positions of the resulting isochromans, as expected.

* Isomerisation is extremely sensitive to the nature of the substituent on the phenyl ring. The presence of 6,8 methoxy groups in resulting isochromans promotes isomerisation at the C-1 stereogenic centre and ultimately causes isomerisation to phthalans, whereas the formation of 5,8-dimethoxy isochromans from the corresponding dioxolanes is affected by the alternative benzylic cleavage of the parent dioxolanes.

* In certain cases, isomerisation can be controlled to give isochromans in excellent yield with desired stereochemistry at C-1.
The work reported in Chapters 2 and 3 establishes that:

* under carefully controlled conditions, isomerisation of 4-(3',5'-dimethoxyphenyl)-2,5-dimethylidioxolanes gives 4-hydroxy-6,8-dimethoxy-1,3-dimethylisochromans exclusively. Isomerisation of the cis-4,5-disubstituted dioxolane can be controlled to afford the desired stereochemistry at the C-1 position, whereas the trans-4,5-disubstituted dioxolane gave the all-cis-isochroman exclusively. These isochromans show further isomerisation to dihydroisobenzofurans.

b) Isomerisation of 4-(2',5'-dimethoxyphenyl)-2,5-dimethylidioxolanes give 4-hydroxy-5,8-dimethoxy-1,3-dimethylisochromans in low yield together with chlorohydrins. This is due to the alternative benzylic bond cleavage of the starting dioxolanes.

c) 4-(2'-Chloro-5'-methoxyphenyl)-2,5-dimethylidioxolanes give 5-chloro-4-hydroxy-8-methoxy-1,3-dimethylisochromans in excellent yield and the isomerisation can be controlled to afford the desired stereochemistry at the C-1 position in the products.

Thus it can be concluded that the Lewis acid catalysed isomerisation of 4,5-disubstituted phenyldioxolanes was influenced by structural and experimental variables. The primary factors are substitution patterns of the phenyl ring. Secondary factors are the stereochemistry of the phenyldioxolane, concentration and temperature. It is difficult to draw any firm conclusions regarding the mechanism of the isomerisation of dioxolanes based on these studies.

Although the syntheses of glucoside B and quinones A and A' themselves have not been addressed using this method, several stereochemically important compounds have been successfully made by isomerising phenyldioxolanes. The important goal of construction of the pyran ring with the correct stereochemistry at the C-1, C-3 and C-4 positions has been achieved. The project has gone a long way towards demonstrating that a route to glucoside B via the isomerisation of dioxolanes may well be feasible. The reaction sequence may be developed further using an appropriate naphthyldioxolane with
a C-4 chloro substituent and then the chloro substituent removed by reductive dechlorination to give a glucoside B analogue (Fig 3.38). The same chlorinated naphthopyran could also be oxidised to afford the dimethyl ether of racemic quinone A.\textsuperscript{17}
References


Chapter 4

Isomerisation of 4,5-disubstituted phenyldioxolanes to isochromans related to kalafungin antibiotics
Chapter 4

Isomerisation of 4,5-disubstituted phenyldioxolanes to isochoromans related to kalafungin antibiotics
Chapter 4

4.1 Introduction

The work discussed in Chapters 2 and 3 clearly demonstrates that it is possible to use the stereoselective isomerisation of aryldioxolanes with titanium tetrachloride, an intramolecular version of the Mukaiyama reaction, for the synthesis of protoaphin-type isochromans. In this Chapter attention is focused on the application of the aforementioned reaction to the construction of the isochroman ring system with a γ-lactone functionality to give compounds which are related to antibiotics of the kalafungin and nanaomycin types. The proposed approach is depicted in Fig 4.1.

As described in Section 2.2, the basic principle behind the present approach was that the stereochemistry of the dioxolanes at the C-4 and C-5 positions can be defined so that the isomerised product will have the desired relative stereochemistry at the C-4 and C-3 positions. To generate the cis relative stereochemistry at the C-4 and C-3 positions of the derived isochromans, it is necessary to start with a trans-4,5-disubstituted phenyldioxolane. Thus the preparation of kalafungin-type pyrano-γ-lactones (210) essentially requires the synthesis of trans-5-carboxymethyl-4-phenyldioxolanes of type (209). This Chapter is mainly concerned with the synthesis of this type of dioxolane with different substitution patterns in the aromatic ring and their subsequent isomerisation to
the corresponding isochromans. The preparation of the *trans*-5-carbomethoxymethyl-4- (3',5'-dimethoxyphenyl)dioxolanes (216) and (217) was examined first.

### 4.2 The proposed synthesis of the *trans*-5-carbomethoxymethyl-4-(3',5'-dimethoxyphenyl)dioxolanes (216) and (217)

The synthetic route to the *trans*-5-carbomethoxymethyl-4-(3',5'-dimethoxyphenyl) dioxolanes (216) and (217) is similar to that of the phenyldioxolanes (201) and (202) discussed in Chapter 3. In this case, however, an intermediate (212) with a four carbon chain, containing a $\beta,\gamma$-unsaturated olefin and a carboxy terminus will be required. Introduction of this type of olefinic functionality could be accomplished by a Wittig reaction using an appropriate phosphonium salt. This olefin (212) could be converted stereoselectively into the corresponding dihydroxy acid (214a) with osmium tetroxide. The preparation of dioxolanes (216) and (217) could then be accomplished by the acetalation of the dihydroxy acid (214a) with 1,1-dimethoxyethane in the presence of (±)-camphorsulphonic acid (see Fig 4.2).

![Diagram](image_url)

**Fig 4.2**

#### 4.2.1 Preparation of butenoic acid (212)

A survey of the literature pertaining to the Wittig reaction was carried out with a view to finding a suitable procedure for the preparation of $\beta,\gamma$-unsaturated carboxylic acids. Corey *et al.* described a method to prepare 4-(3'-methoxyphenyl)-3-pentenoic acid
(222) using a phosphonium salt of 3-chloropropionic acid (221) in a reaction with 3-methoxyacetophenone (220) (Fig. 4.3).1

\[
\text{Cl} - \text{CH} - \text{COOH} + P(\text{Ph})_3
\]

\[
\text{O} + \left[ (\text{Ph})_3^+ \text{CH} - \text{COOH} \right] \text{Cl}^- \rightarrow \text{O} - \text{CH} - \text{CH} - \text{COOH}
\]

Fig 4.3

The product from this reaction had almost the correct side-chain that was required in the present study, apart from the additional methyl group at the C-4 position. Thus it was decided to experiment with 3,5-dimethoxybenzaldehyde (211) and the known phosphonium salt (221). The phosphonium salt (221) was made following the published procedure by a high temperature fusion of triphenylphosphine and 3-chloropropionic acid.1 The resulting glassy solid could either be crystallised by rapid air cooling and ground to a fine powder, or more conveniently dissolved whilst still hot in dry dimethyl sulphoxide (DMSO).2 Addition of 3,5-dimethoxybenzaldehyde (211) in tetrahydrofuran followed by two equivalents of sodium hydride to the phosphonium salt dissolved in DMSO afforded the desired acid (212) in 50% yield together with unreacted aldehyde (211) after 14 h reaction time (Fig 4.4).
Support for the structure of unsaturated acid (212) was obtained from its u.v.
spectrum which showed an intense band at 250 nm resulting from a styrene type of
chromophore. The above band at 250 nm was in good agreement with that obtained for
the trans-1-(3',5'-dimethoxyphenyl)-1-propene (143a), which was synthesised and
characterised for other purposes (see Chapter 2, Section 2.4.1). These u.v. spectral data
support the presence of a C-3 double bond and not a C-2 double bond.3 Elemental
analysis and the mass spectrum of unsaturated acid (212) confirmed the molecular
formula C_{12}H_{14}O_{4}. Furthermore, the analysis of the $^1$H-n.m.r. spectrum of unsaturated
acid (212) indicated the presence of only one isomer with a doublet of triplets at $\delta$ 6.45
(J 15.9 and 1.5 Hz) for the 4-H proton and a doublet of triplets at $\delta$ 6.27 (J 15.9 and 7.2
Hz) for the 3-H proton. This large coupling constant of 15.9 Hz was compatible with a
trans olefinic coupling by analogy with olefin (143a) (Section 2.4.1) and literature
precedent.4

4.2.2 Preparation of hydroxy $\gamma$-lactone (215)

The hydroxylation of the unsaturated acid (212) with osmium tetroxide and
4-methylmorpholine-$N$-oxide was attempted. Although the reaction itself appeared to
proceed to plan, isolation of the hydroxylated product proved troublesome. To help
overcome this, it was decided to prepare the methyl ester of acid (212). Treatment of
(212) with oxalyl chloride gave an unstable acid chloride which was stirred with methanol
without purification to give the unsaturated ester (213). The $^1$H-n.m.r. spectrum of ester
(213) showed the aromatic methoxy groups at δ 3.80 and an ester methoxy group at δ 3.72. The microanalysis confirmed its molecular formula as C_{13}H_{16}O_4.

It was hoped to obtain diol (214b) (see Fig 4.5a) by cis-hydroxylation of unsaturated ester (213) with osmium tetroxide. Thus the unsaturated ester (213) was treated with osmium tetroxide and 4-methylmorpholine-N-oxide. After stirring the reaction mixture for 18 h at room temperature, two compounds (215a) and (215b) were isolated in 87% and 5% yield respectively (Fig 4.5b).

The mass spectrum of the major compound (215a) showed the molecular ion at m/z 238 and the elemental analysis was compatible with a molecular formula C_{12}H_{14}O_5. The i.r. spectrum showed a hydroxy stretching frequency at 3467 cm^{-1} and a carbonyl stretching frequency at 1776 cm^{-1} supporting the presence of a hydroxy γ-lactone ring system. The ^1H-n.m.r. spectrum of compound (215a) showed a pair of geminal coupled protons at δ 2.70 (d, J 17.5 Hz) and δ 2.85 (dd, J 17.5 and 5.4 Hz) for the 3-CH₂
protons. The methine proton 4-H showed vicinal coupling to one of the geminal coupled protons (J 5.4 Hz) and to the 5-H proton (J 3.8 Hz). Similar geminal and vicinal coupling constants (J 17 Hz and 5 Hz for 3-H and J 5 and 4 Hz for 4-H) have been reported for lactone (223) which is a derivative of juglomycin A. Hence, compound (215a) was identified as a hydroxy γ-lactone by comparison of its spectral data with those of lactone (223).

Furthermore, analysis of the n.O.e. spectrum of compound (215a) obtained upon irradiation at δ 4.58 (the signal for the 4-H proton) showed a 10% enhancement of the 5-H proton. Alternatively, irradiation at δ 5.42 (the signal for the 5-H proton) showed an 8% enhancement of the 4-H proton, indicating a close proximity of the 4-H and 5-H protons. These n.O.e. spectral data supported the stereochemical assignment of the hydroxy γ-lactone (215a) as all-cis-configuration, as shown below.

The mass spectrum of the minor compound (215b) also showed the same molecular ion (m/z 238), which suggested that it was stereoisomeric with compound (215a). Its 1H-n.m.r. spectrum showed geminal and vicinal couplings of the two
methylene protons at δ 2.60 (J 17.8 and 4.7 Hz) and δ 2.89 (J 17.8 and 6.6 Hz) respectively. The methine proton, 4-H, showed coupling to both methylene protons at C-3. The structure of hydroxy lactone (215b) was assigned as a trans γ-hydroxy lactone by comparison of its 1H-n.m.r. spectral data with those reported for the coupling between methylene protons at C-3 and methine proton at C-4 (J 18 and 6 Hz and J 18 and 7 Hz) of analogous compound (224).

The above hydroxylation results suggest that the use of osmium tetroxide and 4-methylmorpholine-N-oxide in aqueous acetone favours the formation of dihydroxy ester (214b) which is then directly converted into the hydroxy γ-lactone (215a) under the reaction conditions and with retention of stereochemistry at the asymmetric centres. This would happen if the lactonisation has taken place after the formation of dihydroxy ester (214b); see Fig 4.6.

However, the isolation of a small amount of lactone (215b) (5%) may indicate that the lactonisation can occur prior to the formation of dihydroxy ester at the osmate ester stage (see Fig 4.7). Alternatively, it could have been formed from traces of the cis olefin...
formed in the Wittig reaction though none of this compound could be detected in the $^1$H-n.m.r. spectrum of the Wittig product.

![Diagram of chemical structures](image)

**Fig 4.7**

### 4.2.3 Preparation of trans-4,5-disubstituted phenyldioxolanes (216) and (217)

Treatment of hydroxy γ-lactone (215a) with 1,1-dimethoxyethane and (±)-camphorsulphonic acid (catalytic) in boiling dichloromethane gave the diastereomeric mixture of trans-4,5-disubstituted phenyldioxolanes (216) and (217) in 70% yield, together with the more polar lactone (218) in 7% yield (Fig 4.8). Unreacted starting material was found in small amounts (5%) even after extended reflux for 72 h.

![Diagram of chemical structures](image)

**Fig 4.8**

The $^1$H-n.m.r. spectrum of the diastereomeric mixture of dioxolanes (216) and (217) showed a pair of methyl groups at $\delta 1.55$ and $\delta 1.45$, the integration of which indicated that the products were present in the ratio of 1.3:1. Chromatographic separation
of the mixture afforded the stereochemically pure dioxolane (216). The stereochemistry at the C-2 position of the dioxolane (216) was assigned by analysis of its n.O.e. spectrum. Irradiation at $\delta$ 1.51, the signal for the 2-CH$_3$ group, showed an 11% positive enhancement for the 5-H proton. This indicates a close proximity of the 5-H proton and 2-CH$_3$ groups, and supported the stereochemical assignment of the dioxolane (216). The sample of dioxolane (217) was, however, still contaminated with dioxolane (216) and it was not fully characterised.

$\text{MeO} \quad \text{OMe}$

$\text{COOMe}$

$\text{2-CH}_3 \text{ to 5-H } = 11\%$

$\text{5-CH}_2 \text{ to 4-H } = 10\%$

The elemental analysis of the third compound (218) obtained in 7% yield gave a molecular formula C$_{14}$H$_{16}$O$_5$. The mass spectrum of compound (218) showed the molecular ion at $m/z$ 264 and a fragment ion at $m/z$ 249 as the base peak corresponding to loss of a methyl radical. These mass spectral data were consistent with the presence of an isochroman ring system. A strong carbonyl stretching frequency at 1781 cm$^{-1}$ in the i.r. spectrum of compound (218) supported the presence of the $\gamma$-lactone ring. The $^1$H-n.m.r. spectrum indicated the presence of only two protons ($\delta$ 6.58 and $\delta$ 6.48) in the aromatic region and the absence of a methyl ester group. The spectrum also showed a doublet at $\delta$ 5.07 (J 2.5 Hz), a quartet at $\delta$ 4.79 (J 6.5 Hz) and a doublet of triplets at $\delta$ 4.35 (J 2.5 and 4.6 Hz) corresponding to the 9b-H, 5-H and 3a-H protons of the isochroman ring system respectively. Thus the above data supported the pyrano-$\gamma$-lactone structure for compound (218). The relative stereochemistry of the compound (218) will be discussed in section 4.3.1.
One possible pathway for the formation of pyrano-γ-lactone (218) is indicated in Fig 4.9, which shows how the condensation of the starting hydroxy γ-lactone (215a) with 1,1-dimethoxyethane could form the intermediate oxonium ion (A) under acidic conditions. This intermediate could then cyclise directly to give the pyrano-γ-lactone (218). A similar acid catalysed cyclisation was described by Li and Ellison (see Section 1.4).

Interestingly, the other possible route would be the ring opening of dioxolanes (216) and (217) with (±)-camphorsulphonic acid to give an intermediate oxonium ion (B), which could then cyclise to the pyrano-γ-lactone (218) (Fig 4.10). Since our interest was to synthesise isochromans by isomerisation of phenyldioxolanes, it was decided to examine the isomerisation of dioxolanes (216) and (217) to their corresponding isochromans with (±)-camphorsulphonic acid.

(216) $R_1 = \text{CH}_3$, $R_2 = \text{H}$

(217) $R_1 = \text{H}$, $R_2 = \text{CH}_3$
4.3 Preparation of pyrano-γ-lactones (218) and (219)

The isomerisation reaction of dioxolanes (216) and (217) with (+)-camphorsulphonic acid was performed in dichloromethane with various acid concentrations, all of which were greater with respect to these dioxolanes than in the case of their formation from the lactone (215a) (see Table 4.1). The g.c-mass spectral analysis of the crude products of each experiment showed a mixture of two components (218) and (219), each having the same molecular ions at \( m/z \ 264 \) and a fragment ion at \( m/z \ 249 \) as the base peak. This supports the presence of the isochroman ring system. The increased acid concentration is responsible for promoting the cyclisation of dioxolanes (216) and (217) to pyrano-γ-lactones (218) and (219). A lower acid concentration (4.3 x 10^{-4} mol l^{-1}) was used to prepare dioxolanes (216) and (217) and at this acid concentration only 7% of the pyrano-γ-lactone (218) was obtained, even after 18 h at reflux.

Table 4.1

The ratios of the isochromans (218) and (219) at different acid concentrations

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions(^a)</th>
<th>CSA (^b) mol l(^{-1})</th>
<th>Yield(^c) of Isochromans (218)+ (219)</th>
<th>Isochromans (218):(219)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>r.t, 8 h</td>
<td>5.7 x 10^{-3}</td>
<td>86</td>
<td>6.8:1</td>
</tr>
<tr>
<td>2</td>
<td>r.t, 8 h</td>
<td>5.7 x 10^{-2}</td>
<td>80</td>
<td>1:1.9</td>
</tr>
<tr>
<td>3</td>
<td>r.t, 8 h</td>
<td>8.6 x 10^{-2}</td>
<td>89</td>
<td>1:3.6</td>
</tr>
</tbody>
</table>

\(^a\) 1.3:1 Mixture of phenyldioxolanes (216) and (217) in dichloromethane, at a concentration of 2.3 x 10^{-1} mol l^{-1}.

\(^b\) CSA = (±)-camphorsulphonic acid.

\(^c\) Combined isolated yields of isochromans (218) and (219).

\(^d\) Ratio of isochromans (218) and (219) was determined by g.c. and \(^1\)H-n.m.r. analysis.
After chromatographic purification on silica gel, the combined yield of products (218) and (219) was found to be in the range 80-89%. By analysis of the g.c., and $^1$H-n.m.r. spectra, the ratio of the two components at the lowest acid concentration was found to be 6.8:1 (Entry 1). The major component at this acid concentration was pyranoy-\(\gamma\)-lactone (218). With increasing acid concentration, the ratio changed substantially giving an approximate value of 1:3.6 at the highest acid concentration (Entry 3). High pressure liquid chromatographic (HPLC) separation of the mixture from the highest acid concentration reaction afforded stereochemically pure pyranoy-\(\gamma\)-lactone (219). The satisfactory elemental analysis confirmed its molecular formula as $\text{C}_{14}\text{H}_{16}\text{O}_5$. The structure of compound (219) as a pyranoy-\(\gamma\)-lactone was supported by its i.r. spectrum which showed a band at 1780 cm$^{-1}$ corresponding to the \(\gamma\)-lactone moiety and the $^1$H-n.m.r. spectrum which showed a quartet at $\delta$ 5.10 (J 6.6 Hz), a doublet at $\delta$ 5.01 (J 3.0 Hz) and a doublet of triplets at $\delta$ 4.77 (J 3.0 and 5.4 Hz) for the 5-H, 9b-H and 3a-H protons respectively. The relative stereochemistry at these three centres will be discussed in the next section.

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{image.png}
\caption{(219)}
\end{figure}

The results of the acid catalysed cyclisation of dioxolanes (216) and (217) to pyranoy-\(\gamma\)-lactones reveal that increasing acid concentration affected both the rate of cyclisation and the stereochemistry of the products. The latter effect may be due either to a change in the stereochemistry of the cyclisation itself, or to a subsequent equilibration at the C-5 centre of the primary isochroman product. Such equilibration would be promoted by the position of the two methoxy groups. Unlike the system discussed in Sections 2.5.1 and 2.5.5, cleavage of the C-5 ether bond does not lead here to
dihydroisobenzofurans, since the necessary alternative hydroxy group is not available for ring closure.

4.3.1 Relative stereochemistry of pyrano-γ-lactones (218) and (219)

The observed coupling constant of 2-3 Hz between the 3a-H and 9b-H protons of compounds (218) and (219) confirmed the cis relative stereochemistry between them. In each case, the conformation of the pyran ring and configuration of the C-5 methyl group relative to the substituents at C-3a and C-9b were established by n.O.e. spectroscopy. The n.O.e. spectrum obtained upon irradiation at δ 4.79, the signal for the 5-H proton of pyrano-γ-lactone (218), showed a 7% enhancement of the signal due to the 3a-H proton. The alternative n.O.e. spectrum obtained upon irradiation at δ 4.35, the signal for the 3a-H proton, showed a 10% enhancement of the 5-H proton. This implies that isochroman (218) has the all-cis relationship as shown in Fig 4.11.

\[
\begin{align*}
\text{positive n.O.e.} \\
5\text{-H to } 3a\text{-H} &= 7\% \\
3a\text{-H to } 5\text{-H} &= 10\% \\
3a\text{-H to } 9b\text{-H} &= 12\% \\
\text{MeO to } 9\text{-H} &= 18\% \\
\text{MeO to } 7\text{-H} &= 37\%
\end{align*}
\]

\[
\begin{align*}
\text{positive n.O.e.} \\
5\text{-CH}_3\text{ to } 3a\text{-H} &= 15\% \\
3a\text{-H to } 9b\text{-H} &= 5\% \\
\text{MeO to } 9\text{-H} &= 25\% \\
\text{MeO to } 7\text{-H} &= 48\%
\end{align*}
\]
For compound (219), the n.O.e. spectrum obtained upon irradiation at $\delta$ 1.46, the signal of the C-5 methyl group, showed a 15% enhancement for the signal due to the 3a-H proton. These data confirm the \textit{trans} relative stereochemistry for the C-5 and C-3a substituents of isochroman (219) as depicted in Fig 4.11. Once again, a comparison of the $^1$H-n.m.r. spectra for the two epimers shows that when the pyran methyl is \textit{cis} to the lactone in isomer (218) the proton 3a-H is at higher field ($\delta$ 4.35) than for the isomer (219) ($\delta$ 4.77). The chemical shift difference is about 0.4 ppm as observed for the earlier analogues, although, as would be expected, both values are deshielded in comparison with the 4-hydroxy-1,3-dimethylisochromans.

4.4 Isomerisation of dioxolanes (216) and (217) with titanium tetrachloride

Although the cyclisation reaction was successful using (+)-camphorsulphonic acid, it was also decided to investigate the isomerisation reaction with titanium tetrachloride. Isomerisation of the mixture of phenyldioxolanes (216) and (217) with titanium tetrachloride was investigated at a variety of temperatures. Comparison of $^1$H-n.m.r. spectral data of the crude reaction mixture from each experiment is given in Table 4.2. The results showed that at -78 $^\circ$C, a 1.3:1 mixture of starting dioxolanes (216) and (217) equilibrated to a 1:1.8 mixture in quantitative yield (Entry 1). However, when mixed dioxolanes (216) and (217) were treated with titanium tetrachloride at -78 $^\circ$C and the temperature of the reaction mixture was warm to -30 $^\circ$C and stirred for 30 minutes a mixture of products was obtained (Entry 2). The g.c.-mass analysis of this mixture indicated the presence of dioxolanes (216) and (217), pyran ester (226) and dihydroisobenzofuran (227). Attempted chromatographic separation of this mixture was not successful and hence, it was not further investigated.
Table 4.2

Effect of reaction conditions on isomerisation of dioxolanes (216) and (217)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Dioxolanes (216):(217)a</th>
<th>Conditions</th>
<th>Product Dioxolanes (216):(217)b</th>
<th>Product Dioxolanes (216):(217)c</th>
<th>Product (226)d</th>
<th>Product (227)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3:1</td>
<td>-78 °C, 30 min</td>
<td>1:1.8</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.3:1</td>
<td>-78 °C to -30 °C, 30 min</td>
<td>1:1.5</td>
<td>55</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>1.5:1</td>
<td>-78 °C to r.t. b, 2 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>1.5:1</td>
<td>-78 °C to r.t. b, 2 h</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

a) A mixture of dioxolanes (216) and (217) in dichloromethane at a concentration of 6 x 10^{-3} mol l^{-1}.

b) Temperature at which reaction was quenched with methanol.

c) Ratios as determined by g.c. and 1H-n.m.r. analysis.

d) Combined yields were estimated from g.c. and 1H-n.m.r. spectral analysis.

However, increasing the temperature of the reaction mixture to room temperature afforded only dihydroisobenzofuran (227) (Entries 3 and 4)). The g.c.-mass spectrum of the dihydroisobenzofuran (227) showed an appropriate molecular ion at m/z 296 and the base peak at m/z 193 corresponding to [M^+-(CH(OH)CH2CO2CH3)]. Based on this fragmentation pattern the dihydroisobenzofuran (227) could easily be distinguished from the corresponding isomeric isochromans (226); see Fig 4.12.
The $^1$H-n.m.r. spectrum of dihydroisobenzofuran (227) showed a doublet of quartets at $\delta 5.40$ ($J 2.9$ and 6.2 Hz), a doublet of doublets at $\delta 5.25$ ($J 2.9$ and 5.5 Hz) and a multiplet at $\delta 4.31$ corresponding to the 1-H and 3-H protons and side chain methine proton respectively. It should be noted that only one isomer of dihydroisobenzofuran (227) was observed by analysis of the $^1$H-n.m.r. spectrum. The stereochemistry at the C-1 position relative to the C-3 position of this isomer was assigned as $\text{trans}$ by comparing the coupling constant, $J_{1,3}$ of 2.9 Hz with that of the analogous compound (166-1), described in section 2.5.5.

As described in Chapter 2, the dihydroisobenzofuran (227) could be formed via the first formed isochroman product (226), in which the strong electron donating effect of the methoxy substituents promotes the opening of the C-1 to O-2 bond and leads to the formation of dihydroisobenzofuran (see Section 2.5.1 and Fig 2.15). The titanium tetrachloride cyclisation of dioxolanes (216) and (217) enhances the secondary isomerisation to a dihydroisobenzofuran; however, the use of camphorsulphonic acid directly afforded the corresponding pyrano-$\gamma$-lactones selectively.
4.5 Synthesis of trans-4-(2'-chloro-5'-methoxyphenyl)-5-carbomethoxymethylidioxolanes (233) and (234)

Having found a route that could be used to make a pyran ring with a γ-lactone functionality, and because of the success of the isomerisation of phenyldioxolanes (201) and (202) in Chapter 3, it was decided to use this strategy for the synthesis of 9-chloro-6-methoxy-pyrano-γ-lactones. The synthetic route proposed for the synthesis of trans-4,5-phenyldioxolanes (233) and (234) was similar to that of the previous system described in Section 4.2.

![Chemical structures](image)

The Wittig reaction to make the unsaturated acid (230) was carried out by the method previously described in Section 4.2.1, i.e. addition of two equivalents of sodium hydride to a stirred solution of phosphonium salt (221) and aldehyde (229) in dry dimethyl sulphoxide and tetrahydrofuran. This gave the unsaturated acid (230) in 57% yield together with unreacted aldehyde (229); see Fig 4.13. The $^1$H-n.m.r. spectrum of compound (230) contained a doublet of triplets at $\delta$ 6.88 (J 15.8 and 1.5 Hz) for the 4-H proton and a doublet of triplets at $\delta$ 6.29 (J 15.8 and 7.2 Hz) for the 3-H proton. The olefinic geometry of the acid (230) was determined to be trans by the $^1$H-n.m.r. spectral analysis since the coupling constant of J vic 15.8 Hz was in agreement with trans coupling, as shown in Section 4.2.1 for the analogous compound (212). The mass spectrum and the elemental analysis confirmed the identity of unsaturated acid (230).
Esterification of unsaturated acid (230) was carried out in a manner similar to that described for unsaturated acid (212); i.e. it was first treated with oxalyl chloride to make an unstable acid chloride which was then stirred without purification with methanol to give the ester (231). The $^1$H-n.m.r. spectrum of ester (231) showed an appropriate methyl ester resonance at $\delta$ 3.73 and the mass spectrum of showed a molecular ion at $m/z$ 240/242. Similar spectroscopic properties were observed for the analogous ester (213) in Section 4.2.2.

![Fig 4.14](image)

Treatment of unsaturated ester (231) with a catalytic amount of osmium tetroxide and 4-methylmorpholine-N-oxide afforded the hydroxy $\gamma$-lactone (232) in 75% yield (Fig 4.14). The mass spectrum of hydroxy $\gamma$-lactone (232) showed an appropriate molecular ion at $m/z$ 242/244 and the elemental analysis gave the molecular formula $\text{C}_{11}\text{H}_{11}\text{ClO}_4$, consistent with that of hydroxy $\gamma$-lactone (232). The $^1$H-n.m.r. spectrum of lactone (232) showed a pair of geminal coupled protons at $\delta$ 2.96 (J 17.6 and 5.4 Hz) and $\delta$ 2.72 (J 17.6 Hz) for the 3-CH$_2$ protons. The methine proton, 4-H, showed a vicinal coupling to one of the 3-H protons (J 5.4 Hz) and to the 5-H proton (J 3.4 Hz). These geminal and vicinal coupling constants are in close agreement with those observed for the analogous compound (215a); see Section 4.2.2. From the above spectral data the structure (232) was assigned as depicted in Fig 4.14.

The next step was to prepare the corresponding dioxolanes from hydroxy $\gamma$-lactone (232), by treatment with 1,1-dimethoxyethane and a catalytic quantity of (±)-
camphorsulphonic acid. The acetalation of hydroxy γ-lactone (232) was examined using a similar acid concentration to that employed for lactone (215a). Even after extended reflux for 72 hours a diastereomeric mixture of dioxolane esters (233) and (234) was obtained in 81% yield together with the starting hydroxy γ-lactone (232)(10%) (Fig. 4.15). None of the pyrano-γ-lactones were observed under these conditions. The $^1$H-n.m.r. spectrum of dioxolanes (233) and (234) showed resonances at δ 5.53 and δ 5.38 for the 2-H protons of each epimer, while the 4-H and 5-H proton signals combined for each epimer at δ 5.11 and δ 4.31 respectively. From the $^1$H-n.m.r. spectral analysis the ratio of the two diastereomers (233) and (234) was found to be in approximately 1:1.

Next, the cyclisation of dioxolanes (233) and (234) to pyrano-γ-lactones with (±)-camphorsulphonic acid was investigated. It was discussed in Section 4.3 that on heating the analogous dioxolanes (216) and (217) under reflux with (±)-camphorsulphonic acid in dichloromethane, pyrano-γ-lactones (218) and (219) were formed. In the present case, however, heating of dioxolanes (233) and (234) for 24 h under reflux with camphorsulphonic acid merely gave recovery of starting materials. After extended reflux, for 72 h, the product isolated was hydroxy-γ-lactone (232) in 92% yield. These results indicate that the substitution pattern on the aromatic ring affects the acid catalysed cyclisation of dioxolanes to isochromans.

![Fig 4.15](image_url)

Effect of reaction conditions on the isomerisation of dioxolanes (233) and (234)
4.6 Isomerisation of dioxolanes (233) and (234) with titanium tetrachloride

In earlier studies, it was shown that \textit{trans}-4-(2'-chloro-5'-methoxyphenyl)-5-methylidioxolanes (201) and (202) (see Section 3.7) isomerise efficiently to the corresponding isochromans with titanium tetrachloride. Thus it was decided to examine the isomerisation of dioxolanes (233) and (234) in a similar manner. A 1:1 diastereomeric mixture of dioxolanes (233) and (234) was treated with titanium tetrachloride at a variety of temperatures. A comparison of the g.c. and $^1$H-n.m.r. spectral data of the crude reaction mixture from each experiment is given in Table 4.3. The results show that at -78 °C and -30 °C, the 1:1 mixture of starting dioxolanes (233) and (234) equilibrated to a ratio of 1:3.6 and 1:1.9 respectively; see Entries 1 and 2. The product ratio of pyran ester (235) to diol ester (236) increased when the reaction was allowed to proceed at higher temperatures for longer times (see Entries 3-5).

\textbf{Table 4.3}

Effect of reaction conditions on isomerisation of dioxolanes (233) and (234)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting dioxolanes (233):(234)$^a$</th>
<th>Conditions 2equiv. TiCl$_4$</th>
<th>yield$^c$</th>
<th>Product dioxolanes (233):(234)$^d$</th>
<th>Products (235):(236)$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 1</td>
<td>-78 °C$^b$, 30 min</td>
<td>100</td>
<td>1:3.6</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1 : 1</td>
<td>-30 °C$^b$, 45 min</td>
<td>95</td>
<td>1:1.9</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1 : 1</td>
<td>0 °C$^b$, 45 min</td>
<td>90</td>
<td>-</td>
<td>1:2</td>
</tr>
<tr>
<td>4</td>
<td>1 : 1</td>
<td>0 °C$^b$, 90 min</td>
<td>95</td>
<td>-</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>1 : 1</td>
<td>0 °C to r.t$^b$ 5h</td>
<td>96</td>
<td>-</td>
<td>6:1</td>
</tr>
</tbody>
</table>

\begin{itemize}
  \item \textit{a}) Dioxolanes (233) and (234) in dichloromethane at a concentration of $6 \times 10^{-3}$ mol l$^{-1}$.
  \item \textit{b}) Temperature at which reaction was quenched with methanol.
  \item \textit{c}) Combined yields were estimated from the g.c. and $^1$H-n.m.r. analysis.
  \item \textit{d}) Ratios as determined by g.c. and $^1$H-n.m.r. analysis.
\end{itemize}
The above data suggest that the most efficient conditions for the isomerisation of dioxolanes (233) and (234) to pyran ester (235) were the stirring of the reaction mixture with titanium tetrachloride at room temperature for 5 h (Fig 4.16), whereupon the products (235) and (236) were obtained in a combined yield of 96%. After separating this mixture on a silica gel column, compound (235) was isolated in 64% yield.

The mass spectrum of isochroman (235) showed a molecular ion at (m/z 300/302), a fragment ion pair at m/z 285/287 corresponding to loss of a methyl radical and another ion pair at m/z 267/268 due to further loss of water (Fig 4.17). Assignment as structure (235) rather than the alternative dihydroisobenzofurans (237) was based on a comparison of the mass spectral fragmentation pattern with that of isochromans (203) and (204) (Section 3.7.5). Based on $^1$H-n.m.r. spectral analysis, pyran ester (235) was formed as a single stereoisomer. The $^1$H-n.m.r. spectrum of this showed two aromatic protons at $\delta$ 7.26 (J 8.8 Hz) and $\delta$ 6.78 (J 8.8 Hz) analogous to those of isochroman (203). Furthermore, the spectrum showed a quartet at $\delta$ 4.94 (J 6.2 Hz) for the 1-H...
proton, a doublet at δ 4.69 (J 1.3 Hz) for the 4-H proton, a doublet of triplets at δ 4.02 (J 1.3 and 7.1 Hz) corresponding to the 3-H proton and a singlet at δ 3.72 for the methyl ester group.

\[
\text{MeO} \quad \text{MeOOC} \quad \text{OH}
\]

(237)

The cis relative configuration at the C-3 and C-4 centres of isochroman (235) was confirmed by the coupling constant (J 1.3 Hz) observed between the 3-H and 4-H protons, a value similar to that observed for isochroman (203) (Section 3.7.6). The configuration of the C-1 methyl group relative to the substituents at C-3 and C-4 was established by n.O.e. spectral analysis (see Fig 4.18). Irradiation at δ 4.94, the signal for the 1-H proton, showed a 10% enhancement for the 3-H proton signal and a confirmatory n.O.e. spectrum obtained upon irradiation of the 3-H proton signal showed a similar enhancement for the 1-H proton together with an 11% enhancement for the 4-H proton. Based upon this evidence the structure for the pyran ester (235) was proposed as all-cis (see Fig 4.18).

\[
\text{MeO to 7-H} = 20% 
\]

Fig 4.18

\begin{itemize}
  \item 1-H to 3-H = 10%
  \item 3-H to 1-H = 10%
  \item 3-H to 4-H = 11%
\end{itemize}
The mass spectrum of diol ester (236) showed an appropriate molecular ion at \( m/z \) 274/276 and a fragment ion at \( m/z \) 172/174 corresponding to \([M^+ - (CH(OH)CH_2CO_2CH_3)]\) as the base peak. The \(^1\)H-n.m.r. spectrum contained two aromatic doublets at \( \delta \) 7.24 (J 8.8 Hz) and 7.10 (J 3.0 Hz), and a doublet of doublets at \( \delta \) 6.79 (J 8.8 and 3.0 Hz) analogous to diol (200) described in Chapter 3. In addition, the spectrum showed a signal for the methyl ester group at \( \delta \) 3.70 and two doublets of doublets at \( \delta \) 2.68 (J 17.0 and 7.0 Hz) and 2.54 (J 17.0 and 3.2 Hz) for the methylene protons (2 x 2-H) coupled to the adjacent methine proton. Presumably, diol ester (236) was derived by quenching of the reaction mixture prior to completion of the reaction. It is interesting to note that ester (236) was obtained in this reaction, albeit in low yield, without cyclisation to the hydroxy lactone (232).

At this stage, it was decided to convert pyran ester (235) to its pyrano-\(\gamma\)-lactone (238) in order to compare its spectral data with those of pyrano-\(\gamma\)-lactone (218). When compound (235) was heated under reflux with (+)-camphorsulphonic acid in dichloromethane, the pyrano-\(\gamma\)-lactone (238) was obtained in 83% yield (Fig 4.19).

![Fig 4.19](image)

The i.r. spectrum of pyrano-\(\gamma\)-lactone (238) showed a strong carbonyl stretching frequency at 1781 cm\(^{-1}\) supporting the presence of the \(\gamma\)-lactone ring. Its mass spectrum showed the correct molecular ion \((m/z 268/270)\) and the base peak \((m/z 253/255)\) corresponding to the loss of a methyl group from the molecular ion. The \(^1\)H-n.m.r. spectral data of pyrano-\(\gamma\)-lactone (238) were qualitatively similar to those observed for pyrano-\(\gamma\)-lactone (218) (see Section 4.2.3), apart from the ortho coupled aromatic...
protons. The vicinal coupling constant of 2.2 Hz between the 3a-H and 9b-H protons confirmed their *cis* configuration. The configuration of the C-5 methyl group relative to the substituents at the C-3a and C-9b centres was established by n.O.e. spectral analysis of the precursor (235) (see Fig 4.18). From this evidence, it is quite clear that, despite the *peri*-interaction with the neighbouring methoxy group, the C-5 methyl group of pyrano-γ-lactone (238) has taken up a *pseudo*-equatorial configuration.

In summary then, the titanium tetrachloride catalysed cyclisation of dioxolanes (233) and (234) at elevated temperatures causes them to isomerise selectively to isochroman (235). This cyclisation does not proceed with camphorsulphonic acid as the catalyst.

### 4.7 Synthesis of *trans*-4-(2',5'dimethoxyphenyl)-5-carbomethoxymethylidioxolanes (243) and (244)

A successful synthesis has been demonstrated in Sections 4.3 of the pyrano-γ-lactones (218) and (219) from dioxolanes (216) and (217), and in Section 4.6 of pyrano-γ-lactone (238) from the dioxolanes (233) and (234). Importantly, the cyclisation of dioxolanes (216) and (217) can be controlled to favour either lactone (218) or (219). The critical step next explored was the conversion of the dioxolanes (243) and (244) into the pyrano-γ-lactones (245) and (246) which more closely resemble the naturally occurring compounds such as kalafungin. This was so since these new products possessed a hydroquinone dimethyl ether grouping which could readily be converted into a quinone.

\[
\begin{align*}
\text{(242)} & \quad \text{(MeO)}_2\text{CHMe} \\
\text{MeO} & \quad \text{CSA} \\
\text{MeO} & \quad \text{MeOOC} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
\text{(243)} & \quad R_1 = \text{Me}, \ R_2 = \text{H} \\
\text{(244)} & \quad R_1 = \text{H}, \ R_2 = \text{Me} \\
\text{(245)} & \quad \text{MeO} \\
\end{align*}
\]
As discussed in Chapter 3, the problem apparent for the isomerisation of phenyldioxolanes of type (243) and (244) is that the methoxy substitution ortho to the dioxolane ring promotes the O-3 to C-4 bond cleavage with titanium tetrachloride. However, it was decided to prepare the corresponding hydroxy γ-lactone (242) and the dioxolanes (243) and (244) to examine their capacity to undergo the desired acid-catalysed cyclisation reaction instead of oxygen cleavage.

As a first step towards the synthesis of trans-4,5-disubstituted phenyldioxolanes (243) and (244), the preparation of the unsaturated acid (240) was investigated using aldehyde (239) and phosphonium salt (221) prepared by fusion of triphenylphosphine and 3-chloropropanoic acid, as described in Section 4.2.1. From the crude product mixtures, the unsaturated acid (240) was isolated in 67% yield together with unreacted aldehyde (239) (Fig 4.20). The strong carbonyl stretching frequency at 1710 cm\(^{-1}\) in its i.r. spectrum supported the presence of a carboxylic acid group. The mass spectrum showed an appropriate molecular ion (m/z 222) as the base peak, and the satisfactory elemental analysis confirmed the molecular formula C\(_{12}\)H\(_{14}\)O\(_4\). The \(^1\)H-n.m.r. spectrum contained a doublet of triplets at \(\delta 6.83\) (J 15.9 and 1.5 Hz) for the 4-H proton and a doublet of triplets at \(\delta 6.31\) (J 15.9 and 5.6 Hz) for the 3-H proton. The observed vicinal coupling constant of 15.9 Hz was consistent with a trans olefinic coupling. These spectroscopic data were in agreement with those observed for the analogous acids (212) and (230).

![Fig 4.20](image-url)
Esterification of acid (240) to make the unsaturated ester (241) was then carried out by the method used in Section 4.2.2; i.e. addition of oxalyl chloride to a stirred solution of acid (240) in dichloromethane with the resulting acid chloride concentrated to dryness, and stirred with methanol to give methyl ester (241) in 83% yield. The structure of ester (241) was confirmed by the elemental analysis and comparison of its i.r. and $^1$H-n.m.r. spectra with the analogous unsaturated ester (231).

The cis hydroxylation of ester (241) with osmium tetroxide and 4-methylmorpholine-N-oxide in aqueous acetone gave the hydroxy $\gamma$-lactone (242) exclusively (92%) (compare section 4.2.2 and see Fig 4.21). This compound gave a satisfactory elemental analysis confirming its molecular formula as $\text{C}_{12}\text{H}_{14}\text{O}_{5}$. A strong carbonyl stretching frequency at 1772 cm$^{-1}$ in its i.r. spectrum supported the presence of the $\gamma$-lactone moiety. The relative stereochemistry at the C-4 and C-5 positions of lactone (242) was assigned by comparison of its $^1$H-n.m.r. spectrum with the spectrum of the analogous hydroxy $\gamma$-lactone (232) (Section 4.5).

\[
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{MeO} \\
\text{COOMe} \\
\text{C-C} \\
\text{O} \\
\text{MeO} \\
\end{array} \quad \overset{\text{O}_3\text{O}_4}{\text{MMO}} \\
\begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{H} \\
\text{O} \\
\text{HO} \\
\end{array}
\]

Fig 4.21

The hydroxy $\gamma$-lactone (242) was treated with 1,1-dimethoxyethane and (+)-camphorsulphonic acid in dichloromethane. After heating under reflux for 72 h, a 1:1 mixture of dioxolane esters (243) and (244) were obtained in 60% yield together with 31% unreacted hydroxy $\gamma$-lactone (242) and 5% pyrano-$\gamma$-lactone (245) (Fig 4.22). A preparative formation of pyrano-$\gamma$-lactone (245) was achieved with phosphoric acid and will be discussed in Section 4.8.
The mass spectrum of the mixture of dioxolane esters (243) and (244) showed a strong molecular ion \((m/z 296)\), and elemental analysis confirmed their molecular formula as \(C_{15}H_{20}O_6\). The \(^1\)H-n.m.r. spectrum of dioxolanes (243 and 244) showed the presence of the two methyl groups at \(\delta 1.51\) and \(\delta 1.47\) due to two diastereomers in an approximate ratio of 1:1, as determined by comparison of the integrals of these two signals. Thus the successful synthesis of 4,5-trans-phenyldioxolane esters (243) and (244) had been accomplished. The next step was the investigation of the isomerisation of these dioxolanes to the corresponding isochromans.

### 4.8 Isomerisation of dioxolanes (243) and (244)

It was discussed in Chapter 3 how the isomerisation of mixed dioxolanes (181) and (182) with titanium tetrachloride favoured the cleavage of both the O-3 to C-4 bond and the C-2 to O-3 bond. The cleavage of the O-3 to C-4 bond resulted in the formation of halohydrins (177) while cleavage of the O-3 to C-2 bond produced the desired isochromans (184). It seemed reasonable to assume that the titanium tetrachloride catalysed ring opening of mixed dioxolane esters (243) and (244) would behave in a manner similar to dioxolanes (181) and (182). However, treatment of a 1:1 mixture of dioxolane esters (243) and (244) with titanium tetrachloride afforded a number of products. Analyses of this mixture by g.c., g.c.-mass and \(^1\)H-n.m.r. spectroscopy indicated an isomeric mixture of hydroxy \(\gamma\)-lactones and an isomeric mixture of diol esters. Attempted chromatographic separation of this mixture was not successful and it was not further investigated.
The condensation of the hydroquinone from \( \beta \)-hydroxy ester (23) with acetaldehyde in proton acids to give benzoisochromans (24) was reported in the literature and described in section 1.4. At this stage, we decided to examine the analogous possibility of converting the lactone (242) itself into the desired pyrano-\( \gamma \)-lactone (245) as shown in Fig 4.23.

Thus, a solution of hydroxy \( \gamma \)-lactone (242) and freshly distilled acetaldehyde was treated with phosphoric acid. This was stirred for 22 h and the resultant crude product chromatographed to give a single product in 76% yield. The mass spectrum of this product showed a molecular ion at \( m/z \) 264 corresponding to the pyrano-\( \gamma \)-lactone (245) and a fragment ion (\( m/z \) 249) as the base peak. The i.r. spectrum of pyrano-\( \gamma \)-lactone (245) showed a strong stretching frequency at 1786 cm\(^{-1} \) supporting the presence of a \( \gamma \)-lactone functionality. The evidence for the presence of an isochroman structure was obtained from the analysis of the i.r, mass and \( ^{1} \text{H}-\text{n.m.r.} \) spectral data.
The relative stereochemistry of the pyrano-γ-lactone (245) was also determined. It was found using n.O.e. experiments that irradiation of the 3a-H proton gave an 11\% enhancement for the 5-H proton. This implies the \textit{cis} configuration for the two groups at the C-5 and C-3a positions. Complementary n.O.e. spectra were obtained by irradiation of each of the other two pyran ring protons which indicated the relative \textit{cis} configuration for the substituents at C-3a and C-9b. This implies that the pyrano-γ-lactone (245) has an all-\textit{cis} configuration.

Next, pyrano-γ-lactone (245) was oxidatively demethylated with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile to afford the corresponding quinone (247); see Fig 4.24. The long range coupling constant of 1.8 Hz between the 5-H and 9b-H protons of quinone (247) was compatible with the given relative configuration for the \textit{pseudo}-axial 5-H and \textit{pseudo}-equatorial 9b-H protons.
Quinone (247) was then converted into naphthoquinone (248) by a Diels-Alder reaction with 1-acetoxybuta-1,3-diene followed by treatment with sodium carbonate to afford the known compound, 5-epi-7-deoxykalafungin (248) in 66% yield. The structure of this deoxykalafungin (248) was confirmed by comparison of its \textsuperscript{1}H-n.m.r. and mass spectral data with those reported.\textsuperscript{10,11} This evidence confirmed the structure of quinone (247) and hence that of isochroman (245).

In view of this success, it was decided to examine the isomerisation and lactonisation reaction of dioxolanes (243) and (244) under phosphoric acid catalysis. The mixture of dioxolanes (243) and (244) was treated with phosphoric acid and stirred at room temperature for 18 h. The resultant crude product was chromatographed to afford the desired pyrano-\(\gamma\)-lactones (245) and (246) in 70% yield (Fig 4.26). Analysis of the \textsuperscript{1}H-n.m.r. spectrum of the mixture showed a 1:1 ratio of pyrano-\(\gamma\)-lactones (245) to (246) by comparing the integrals of the two respective methyl groups at \(\delta\) 1.46 and \(\delta\)
1.57. According to Li and Ellison,\textsuperscript{7} treatment of the mixture of naphthopyranquinones related to isochromans (245) and (246) with sulphuric acid causes epimerisation at the C-5 methyl group to furnish the quinonoid isomer related to isochroman (246) as the major product with the correct stereochemistry of the methyl group for a synthesis of kalafungin itself. However, owing to a lack of time this was not further explored.

4.9 Conclusion and outlook

In conclusion, the acid catalysed isomerisation and lactonisation of \textit{trans}-5-carbomethoxymethyl-4-phenyldioxolanes is a viable synthetic tool for the stereoselective formation of the pyrano-\textgamma-lactones. The results described in Chapter 4 establish that:

* in all cases, the stereochemistry of the C-3a and C-9b positions of these pyrano-\gamma-lactones is guided by the stereochemistry at the C-5 and C-4 positions of the dioxolane precursors.

* The isomerisation reaction is extremely sensitive to the nature of the substituents on the phenyl ring and to the nature of the acid; \textit{i.e.} 3',5'-dimethoxyphenyl dioxolanes and 2',5'-dimethoxyphenyl-dioxolanes cyclise efficiently to their corresponding pyrano-\gamma-lactones with proton acids, whereas 2'-chloro-5'-methoxyphenyldioxolanes cyclise to hydroxy isochromans with Lewis acid.

* In certain cases, isomerisation can be controlled to afford the desired stereochemistry at the C-5 position.

As described in Section 4.3, 4,5-\textit{trans}-5-carboxymethyl-4-(3',5'-dimethoxyphenyl)-dioxolanes (216) and (217) readily isomerise and lactonise to their pyrano-lactones (218) and (219) with camphorsulphonic acid. Moreover, the stereochemistry at the C-1 centre can be controlled to favour either the pyrano-\gamma-lactone
(218) or the C-5 epimer (219). However, the isomerisation of dioxolanes (216) and (217) to the isochromans with titanium tetrachloride is difficult to achieve.

Unlike dioxolanes (216) and (217), 4,5-trans-5-carboxymethyl-4-(2'-chloro-5'-methoxyphenyl)-dioxolanes (233) and (234) isomerise with titanium tetrachloride to give isochroman ester (235) selectively. However, this isomerisation reaction did not proceed with camphorsulphonic acid.

The investigations described in Section 4.8 demonstrate that the isomerisation of 4,5-trans-5-carboxymethyl-4-(2',5'-dimethoxyphenyl)-dioxolanes (243) and (244) with camphorsulphonic acid or titanium tetrachloride to the corresponding isochromans is not possible. It is interesting to note that they would, however, isomerise and lactonise with phosphoric acid to give pyrano-γ-lactone (245) in good yield.

Furthermore, the work described in Section 4.8 demonstrates that the formation of pyrano-γ-lactone can be achieved via the hydroxy γ-lactone precursor (242). This efficient approach involves the condensation of lactone (242) with acetaldehyde in phosphoric acid to give the pyrano-γ-lactone in good yield. Although the product favoured by this method is the all-cis-isomer (245) in contrast to the method in Fig 4.26, this fact presents no serious problem for kalafungin synthesis since the cis-isomer can be isomerised to the thermodynamically more stable trans-isomer at a later stage of the synthesis.

It is clear that this approach provides a useful and short alternative route to the synthesis of kalafungin-type antibiotics. Moreover, this approach has several advantages. A high overall yield has been achieved even though each step has not been optimised, while commercially available starting materials are used and the procedures are amenable to larger scale synthesis.
Finally, the research reported in this thesis reveals the synthetic potential of the stereoselective isomerisation of aryldioxolanes, an intramolecular version of the Mukaiyama reaction, to the benzoisochroman class of antibiotics. Although it was not attempted to synthesise kalafungin owing to lack of time, several important pyrano-γ-lactones were synthesised together with a derivative of kalafungin.
References


Chapter 5

Experimental
General Notes:

1. Melting points were determined on a Reichert hot-stage microscope and were uncorrected.

2. Elemental analyses were carried out by the ANU Analytical Service Unit.

3. Electrical Impact (EI) Mass Spectra were measured on a VG Micromass 7070 F Mass Spectrometer operating at 70 eV. The molecular ion (M⁺) (where appropriate) and selected fragment ions are reported as their mass/charge ratios (m/z) followed by their relative intensities as compared with the base (100%) fragment. All Mass spectra recorded are EI unless otherwise stated. High resolution Mass spectra (Exact Mass) were determined on an AEI MS 902 High Resolution Mass Spectrometer.

4. Infrared spectra were measured on a Perkin Elmer 683 Infrared Spectrophotometer. Samples were run as liquid films (neat) or as a solution in CCl₄ or CHCl₃ in 0.5 mm NaCl cells. Significant peaks were reported (cm⁻¹).

5. Ultraviolet spectra were measured on a Varian DBS-90 UV-Visible spectrophotometer.

6. Gas liquid chromatography (gc) was carried out with the following columns with helium as the carrier gas:
   a. 2m x 1.5mm, 2% OV-17 on Gaschrom Q (60-80 mesh).
   b. 25m x 0.2mm, Vitreous Silica Capillary Column (SGE25QC2/BP1-1.0).
   c. 25m x 0.2mm, Vitreous Silica Capillary Column (SGE25QC2/BP5-1.0).
   GC analyses were performed on a Varian 3400 and 6000 gas chromatograph equipped with a Flame Ionisation Detector and all compounds assumed to have identical response. The % yields of products were calculated using peak areas.

   d. G.c.-mass analyses were performed on a Hewlett Packard 5970 mass spectrometer employing electron impact ionisation and a Hewlett Packard 5890 gas chromatograph, using a 12 mx 0.2 mm HP-1 Capillary Column with helium as the carrier gas. For g.c.-mass analysis, temperature of the g.c. column was usually run from 50 °C to 200 °C at the rate of 10 °C/minute.
7. Thin layer chromatography was conducted on Whatman silica precoated microscopic slides (75 x 25mm). Preparative Thin Layer Chromatography was performed on Merck precoated glass plates. Chromatograms were visualised under UV light, or upon exposure to iodine vapour, or by spraying with a colour reagent (5% vanillin in sulphuric acid) followed by heating at 200°C.

8. Column chromatography was carried out by one of the following:
(a) flash chromatography on silica (Merck mesh 0.004-0.063 mm) as described by Still et al. 1
(b) Chromatotron (model 7924T) with 1 and 2 mm rotors coated with Merck silica gel 60PF254.
(c) Normal phase high pressure liquid chromatography with Waters 510 High Pressure Liquid Chromatography. Compounds were detected with Waters differential refractometer R401. A Waters Radial-PAK cartridge 5µ column was used.

9. Routine $^1$H and $^{13}$C n.m.r. spectra were recorded on the following instruments: Jeol FX-200 ($^{13}$C n.m.r. at 50.1 MHz), Varian VXR-300 ($^{13}$C n.m.r. at 75 MHz), Gemini-300 ($^{13}$C n.m.r. at 75 MHz). Spectra were usually recorded in deuterochloroform (CDCl$_3$, 99.8% deuterium incorporation) unless otherwise stated. For $^1$H-n.m.r. spectra, chemical shifts (δ) are reported in parts per million (ppm) down field from the internal standard tetramethylsilane (TMS, δ 0.00ppm), followed by their intensities (number of protons) and coupling constants. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), etc. For $^{13}$C n.m.r. spectra recorded in CDCl$_3$, the centre line of the triplet due to CDCl$_3$ was referenced to 77.0 ppm.

10. Nuclear Overhauser enhancement (nOe) experiments (1D and 2D) were conducted on a Varian VXR-500 and Gemini-300. One dimensional nOe data were obtained in the interleave mode by taking difference spectra with data sets using an on resonance and an off resonance selective pre-irradiation pulse. Two dimensional noesy spectra were acquired in the pure absorption mode with 2048 data points in the t2 dimension stored in alternate blocks and 128 FID’s in the t1 dimension. FID’s were apodized by either at 45° sine bell or a 45° squared sine bell in the first dimension and by gaussian multiplication in
the second dimension. Samples were made up in CDCl₃ (99.6% deuterium incorporation) in special Wilmad Taperlok Nmr tubes and were degassed by freeze-thaw methods.

11. Solvents and reagents were purified according to published procedures and solvents were dried over sodium wire or molecular sieves 3Å or 4Å. Organic extracts were dried using anhydrous sodium sulphate or magnesium sulphate and the bulk of the solvent removed under reduced pressure using a Büchi Rotavapor.

References


trans-1-(3',5'-Dimethoxyphenyl)-1-propene (143a)

Method 1

To a stirred suspension of ethyltriphenylphosphonium bromide (800 mg, 2.20 mmol) in dry tetrahydrofuran (20 ml) was added dropwise n-butyllithium (1.6 M solution in hexane) (1.8 ml, 2.20 mmol) at -78 °C in an atmosphere of nitrogen. The resultant orange solution was stirred at 0 °C for 5 minutes, and then cooled to -78 °C. A solution of 3,5-dimethoxybenzaldehyde (142) (300 mg, 1.80 mmol) in dry tetrahydrofuran (2 ml) was then added dropwise to the reaction mixture. The resultant solution was stirred at -78 °C for 15 minutes, allowed to warm to room temperature and then stirred for another 3 h. The reaction was quenched with water and then diethyl ether was added. The organic layer was washed several times with aqueous sodium chloride, dried and evaporated to give a brown oil, which was chromatographed on silica gel using 19:1 hexane/ethyl acetate to afford a 2:1 mixture of E- and Z-olefins (143a) and (143b) (270 mg, 84%) as a colourless oil. Following the procedure of Giles and Sargent\(^1\) the mixture of E- and Z-olefins (270 mg, 1.51 mmol) was added to a stirred solution of palladium bisacetonitrile dichloride (5 mg) in chloroform (10 ml) at room temperature. An aliquot (0.5 ml) of reaction mixture was taken out at 30 minutes intervals and analysed by g.c. After 2 h, no further change could be detected in the g.c and \(^1\)H-n.m.r. spectrum. The solvent was evaporated and the residue was rapidly chromatographed through a short column of silica gel using 19:1 hexane/ethyl acetate as eluent to give an oily product. This was crystallised from light petroleum (60°-80 °C) to afford the E-isomer (143a) (260 mg, 96%), m.p. 55-56 °C. (Found: C, 73.8; H, 8.1. \(\text{C}_{11}\text{H}_{14}\text{O}_{2}\) requires C, 74.1; H, 7.9%); \(\lambda_{\text{max}}\) nm (MeOH) 255 (log \(\epsilon\) 4.4), 300 (log \(\epsilon\) 3.5); \(\delta_{\text{H}}\) (CDCl\(_3\)) 6.52 (2H, d, J 2.3 Hz, 2'-H and 6'-H), 6.40 (1H, dq, J 15.0 and 1.6 Hz, 1-H), 6.35 (1H, t, J 2.3 Hz, 4'-H), 6.27 (1H, dq, J 15.0 and 4.6 Hz, 2-H), 3.80 (6H, s, 2 x OCH\(_3\)), 1.92 (3H, dd, J 4.6 and 1.6 Hz, CHCH\(_3\)); \(\delta_{\text{13C}}\) (CDCl\(_3\)) 160.8 (C-3' and C-5'), 139.9 (C-1'), 130.0 (C-1), 126.2 (C-2), 103.6 (C-2' and C-6'), 99.0 (C-4'), 55.2 (2 x OCH\(_3\)), 18.5 (CHCH\(_3\)); \(m/z\) 178 (M\(^+\), 100%), 163 (16), 147 (43), 135 (10), 121 (14), 103 (20).
Method 2

Following the procedure of Schlosser and Christmann, 2 phenyllithium (2 M solution in cyclohexane) (6.0 ml, 12 mmol) was added dropwise to a stirred suspension of ethyltriphenylphosphonium bromide (5 g, 13.0 mmol) in dry tetrahydrofuran (THF) (15 ml) at -78 °C in an atmosphere of nitrogen. After 10 minutes, 3,5-dimethoxybenzaldehyde (142) in THF (10 ml) (2.0 g, 12 mmol) was added and the mixture stirred for another 5 minutes. More phenyllithium (6.0 ml, 12 mmol) was then added to the reaction mixture which was allowed to warm to 0 °C before the addition of t-butyl alcohol (3 ml) followed by potassium-t-butoxide in THF (3 ml). After 3 h, the reaction mixture was centrifuged and the supernatant layer was washed with dilute hydrochloric acid (10%) and then water (3 x 50 ml), dried and evaporated to afford a yellow oil (2 g). This was purified by chromatography on silica gel using 19:1 hexane/ethyl acetate as eluent to give the title compound (143a) as a white solid (1.4 g, 65%), crystallised from light petroleum (60°-80 °C), m.p. 55-56 °C identical with material described above.

trans-1-(3',5'-Dimethoxyphenyl)-1,2-epoxypropane (144)

A solution of meta-chloroperbenzoic acid (400 mg, 2.32 mmol) in chloroform (30 ml) was added dropwise to a solution of olefin (143a) (300 mg, 1.68 mmol) in chloroform (5 ml) at 0 °C and this was stirred for 24 h. The reaction mixture was filtered and the filtrate poured into a saturated sodium bicarbonate solution (15 ml). The organic phase was separated and the aqueous phase was extracted with cold chloroform (3 x 10 ml). The combined organic extracts were washed with water, dried, filtered and concentrated to afford an orange oil. This was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give three compounds: epoxide (144) (120 mg, 37%), which was crystallised from light petroleum (60-80 °C), m.p. 60-61 °C. (Found: C, 68.0; H, 7.6. C_{11}H_{14}O_{3} requires C, 68.0; H, 7.3%); δ_{H} (CDCl_{3}) 6.45 (2H, d, J 2.3 Hz, 2' and 6'-H), 6.40 (1H, t, J 2.3 Hz, 4'-H), 3.79 (6H, s, 2 x OCH_{3}), 3.55 (1H, d,
J 2.0 Hz, 1-H), 3.05 (1H, dq, J 2.0 and 5.1 Hz, 2-H), 1.45 (3H, d, J 5.1 Hz, CHCH₃); δ¹³C (CDCl₃) 160.9 (C-3' and C-5'), 140.3 (C-1'), 103.2 (C-2' and C-6'), 100.0 (C-4'), 59.5 and 58.8 (C-1, C-2), 55.5 (2 x OCH₃), 17.6 (CHCH₃); m/z 194 (M⁺, 53%), 171 (100%), 165 (23), 151 (13), 135 (20);
olefin (145) as a colourless oil (18 mg, 5.5%), δH (CDCl₃) 6.73 (1H, dq, J 15.0 and 1.6 Hz, 1-H), 6.51 (1H, d, J 2.3 Hz, 6'-H), 6.37 (1H, d, J 2.3 Hz, 4'-H), 6.28 (1H, dq, J 15.0 and 4.6 Hz, 2-H), 5.48 (1H, s, 2'-OH), 3.88 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 1.92 (3H, dd, J 4.6 and 1.6 Hz, CHCH₃); m/z 194 (M⁺, 100%), 179 (36), 151 (15), 137 (7); and
hydroxy ester (146) (140 mg, 17%), ¹H-n.m.r. spectrum of the diastereomeric mixture of (146) showed significant resonances at δH (CDCl₃) 8.05, 7.54, 7.35, 6.48 (14H, Ar-H of both isomers), 6.25 and 6.21 (each 1H, d, J 4.0 and 6.0 Hz 1-H of each isomer), 4.35 (2H, m, 2-H of both isomers), 3.82 (2 x OMe), 3.68 (2 x OMe), 1.25 (CHCH₃ of both isomers); m/z 352 (M⁺{Cl}, 1%), 350 (M⁺{Cl}, 3), 308 (5), 306 (13), 167 (41), 141 (29), 139 (100), 111 (20).

This procedure was repeated with anhydrous sodium bicarbonate (500 mg) in the reaction mixture and epoxide (144) was isolated in 66% yield.

rel-(1S,2R)-1-(3',5'-Dimethoxyphenyl)-1,2-propanediol (147)

A solution of epoxide (120 mg, 0.62 mmol) in dimethyl sulphoxide (7 ml) and potassium hydroxide (0.4 N, 3 ml) was stirred at 80 °C. After 24 h, the resulting solution was cooled to room temperature, poured into water and extracted with ethyl acetate (4 x 20 ml). The combined organic extracts were washed with water, then dried and evaporated to afford an orange oil (130 mg). This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to give the title compound (147) as a light orange oil (105 mg, 79%). (Found: C, 62.0; H, 7.9. C₁₁H₁₆O₄ requires C, 62.25; H, 7.6%); δH (CDCl₃) 6.52 (2H, d, J 2.3 Hz, 2'-H and 6'-H), 6.37 (1H, t, J 2.3 Hz, 4'-H), 4.60 (1H, d, J 4.4 Hz, 1-H), 3.96 (1H, dq, J 4.4 and 6.4 Hz, 2-H), 3.70 (6H, s,
2 x OCH₃), 1.09 (3H, d, J 6.4 Hz, CHCH₃); δ¹³C (CDCl₃) 160.7 (C-3’ and C-5’), 143.1 (C-1’), 104.6 (C-2’ and C-6’), 99.6 (C-4’), 77.4 (C-1), 71.2 (C-2), 55.3 (2 x OCH₃), 17.1 (CHCH₃); m/z 212 (M⁺, 25%), 194 (4), 169 (77), 139 (100), 124 (22).

rel-(2R,4S,5R)-4-(3’ ,5’ -Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolane (148)

Diol (147) (60 mg, 0.28 mmol) in dry dichloromethane (10 ml) was treated with 1,1-dimethoxyethane (0.04 ml) and (+)-camphorsulphonic acid (10 mg, 0.04 mmol). After heating under reflux for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to afford a colourless oil, which was purified by chromatography on silica gel using 6:1 hexane/ethyl acetate as eluent to give the title compound (148) as a colourless oil (50 mg, 74%). (Found: C, 65.25; H, 7.4. C₁₃H₁₈O₄ requires C, 65.5; H, 7.6%); δH (CDCl₃) 6.44 (2H, d, J 2.2 Hz, 2'-H and 6'-H), 6.39 (1H, t, J 4.9 Hz, 2-H), 4.94 (1H, d, J 7.0 Hz, 4-H), 4.33 (1H, dq, J 7.0 and 6.4 Hz, 5-H), 3.78 (6H, s, 2 x OCH₃), 1.55 (3H, d, J 4.9 Hz, 2-CH₃), 0.99 (3H, d, J 6.4 Hz, 5-CH₃); δ¹³C (CDCl₃) 160.4 (C-3’ and C-5’), 140.9 (C-1’), 104.9 (C-2’ and C-6’), 100.6 (C-4’), 99.4 (C-2), 80.8 (C-5), 76.2 (C-4), 55.1 (2 x OCH₃), 19.5 (CH₃-2), 16.0 (CH₃-5); m/z 238 (M⁺, 25%), 194 (57), 179 (100), 165 (22), 163 (9).

rel-(1R,3R,4S)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochroman (151) and rel-(1S,3R,4S)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochroman (152)

Dioxolane (148) (30 mg, 0.13 mmol) in dry dichloromethane (20 ml) was treated with titanium tetrachloride (16.4 µl, 0.26 mmol) at -78 °C in an atmosphere of nitrogen. The resulting reaction mixture was stirred at -78 °C for 30 minutes and quenched with
methanol (0.1 ml). A saturated aqueous sodium bicarbonate solution (2 ml) was added and the resultant mixture poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil. This was analysed by g.c. and g.c.-mass spectroscopy which indicated a 4:1 mixture of isochroman isomers (151) and (152). This mixture was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give two compounds: compound (151) as a white solid (21 mg, 70%), which was crystallised from dichloromethane/hexane, m.p. 134-135 °C. (Found: C, 65.6; H, 7.8. C_{13}H_{18}O_{4} requires C, 65.5; H, 7.6%); \( \delta H \) (CDCl$_3$) 6.69 (1H, d, J 2.3 Hz, 5-H), 6.35 (1H, d, J 2.3 Hz, 7-H), 4.96 (1H, q, J 6.5 Hz, 1-H), 4.23 (1H, d, J 8.0 Hz, 4-H), 3.85 (1H, dq, J 8.0 and 6.3 Hz, 3-H), 3.80 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 1.56 (3H, d, J 6.5 Hz, 1-CH$_3$), 1.34 (3H, d, J 6.3 Hz, 3-CH$_3$); \( \delta^{13}C \) (CDCl$_3$) 159.9 and 156.3 (C-6, C-8), 138.0 (C-4a), 120.9 (C-8a), 101.7 (C-5), 97.9 (C-7), 71.3, 68.8 and 67.7 (C-1, C-3, C-4), 55.2 (OCH$_3$), 55.1 (OCH$_3$), 19.0 and 18.0 (CH$_3$-1 and CH$_3$-3); m/z 238 (M$, 7\%$), 223 (44), 220 (17), 205 (100), 195 (7), 179 (20); and

compound (152) as a colourless oil (5 mg, 17%). (Found: M$, 238.1205, C_{13}H_{18}O_{4} requires M$, 238.1205); \( \delta H \) (CDCl$_3$) 6.76 (1H, d, J 2.4 Hz, 5-H), 6.38 (1H, d, J 2.4 Hz, 7-H), 4.92 (1H, dq, J 6.3 and 1.5 Hz, 1-H), 4.31 (1H, dd, J 1.5 and 9.0 Hz, 4-H), 3.85 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.34 (1H, dq, J 9.0 and 6.2 Hz, 3-H), 1.48 (3H, d, J 6.3 Hz, 1-CH$_3$), 1.42 (3H, d, J 6.2 Hz, 3-CH$_3$); \( \delta^{13}C \) (CDCl$_3$) 159.6 and 156.4 (C-6 and C-8), 140.0 (C-4a), 120.3 (C-8a), 100.4 and 97.7 (C-5, C-7), 74.1, 71.2 and 70.8 (C-1, C-4, C-3), 55.2 (OCH$_3$), 55.1 (OCH$_3$), 21.2 and 18.2 (CH$_3$-1 and CH$_3$-3); m/z 238 (M$, 8\%$), 223 (23), 220 (18), 205 (100), 195 (7), 179 (26).

The above reaction was repeated using dioxolane (148) (30 mg, 0.13 mmol) in dry dichloromethane (20 ml). This was treated with titanium tetrachloride (16.4 µl, 0.26 mmol) at -78 °C and the temperature of the reaction mixture was immediately to -30 °C. The mixture was stirred at -30 °C for 30 minutes. The crude residue (30 mg) obtained
was analysed by g.c.-mass and \textsuperscript{1}H-n.m.r. spectroscopy which indicated a 1:7 mixture of isochromans (151) and (152); see Table 2.1. This was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give the compound (151) as a white solid (3 mg, 9%) and compound (152) as a colourless oil (22 mg, 72%).

Similarly, a 4:1 mixture of isochromans (151) and (152) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C for 60 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C.

Once again a sample of 4:1 mixture of isochromans (151) and (152) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was treated with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C, then the reaction mixture was warm to -30 °C and stirred for 20 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C. This procedure was repeated once again, i.e., a 4:1 mixture of isochromans (151) and (152) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was treated with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C then the reaction mixture was warm to 0 °C and stirred for 10 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C.

All the samples were neutralised with saturated aqueous sodium bicarbonate solution, washed with water, dried and evaporated. The crude residues were analysed by g.c and g.c.-mass spectroscopy which indicated retention times of 15.46 and 16.12 minutes for two isochroman isomers (203) and (204) respectively. The results of g.c, g.c.-mass and \textsuperscript{1}H-n.m.r. spectroscopic analyses are given in Table 2.1.
rel-(1S,3R,4S)-4-Acetoxy-6,8-dimethoxy-1,3-dimethylisochroman (152-1)

A solution of pyran (152) (25 mg, 0.11 mmol) in acetic anhydride (2 ml) and pyridine (0.5 ml) was stirred at 55 °C for 1 h. The mixture was poured into an ice cold dilute hydrochloric acid solution (10 ml). This was extracted with dichloromethane, washed with water, dried and concentrated. Chromatography on silica gel using 6:1 hexane/ethyl acetate as the eluent yielded the acetate (152-1) (23 mg, 78%), which was crystallised from diethyl ether, m.p. 74-75 °C. (Found: M+, 280.1311, C_{15}H_{20}O_{5} requires M+, 280.1312); δ_{H} (CDCl_{3}) 6.31 (1H, d, J 2.1 Hz, 5-H), 6.17 (1H, d, J 2.1 Hz, 7-H), 5.67 (1H, dd, J 1.5 and 9.0 Hz, 4-H), 4.86 (1H, dq, J 6.0 and 1.5 Hz, 1-H), 3.72 (3H, s, OCH_{3}), 3.70 (3H, s, OCH_{3}), 3.50 (1H, dq, J 9.0 and 6.3 Hz, 3-H), 2.12 (3H, s, 4-0Ac), 1.41 (3H, d, J 6.0 Hz, 1-CH_{3}), 1.21 (3H, d, J 6.3 Hz, 3-CH_{3}); m/z 280 (M+, 1.5%), 220 (19), 206 (13), 205 (100), 194 (11), 193 (13).

rel-(1R,2R)-1-(3',5'-Dimethoxyphenyl)-1,2-propanediol (153)

E-Olefin (143a) (350 mg, 1.95 mmol) in a 2:1 mixture of acetone/water (9 ml) was treated with 4-methylmorpholine-N-oxide (270 mg, 2.30 mmol) and osmium tetroxide (5 mg) in t-butyl alcohol (1ml) at 0 °C. After stirring for 24 h, acetone was removed under vacuum at room temperature and the remaining aqueous layer poured into dilute hydrochloric acid (2 M, 5 ml). The organic materials were extracted into ethyl acetate (5 x 20 ml) and the combined extracts washed with water/brine, dried and evaporated to afford a crude oil (400 mg). This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to give the title compound (153) as a light orange oil (325 mg, 77%). (Found: C, 62.0; H, 7.9. C_{11}H_{16}O_{4} requires C, 62.25; H, 7.6%); δ_{H} (CDCl_{3}) 6.50 (2H, d, J 2.3 Hz, 2'-H and 6'-H), 6.37 (1H, t, J 2.3 Hz, 4'-H), 4.33 (1H, d, J 7.1 Hz, 1-H), 3.87 (1H, dq, J 7.1 and 6.5 Hz, 2-H), 3.81 (6H, s, 2 x OCH_{3}), 1.11 (3H, d, J 6.5 Hz, CHCH_{3}); δ^{13}C (CDCl_{3}) 160.7 (C-3' and C-5').


143.1 (C-1') 104.7 (C-2' and C-6'), 99.9 (C-4'), 79.4 (C-1), 72.0 (C-2), 55.3 (2 x OCH₃), 18.8 (CH(CH₃)); m/z 212 (M⁺, 11%), 168 (69), 139 (100), 124 (21).

rel-(2S,4R,5R) and rel-(2R,4R,5R)-4-(3',5'-Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes (154)

Diol (153) (150 mg, 0.71 mmol) in dry dichloromethane (20 ml) was treated with 1,1-dimethoxyethane (0.1 ml) and (+)-camphorsulphonic acid (20 mg, 0.09 mmol). After heating under reflux for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution (1 ml) and poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to afford a colourless oil which was purified by chromatography on silica gel using 6:1 hexane/ethyl acetate as eluent to give a 1:1 isomeric mixture of dioxolanes (154) as a colourless oil (110 mg, 71%). (Found: C, 65.3; H, 7.4. C₁₃H₁₉O₄ requires C, 65.5; H, 7.6%; δH (CDCl₃) 6.6 to 6.4 (6H, m, 2'-H, 4'-H and 6'-H of both isomers), 5.45 and 5.39 (each 1H, q, J 4.8 and 4.7 Hz respectively, 2-H of each isomer), 4.43 and 4.40 (each 1H, d, J 5.1 and 5.8 Hz, 4-H of each isomer), 3.88 (2H, m, 5-H of both isomers), 3.80 (12H, s, OCH₃ of both isomers) 1.52 and 1.48 (each 3H, d, J 4.8 and 4.7 Hz respectively, 2-CH₃ of each isomer), 1.42 and 1.35 (each 3H, d, J 6.1 and 6.3 Hz respectively, 5-CH₃ of each isomer); m/z 238 (M⁺, 12%), 194 (47), 178 (52) , 179 (100), 165 (18), 151 (10).

rel-(1R,3R,4R)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochroman (157) and rel-(1S,3R,4R)-4-Hydroxy-6,8-dimethoxy-1,3-dimethylisochroman (158)

A mixture of dioxolanes (154) (30 mg, 0.13 mmol) in dry dichloromethane (20 ml) was treated with titanium tetrachloride (27.6 µl, 0.26 mmol) at -78 °C in an atmosphere of nitrogen. After stirring at -78 °C for 30 minutes, the reaction was quenched with methanol (0.1 ml). A saturated aqueous sodium bicarbonate solution
(2ml) was added and the resultant mixture poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil. This was analysed by g.c. and g.c.-mass spectroscopy which indicated a 1:7 mixture of isochroman isomers (157) and (158). This mixture was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to afford two compounds: compound (157) as a white solid (3 mg, 8%), which was crystallised from dichloromethane/hexane, m.p. 101-102 °C. (Found: C, 65.6; H, 7.8. C_{13}H_{18}O_4 requires C, 65.5; H, 7.6%); δ\textsubscript{H} (CDCl\textsubscript{3}) 6.50 (1H, d, J 2.3 Hz, 5-H), 6.39 (1H, d, J 2.3 Hz, 7-H), 5.03 (1H, q, J 6.5 Hz, 1-H), 4.10 (1H, m, 4-H and 3-H), 3.80 (3H, s, OCH\textsubscript{3}), 3.77 (3H, s, OCH\textsubscript{3}), 1.45 (3H, d, J 6.5 Hz, 1-CH\textsubscript{3}), 1.36 (3H, d, J 6.3 Hz, 3-CH\textsubscript{3}); m/z 238 (M\textsuperscript{+}, 9%), 223 (57), 205 (100), 194 (12), 179 (30); and

compound (158) as a colourless oil (22mg, 72%), which was crystallised from dichloromethane/hexane, m.p. 70-71 °C. (Found: C, 65.25; H, 7.9. C_{13}H_{18}O_4 requires C, 65.5; H, 7.6%); δ\textsubscript{H} (CDCl\textsubscript{3}) 6.48 (1H, d, J 2.4 Hz, 5-H), 6.41 (1H, d, J 2.4 Hz, 7-H), 4.87 (1H, q, J 6.3 Hz, 1-H), 4.12 (1H, d, J 1.6, 4-H), 3.81 (3H, s, OCH\textsubscript{3}), 3.78 (3H, s, OCH\textsubscript{3}), 3.72 (1H, dq, J 1.6 and 6.6 Hz, 3-H), 1.54 (3H, d, J 6.3 Hz, 1-CH\textsubscript{3}), 1.35 (3H, d, J 6.6 Hz, 3-CH\textsubscript{3}); δ\textsuperscript{13}C (CDCl\textsubscript{3}) 159.3 and 156.4 (C-6, C-8), 138.6 (C-4a), 120.0 (C-8a), 104.6 (C-5), 99.0 (C-7), 71.9, 71.2 and 69.6 (C-1, C-3, C-4), 55.3 (OCH\textsubscript{3}), 55.1 (OCH\textsubscript{3}), 21.3 and 16.9 (CH\textsubscript{3}-1 and CH\textsubscript{3}-3); m/z 238 (M\textsuperscript{+}, 11%), 223 (100), 205 (34), 194 (21), 179 (45), 165 (11).

Dihydroisobenzofuran (162)

Dioxolane (148) (30 mg, 0.13 mmol) in dry dichloromethane (20 ml) was treated with titanium tetrachloride (27.6 µl, 0.26 mmol) at -78 °C in an atmosphere of nitrogen. After one minute, the resulting solution was immediately changed into a cold bath at 0 °C and stirred for 10 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate solution (1 ml) and poured into water. The organic layer was separated and
the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to afford a colourless oil which was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give dihydroisobenzofurans (162) as a colourless oil (20 mg, 67%). This was analysed by g.c. and g.c.-mass spectroscopy which indicated a 4:1 mixture of dihyroisobenzofuran isomers (162). (Found: \( M^+ \), 238.1205, \( \text{C}_{13}\text{H}_{18}\text{O}_4 \) requires \( M^+ \), 238.1205); The \( ^1\text{H}-\text{n.m.r.} \) spectrum of the major isomer showed significant resonances at \( \delta_H \) (CDCl\(_3\)) 6.38 (2H, m, 4-H and 6-H), 5.42 (1H, dq, J 6.2 and 3.1 Hz, 1-H), 5.25 (1H, dd, J 3.3 and 3.1 Hz, 3-H), 3.95 (1H, m, 3'-H), 3.81 (3H, s, OCH\(_3\)), 3.80 (3H, s, OCH\(_3\)), 1.49 (3H, d, J 6.2 Hz, 1-CH\(_3\)), 1.13 (3H, d, J 6.5 Hz, 3'-CH\(_3\)); \( m/z \) 238 (\( M^+ \), 81%), 193 (100), 175 (7), 165 (7).

rel-(1R,3R,4R)-4-Acetoxy-6,8-dimethoxy-1,3-dimethylisochroman (165)

A solution of pyran (157) (6 mg, 0.11 mmol) in acetic anhydride (2 ml) and pyridine (0.5 ml) was stirred at 55 °C for 1 h. The resultant mixture was poured into an ice cold dilute hydrochloric acid (10 ml). This was extracted with dichloromethane, washed with water, dried and concentrated. Chromatography on silica gel with 6:1 hexane/ethyl acetate as the eluent yielded the acetate (165) as an oil (6 mg, 85%), (Found: C, 64.4; H, 6.9. \( \text{C}_{15}\text{H}_{20}\text{O}_5 \) requires C, 64.3; H, 7.1%); \( \delta_H \) (CDCl\(_3\)) 6.46 (1H, d, J 2.1 Hz, 5-H), 6.43 (1H, d, J 2.1 Hz, 7-H), 5.74 (1H, d, J 2.1 Hz, 4-H), 5.12 (1H, q, J 6.5 Hz, 1-H), 4.22 (1H, dq, J 2.1 and 6.3 Hz, 3-H), 3.80 (3H, s, OCH\(_3\)), 3.78 (3H, s, OCH\(_3\)), 2.12 (3H, s, 4-OAc), 1.46 (3H, d, J 6.5 Hz, 1-CH\(_3\)), 1.25 (3H, d, J 6.3 Hz, 3-CH\(_3\)); \( m/z \) 280 (\( M^+ \), 1.1%), 265 (8), 220 (15), 206 (12), 205 (85), 193 (10), 43 (100).

Dihydroisobenzofuran (166)

A mixture of dioxolanes (154) (30 mg, 0.13 mmol) in dry dichloromethane (15 ml) was treated with titanium tetrachloride (27.6 µl, 0.26 mmol) at -78 °C in an atmosphere of nitrogen. After one minute, the resulting solution was warmed to 0 °C and
stirred for 10 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate solution (2 ml) and poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to afford a colourless oil which was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give the dihydroisobenzofurans (166) as a colourless oil (21 mg, 70%). This was analysed by g.c. and g.c.-mass spectroscopy which indicated a 6:1 mixture of dihydroisobenzofuran (166). (Found: M⁺, 238.1205, C₁₃H₁₈O₄ requires M⁺, 238.1205); The ¹H-n.m.r. spectrum of the major isomer showed significant resonances at δ_H (CDCl₃) 6.37 (2H, m, 4-H and 6-H), 5.39 (1H, dq, J 2.9 and 6.3 Hz, 1-H), 5.03 (1H, dd, J 2.9 and 7.3 Hz, 3-H), 3.88 (1H, m, 3'-H), 3.81 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 1.48 (3H, d, J 6.3 Hz, 1-CH₃), 1.33 (3H, d, J 6.5 Hz, 3'-CH₃); m/z 238 (M⁺, 7%), 205 (22), 193 (100), 175 (7), 165 (11).

The above reaction was repeated on a solution of dioxolanes (10 mg, 0.05 mmol) in dry dichloromethane (7 ml), which was treated with titanium tetrachloride (9.2 µl, 0.1 mmol) at -78 °C in an atmosphere of nitrogen. After one minute, the resulting solution was immediately warmed to -30 °C and stirred for 30 minutes at -30 °C. The reaction was quenched with saturated aqueous sodium bicarbonate solution (0.5 ml) and poured into water. The crude residue obtained was analysed by g.c., g.c.-mass and ¹H-n.m.r. spectroscopy which indicated a mixture of compound (157) (10%), compound (158) (56%) and compound (166) (34%).

The above reaction was repeated on a solution of isochroman (158) (10 mg, 0.05 mmol) in dry dichloromethane (7 ml), which was treated with titanium tetrachloride (9.2 µl, 0.1 mmol) at -78 °C in an atmosphere of nitrogen. After one minute, the resulting solution was immediately warmed to 0 °C and stirred for 10 minutes. The crude residue (10 mg) was analysed by g.c.-mass and ¹H-n.m.r. spectroscopy which indicated a 6:1 mixture of dihydroisobenzofurans (166). This was purified by chromatography on silica...
gel using 4:1 hexane/ethyl acetate to afford the title compound (166) (6 mg, 60%). The results of g.c, g.c.-mass and $^1$H-n.m.r. spectroscopic analyses are given in Table 2.3.

**Bromopyrans (169) and (170)**

Isochroman (158) (70 mg, 0.29 mmol) was dissolved in dry benzene (5 ml) and treated with phosphorus tribromide (0.11 ml, 1.16 mmol) in an atmosphere of nitrogen. After 30 minutes, the resulting solution was quenched with a dilute solution of sodium bicarbonate (1 ml) and poured into water (20 ml). This was extracted with dichloromethane, washed with water, dried and concentrated to afford the crude product (75 mg). This was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give the bromopyran (169) (40 mg, 45%) and bromopyran (170) (20 mg, 22%). The $^1$H-n.m.r. analysis of bromopyrans (169) and (170) showed that each of these compounds was an epimeric mixture at C-1. The $^1$H-n.m.r. spectrum of the epimeric mixture of bromopyrans (169) showed resonances at δH (CDCl$_3$) 6.81, 6.68, 6.37 and 6.32 (each 1H, d, J 2.2 Hz, Ar-H of each isomer), 4.95 (6H, m, 4-H, 1-H and 3-H), 4.29 (1H, dq, J 8.2 and 6.2 Hz, 3-H). The $^1$H-n.m.r. spectrum of bromopyrans (170) showed resonances at δH (CDCl$_3$) 6.43 to 6.36 (4H, m, Ar-H of both isomers), 5.13 and 5.07 (each 1H, q, J 6.6 and 6.2 Hz, 1-H of both isomers), 5.00 (2H, d, J 1.9 Hz, 4-H of both isomers) 3.98 (2H, dq, J 5.7 and 1.9 Hz, 3-H of both isomers). The g.c. mass spectral fragmentation pattern of the four stereoisomers were identical, m/z 302 (M+$^{81}$Br, 9%), 300 (M+$^{79}$Br, 8), 287 (88), 285 (88), 206 (31), 205 (75), 191 (41), 179 (22), 177 (27).

**rel-(1S,3R)-6,8-Dimethoxy-1,3-dimethylisochroman (167)**

An isomeric mixture of compounds (169) and (170) (60 mg, 0.2 mmol) in ethanol and water (3:1) (12 ml) was stirred with Raney nickel catalyst (100 mg, 50% in water) at 60 °C. After 15 minutes, the catalyst was filtered off and washed exhaustively.
with dichloromethane. The combined organic fraction was washed with water, dried and concentrated to afford the crude product (40 mg). This was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give pyran (167) (18 mg, 40%). (Found: M+, 222.1256, C_{13}H_{18}O_{3} requires M+, 222.1254); δ_{H} (CDCl_{3}) 6.32 (1H, d, J 2.4 Hz, 5-H), 6.22 (1H, d, J 2.4 Hz, 7-H), 4.93 (1H, dq, J 1.5 and 6.3 Hz, 1-H), 3.78 (3H, s, OCH_{3}), 3.77 (3H, s, OCH_{3}), 3.66 (1H, m, 3-H), 2.66 (1H, ddd, J 17.1, 10.5 and 1.5 Hz, 4-Ha'), 2.52 (1H, d (broad), J 17.1 Hz, 4-He'), 1.51 (3H, d, J 6.3 Hz, 1-CH_{3}), 1.32 (3H, d, J 6.2 Hz, 3-CH_{3}); m/z 222 (M+, 7%), 208 (15), 207 (100), 192 (6), 189 (7).

The olefin (172) (30 mg, 1.54 mmol) in a 2:1 mixture of acetonitrile/water (1 mL) was treated with 3-methylphosphonic acid (349 mg, 2.16 mmol) and sodium bicarbonate
cis-1-(2',5'-Dimethoxyphenyl)-1-propene (173)

Sodium hydride (55-60% dispersion in mineral oil, 200 mg) was stirred with dimethyl sulphoxide (0.5 ml) and tetrahydrofuran (2 ml) at 60 °C for 2 h in an atmosphere of argon. This mixture was cooled to room temperature and ethyltriphenylphosphonium bromide (1.8 g, 5.20 mmol) in tetrahydrofuran (10 ml) was added and stirred for 15 minutes. The aldehyde (172) (500 mg, 3.01 mmol) in THF (20 ml) was added and the mixture stirred at 60 °C for a further 1 h. The reaction mixture was centrifuged and the supernatant layer separated. This organic layer was washed with dilute hydrochloric acid (10%), dried, filtered and evaporated to afford a brown oil which was purified by chromatography on silica gel using 15:1 hexane/ethyl acetate as eluent to give a 4:1 mixture of Z- and E-olefins as a colourless oil (450 mg, 84%). (Found: C, 74.4; H, 7.9. 

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\text{C}_{11}\text{H}_{14}\text{O}_2 \text{ requires C, 74.1; H, 7.9%}; \]

The \(^1\)H-n.m.r. spectrum of major isomer (173) showed; \(\delta^H\) (CDCl\(_3\)) 6.83 (1H, d, J 2.8 Hz, 6'-H), 6.81 (1H, dd, J 7.8 and 2.8 Hz, 4'-H), 6.68 (1H, d, J 7.8 Hz, 3'-H), 6.47 (1H, dq, J 11.4 and 1.2 Hz, 1-H), 5.88 (1H, dq, J 11.4 and 7.1 Hz, 2-H), 3.80 (6H, s, 2 x OCH\(_3\)), 1.85 (3H, dd, J 7.1 and 1.2 Hz, CHCH\(_3\)); \(\delta^1\)C (CDCl\(_3\)) 152.9 and 151.3 (C-5', C-2'), 127.3 and 127.1 (C-1, C-1'), 125.1 (C-2), 116.2 (C-6'), 112.1 and 111.2 (C-3', C-4'), 56.0 (OCH\(_3\)), 55.7 (OCH\(_3\)), 13.9 (CHCH\(_3\)); m/z 178 (M\(^+\), 100%), 163 (10), 135 (10), 121 (14), 103 (20). The \(^1\)H-n.m.r. spectrum of minor isomer showed; \(\delta^H\) (CDCl\(_3\)) 6.98 (1H, d, J 2.8 Hz, 6'-H), 6.79 (2H, m, 3'-H and 4'-H), 6.68 (1H, dq, J 16.0 and 1.2 Hz, 1-H), 6.24 (1H, dq, J 16.0 and 6.6 Hz, 2-H), 3.80 (6H, s, 2 x OCH\(_3\)), 1.91 (3H, dd, J 6.6 and 1.2 Hz, CHCH\(_3\))

rel-(1S,2R)-1-(2',5'-Dimethoxyphenyl)-1,2-propanediol (174)

Olefin (173) (320 mg, 1.54 mmol) in a 2:1 mixture of acetone/water (9 ml) was treated with 4-methylmorpholine-N-oxide (246 mg, 2.10 mmol) and osmium tetroxide
(5 mg) in t-butanol (1 ml) at 0 °C. After stirring for 24 h, the acetone was removed under vacuum at room temperature. The remaining aqueous layer was poured into dilute hydrochloric acid (2 M, 5 ml) and the organic materials extracted into ethyl acetate (5 x 20 ml). The combined extracts were washed with water, dried and evaporated to afford a crude oil (310 mg). This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to yield a 7:1 mixture of diastereomers as an orange oil (270 mg, 69%). (Found: C, 62.0; H, 7.9. C11H16O4 requires C, 62.25; H, 7.6%); the 1H-n.m.r. spectrum of the major isomer (174) showed; δH (CDCl3) 7.00 (1H, d, J 2.2 Hz, 6'-H), 6.80 (2H, narrow m, 3'-H and 4'-H), 4.89 (1H, d, J 7.2 Hz, 1-H), 4.12 (1H, dq, J 7.2 and 6.4 Hz, 2-H), 3.78 (3H, s, OCH3), 3.77 (3H, s, OCH3), 1.09 (3H, d, J 6.4 Hz, CHCH3); δ13C (CDCl3) 153.1 and 150.6 (C-5', C-2'), 129.6 (C-1'), 113.9 and 112.9 (C-3', C-4'), 111.3 (C-6'), 73.8 (C-1), 70.0 (C-2), 55.8 (OCH3), 55.5 (OCH3), 17.2 (CHCH3); m/z 212 (M+, 12%), 168 (22), 167 (100), 139 (40), 137 (32), 124 (23). The 1H-n.m.r. spectrum of the minor isomer (180) showed; δH (CDCl3) 6.87 (1H, d, J 2.6 Hz, 6'-H), 6.80 (2H, narrow m, 3'-H and 4'-H), 4.53 (1H, weak, 1-H), 4.12 (1H, weak, 2-H), 3.78 and 3.77 (each 3H, s, 2 x OCH3), 1.07 (3H, d, J 6.3 Hz, CHCH3);

rel-(2R,4S,5R)-4-(2',5'-Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolane (175)

The diol (174) (200 mg, 0.94 mmol) in dry dichloromethane (20 ml) was treated with 1,1-dimethoxyethane (0.13 ml) and (±)-camphorsulphonic acid (10 mg, 0.042 mmol) in a manner similar to compound (153). The crude product (190 mg) was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give the title compound (175) as a colourless oil (162 mg, 72%). (Found: C, 65.5; H, 7.9. C13H18O4 requires C, 65.5; H, 7.6%); δH (CDCl3) 7.07 (1H, d, J 2.1 Hz, 6'-H), 6.79 (2H, narrow m, 3'-H and 4'-H), 5.35 (1H, d, J 7.2 Hz, 4-H), 5.18 (1H, q, J 4.9 Hz, 2-H), 4.44 (1H, dq, J 7.2 and 6.3 Hz, 5-H), 3.78 (3H, s, OCH3), 3.77 (3H, s, OCH3), 1.54 (3H, d, J 4.9 Hz, 2-CH3), 0.81 (3H, d, J 6.3 Hz, 5-CH3); δ13C (CDCl3) 153.5
and 149.9 (C-5', C-2'), 126.2 (C-1'), 113.9 and 112.5 (C-3', C-4'), 110.5 (C-6'), 99.6 (C-4), 75.5 and 74.8 (C-5, C-2), 55.1 (2 x OCH3), 19.5 (CH3-2), 15.5 (CH3-5); m/z 238 (M+, 35%), 194 (84), 179 (22), 165 (41), 163 (100), 151 (18), 135 (86), 44 (99).

rel-(1R,3R,4S)-4-Hydroxy-5,8-dimethoxy-1,3-dimethylisochroman (176)

To a stirred solution of dioxolane (175) (55 mg, 0.22 mmol) in dry dichloromethane (35 ml) was added titanium tetrachloride (25.3 µl, 0.22 mmol) at -78 °C. After stirring at -78 °C for 30 minutes, the resulting reaction mixture was quenched with methanol (0.1 ml) and a saturated aqueous sodium bicarbonate solution (0.5 ml) was added. The resultant mixture was poured into water, the organic layer separated and aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil (50 mg). This was analysed by g.c. and g.c.-mass spectroscopy which indicated a number of products. These products were purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give three compounds: unreacted starting dioxolane (175) (11 mg, 20%) (the 1H-n.m.r. and mass spectra were in agreement with those quoted above); isochroman (176) as a colourless oil (10 mg, 18%). (Found: M+, 238.1205, C13H18O4 requires M+, 238.1205); δH (CDCl3) 6.82 and 6.72 (1H, d, J 9.0 Hz, 6-H and 7-H), 5.01 (1H, q, J 6.6 Hz, 1-H), 4.55 (1H, d, J 7.9 Hz, 4-H), 3.98 (1H, dq, J 7.9 and 6.2 Hz, 3-H), 3.85 (3H, s, OCH3), 3.76 (3H, s, OCH3), 1.55 (3H, d, J 6.6 Hz, 1-CH3), 1.49 (3H, d, J 6.2 Hz, 3-CH3); m/z 238 (M+, 19%), 220 (29), 205 (100), 179 (15), 175 (22); and chlorohydrins (177) as a colourless oil (isomeric mixture) (25 mg, 45%), δH (CDCl3) 7.15 and 7.05 (each 1H, d, J 2.1 Hz, 6'-H of each isomer), 6.82 (4H, m, 3'-H and 4'-H of both isomers), 5.43 and 5.42 (each 1H, d, J 6.0 and 6.4 Hz, 1-H of each isomer), 4.15 (2H, dq overlapped, 2-H of both isomers), 3.80 and 3.76 (each 6H, 2 x OCH3 of each isomer), 1.25 and 1.14 (each 3H, d, J 6.0 and 6.4 Hz, CHCH3 of each
isomer). The g.c.-mass spectrum of the mixture of chlorohydrins (177) showed six components: two isomers of chlorohydrins (177) with retention times 13.4 and 13.5 minutes and identical fragmentation patterns at m/z 232 (M+{37Cl}, 10%), 230 (M+{35Cl}, 31), 194 (27), 188 (28), 186 (84), 171(36), 151 (100); epoxide (178) and its diastereomer with retention times 11.4 and 11.6 minutes and identical fragmentation patterns at m/z 194 (M+, 98%), 179 (13), 165 (47), 151 (100); ketone (178-1) with retention time 11.5 minutes and m/z 194 (M+, 56%), 165 (100), 150 (60); and ketone (178-2) with retention time 11.8 minutes and m/z 194 (M+, 80%), 151 (100), 121 (53).

cis-1-(2',5'-Dimethoxyphenyl)-1,2-epoxypropane (178)

A solution of meta-chloroperbenzoic acid\(^3\) (500 mg, 2.91 mmol) in chloroform (30 ml) was added dropwise to a solution of olefin (173) (450 mg, 2.52 mmol) in chloroform (10 ml) at 0 °C and the reaction mixture stirred with sodium bicarbonate (100 mg) for 24 h. This mixture was filtered and the filtrate was poured into saturated sodium bicarbonate solution (15 ml). The organic phase was separated and the aqueous phase extracted with cold chloroform (3 x 10 ml). The combined organic extracts were washed with water, dried, filtered and concentrated to give an orange oil (800 mg) which was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to afford two compounds: compound (178) as a white solid (300 mg, 66%) which was crystallised from light petroleum (60-80 °C), m.p. 65-66 °C. (Found: C, 68.0; H, 7.6. \(\text{C}_{11}\text{H}_{14}\text{O}_3\) requires C, 68.0; H, 7.3%); \(\delta\_H (\text{CDCl}_3) 6.83\) (1H, d, J 2.2 Hz, 6'-H), 6.78 (2H, narrow m, 3'-H and 4'-H), 4.16 (1H, d, J 4.9 Hz, 1-H), 3.80 (3H, s, OCH\(_3\)_), 3.76 (3H, s, OCH\(_3\)_), 3.38 (1H, dq, J 4.9 and 5.2 Hz, 2-H), 1.06 (3H, d, J 5.2 Hz, CH\(_2\CH_3\)_); \(\delta\_^{13}C (\text{CDCl}_3) 153.0 \text{ and } 152.0\) (C-5', C-2'), 125.0 (C-1'), 113.4 and 113.0 (C-3', C-4'), 110.9 (C-6'), 55.8 (OCH\(_3\)_), 55.7 (OCH\(_3\)_), 55.1 and 54.7 (C-1, C-2), 12.6 (CH\(_2\CH_3\)_); m/z 194 (M+, 46%), 179 (11), 165 (20), 163 (43), 151 (32), 135 (100); and hydroxy ester (179) (13 mg, 7%) \(^1\)H-n.m.r. spectrum of diastereomeric mixture (179) showed significant resonances at \(\delta\_H (\text{CDCl}_3) 8.07, 7.97, 7.41, 7.38, 6.92, 6.84,\)
6.78 (14H, Ar-H of both isomers), 6.38 and 6.26 (each 1H, d, 3.9 and 5.9 Hz, 1-H of each isomer), 4.23 (2H, m, 2-H of both isomers), 3.84 (6H, s, OMe), 3.72 (6H, s, OMe), 1.20 (6H, d, J 6.5 Hz, CHCH₃ of both isomers); m/z 350 (M+, 2%), 306 (9), 167 (23), 151 (6), 140 (28), 139 (100), 111 (24).

rel-(1R,2R)-1-(2',5'-Dimethoxyphenyl)-1,2-propanediol (180)

A solution of epoxide (178) (300 mg, 1.55 mmol) in dimethyl sulphoxide 4(15 ml) and potassium hydroxide (0.4 N, 6 ml) was stirred at 80 °C. After 24 h, the resulting solution was cooled to room temperature, poured into water and extracted with ethyl acetate (4 x 20 ml). The combined organic extracts were washed with water, dried and evaporated to afford an orange oil. This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to give the title compound (180) as a light orange oil (250 mg, 76%); (Found: C, 62.6; H, 7.9. C₁₁H₁₆O₄ requires C, 62.25; H, 7.6%); δH (CDCl₃) 6.87 (1H, d, J 2.6 Hz, 6'-H), 6.80 (2H, narrow m, 3'-H and 4'-H), 4.53 (1H, d, J 7.1 Hz, 1-H), 3.95 (1H, dq, J 7.1 and 6.3 Hz, 2-H), 3.80 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 1.07 (3H, d, J 6.3 Hz, CHCH₃); m/z 212 (M+, 11%), 168 (22), 167 (100), 139 (52), 137 (34), 124 (23).

rel-(2R,4R,5R) and rel-(2S,4R,5R)-4-(2',5'-Dimethoxyphenyl)-2,5-dimethyl-1,3-dioxolanes (181) and (182)

The diol (180) (230 mg, 1.08 mmol) in dry dichloromethane (25 ml) was treated with 1,1-dimethoxyethane (0.16 ml) and (+)-camphorsulphonic acid (10 mg) in a manner similar to that for compound (153). The crude product (230 mg) was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give approximately a 2:1 mixture of dioxolanes (181) and (182) as a colourless oil (200 mg, 77%); δH (CDCl₃) 7.12 (2H, d, J 2.5 Hz, 6'-H of both isomers), 6.78 (4H, narrow m, 3'-H and 4'-H of both isomers), 5.38 (2H, m, 2-H of both isomers), 4.95 and 4.87
(each 1H, d, J 7.0 Hz, 4-H of both isomers), 3.93 (2H, dq, J 7.0 and 5.0 Hz, 5-H of both isomers), 3.79 and 3.76 (each 6H, s, OCH₃ of both isomers), 1.50, 1.42, 1.36 and 1.34 (each 3H, d, J 5.0 and 6.4 Hz, 2-CH₃ and 5-CH₃ of both isomers); m/z 238 (M⁺, 14%), 194 (36), 179 (10), 165 (18), 163 (39), 151 (8), 135 (46), 44 (100).

Attempted chromatographic separation of diastereomeric mixture (100 mg) afforded a single diastereomer (40 mg, 40%), (Found: C, 65.5; H, 7.6. C₁₃H₁₈O₄ requires C, 65.5; H, 7.6%). δ_H (CDCl₃) 7.12 (1H, d, J 2.5 Hz, 6'-H), 6.80 (2H, narrow m, 3'-H and 4'-H), 5.38 (1H, q, J 5.0 Hz, 2-H), 4.96 (1H, d, J 6.0 Hz, 4-H), 3.97 (1H, dq, J 6.0 and 6.4 Hz, 5-H), 3.79 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 1.50 (3H, d, J 5.0 Hz, 2-CH₃) 1.36 (3H, d, J 6.4 Hz, 5-CH₃);

rel-(1S,3R,4R)-4-Hydroxy-5,8-dimethoxy-1,3-dimethylisochroman (184)

To a stirred solution of a 2:1 mixture of dioxolanes (181) and (182) (40 mg, 0.22 mmol) in dry dichloromethane (15 ml) was added titanium tetrachloride (18.4 µl, 0.22 mmol) at -78 °C. After stirring at -78 °C for 30 minutes, the resulting reaction mixture was quenched with methanol (0.1 ml) and a saturated aqueous sodium bicarbonate solution (2 ml). The resultant mixture was poured into water, the organic layer separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil (38 mg). This was analysed by g.c. and g.c.-mass spectroscopy which indicated a number of products. These products were purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give three compounds: unreacted starting dioxolanes (181) and (182) (8 mg, 20%) (the ¹H-n.m.r. and mass spectra were in agreement with those of the starting dioxolanes); a diastereomeric mixture of chlorohydrins (177) as a colourless oil (12 mg, 31%) (the ¹H-n.m.r and g.c.-mass data are given above); and isochroman (184) as a colourless oil (18 mg, 45%). (Found: C, 65.6; H, 7.9. C₁₃H₁₈O₄ requires C, 65.5; H, 7.6%); δ_H (CDCl₃) 6.77 and 6.73 (each 1H, d, J 8.5 Hz, 2'-H).
Hz, 6-H and 7-H), 4.93 (1H, q, J 6.3 Hz, 1-H), 4.58 (1H, d, J 1.6 Hz, 4-H), 3.84
(3H, s, OCH3), 3.78 (3H, s, OCH3), 3.56 (1H, dq, J 1.6 and 6.3 Hz, 3-H), 1.58 (3H, d, J 6.3 Hz, 1-CH3), 1.39 (3H, d, J 6.3 Hz, 3-CH3); δ13C (CDCl3) 151.5 and 150.2
(C-8, C-5), 129.3 and 126.9 (C-8a, C-4a), 112.3 and 108.9 (C-6, C-7), 72.2, 71.1 and 63.8 (C-1, C-3, C-4), 55.8 (OCH3), 55.6 (OCH3), 21.6 (1-CH3), 16.7 (3-CH3); m/z 238 (M+, 19%), 220 (29), 205 (100), 179 (15), 175 (22).

The above procedure was repeated using dioxolanes (181) and (182) (40 mg, 0.22 mmol) and the reaction mixture stirred at 0 °C for 10 minutes before quenching with methanol (0.1 ml). The 1H-n.m.r. spectral analysis of the crude residue showed a 3:1 mixture of halohydrins (177) (20 mg, 38%) and dehydrated pyran product (185) (20 mg, 36%) (Found: M+, 220.1099, C13H16O3 requires 220.1099); δH (CDCl3) 6.65 and 6.58 (1H, d, J 9.0 Hz, 6-H and 7-H), 5.81 (1H, s, 4-H), 5.61 (1H, q, J 6.0 Hz, 1-H), 3.79 (3H, s, OCH3), 3.76 (3H, s, OCH3), 1.91 (3H, s, 3-CH3), 1.35 (3H, d, J 6.0 Hz, 1-CH3); m/z 220 (M+, 9%), 205 (21), 149 (27), 57 (100).

rel-(1S,3R,4R)-4-Hydroxy-1,3-dimethylisochroman-5,8-dione (187)

To a stirred solution of isochroman (184) (20 mg, 0.08 mmol) and silver(II) oxide (50 mg) in dioxane (2 ml) was added nitric acid (6 M, 0.2 ml). The reaction mixture was stirred for 5 minutes and a mixture of chloroform (6 ml) and water (2 ml) was then added. The organic phase was separated, washed with water, dried, and evaporated to afford an orange residue. This was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give the title compound (187) as an yellow oil (13 mg, 75%), δH (CDCl3) 6.80 and 6.74 (each 1H, d, J 10.0 Hz, 6-H and 7-H), 4.64 (1H, dq, J 1.5 and 6.0 Hz, 1-H), 4.38 (1H, dd, J 1.6 and 1.5 Hz, 4-H), 3.57 (1H, dq, J 1.6 and 6.3 Hz, 3-H), 1.53 (3H, d, J 6.0 Hz, 1-CH3), 1.37 (3H, d, J 6.3 Hz, 3-CH3); δ13C (CDCl3) 187.3 and 186.3 (C-8 and C-5), 145.3 and 139.8 (C-8a, C-4a), 137.3 and 136.1 (C-6, C-7), 72.2, 69.8 and 61.5 (C-1, C-3, C-4), 20.3 (1-CH3), 15.9 (3-CH3); m/z 210 (M+ + 2, 10%), 208 (5), 193 (27), 164 (100), 136 (64).
2-Chloro-5-methoxybenzyld bromide (190)

A solution of N-bromosuccinimide (6.5 g, 0.2 mol) and 4-chloro-3-methylanisole (15.6 g, 0.1 mol) in carbon tetrachloride (150 ml) was treated with AIBN (1.6 g, 0.01 mol). The reaction mixture was irradiated with a 250 W lamp for 3 h and filtered to remove unwanted solids. The solid residue was washed with carbon tetrachloride (50 ml) and the filtrate and washings were combined and evaporated to dryness to afford a white solid (15 g, 64%). This was crystallised from hexane, m.p. 54-55 °C, δH (CDCl3) 7.25 (1H, d, J 9.0 Hz, 3-H), 6.92 (1H, d, J 3.0 Hz, 6-H), 6.77 (1H, dd, J 9.0 and 3.0 Hz, 4-H), 4.51 (2H, s, CH2Br), 3.76 (3H, s, OCH3); m/z 238 (M+{81Br + 37Cl}, 2%), 236 (M+{79Br + 37Cl} and M+{81Br + 35Cl}, 7), 234 (M+{79Br + 35Cl}, 6), 157 (31), 155 (100). These data correspond with those provided in the literature.12

2-Chloro-5-methoxybenzaldehyde (191)

A solution of hexamine (19 g, 0.14 mol) and benzyl bromide (190) (10 g, 0.42 mol) in chloroform (300 ml) was heated under reflux on a steam bath for 30 minutes. A white precipitation was observed during this period. The solvent (100 ml) was distilled off and acetone (100 ml) was added to the reaction mixture. This mixture was cooled in an ice bath until precipitation was completed. The precipitate was collected on a Buchner funnel, dried in air and heated under reflux for 1 h with acetic acid (50%, 100 ml). Water and then concentrated hydrochloric acid (4:1) were added and boiling continued for another 5 minutes. The resultant mixture was cooled in an ice bath to afford aldehyde (191) as a light yellow solid (5 g, 70%), m.p. 62-63 °C. (Found: C, 56.1; H, 4.0; Cl, 20.8. C8H7ClO2 requires C, 56.3; H, 4.1; Cl, 20.8%); δH (CDCl3) 10.38 (1H, s, CHO), 7.33 (1H, d, J 3.0 Hz, 6-H), 7.29 (1H, d, J 9.0 Hz, 3-H), 7.02 (1H, dd, J 9.0 and 3.0 Hz, 4-H), 3.76 (3H, s, OCH3); δ13C (CDCl3) 189.7 (CO), 158.4 (C-5), 132.5 (C-1), 131.4 (C-3), 128.0 (C-2), 122.8 (C-6), 111.7 (C-4), 55.7 (OCH3); m/z 172 (M+{37Cl}, 31%), 170 (M+{35Cl}, 100), 169 (88), 141 (17). These data correspond with those provided in the literature.12
trans-1-(2'-Chloro-5'-methoxyphenyl)-1-propene (196)

Sodium hydride (55-60 %) dispersion in mineral oil (400 mg) was stirred with dimethyl sulphoxide (1 ml) and tetrahydrofuran (4 ml) at 60 °C for 2 h in an atmosphere of argon. This mixture was cooled to room temperature and ethyltriphenylphosphonium bromide (3.2 g, 8.80 mmol) in tetrahydrofuran (10 ml) was added and stirred for 15 minutes. Then the aldehyde (191) (1 g, 6.02 mmol) in tetrahydrofuran (40 ml) was added and the mixture stirred at 60 °C for another 1 h. The reaction mixture was centrifuged and the supernatant layer was separated. This organic layer was washed with dilute hydrochloric acid (10%), dried, filtered and evaporated to afford a brown oil which was purified by chromatography on silica gel using 15:1 hexane/ethyl acetate as eluent to give a 1:1 mixture of E- and Z-olefins as a colourless oil (850 mg, 80%). This was analysed by g.c. which also indicated a 1:1 mixture of two components with retention times of 11.44 minutes (48%) and 11.92 minutes (51%), δH (CDCl3) 7.32 and 7.28 (each 1H, d, J 8.8 Hz, 3'-H of each isomer), 7.06 and 6.91 (each 1H, d, J 3.1 Hz, 6'-H of each isomer), 6.77 (1H, dq, J 16.0 and 1.8 Hz, trans 1-H), 6.72 (2H, dd, J 8.8 and 3.1 Hz, 4'-H of both isomers), 6.55 (1H, dq, J 11.5 and 1.8 Hz, cis 1-H), 6.27 (1H, dq, J 16.0 and 6.6 Hz, trans 2-H), 5.96 (1H, dq, J 11.5 and 7.1 Hz, cis 2-H), 3.84 (6H, s, OCH3), 1.98 (3H, dd, J 6.6 and 1.8 Hz, CHCH3), 1.85 (3H, dd, J 7.1 and 1.8 Hz, CHCH3). The mixture of E- and Z-olefins (1:1) in ethanol (10 ml) was treated with palladium bisacetonitrile dichloride (10 mg) and heated under reflux for 2 h.1 The mixture was filtered to remove the catalyst and the filtrate evaporated to a residue which was chromatographed on silica gel with 15:1 hexane/ethyl acetate as eluent to give an oily mixture containing the E-olefin (196) (93% by g.c.) and the Z-olefin (7% by g.c.). (Found: C, 65.8; H, 6.1; Cl, 19.4. C10H11ClO requires C, 65.8; H, 6.2 ; Cl, 19.3%); The 1H-n.m.r. of the major component (196) showed; δH (CDCl3) 7.25 (1H, d, J 8.8 Hz, 3'-H), 7.03 (1H, d, J 2.9 Hz, 6'-H), 6.78 (1H, dq, J 16.0 and 1.8 Hz, 1-H), 6.72 (1H, dd, J 8.8 and 2.9 Hz, 4'-H), 6.24 (1H, dq, J 16.0 and 6.6 Hz, 2-H), 3.81 (3H, s, OCH3), 1.95 (3H, dd, J 6.6 and 1.8 Hz, CHCH3); δ13C (CDCl3) 158.2 (C-5'), 136.6 and 133.8 (C-1', C-2'), 130.1 (C-1), 128.5 (C-6'), 127.3 (C-2), 113.8 (C-3'), 111.4
trans-1-(2'-Chloro-5'-methoxyphenyl)-1,2-epoxypropane (197)

A solution of meta-chloroperbenzoic acid 3 (600 mg, 3.49 mmol) in chloroform (20 ml) at 0 °C was added dropwise to a solution of olefin (196) (450 mg, 2.71 mmol) in chloroform (10 ml) and then stirred with sodium bicarbonate (100 mg) for 24 h. The reaction mixture was filtered and the filtrate poured into a saturated sodium bicarbonate solution (15 ml). The organic phase was separated and the aqueous phase extracted with cold chloroform (3 x 10 ml). The combined organic extracts were washed with water, dried, filtered and concentrated to give an orange oil (500 mg). This was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to afford the title compound (197) as an orange oil (440 mg, 90%). (Found: C, 60.7; H, 5.3; Cl, 17.6. C_{10}H_{11}ClO_2 requires C, 60.5; H, 5.6; Cl, 17.85%); δ_H (CDCl_3) 7.23 (1H, d, J 8.5 Hz, 3'-H), 6.76 (1H, d, J 2.3 Hz, 6'-H), 6.74 (1H, dd, J 8.5 and 2.3 Hz, 4'-H), 3.88 (1H, d, J 2.0 Hz, 1-H), 3.76 (3H, s, OCH_3), 2.87 (1H, dq, J 2.0 and 5.1 Hz, 2-H), 1.50 (3H, d, J 5.1 Hz, CHCH_3); δ_{13C} (CDCl_3) 159.3 (C-5'), 137.2 (C-2'), 130.3 and 130.2 (C-3' and C-1'), 115.5 and 111.1 (C-4', C-6'), 59.3 and 57.6 (C-1, C-2), 56.1 (OCH_3), 18.4 (CH_3); m/z 200 (M+{^{37}Cl}, 13%), 198 (M+{^{35}Cl}, 35), 183 (11.5), 169 (32), 167 (55), 154 (14), 119 (100).

rel-(1S,2R)-1-(2'-Chloro-5'-methoxyphenyl)-1,2-propanediol (198)

A solution of epoxide (197) (350 mg, 1.77 mmol) in dimethyl sulphoxide 4 (15 ml) and potassium hydroxide (0.4 M, 6 ml) was stirred at 80 °C. After 24 h, the resulting solution was cooled to room temperature and poured into water and extracted with ethyl acetate (4 x 20 ml). The combined organic extracts were washed with water, dried and evaporated to give an orange oil. This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to afford the title compound (198) as a
light orange oil (330 mg, 86%). (Found: C, 55.7; H, 6.2; Cl, 16.2. C10H13ClO3 requires C, 55.4; H, 6.05; Cl, 16.4%); δH (CDCl3) 7.27 (1H, d, J 8.7 Hz, 3'-H), 7.23 (1H, d, J 2.9 Hz, 6'-H), 6.81 (1H, dd, J 8.7 and 2.9 Hz, 4'-H), 5.22 (1H, d, J 3.2 Hz, 1-H), 4.26 (1H, dq, J 3.2 and 6.5 Hz, 2-H), 3.85 (3H, s, OCH3), 1.10 (3H, d, J 6.5 Hz, CHCH3); δ 13C (CDCl3) 158.3 (C-5'), 139.0 (C-2'), 129.7 (C-3') 123.2 (C-1'), 114.3 and 113.3 (C-4', C-6'), 73.4 (C-1), 69.1 (C-2), 55.4 (OCH3), 15.9 (CHCH3); m/z 218 (M+ [{37}Cl], 2%), 216 (M+ [{35}Cl], 5), 174 (21), 173 (15), 172 (69), 171 (29), 143 (37), 137 (34), 109 (38), 77 (51), 44 (100).

rel-(2R,4S,5R)-4-(2'-Chloro-5'-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane (199)

Diol (198) (250 mg, 1.16 mmol) in dry dichloromethane (25 ml) was treated with 1,1-dimethoxyethane (0.16 ml) and (+)-camphorsulphonic acid (10 mg, 0.04 mmol) in a manner similar to compound (147). The crude product (230 mg) was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give the title compound (199) as a colourless oil (260 mg, 92%). (Found: M+, 242.0711. C12H15ClO3 requires 242.0710); δH (CDCl3) 7.30 (1H, d, J 8.7 Hz, 3'-H), 7.17 (1H, d, J 3.1 Hz, 6'-H), 6.85 (1H, dd, J 8.7 and 3.1 Hz, 4'-H), 5.48 (1H, d, J 7.2 Hz, 4-H), 5.26 (1H, q, J 4.7 Hz, 2-H), 4.60 (1H, dq, J 7.2 and 6.4 Hz, 5-H), 3.89 (3H, s, OCH3), 1.64 (3H, d, J 4.7 Hz, 2-CH3), 0.95 (3H, d, J 6.4 Hz, 5-CH3); δ 13C (CDCl3) 158.3 (C-5'), 137.2 (C-2'), 129.6 (C-3'), 123.0 (C-1'), 114.3 and 113.6 (C-4', C-6'), 100.0 (C-2), 76.5 and 75.2 (C-4, C-5), 55.4 (OCH3), 19.7 (CH3-2), 16.3 (CH3-5); m/z 244 (M+ [{37}Cl], 3%), 242 (M+ [{35}Cl], 9), 198 (55), 169 (40), 167 (77), 154 (14), 119 (38), 77 (16), 72 (100), 44 (78).

rel-(1R,2R)-1-(2'-Chloro-5'-methoxyphenyl)-1,2-propanediol (200)

Olefins (196) (13:1 E to Z)(200 mg, 1.08 mmol) in a 2:1 mixture of acetone/water (6 ml) was treated with 4-methylmorpholine-N-oxide 6 (155 mg, 1.32
mmol) and osmium tetroxide (5 mg) in t-butanol (0.5 ml) at 0 °C. After stirring for 24 h, acetone was removed under vacuum at room temperature. The remaining aqueous layer was poured into dilute hydrochloric acid (2 M, 5 ml) and extracted into ethyl acetate (5 x 20 ml). The combined organic extracts were washed with water/brine, dried and evaporated to afford a crude oil. This was purified by chromatography on silica gel using 1:1 hexane/ethyl acetate as eluent to give the title compound (200) as a light orange oil (200 mg, 80%). (Found: M+, 216.0553. C_{10}H_{13}ClO_{3} requires 216.0552); δ_{H} (CDCl3) 7.25 (1H, d, J 8.9 Hz, 3'-H), 7.03 (1H, d, J 3.0 Hz, 6'-H), 6.77 (1H, dd, J 8.9 and 3.0 Hz, 4'-H), 4.90 (1H, d, J 5.5 Hz, 1'-H), 3.92 (1H, dq, J 5.5 and 6.6 Hz, 2'-H), 3.78 (3H, s, OCH3), 1.19 (3H, d, J 6.6 Hz, CHCH3); δ_{13C} (CDCl3) 158.5 (C-5'), 139.8 (C-2'), 130.1 (C-3'), 123.8 (C-1'), 114.7 and 113.2 (C-4', C-6'), 74.4 (C-1), 71.5 (C-2), 55.5 (OCH3), 18.7 (CHCH3); m/z 218 (M+(37Cl), 1%), 216 (M+(35Cl), 3), 174 (27), 172 (87), 145 (16), 143 (55), 137 (47), 109 (50), 108 (69), 77 (58), 44 (100).

rel-(2R,4R,5R)-4-(2'-Chloro-5'-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane (201) and rel-(2S,4R,5R)-4-(2'-Chloro-5'-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane (202)

Diol (200) (200 mg, 0.93 mmol) in dry dichloromethane (20 ml) was treated with 1,1-dimethoxyethane (0.10 ml) and (+)-camphorsulphonic acid (10 mg, 0.043 mmol) in a manner similar to compound (153). The crude product (200 mg) was purified by chromatography on silica gel using 9:1 hexane/ethyl acetate as eluent to give a 2:1 diastereomeric mixture of dioxolanes (201) and (202) as a colourless oil (190 mg, 85%). Further chromatography on the mixture of dioxolanes (201) and (202) in 9:1 hexane/ethyl acetate afforded the single diastereomer (201) as a colourless oil (105 mg, 55%). (Found: C, 59.2; H, 6.2; Cl, 14.6. C_{12}H_{15}ClO_{3} requires C, 59.4; H, 6.2 ; Cl, 14.6%); δ_{H} (CDCl3) 7.24 (1H, d, J 8.8 Hz, 3'-H), 7.03 (1H, d, J 3.1 Hz, 6'-H), 6.77 (1H, dd, J 8.8 and 3.1 Hz, 4'-H), 5.49 (1H, q, J 4.7 Hz, 2-H), 4.97 (1H, d, J 7.4 Hz, 4-H), 3.91 (1H, dq, J 7.4 and 6.1 Hz, 5-H), 3.80 (3H, s, OCH3), 1.49 (3H, d, J 6.1 Hz, 5-CH3),
1.46 (3H, d, J 4.7 Hz, 2-CH3); δ 13C (CDCl3) 158.6 (C-5'), 138.0 (C-2'), 130.3 (C-3') 123.7 (C-1'), 114.5 and 112.9 (C-4', C-6'), 102.2 (C-2), 81.5 and 80.4 (C-4 and C-5), 55.5 (OCH3), 20.8 (CH3-2), 17.5 (CH3-5); m/z 244 (M+{37Cl}, 2%), 242 (M+{35Cl}, 4), 198 (28), 169 (19), 167 (33), 154 (14), 119 (15), 77 (16), 72 (80), 42 (100); and
dioxolanes (202) (95%) and (201) (5%) as a colourless oil (40 mg, 21%) δH (CDCl3) 7.24 (1H, d, J 8.8 Hz, 3'-H), 7.14 (1H, d, J 3.1 Hz, 6'-H), 6.78 (1H, dd, J 8.8 and 3.1 Hz, 4'-H), 5.42 (1H, q, J 4.8 Hz, 2-H), 5.02 (1H, d, J 5.4 Hz, 4-H), 4.03 (1H, dq, J 5.4 and 6.5 Hz, 5-H), 3.80 (3H, s, OCH3), 1.54 (3H, d, J 4.8 Hz, 2-CH3), 1.43 (3H, d, J 6.5 Hz, 5-CH3); mass spectral fragmentation pattern identical to isomer (201).

rel-[1S,3R,4R]-5-Chloro-4-hydroxy-8-methoxy-1,3-dimethylisochroman (203) and rel-[1R,3R,4R]-5-Chloro-4-hydroxy-8-methoxy-1,3-dimethylisochroman (204)

Titanium tetrachloride (47.0 µl, 0.4 mmol) was added to a stirred solution of 2; 1 mixture of dioxolanes (201) and (202) (50 mg, 0.2 mmol) in dry dichloromethane (60 ml) at -78 °C in an atmosphere of argon. After 30 minutes, the reaction was quenched with methanol (0.1 ml). The resultant solution was neutralised with saturated aqueous sodium bi carbonate solution, washed with water, dried and evaporated. The crude residue obtained was analysed by g.c. and 1H-n.m.r. spectroscopy which indicated a 1:1.7 diastereomeric mixture of isochromans (203) and (204). Chromatography of this mixture on silica gel using 4:1 hexane/ethyl acetate afforded two compounds;

isochroman (203) as a colourless oil (13 mg, 26%). (Found: C, 59.35; H, 6.4; Cl, 14.95. C12H15ClO3 requires C, 59.4; H, 6.2; Cl, 14.6%); δH (CDCl3) 7.28 (1H, d, J 8.8 Hz, 6-H), 6.78 (1H, d, J 8.8 Hz, 7-H), 4.93 (1H, q, J 6.2 Hz, 1-H), 4.56 (1H, d, J 1.2 Hz, 4-H), 3.81 (3H, s, OCH3), 3.68 (1H, dq, J 1.2 and 6.3 Hz, 3-H), 1.56 (3H, d, J 6.2 Hz, 1-CH3), 1.40 (3H, d, J 6.3 Hz, 3-CH3); δ 13C (CDCl3) 154.7 (C-8),
isochroman (204) as a white solid (25 mg, 50%), m.p. 107-108 °C. (Found: C, 59.7; H, 6.4; Cl, 14.4. C\textsubscript{12}H\textsubscript{15}ClO\textsubscript{3} requires C, 59.4; H, 6.2; Cl, 14.6%); \(\delta\textsubscript{H} (\text{CDCl}_3)\) 7.28 (1H, d, J 8.8 Hz, 6-H), 6.75 (1H, d, J 8.8 Hz, 7-H), 5.09 (1H, q, J 6.6 Hz, 1-H), 4.50 (1H, d, J 1.7 Hz, 4-H), 4.11 (1H, dq, J 1.7 and 6.5 Hz, 3-H), 3.81 (3H, s, OCH\textsubscript{3}), 1.48 (3H, d, J 6.6 Hz, 1-CH\textsubscript{3}), 1.40 (3H, d, J 6.5 Hz, 3-CH\textsubscript{3}); \(\delta\textsubscript{13C} (\text{CDCl}_3)\) 153.9 (C-8), 133.9 (C-5), 129.7 (C-4a), 128.1 (C-6), 126.0 (C-8a), 110.6 (C-7), 68.5, 66.2 and 65.0 (C-1, C-3, C-4), 55.4 (OCH\textsubscript{3}), 17.8 (CH\textsubscript{3}-1), 16.9 (CH\textsubscript{3}-3); m/z 244 (M\textsuperscript{+}(\text{37Cl}), 4%), 242 (M\textsuperscript{+}(\text{35Cl}), 11), 227 (35), 209 (38), 200 (22), 198 (68), 42 (100).

Another sample of a 2.6:1 mixture of dioxolanes (201) and (202) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -95 °C for 60 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -95 °C. The crude residue was analysed by g.c and g.c.-mass spectroscopy which indicated retention times of 15.46 and 16.12 minutes for the two isochroman isomers (203) and (204) respectively. The results of the g.c. and \textsuperscript{1}H-n.m.r. spectral analysis are given in the Table 3.1.

**Isomerisation of dioxolane (201)**

To a stirred solution of dioxolane (201) (100 mg, 0.41 mmol) in dry dichloromethane (66 ml) was added titanium tetrachloride (75.2 µl, 0.80 mmol) at -95 °C in an atmosphere of argon. Two portions (5 ml each) of reaction mixture were syringed out and immediately quenched with methanol (0.1 ml) after 2 minutes and 12 minutes. The rest of the reaction mixture was warmed to -78 °C and kept for 30 minutes and then quenched with methanol (0.1 ml).
Another sample of dioxolane (201) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -95 °C for 60 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -95 °C.

Once again a sample of dioxolane (201) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C for 2 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C. This procedure was repeated under the following temperature and time conditions:

a) at -78 °C for 30 minutes;
b) at -78 °C for 30 minutes and at 0 °C for 30 minutes;
c) at -78 °C for 30 minutes, at 0 °C for 30 minutes and at room temperature for 60 minutes; and
d) dioxolane (201) (15 mg, 0.06 mmol) in dichloromethane (20 ml) at -78 °C for 30 minutes.

All the samples were neutralised with saturated aqueous sodium bicarbonate solution, washed with water, dried and evaporated. The crude residues were analysed by g.c. and g.c.-mass spectroscopy which indicated retention times of 15.46 and 16.12 minutes for the two isochroman isomers (203) and (204) respectively. The results of the g.c. and 1H-n.m.r. spectral analysis are given in the Table 3.2.

**Isomerisation of isochroman (203)**

Isochroman (203) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was treated with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C. After 2 minutes the temperature of the reaction mixture was warm up 0 °C and stirred for 30 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at 0 °C. The crude residue was analysed by g.c. and g.c.-mass spectroscopy which
indicated retention time of 15.46 minutes for isochroman (203). The $^1$H-n.m.r. spectral data were entirely consistent with those observed for isochroman (203).

**Isomerisation of dioxolane (202)**

To a stirred solution of dioxolane (202) (15 mg, 0.06 mmol) in dry dichloromethane (10 ml) was added titanium tetrachloride (14.1 µl, 0.12 mmol) at -95 °C in an atmosphere of argon and stirred for 12 minutes. The resultant solution was quenched with methanol (0.1 ml) at -95 °C.

Another sample of dioxolane (202) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -95 °C for 60 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -95 °C.

Once again a sample of dioxolane (202) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C for 5 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C. This procedure was repeated under the following temperature and time conditions:

a) at -78 °C for 30 minutes;

b) dioxolane (201) (15 mg, 0.06 mmol) in dichloromethane (20 ml) at -78 °C for 30 minutes.

All the samples were neutralised with saturated aqueous sodium bicarbonate solution, washed with water, dried and evaporated. The crude residues were analysed by g.c and g.c.-mass spectroscopy which indicated retention times of 15.46 and 16.12 minutes for two isochroman isomers (203) and (204) respectively. The results of g.c, g.c.-mass and $^1$H-n.m.r. spectroscopic analyses are given in Table 3.3.
Titanium tetrachloride (47.0 µl, 0.40 mmol) was added to a stirred solution of dioxolane (199) (50 mg, 0.20 mmol) in dry dichloromethane (33 ml) at -95 °C in an atmosphere of argon. After 15 minutes, a portion (10 ml) of reaction mixture was syringed out and immediately quenched with methanol (0.1 ml). The rest of the reaction mixture was kept at -95 °C for 60 minutes and then quenched with methanol (0.1 ml).

Another sample of dioxolane (199) (15 mg, 0.06 mmol) in dichloromethane (10 ml) was stirred with titanium tetrachloride (14.1 µl, 0.12 mmol) at -78 °C for 30 minutes in an atmosphere of argon. The resultant solution was quenched with methanol (0.1 ml) at -78 °C. This procedure was repeated under the same conditions, but at low concentration of dioxolane; i.e. the dioxolane (199) (15 mg, 0.06 mmol) in dichloromethane (20 ml). All the samples were neutralised with saturated aqueous sodium bicarbonate solution, washed with water, dried and evaporated. The crude residues were analysed by g.c. and 1H-n.m.r. spectroscopy which indicated a mixture of diol (198), dioxolane (199) and isochroman (207) (see Table 3.4). These crude residues obtained at -78 °C were combined and purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to afford isochroman (207) as a white solid (23 mg, 75%), m.p. 108-110 °C, (Found: C, 59.2; H, 6.0; Cl, 14.9. C_{12}H_{15}ClO_{3} requires C, 59.4; H, 6.2; Cl, 14.6%); δ_{H} (CDCl_{3}) 7.25 (1H, d, J 8.8 Hz, 6-H), 6.75 (1H, d, J 8.8 Hz, 7-H), 4.96 (1H, q, J 6.3 Hz, 1-H), 4.57 (1H, d, J 6.0 Hz, 4-H), 4.16 (1H, dq, J 6.0 and 6.5 Hz, 3-H), 3.81 (3H, s, OCH_{3}), 1.56 (3H, d, J 6.3 Hz, 1-CH_{3}), 1.27 (3H, d, J 6.5 Hz, 3-CH_{3}); δ^{13}C (CDCl_{3}) 153.9 (C-8), 133.0 (C-5), 130.5 (C-4a), 128.2 (C-6), 125.7 (C-8a), 110.5 (C-7), 69.9, 68.3 and 66.2 (C-1, C-3, C-4), 55.4 (OCH_{3}), 19.6 (CH_{3}-3), 17.6 (CH_{3}-1); m/z 244 (M+ [^{37}Cl], 8%), 242 (M+ [^{35}Cl], 24), 229 (35), 227 (100), 211 (13), 209 (34), 198 (58), 183 (56), 169 (29).
Following the procedure of Beckwith and Goh\(^{13}\), a mixture of isochroman (204) (10 mg, 0.04 mmol), di-\(t\)-butyl peroxide (DTBP) (4 \(\mu l\), 0.02 mmol) and lithium aluminium hydride (50 mg) in dry tetrahydrofuran (10 ml) was irradiated with a 250 W high-pressure Hg lamp for 5 h, cooled, diluted with aqueous hydrochloric acid and extracted with ether. The organic extracts were dried and evaporated to give a colourless oil (5 mg, 58\%) which was analysed by g.c.-mass and \(^1\)H-n.m.r. spectroscopy, \(\delta\)\(_H\) (CDCl\(_3\)) 7.25 (1H, dd, J 8.8 and 8.8 Hz, 6-H), 7.00 and 6.80 (1H, d, J 8.8 Hz, 5-H and 7-H), 5.09 (1H, q, J 6.6 Hz, 1-H), 4.18 (1H, d, J 1.7 Hz, 4-H), 4.11 (1H, dq, J 1.7 and 6.5 Hz, 3-H), 3.81 (3H, s, OCH\(_3\)), 1.50 (3H, d, J 6.6 Hz, 1-CH\(_3\)), 1.45 (3H, d, J 6.5 Hz, 3-CH\(_3\)); \(m/z\) 208 (M\(^+\), 15\%), 193 (27), 175 (45), 164 (100).
Experimental: Chapter 4

trans-4-(3',5'-Dimethoxyphenyl)-3-butenoic acid (212)

3,5-dimethoxybenzaldehyde (5.2 g, 30 mmol) in dry tetrahydrofuran (100 ml) was added in portions to a stirred solution of 3-triphenylphosphoniumpropanoic acid chloride\(^1\) (12.5 g, 30 mmol) in dry dimethyl sulphoxide (100 ml) at room temperature. The mixture was cooled to 0 °C and sodium hydride (1.0 g, 60% dispersion in oil) was added in portions. The reaction was allowed to warm to room temperature and stirred continuously for 14 h. A solution of sodium hydroxide (10%) was added and this aqueous solution was first washed with toluene (5 x 100 ml) then with diethyl ether (2 x 100 ml). The aqueous solution was acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 150 ml). The combined organic extracts were washed with dilute hydrochloric acid, dried and evaporated to give a brown oil (4 g).

This was purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give the unreacted aldehyde (191) (1.5 g, 29%) and the title compound (212) as a yellow oil (3.50 g, 50%), crystallised from dichloromethane, m.p. 53-54 °C. (Found: C, 64.9; H, 6.5. \(\text{C}_{12}\text{H}_{14}\text{O}_{4}\) requires C, 64.9; H, 6.4%); \(\lambda_{\text{max}}\) nm (MeOH) 250 (log \(\varepsilon\) 4.3), 300 (log \(\varepsilon\) 3.4); \(\nu_{\text{max}}\) (neat) 1710 (COOH), 1653 (C=C), 1596 cm\(^{-1}\) (1,3,5-trisubstituted benzene); \(\delta_{\text{H}}\) (CDCl\(_3\)) 6.53 (2H, d, J 2.2 Hz, 2' and 6'-H), 6.45 (1H, dt, J 15.9 and 1.5 Hz, 4-H), 6.38 (1H, t, J 2.2 Hz, 4'-H), 6.27 (1H, dt, J 15.9 and 7.2 Hz, 3-H), 3.80 (6H, s, 2 x OCH\(_3\)), 3.30 (2H, dd, J 7.2 and 1.5 Hz, 2-CH\(_2\)); \(\delta\) \(^{13}\text{C}\) (CDCl\(_3\)) 177.6 (C-1), 160.8 (C-3' and C-5'), 138.6 (C-1'), 133.9 (C-4), 121.4 (C-3), 104.4 (C-2' and C-6'), 100.0 (C-4'), 55.3 (2 x CH\(_3\)O), 37.9 (C-2); \(m/z\) 222 (M\(^{+}\), 82%), 182 (31), 177 (100), 168 (46), 161 (22), 147 (22), 146 (24), 139 (28), 109 (26), 103 (21), 91 (43), 79 (21), 77 (49), 69 (29).
Methyl trans-4-(3',5'-Dimethoxyphenyl)-3-butenoate (213)

Phenylbutenoic acid (212) (1.70 g, 7 mmol) in dry dichloromethane (15 ml) was treated with oxalyl chloride (1.0 g, 8 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred continuously for 2 h. The mixture was then heated under reflux for 12 h and the solvent was removed by distillation under reduced pressure. This product was stirred for 2 h with methanol (20 ml) which was removed by distillation under reduced pressure to afford the crude ester (1.7 g). This was purified by chromatography on silica gel using 6:1 hexane/ethyl acetate as eluent to give the title compound (213) as a yellow oil (1.50 g, 83%). (Found: C, 66.2; H, 6.9. C_{13}H_{16}O_{4} requires C, 66.1; H 6.8%). δ_{H} (CDCl_{3}) 6.53 (2H, d, J 2.2 Hz, 2' and 6'-H), 6.45 (1H, dt, J 15.9 and 1.5 Hz, 4-H), 6.38 (1H, t, J 2.2 Hz, 4'-H), 6.27 (1H, dt, J 15.9 and 7.2 Hz, 3-H), 3.80 (6H, s, 2 x OCH_{3}), 3.72 (3 H, s, COOCH_{3}), 3.25 (2H, dd, J 7.2 and 1.5 Hz, 2-CH_{2}); δ_{13}C (CDCl_{3}) 171.8 (C=O), 160 (C-3' and C-5'), 138.7 (C-1'), 134.4 (C-4), 122 (C-3), 104 (C-2' and C-6'), 99.8 (C-4'), 55.2 (2 x OCH_{3}), 51.8 (COOCH_{3}), 38.0 (C-2); m/z 236 (M^+, 49%), 177 (100), 176 (54), 161 (21), 146 (23), 91 (36), 77(26), 65 (24), 59 (25).

rel-[4R,5R]-2,3,4,5-Tetrahydro-4-hydroxy-5-(3',5'-Dimethoxyphenyl)-2H-furan-2-one (215a)

Olefin ester (213) (1.50 g, 6.3 mmol) in acetone (20 ml) was added to a solution of osmium tetroxide (5 mg) and 4-methylmorpholine-N-oxide (0.85 g, 7.3 mmol) in water at 0 °C. The reaction was allowed to warm to room temperature and was stirred continuously for 18 h. Acetone was removed under reduced pressure. The aqueous solution was acidified with dilute hydrochloric acid (2 M, 20 ml). The organic materials were extracted into ethyl acetate (5 x 50 ml), and the combined extracts were washed with water (3 x 100 ml), dried, filtered, and solvent removed by the distillation under reduced pressure to give a light brown oil (1.4 g). This was purified by chromatography on silica gel using 3:2 hexane/ethyl acetate as eluent to afford two compounds: the title compound
(215a) as a colourless oil (1.32 g, 87%). (Found: C, 60.5; H, 6.1. C₁₂H₁₄O₅ requires C, 60.5; H, 5.9%); νmax (neat) 3467 (OH), 1776 (C=O, lactone), 1599 cm⁻¹ (1,3,5-trisubstituted benzene), δH (CDCl₃) 6.50 (2H, d, J 2.2 Hz, 2' and 6'-H), 6.43 (1H, t, J 2.2 Hz, 4'-H), 5.42 (1H, d, J 3.8 Hz, 5-H), 4.58 (1H, dt, J 3.8 and 5.4 Hz, 4-H), 3.78 (6H, s, 2 x OCH₃), 2.85 (1H, dd, J 17.5 and 5.4 Hz, 3-H), 2.70 (1H, d, J 17.5 Hz, 3-H); δ¹³C (CDCl₃) 175.2 (C-2), 161.2 (C-3' and C-5'), 135.1 (C-1'), 103.8 (C-2' and C-6'), 100.8 (C-4'), 85.1 (C-5), 70.1 (C-4), 55.5 (2 x OCH₃), 38.5 (C-3); m/z 238 (M⁺, 24%), 167 (43), 166 (100), 139 (36), 135 (14), 109 (33), 77 (20); and Compound (215b) as a brown solid (80 mg, 5%), which was crystallised from dichloromethane, m.p. 120-121 °C. δH (CDCl₃) 6.47 (2H, d, J 2.2 Hz, 2' and 6'-H), 6.43 (1H, t, J 2.2 Hz, 4'-H), 5.30 (1H, d, J 3.7 Hz, 5-H), 4.47 (1H, m, 4-H), 3.81 (6H, s, 2 x OCH₃), 2.89 (1H, dd, J 17.8 and 6.6 Hz, 3-H), 2.60 (1H, dd, J 17.8 and 4.7 Hz, 3-H); m/z 238 (M⁺, 43%), 167 (47), 166 (100), 139 (33), 135 (14), 109 (18), 77 (15).

rel-(2S,4R,5R)-5-Carbomethoxymethyl-4-(3',5'-dimethoxyphenyl)-2-methyl-1,3-dioxolane (216) and rel-(2R,4R,5R)-5-Carbomethoxymethyl-4-(3',5'-dimethoxyphenyl)-2-methyl-1,3-dioxolane (217)

Lactone (215a) (500 mg, 2.1 mmol) in dry dichloromethane (100 ml) was treated with 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (+)-camphorsulphonic acid (10 mg, 0.043 mmol). The mixture was then heated under reflux for 72 h. The reaction was quenched with saturated sodium bicarbonate solution (5 ml), poured into cold water and extracted with dichloromethane (3 x 100 ml). These combined extracts were dried (MgSO₄), filtered and the solvent removed by distillation under reduced pressure to give a colourless oil. This oil was chromatographed on silica gel using 4:1 hexane/ethyl acetate as eluent to afford a 1:3:1 diastereomeric mixture of the dioxolanes (216) and (217) as a colourless oil (436 mg, 70%). (Found: C, 61.0; H, 6.9. C₁₅H₂₀O₆ requires C, 60.8; H, 6.8%), δH (CDCl₃) 6.55 and 6.49 (each 2 H, d, J 2.0 Hz, 2' and 6'-H of both isomers), 6.40 (2H, t, J 2.0 Hz, 4'-H of both isomers), 5.46 and 5.35 (each 1H, q,
J 4.9 Hz, 2-H of each isomer), 4.59 and 4.57 (each 1 H, d, J 6.6 Hz, 4-H of each isomer), 4.27 (2H, m, 5-H of both isomers), 3.80 (12H, s, OCH3 of both isomers), 3.67 (6H, s, COOCH3 of both isomers), 2.68 (4H, m, CH2 of both isomers), 1.55 and 1.45 (each 3H, d, J 4.9 Hz, 2-CH3 of each isomer); m/z 296 (M+, 8%), 193 (22), 179 (43), 165 (18), 151 (32), 87 (30), 77 (24), 59 (100), and compound (218) with lower Rf was obtained as a white powder (34 mg, 7%). The 1H-n.m.r. and mass spectral analyses are given below. Further chromatography on the mixture of dioxolanes (216) and (217) (100 mg) in 5:1 hexane/ethyl acetate afforded the single diastereomer (216) (20 mg, 20%); 6H (CDCl3) 6.53 (2H, d, J 2.2 Hz, 2’ and 6’-H), 6.41 (1H, t, J 2.2 Hz, 4’-H), 5.38 (1H, q, J 4.9 Hz, 2-H), 4.60 (1H, d, J 6.9 Hz, 4-H), 4.26 (1H, dt, 17.0 and 6.9 Hz, 5-H), 3.79 (6H, s, 2 x OCH3), 3.67 (3H, s, COOCH3), 2.67 (2H, dd, J 17.5 and 4.7 Hz, 3-H), 1.51 (3H, d, J 4.9 Hz, 2-CH3). The 1H-n.m.r. spectrum of diastereomer (217) showed about 25% contamination of isomer (216).


Phenyldioxolanes (216) and (217) (100 mg, 0.34 mmol) in dry dichloromethane (15 ml) were treated with (+)-camphorsulphonic acid (20 mg, 0.086 mmol) and heated under reflux for 18 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (1 ml) and extracted with dichloromethane (3x10 ml). The combined organic extracts were dried, filtered and concentrated to give a colourless solid (90 mg). This was purified by chromatography on silica gel using 3:2 hexane/ethyl acetate as eluent to afford a 6.8:1 mixture of γ-lactonopyrans (218) and (219) as a colourless oil (80 mg, 86%). The above reaction was repeated using dioxolanes (216) and (217) (100 mg, 0.34 mmol) in dry dichloromethane (15 ml). were treated with (+)-camphorsulphonic acid (300 mg, 1.29 mmol) and heated under reflux for 18 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (1 ml) and extracted with
dichloromethane (3x10 ml) The crude residue obtained was analysed by g.c.-mass and 
$^1$H-n.m.r. spectroscopy which indicated a 1:3.6 mixture of $\gamma$-lactonopyrans (218) and (219) as a colourless oil (82 mg, 89%); see Table 4.1. This mixture was separated by 
HPLC using 4:1 hexane/tetrahydrofuran as eluent to afford two compounds: compound 
(218) (15 mg, 18%), which was crystallised from dichloromethane/hexane, m.p. 138-
140 °C. (Found: C, 63.3; H, 6.1. C$_{14}$H$_{16}$O$_5$ requires C, 63.6; H, 6.1%), $\nu$$_{\text{max}}$ (KBr 
disc) 1781 (C=O), 1600 (C=C ring), 1280 (C-O-C five membered ring), 1244 (C-O-C 
six membered ring); $\delta$$_H$ (CDCl$_3$) 6.58 (1H, d, J 2.3 Hz, 9-H), 6.48 (1H, d, J 2.3 Hz, 
7-H), 5.07 (1H, d, J 2.5 Hz, 9b-H), 4.79 (1H, q, J 6.5 Hz, 5-H), 4.35 (1H, dd, J 2.5 
and 4.6 Hz, 3a-H), 3.82 (3-H, s, OCH$_3$), 3.80 (3-H, s, OCH$_3$), 2.88 (1H, dd, J 17.5 
and 4.6 Hz, 3-H), 2.74 (1H, d, J 17.5 Hz, 3-H), 1.56 (3H, d, J 6.5 Hz, 5-CH$_3$); $\delta$$_{13}$C 
(CDCl$_3$) 175.3 (C-2), 159.4 and 157.1 (C-8, C-6), 129.1 (C-9a), 121.8 (C-5a), 105.6 
(C-9), 100.4 (C-7), 76.9, 70.9 and 69.8 (C-3a, C-5, C-9b), 55.5 (OCH$_3$), 55.3 
(OCH$_3$), 38.3 (C-3), 21.3 (CH$_3$); and 
compound (219) (47 mg, 57%), which was crystallised from dichloromethane-
hexane, m.p. 127-128 °C. (Found: C, 63.7; H, 6.3. C$_{14}$H$_{16}$O$_5$ requires C, 63.6; H, 
6.1%); $\nu$$_{\text{max}}$ (KBr disc) 1780 (C=O), 1612 (C=C ring), 1279 (C-O-C five membered 
ring), 1205 (C-O-C six membered ring); $\delta$$_H$ (CDCl$_3$) 6.58 (1H, d, J 2.1 Hz, 9-H), 6.46 
(1H, d, 2.1 Hz, 7-H), 5.10 (1H,q, J 6.6 Hz, 5-H), 5.01 (1H, d, J 3.0 Hz, 9b-H), 4.77 
(1H, dd, J 5.4 and 3.0 Hz, 3a-H), 3.82 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 2.99 (1H, 
dd, J 17.8 and 5.4 Hz, 3-H), 2.69 (1H, d, J 17.8 Hz, 3-H), 1.46 (3H, d, J 6.6 Hz, 5-
CH$_3$); $\delta$$_{13}$C (CDCl$_3$) 174.8 (C-2), 159.6 and 155.9 (C-6, C-8), 128.2 (C-5a), 121.6 
(C-9a), 104.9 (C-9), 99.7 (C-7) 75.5, 67.3 and 65.8 (C-3a, C-5, C-9b), 55.4 (2x 
OCH$_3$), 37.7 (C-3), 18.5 (CH$_3$); m/z 264 (M$^+$,10%), 249 (100), 221 (2), 193 (3), 177 
(7), 162 (10), 71 (15), 63 (11);
Methyl 4-hydroxy-6,8-dimethoxy-1-methylisochroman-3-ylacetate (226) and dihydroisobenzofuran (227)

To a stirred solution of 1.3:1 mixture of dioxolanes (216) and (217) (50 mg, 0.17 mmol) in dry dichloromethane (25 ml) was added titanium tetrachloride (0.05 ml, 0.34 mmol) at -78 °C. The temperature of the reaction mixture was brought to -30 °C and stirred for 30 minutes. The resulting reaction mixture was quenched with methanol (0.1 ml) and saturated aqueous sodium bicarbonate (2 ml) and then poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil. This was analysed by g.c., g.c.-mass and 1H-n.m.r. spectroscopy, which indicated a mixture of three compounds; dioxolanes (216) and (217) with retention time at 11.5 minutes (55%) (the 1H-n.m.r. and g.c.-mass spectra were in agreement with those of the starting dioxolanes): isochroman (226) with retention time 12.7 (15%); g.c.-mass spectrum m/z 296 (13), 281 (100), 221 (6); and dihydroisobenzofuran (227) with retention time 12.5 (25%). The above reaction was repeated using solution of 1.3:1 mixture of dioxolanes (216) and (217) (50 mg, 0.17 mmol) in dry dichloromethane (25 ml) at room temperature for 2 h. The crude residue (40 mg) obtained was analysed by g.c., g.c.-mass and 1H-n.m.r. spectroscopy, which indicated dihydroisobenzofuran isomer (227) δH (CDCl3) 6.43 (1H, d, J 2.5 Hz, 4-H), 6.36 (1H, d, J 2.5 Hz, 6-H), 5.40 (1H, dq, J 2.9 and 6.2 Hz, 1-H), 5.25 (1H, dd, J 2.9 and 5.5 Hz, 3-H), 4.31 (1H, m, 3'-H), 3.82 (3H, s, OCH3), 3.80 (3H, s, OCH3), 3.71 (1H, m, CH(OH)CH2), 3.70 (3H, s, COOCH3), 2.57 (2H, m, -CH2), 1.45 (3H, d, J 6.2 Hz, 1-CH3); m/z 296 (M+, 4%), 278 (21), 193 (100), 151 (7). Attempted chromatography of crude dihydroisobenzofuran (227) on silica gel or neutral alumina was not successful.

trans-4-(2'-Chloro-5'-methoxyphenyl)-3-butenolic acid (230)

2-Chloro-5-methoxybenzaldehyde (191) (3.0 g, 17.6 mmol) in dry tetrahydrofuran (100 ml) was added to a stirred solution of 3-triphenylphosphonium
propanoic acid chloride\textsuperscript{14} (7.5 g, 18.0 mmol) in dry dimethyl sulphoxide (100 ml). The mixture was cooled to 0 °C and sodium hydride (0.50 g, 60% dispersion in oil) was added in portions. The reaction was allowed to warm to room temperature and stirred continuously for 14 h. A solution of sodium hydroxide (10%) was added and the solution washed with toluene (5 x 100 ml) and diethyl ether (2 x 100 ml). The aqueous solution was acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 150 ml). The combined organic extracts were washed with dilute hydrochloric acid, dried and evaporated to give a brown oil (3 g). This was purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to afford the unreacted aldehyde (191) (1.0 g, 33%) and the title compound (230) as a yellow oil (1.7 g, 50%), which was crystallised from dichloromethane, m.p. 92-94 °C. (Found: C, 58.2; H, 4.8; Cl, 15.7. C\textsubscript{11}H\textsubscript{11}ClO\textsubscript{3} requires C, 58.3; H, 4.9; Cl, 15.6%); \textnu\textsubscript{max} (neat) 1710 (COOH), 1653 (C=C), 1596 cm\textsuperscript{-1} (1,3,5-trisubstituted benzene); \delta\textsubscript{H} (CDCl\textsubscript{3}) 7.23 (2H, d, J 8.8 Hz, 3'-H), 7.06 (1H, d, J 3.0 Hz, 6'-H), 6.88 (1H, dt, J 15.8 and 1.5 Hz, 4-H), 6.76 (1H, dd, J 8.8 and 3.0 Hz, 4'-H), 6.29 (1H, dt, J 15.8 and 7.2 Hz, 3-H), 3.81 (3H, s, OCH\textsubscript{3}), 3.37 (2H, dd, J 7.1 and 1.5 Hz, CH\textsubscript{2}); \delta\textsuperscript{13C} (CDCl\textsubscript{3}) 177.8 (C-1), 158.3 (C-5'), 135.3 (C-2'), 130.2 (C-1'), 124.5 and 123.7 (C-3, C-4), 114.9 (C-4' and C-6'), 111.6 (C-3'), 55.5 (CH\textsubscript{3}O), 38.0 (C-2); \textit{m/z} 228 (M\textsuperscript{+}\{\textsuperscript{37}Cl\}, 21%), 226 (M\textsuperscript{+}\{\textsuperscript{35}Cl\}, 65), 186 (29), 181 (45), 146 (100), 145 (47), 131 (30), 115 (45), 103 (49), 102 (24), 77 (51), 63 (49).

\textbf{Methyl trans-4-(2'-Chloro-5'-methoxyphenyl)-3-butenoate (231)}

Phenylbutenoic acid (230) (1.7 g, 7.50 mmol) in dry dichloromethane (15 ml) was treated with oxalyl chloride\textsuperscript{15} (1.0 g, 8.0 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 2 h. The mixture was then heated under reflux for 12 h, the solvent removed by distillation under reduced pressure and the residue stirred with methanol (20 ml) for 2 h. Methanol was removed by distillation under reduced pressure to afford a crude ester (1.7 g). This was purified by chromatography on silica gel using 6:1 hexane/ethyl acetate as eluent to give the title...
compound (231) as a yellow oil (1.5 g, 83%). (Found: C, 59.5; H, 5.7; Cl, 14.9. C_{12}H_{13}ClO_3 requires C, 59.8; H, 5.4; Cl, 14.7%); δ_H (CDCl_3) 7.25 (2H, d, J 8.8 Hz, 3'-H), 7.06 (1H, d, J 3.0 Hz, 6'-H), 6.83 (1H, dd, J 15.8 and 1.5 Hz, 4-H), 6.73 (1H, dd, J 8.8 and 3.0 Hz, 4'-H), 6.29 (1H, dt, J 15.8 and 7.1 Hz, 3-H), 3.80 (3H, s, OCH_3), 3.73 (3H, s, COOCH_3), 3.31 (2H, dd, J 7.1 and 1.5 Hz, CH_2); δ^{13}C (CDCl_3) 171.1 (C-1), 158.2 (C-5'), 135.5 (C-2'), 130.2 and 129.4 (C-4, C-3), 124.5 (C-1'), 114.8 (C-4' and C-6'), 111.5 (C-3'), 55.5 (CH_3O), 51.9 (COOCH_3), 38.0 (C-2); m/z 242 (M+^{37}Cl, 21%), 240 (M+^{35}Cl, 63), 183 (21), 181 (68), 146 (100), 145 (39), 131 (28), 115 (33), 103 (47), 102 (23), 77 (34), 51 (30).

rel-[4R,5R]-2,3,4,5-Tetrahydro-4-hydroxy-5-(2'-Chloro-5'-methoxyphenyl)-2H-furan-2-one (232)

Olefin ester (231) (600 mg, 2.49 mmol) in acetone (10 ml) was added to a solution of osmium tetroxide (5 mg) and 4-methylmorpholine-N-oxide (540 mg, 4.60 mmol) in water (30 ml) at 0°C. The reaction was allowed to warm to room temperature and stirred continuously for 18 h. Acetone was removed under reduced pressure. The aqueous solution was acidified with dilute hydrochloric acid (2 M, 20 ml). The organic materials were extracted into ethyl acetate (5 x 50 ml) and the combined extracts were washed with water (3 x 100 ml), dried, filtered and the solvent removed by distillation under reduced pressure to give a light brown oil (1.4 g). This was purified by chromatography on silica gel using 3:2 hexane/ethyl acetate as eluent to afford the title compound (232) as a colourless oil (450 mg, 75%). (Found: C, 54.6; H, 4.8; Cl, 14.7. C_{11}H_{11}ClO_3 requires C, 54.45; H, 4.6; Cl, 14.6%); ν_{max} (KBr disc) 3525 (OH), 1770 (C=O, lactone), 1596 cm^{-1}(1,3,5-trisubstituted benzene); δ_H (CDCl_3) 7.29 (1H, d, J 8.8 Hz, 3'-H), 7.10 (1H, d, J 3.1 Hz, 6'-H), 6.86 (1H, dd, J 8.8 and 3.1 Hz, 4'-H), 5.76 (1H, d, J 3.4 Hz, 5-H), 4.93 (1H, dt, J 3.4 and 5.4 Hz, 4-H), 3.80 (3H, s, OCH_3), 2.96 (2H, dd, J 17.6 and 5.4 Hz, 3-H), 2.72 (1H, d, J 17.6 Hz, 3-H); δ^{13}C (CDCl_3) 174.9 (C-1), 158.7 (C-5'), 131.9 (C-2'), 130.3 (C-3'), 121.9 (C-1'), 116.4 and 113.2 (C-4', C-6'), 82.6 (C-
Lactone (232) (600 mg, 2.48 mmol) in dry dichloromethane (100 ml) was treated with 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (+)-camphorsulphonic acid5 (10 mg, 0.043 mmol). The mixture was then heated under reflux for 72 h. The reaction was quenched with saturated sodium bicarbonate solution (5 ml), poured into cold water and extracted with dichloromethane (3 x 100 ml). These combined extracts were dried, filtered and the solvent removed by distillation under reduced pressure to give a colourless oil. This oil was chromatographed on silica gel using 4:1 hexane/ethyl acetate as eluent to afford unreacted hydroxy lactone (232) (40 mg, 10%) and a 1:1 diastereomeric mixture of the dioxolanes (233) and (234) as a colourless oil (550 mg, 81%). (Found: M+ 44, 256.0502, C12H13ClO4 requires M+ 44, 256.0502); δH (CDCl3) 7.23 (2H, d, J 9.1 Hz, 3'-H of both isomers), 7.14 and 7.05 (each 1H, d, J 3.1 Hz, 6'-H of each isomer), 6.78 (2H, dd, J 9.1 and 3.1 Hz, 4'-H of both isomers), 5.53 and 5.38 (each 1H, q, J 4.9 Hz, 2-H of each isomer), 5.11 (2H, d, J 6.9 Hz, 4-H of both isomers), 4.31 (2H, m, 5-H of both isomers), 3.80 (6H, s, OCH3 of both isomers), 3.60 (6H, s, COOCH3 of both isomers), 2.80 (4H, m, CH2 of both isomers); m/z 302 (M+{37Cl}, 2%), 300 (M+{35Cl}, 6), 265 (8), 258 (15), 256 (47), 226 (25), 197 (18), 183 (22), 169 (45), 167 (57), 155 (36), 119 (28), 91 (25), 77 (23), 59 (100).

rel-[1S,3R,4R]-Methyl 5-chloro-4-hydroxy-8-methoxy-1-methylisochroman-3-ylacetate (235)

To a stirred solution of dioxolanes (233) and (234) (250 mg, 1.03 mmol) in dichloromethane (40 ml) was added titanium tetrachloride (0.23 ml, 2.06 mmol) at 0 °C in an atmosphere of argon. After stirring at room temperature for 5 h, the resulting solution
was quenched with saturated aqueous sodium bicarbonate (2 ml) and the resultant mixture poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a colourless oil. This was analysed by g.c. and g.c.-mass spectroscopy, which indicated a mixture of two compounds which was purified by chromatography on silica gel using 3:2 hexane/ethyl acetate as eluent to give two compounds: compound (235) as a colourless oil (160 mg, 64%). (Found: C, 55.9; H, 5.9; Cl, 11.9 C_{14}H_{17}ClO_5 requires C, 55.9; H, 5.7; Cl, 11.8 %); δ_H (CDCl_3) 7.26 (1H, d, J 8.8 Hz, 6-H), 6.78 (1H, d, J 8.8 Hz, 7-H), 4.94 (1H, q, J 6.2 Hz, 1-H), 4.69 (1H, d, J 1.3 Hz, 4-H), 4.02 (1H, dt, J 1.3 and 7.1 Hz, 3-H), 3.80 (3H, s, OCH_3), 3.72 (3H, s, COOCH_3), 2.84 (2H, dd, J 1.3 and 7.1 Hz, CH_2), 1.54 (3H, d, J 6.2 Hz, 1-CH_3); m/z 302 (M^+{^{37}Cl}, 2%), 300 (M^+{^{35}Cl} 6), 287 (5) 285 (15), 253 (10), 225 (12), 209 (18), 200 (32), 198 (100), 183 (27), 169 (36); and diol ester (236) as a colourless oil (30 mg, 12%), δ_H (CDCl_3) 7.24 (1H, d, J 8.8 Hz, 3'-H), 7.10 (1H, d, J 3.0 Hz, 6'-H), 6.79 (1H, dd, J 8.8 and 3.0 Hz, 4'-H), 5.02 (1H, d, J 5.7 Hz, 4-H), 4.15 (1H, m, 3-H), 3.80 (3H, s, OCH_3), 3.70 (3H, s, COOCH_3), 2.68 (1H, dd, J 17.0 and 7.5 Hz, 2-CH_2), 2.54 (1H, dd, J 17.0 and 3.2 Hz, 2-CH_2); m/z 274 (M^+{^{35}Cl}, 1%), 256 (12), 283 (12), 174 (30), 172 (100).


Isochroman (235) (150 mg, 0.62 mmol) in dichloromethane (10 ml) was treated with (±)-camphorsulphonic acid (100 mg, 0.43 mmol). This mixture was heated under reflux for 3 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (2 ml). The organic layer was separated, washed with water, dried and evaporated to give a colourless oil. This was chromatographed on silica gel using 3:1 hexane/ethyl acetate as eluent to afford the title compound (238) as a colourless oil (112 mg, 83%). (Found: C, 57.8; H, 4.9; Cl, 13.5 C_{13}H_{13}ClO_4 requires C, 58.1; H, 4.9 ;
trans-4-(2',5'-Dimethoxyphenyl)-3-butenoic acid (240)

2,5-dimethoxybenzaldehyde (239) (2.0 g, 12.05 mmol) in dry tetrahydrofuran (200 ml) was added in portions to a stirred solution of 3-triphenylphosphoniumpropanoic acid chloride14 (5.0 g, 12.05 mmol) in dry dimethyl sulphoxide (100 ml) at room temperature. The mixture was cooled to 0 °C and sodium hydride (0.35 g, 60% dispersion in oil) was added in portions. The reaction was allowed to warm to room temperature and stirred continuously for 14 h. A solution of sodium hydroxide (10%) was added and the mixture washed with toluene (5 x 100 ml) and diethyl ether (2 x 100 ml), acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 x 150 ml). These combined organic extracts were washed with dilute hydrochloric acid, dried and evaporated to afford a brown oil (4g). This was purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give the unreacted aldehyde (239) (0.3 g, 15%) and the title compound (240) as a yellow oil (1.8 g, 67%). (Found: C, 65.0; H, 6.4. C12H14O4 requires C, 64.85; H, 6.35%; v_max (neat) 1710 (COOH ), 1653 (C=O ring), 1596 cm⁻¹ (1,3,5-trisubstituted benzene); δH (CDCl3) 7.02 (1H, d, J 2.3 Hz, 6'-H), 6.83 (1H, dt, J 15.9 and 1.5 Hz, 4-H), 6.80 (2H, narrow m, 3' and 4'-H), 6.31 (1H, dt, J 15.9 and 5.6 Hz, 3-H), 3.82 (3H, s, OCH3), 3.80 (3H, s, OCH3), 3.34 (2H, dd, J 5.6 and 1.5 Hz, 2-CH2); δ 13C (CDCl3) 177.6 (C-1), 153.8 and 151.1 (C-2' and C-5'), 128 (C-4), 126.5 (C-1'), 121.7 -(C-3), 113.8 (C-6'), 112.2 and 112.1
(C-3’, C-4’), 56.2 (CH$_3$O), 55.7 (CH$_3$O), 38.3 (C-2); $m/z$ 222 (M$^+$, 100%), 177 (45), 161 (77), 147 (15), 146 (15), 91 (27), 77 (21), 65 (25), 55 (19).

**Methyl trans-4-(2',5'-Dimethoxyphenyl)-3-butenoate (241)**

Phenylbutenoic acid (240) (1.7 g, 7.0 mmol) in dry dichloromethane (15 ml) was treated with oxalyl chloride (1.0 g, 8 mmol) in a manner similar to that used in the preparation of ester (213). The crude product was purified by chromatography on silica gel using 6:1 hexane/ethyl acetate as eluent to give the title compound (241) as a yellow oil (1.5 g, 83%). (Found: C, 66.25; H, 7.15. C$_{13}$H$_{16}$O$_4$ requires C, 66.1; H, 6.8%); $\nu$$_{max}$ (neat) 1750 (COOCH$_3$), 1653 (C=C ring); $\delta$$_H$ (CDCl$_3$) 7.01 (1H, d, J 2.3 Hz, 6'-H), 6.82 (1H, dt, J 15.9 and 1.4 Hz, 4'-H), 6.78 (2H, narrow m, 3' and 4'-H), 6.30 (1H, dt, J 15.9 and 5.6 Hz, 3-H), 3.80 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.72 (3H, s, COOCH$_3$), 3.28 (2H, dd, J 5.6 and 1.4 Hz, CH$_2$); $\delta$ 13C (CDCl$_3$) 172.1 (C-1), 153.6 and 150.9 (C-2', C-5'), 128.0 and 126.6 (C-1', C-4), 122.4 (C-3), 113.6 (C-6'), 112.1 and 111.9 (C-3', C-4'), 56.1 (OCH$_3$), 55.6 (OCH$_3$), 51.8 (COOCH$_3$), 31.5 (C-2); $m/z$ 236 (M$^+$, 95%), 181 (11), 177 (100), 162 (23), 161 (84), 147 (20), 146 (24), 121 (17), 103 (12), 91 (32), 77 (19), 65 (29).

**rel-[4R,5R]-2,3,4,5-Tetrahydro-4-hydroxy-5-(2',5'-dimethoxyphenyl)-2H-furan-2-one (242)**

Olefin ester (241) (400 mg, 1.69 mmol) in acetone (10 ml) was added to a solution of osmium tetroxide (5 mg) and 4-methylmorpholine-N-oxide 6 (226 mg, 1.94 mmol) in water (30 ml) at 0°C. The reaction was allowed to warm to room temperature and was stirred continuously for 18 h. Acetone was removed by distillation under reduced pressure. The aqueous solution was acidified with dilute hydrochloric acid (2 M, 20 ml) and the organic materials were extracted into ethyl acetate (5 x 50 ml) and the combined extracts were washed with water (3 x 100 ml), dried, filtered, and evaporated to give a light brown oil (1.0 g). This was purified by chromatography on silica gel.
using 3:2 hexane/ethyl acetate as eluent to afford the title compound (242) as a colourless oil (370 mg, 92%). (Found: C, 60.25; H, 6.1; C_{12}H_{14}O_5 requires C, 60.5; H, 5.9%); \(v_{\text{max}}\) (neat) 3420 (OH), 1772 (C=O, lactone), 1612 cm\(^{-1}\) (C=C ring); \(\delta_H\) (CDCl\(_3\)) 7.06 (1H, d, J 2.2 Hz, 6'-H), 6.84 (2H, narrow m, 3'-H and 4'-H), 5.72 (1H, d, J 3.5 Hz, 5'-H), 4.78 (1H, dt, J 3.5 and 5.3 Hz, 4'-H), 3.80 (3H, s, OCH\(_3\)), 3.76 (3H, s, OCH\(_3\)), 2.87 (1H, dd, J 17.5 and 5.3 Hz, 3'-H), 2.66 (1H, d, J 17.5 Hz, 3'-H); \(\delta_{\text{13C}}\) (CDCl\(_3\)) 175.4 (C-2), 153.8 and 149.6 (C-2', C-5'), 122.1 (C-1'), 114.8 (C-6'), 112.9 and 111.3 (C-3', C-4'), 81.8 (C-5), 68.7 (C-4), 55.8 (2 x OCH\(_3\)), 38.2 (C-3); \textit{mlz} 238 (M\(^+\), 100%), 167 (97), 166 (96), 152 (14), 151 (35), 139 (38), 137 (35), 120 (22).

\textit{rel-(2S,4R,5R) and rel-(2R,4R,5R)-5-Carbomethoxymethyl-4-(2',5'-dimethoxyphenyl)-2-methyl-1,3-dioxolanes (243) and (244)}

Lactone (242) (320 mg, 1.34 mmol) in dry dichloromethene (100 ml) was treated with 1,1-dimethoxyethane (400 mg, 4.1 mmol) and (+)-camphorsulphonic acid (10 mg, 0.043 mmol). The mixture was then heated under reflux for 72 h. The crude product was purified by chromatography on silica gel using 4:1 hexane/ethyl acetate as eluent to give the starting lactone (242) (100 mg, 31%), pyrano-\(\gamma\)-lactone (245) (17mg, 5%) and the title compounds (243) and (244) in a ratio of 1:1 as a colourless oily mixture (190 mg, 60%). (Found: C, 60.8; H, 6.9. C\(_{15}\)H\(_{20}\)O\(_6\) requires C, 60.8; H, 6.8%); \(v_{\text{max}}\) (KBr disc) 1685 (C=O, ester), 1654 cm\(^{-1}\) (C=C ring); \(\delta_H\) (CDCl\(_3\)) 7.12 and 7.02 (each 1H, d, J 2.2 Hz, 6'-H of each isomer), 6.78 (4H, narrow m, 3'-H and 4'-H of both isomers), 5.41 and 5.34 (each 1H, q, J 4.7 Hz, 2'-H of each isomer), 5.04 and 4.98 (each 1H, d, J 6.0 Hz, 4'-H of each isomer), 4.28 (2H, m, 5'-H of both isomers), 3.78 (6H, s, OCH\(_3\) of both isomers), 3.76 (6H, s, OCH\(_3\) of both isomers), 3.68 (6H, s, COOCH\(_3\) of both isomers), 2.85 (4H, m, CH\(_2\) of both isomers), 1.51 and 1.47 (each 3H, d, J 4.8 Hz, 1-CH\(_3\) of each isomer); \textit{mlz} 296 (M\(^+\), 42%), 252 (37), 194 (30), 193 (59), 179 (29), 165 (52), 161 (26), 151 (54), 153 (48), 87 (35), 59 (100).
Treatment of dioxolanes (243) and (244) with titanium tetrachloride

Dioxolanes (243) and (244) (150 mg, 0.05 mmol) in dry dichloromethane (25 ml) and titanium tetrachloride (0.14 ml, 0.1 mmol) were stirred at 0 °C for 3 h. The reaction was quenched with methanol (0.05 ml) at 0 °C. Saturated aqueous sodium bicarbonate solution (2 ml) was added and the resultant mixture poured into water. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give a crude residue (80 mg). This was analysed by g.c., g.c.-mass and ¹H-n.m.r. spectroscopy which indicated a mixture of hydroxy lactones and diol ester. As observed from the g.c.-mass spectrum, the retention times of the lactones were 12.6 and 12.9 minutes while those of the two isomers of diol esters were 17.2 and 17.6 minutes, in each case the g.c.-mass fragmentation patterns of the two isomeric lactones were identical; m/z 238 (M⁺, 40%), 194 (100), 163 (90), 135 (50), 91 (20), 71 (20); diol esters m/z 322 (10%), 264 (12), 252 (40), 186 (20), 151 (100), 121 (30), 91 (15).

rel-[3aR,5S,9bR]-3,3a,5,9b-Tetrahydro-6,9-dimethoxy-5-methyl-2H-furo[3,2-b]benzo[d]pyran-2-one (245)

To a stirred solution of lactone (242) (600 mg, 2.52 mmol) in freshly distilled acetaldehyde (110 mg, 2.50 mmol) was added ortho-phosphoric acid (6 ml). After keeping the reaction mixture at room temperature for 22 h, water (100 ml) added. The aqueous solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were washed with water, dried, and evaporated to give a brown residue. This residue was dissolved in toluene (7 ml) and hexane (30 ml) added. The resultant precipitate was filtered and the filtrate concentrated to afford an orange residue. This residue was purified by chromatography on silica gel using 2:1 hexane/ethyl acetate as eluent to give the title compound (245) as a yellow oil (532 mg, 76%). (Found: M⁺, 264.0998. C₁₄H₁₆ClO₅ requires 264.0998); ν max (KBr disc) 1786 (C=O, γ-lactone), 1602 cm⁻¹ (C=C ring); δ H (CDCl₃) 6.89 and 6.78 (each 1H, d, J 8.9 Hz, 8-H and 7-H),
5.32 (1H, d, J 2.3 Hz, 9b-H), 4.84 (1H, q, J 6.5 Hz, 5-H), 4.28 (1H, dt, J 2.3 and 4.3 Hz, 3a-H), 3.84 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 2.84 (1H, dd, J 17.2 and 4.3 Hz, 3-H), 2.69 (1H, d, J 17.2 Hz, 3-H), 1.57 (3H, d, J 6.5 Hz, 5-CH₃);

δ¹³C (CDCl₃) 175.7 (C-2), 152.7 and 149.7 (C-6, C-9), 130.3 (C-5a), 117.7 (C-9a), 112.3 and 108.9 (C-7, C-8), 72.5, 70.9 and 69.6 (C-3a, C-5, C-9b), 56.1 (OCH₃), 55.6 (OCH₃) 38.2 (C-3), 21.1 (C-5-CH₃; m/z 264 (M⁺, 50%), 249 (100), 221 (12), 165 (15), 91 (19), 77 (22).

rel-[3aR,5S,9bR]- and rel-[3aR,5R,9bR]-3,3a,5,9b-Tetrahydro-6,9-dimethoxy-5-methyl-2H-furo[3,2-b]benzo[d]pyran-2-one (245) and (246)

Dioxolanes (243) and (244) (150 mg, 0.05 mmol) was treated with orthophosphoric acid (2 ml). After keeping the reaction mixture at room temperature for 18 h, water (50 ml) added. The aqueous solution was extracted with dichloromethane (3 x 20 ml) and the combined organic extracts were washed with water, dried, and evaporated to afford a brown residue. This residue was dissolved in toluene (7 ml) and hexane (20 ml) added. The resultant precipitate was filtered and the filtrate concentrated to afford an orange residue. This residue was purified by chromatography on silica gel using 2:1 hexane/ethyl acetate as eluent to give the title compounds (245) and (246) as a yellow oil (119 mg, 70%). δH (CDCl₃) 6.89 to 6.78 (4H, m, 8-H and 7-H of both isomers), 5.33 (2H, d, J 2.9 Hz, 9b-H of both isomers), 5.14 and 4.85 (each 1H, q, J 6.5 Hz, 5-H of each isomer), 4.69 (1H, dt, J 2.9 and 5.0 Hz, 3a-H), 4.28 (1H, dt, J 2.9 and 4.3 Hz, 3a-H), 3.84 (6H, s, OCH₃ of both isomers), 3.78 (6H, s, OCH₃ of both isomers), 2.92 (1H, dd, J 17.2 and 5.0 Hz, 3-H), 2.84 (1H, dd, J 17.2 and 4.3 Hz, 3-H), 2.70 and 2.65 (each 1H, d, J 17.2 Hz, 3-H of each isomer), 1.57 and 1.46 (each 3H, d, J 6.5 Hz, 5-CH₃ of each isomer).
To a stirred solution of pyran-γ-lactone (245) (200 mg, 0.75 mmol) in acetonitrile (15 ml) and water (20 ml) was added cerium ammonium nitrate (870 mg, 1.59 mmol) in water (1.5 ml) during five minutes at room temperature. The reaction mixture was stirred for a further 30 minutes then extracted with dichloromethane (3 x 10 ml). The combined organic extracts were washed with water, dried and evaporated to afford an orange residue. This was purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give the title compound (247) as an orange oil (120 mg, 69%). (Found: M⁺, 234.0529. C₁₂H₁₀O₅ requires 234.0528); δH (CDCl₃) 6.87 and 6.83 (1H, d, J 8.3 Hz, 8-H and 7-H), 5.10 (1H, dd, J 2.5 and 1.8 Hz, 9b-H), 4.64 (1H, dq, J 1.8 and 6.5 Hz, 5-H), 4.32 (1H, dt, J 2.5 and 4.7 Hz, 3a-H), 2.87 (1H, dd, J 17.5 and 4.7 Hz, 3-H), 2.69 (1H, d, J 17.5 Hz, 3-H), 1.57 (3H, d, J 6.5 Hz, 5-CH₃); m/z 234 (M⁺, 28%), 219 (22), 191 (24), 179 (39), 91 (24), 77 (33), 55 (100).

A solution of quinone (247) (30 mg, 0.13 mmol) and 1-acetoxybutadiene (60 mg, 0.54 mmol) in benzene (5 ml) was heated at 60 °C for 5 h. The mixture was evaporated to dryness, and the residual oil dissolved in ethanol (3 ml). To this solution was added 1% sodium carbonate solution (0.3 ml) and the mixture stirred at room temperature for a further 5 h. This was diluted with ethyl acetate (10 ml), washed with water, dried and evaporated to give a crude oil, which was purified by chromatography on silica gel using 3:1 hexane/ethyl acetate as eluent to give the title compound (248) as an orange oil (24 mg, 66%), which was crystallised from hexane/diethyl ether, m.p. 191-193 °C. lit. 190-193 °C (decomp). δH (CDCl₃) 8.17 - 8.07 (2H, m, 7-H and 10-H), 7.79 (2H, m, 8-H and 9-H), 5.30 (1H, dd, J 2.5 and 1.6 Hz, 11b-H), 4.78 (1H, dq, J 1.6 and 6.6 Hz, 5-H), 4.34 (1H, dd, J 2.5 and 4.7 Hz, 3a-H), 2.87 (1H, dd, J...
17.5 and 4.7 Hz, 3-H), 2.69 (1H, d, J 17.5 Hz, 3-H), 1.60 (3H, d, J 6.6 Hz, 1-CH₃);
m/z 284 (M⁺, 4%), 269 (2), 240 (4), 185 (10), 149 (11). These data correspond with
those provided in the literature.²⁹

126.


637.

References


ERRATA

p. iii Line 1* "estabilshed" should read "established"
p. iv Line 7 should read "these compounds more closely resemble"
p. 3 Line 9 "Eleutherin bulbosa" should read "Eleutherine bulbosa"
p. 5 Line 5 "7-O-methyl kalafungin" should read "7-O-methylkalafungin"
p. 9 Line 2* "C-glucoside" should read "C-glycoside"
p. 10 Line 6 should read "originally used by Schmid"
p. 11 Line 4 "lithim" should read "lithium"
p. 13 Line 3 should read "protected juglone (34)"
p. 17 Line 4 "naphthaquinone" should read "naphthoquinone"
p. 22 Line 1 "Aphis nerri" should read "Aphis nerii"
p. 22 Line 2 "emulsion" should read "emulsin"
p. 26 Line 1 should read "methyl ether (79)"
p. 27 Line 6* should read "Z and E-olefins" and line 5* should read "E-olefin"
p. 34 Line 1 "dioxopanes" should read "dioxepanes"
p. 46 Line 9 should read "T. Mukaiyama, K. Banno and K. Narasaka"
p. 79 Line 6 "chemicl" should read "chemical"
p. 101 Line 2* and p. 102 line 6* "benzyl bromide" should read "the benzyl bromide"
p. 102 Line 6 should read "was subsequently hydrolysed"
p. 106 Line 6* should read "signals from the dioxolane ring protons"
p. 126 Line 2 "biproduct" should read "by-product"
p. 129 Line 1 "4188" should read "4185".
p. 166 Line 7* "responce" should read "response"
p. 169 Line 12 should read "saturated aqueous sodium chloride"
p. 170 Line 8 should read "potassium t-butoxide (3 ml)"
p. 171 line 3-4 should read "m/z 194 (M+, 53%), 179 (100)"
p. 178 Line 5, p. 179 line 7 and p 205 line 4* should read "dihydroisobenzofuran"
p. 187 Line 4* "diastreomeric" should read "diastereomeric"
p. 199 Line 5 "hydrochlorioic" should read "hydrochloric"
p. 202 Line 9 "brwon" should read "brown"
p. 210 Line 1 "latone" should read "lactone"
p. 213 Line 9* should read "water (100 ml) was added"

* from the bottom of page