PROTOCOLS TOWARDS THE SYNTHESIS OF CHIRAL ISOCHROMANQUINONES

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KEYWORDS

Benzo[c]pyrans

Isochromanquinones

Chiral Reduction

Cyclization

4-Hydroxy-benzo[c]pyran

4-Hydroxyisochromanquinones

Enantiomeric Excess

Mosher Ester

Oxazaborolidine

Fremy's Salt

ABSTRACT

Very few protocols have been developed for the synthesis of chiral isochromanols. In recent years the active group of Giles *et al.* have developed a very successful and highly efficient protocol using (*S*)-ethyl lactate as chiral building block which fixes resultant chirality at C-3 of the pyran ring. Following a most efficient separation of diastereoisomers at the enantiomeric C-1 centre and a highly stereospecific ring closure at the aryl ring the Giles' group were able to after oxidation synthesize both chirally pure 4-hydroxy-isochromanquinones as well as the chirally pure quinones A and A' after Diels Alder cycloadditions with appropriate dienes.

In the present approach a dialkoxylated *ortho* alkenyl acetyl benzene was reduced to the chiral (R)-1'-hydroxyethyl anlogue and the enantiomeric excesses were determined and varied from 64 – 80 % depending on the substituents. The notion was that the chiral centre, now at the C-1 equivalent position of the pyran ring, would induce preferred chirality at C-3 during the cyclisation of the dialkoxylated *ortho* alkenyl hydroxyethyl benzene. Initial attempts at chiral reduction for the non-conjugated prop-2'-enyl isomer lead to a 7 % yield of the chiral alcohol together with a large array of other products which were identified. Similar reduction on the conjugated prop-1'-enyl isomer proved to be much more successful but in this case a dimeric product was always produced which was identified.

Mercury(II) mediated ring closure under an atmosphere of nitrogen afforded in the main two chiral isochromanes and a benzofuran which could not be effectively separated at this stage. Chemically pure samples where possible were isolated and fully characterized.

Debenzylation of the 3-benzyloxy analogues of the isochromanes afforded the corresponding phenols which, were then oxidized to the quinones and these were separated on the chromatotron to afford pure samples of two isochromanquinones as well as a benzofuranquinone. The enantiomeric excesses of the isochromanquinones were measured between 48 – 69 %.

Finally the mercury(II) mediated synthesis of 4-hydroxyisochromanes was applied to our precursors in order to obtain chiral 4-hydroxyisochromanquinones in the hope that these would have higher biological activity compared to the non-hydroxylated analogues. It was found that the method had to be modified somewhat before hydroxylation took place. At the outset of this method of cyclisation followed by hydroxylation under an atmosphere of oxygen, it was unknown to what extent induced chirality at C-4 would occur.

In this way we were able to isolate (*R*)(*S*)(*R*)-5-benzyloxy-6-methoxy-1,3-dimethyl isochroman-4-ol in chirally pure form which was fully characterized and from the chiral shift reagent (Europium tris[3-heptafluoropropylhydromethoxymethylene (+) camphorate]) it appeared that the molecule was chirally pure. Debenzylation followed by Fremy salt oxidation lead to the isolation and characterization of (*R*)(*S*)(*R*)-4-hydoxy-6-methoxy-1,3-dimethylisochromanquinone which also, from comparative spectra containing europium shift reagent appeared to be chirally pure.

All quinonoid compounds have been evaluated and results compared to the racemic isomers. In the cases of the racemic 4-deoxy- compared to the chiral 4-deoxy pyranquinones and racemic 4-hydroxy- compared to the chiral 4-hydroxypyranquinones there was no marked difference in inhibitory activity. However the 4-hydroxypyranquinones were more inhibitory compared to the 4-deoxy analogues.

DECLARATION

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

MOHAMMED NAZEEM JAHED JUNE 2001

SIGNED.....

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Professor Ivan R Green for his encouragement, guidance, advice and support throughout this project.

To My Parents, Thank You! for your unlimited support and encouragement during my years of study.

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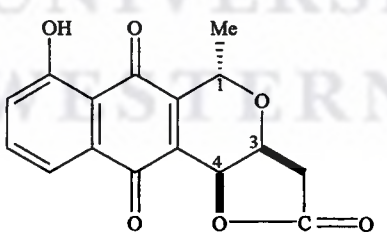
SECTION 1. INTRODUCTION

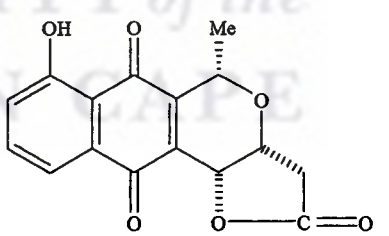
The synthesis of quinones is a very important topic, which is showing a continuing interest because the quinone subunit is contained in a significant number of biologically important natural products. This subunit is present in anticancer agents, antibiotics, antifungal and anticoccidal agents[1].

1.1. Benzoisochromanquinones. Natural occurrence and biological activity

The isolation, characterization and structural determination of nanaomycins A, B and C from *Streptomyces rosa* var. *notoensis* has been reported by Omura and co-workers in 1974[2], who also demonstrated that these compounds are powerful antifungal antibiotics. In 1976 Omura reported the isolation of nanaomycin D **1**, the conversion of nanaomycin A **3** into nanaomycin D **1**, and the evidence that nanaomycin D **1** is the enantiomer of kalafungin **2**, obtained from *Streptomyces tanashiensis*[3].

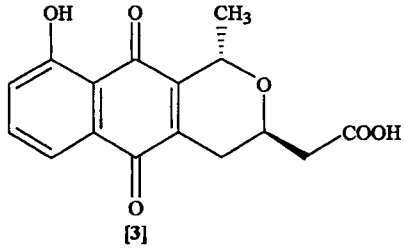


(1S, 3S, 4S)
[1]



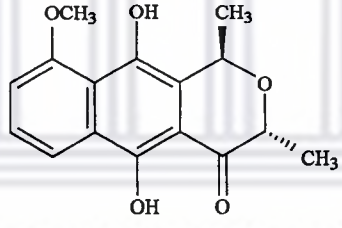
(1R, 3R, 4R)
[2]

Nanaomycin A **3**, a member of the family of pyranonaphthoquinone antibiotics, exhibits significant antimicrobial[2] activity and bears potential antineoplastic activity[4].



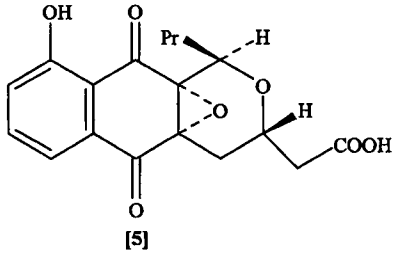
[3]

Hongconin **4** belongs to the broad family of naphthohydropyranquinones and has been used by people in southern China especially for coronary disorders. Hongconin was isolated from the rhisome of *Eleutherine americana Merr et Heyne* (Iridaceae) and showed cardioprotective activity against angina pectoris in preliminary clinical trials[5].

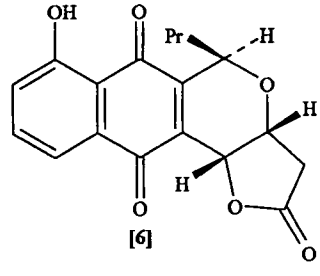


[4]

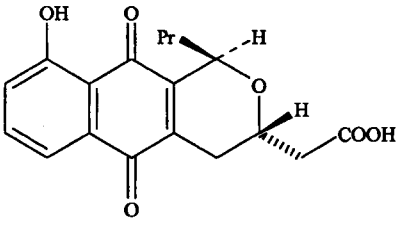
Frenocilins A **5**, B **6** and deoxyfrenolicin **7** are members of the pyranonaphthoquinone family of antibiotics, which were isolated from *Streptomyces fradiae*[6,7].



[5]



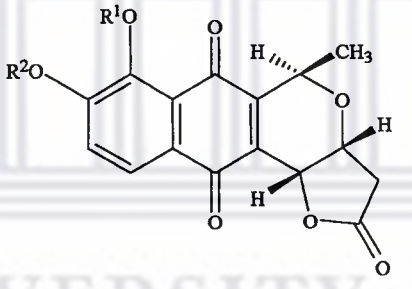
[6]



[7]

These natural products are related to kalafungin **2** and nanaomycin A **3** and are antimicrobial agents upon bioreduction[8].

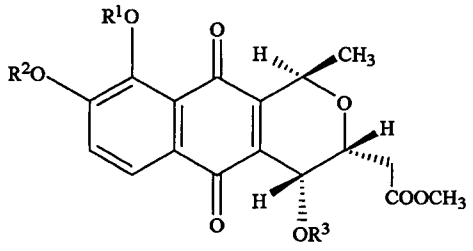
The arizonins (**8-13**) were first isolated from the fermentation broth of Actionoplanes sp. AB66OD-122 by Hochlowski *et al.*[9,10] and were found to exhibit antimicrobial activity against pathogenic strains of Gram-positive bacteria.



Arizonin A1 **8**, Arizonin B1 **9**, Arizonin C1 **10**

Arizonin A1, $R^1 = CH_3$, $R^2 = H$; Arizonin B1, $R^1 = H$, $R^2 = CH_3$;

Arizonin C1, $R^1 = R^2 = CH_3$



Arizonin A2 **11**, Arizonin B2 **12**, Arizonin C3 **13**

Arizonin A2, $R^1 = CH_3$, $R^2 = R^3 = H$; Arizonin B2, $R^1 = H$, $R_2 = CH_3$, $R^3 = H$

Arizonin C3, $R^1 = R^2 = R^3 = CH_3$

1.2. Bioactivation

Bioactivation as a mechanism of drug action consists in the transformation of biologically inactive compounds into active ones subsequent to an *in vivo* transformation. Certain compounds can function as bioreductive alkylating agents, that is, compounds which became potent alkylating agents after they undergo a reduction *in vivo*.

Bioreductive Alkylation

The four simple models that can be used to catalog potential bioreductive alkylating agents[4] are:

Model 1 – Activated eneamines

Model 2 – Vinylogous quinone methides

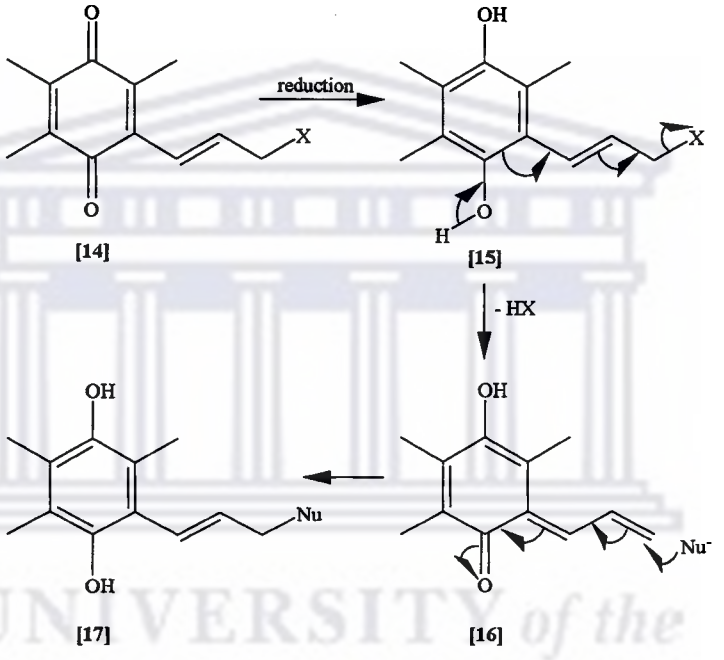
Model 3 – Simple quinone methides

Model 4 - α-methylene lactones or lactams

For our purposes we will only discuss models 2 and 3 since they are applicable to quinones.

Model 2 – Vinylogous quinone methides[2]

The alkenyl- substituted quinones, such as **14**, which are functionalized with a leaving group X at the 3 position on the side chain, could be reduced *in vivo* to the hydroquinone **15** (Scheme 1).

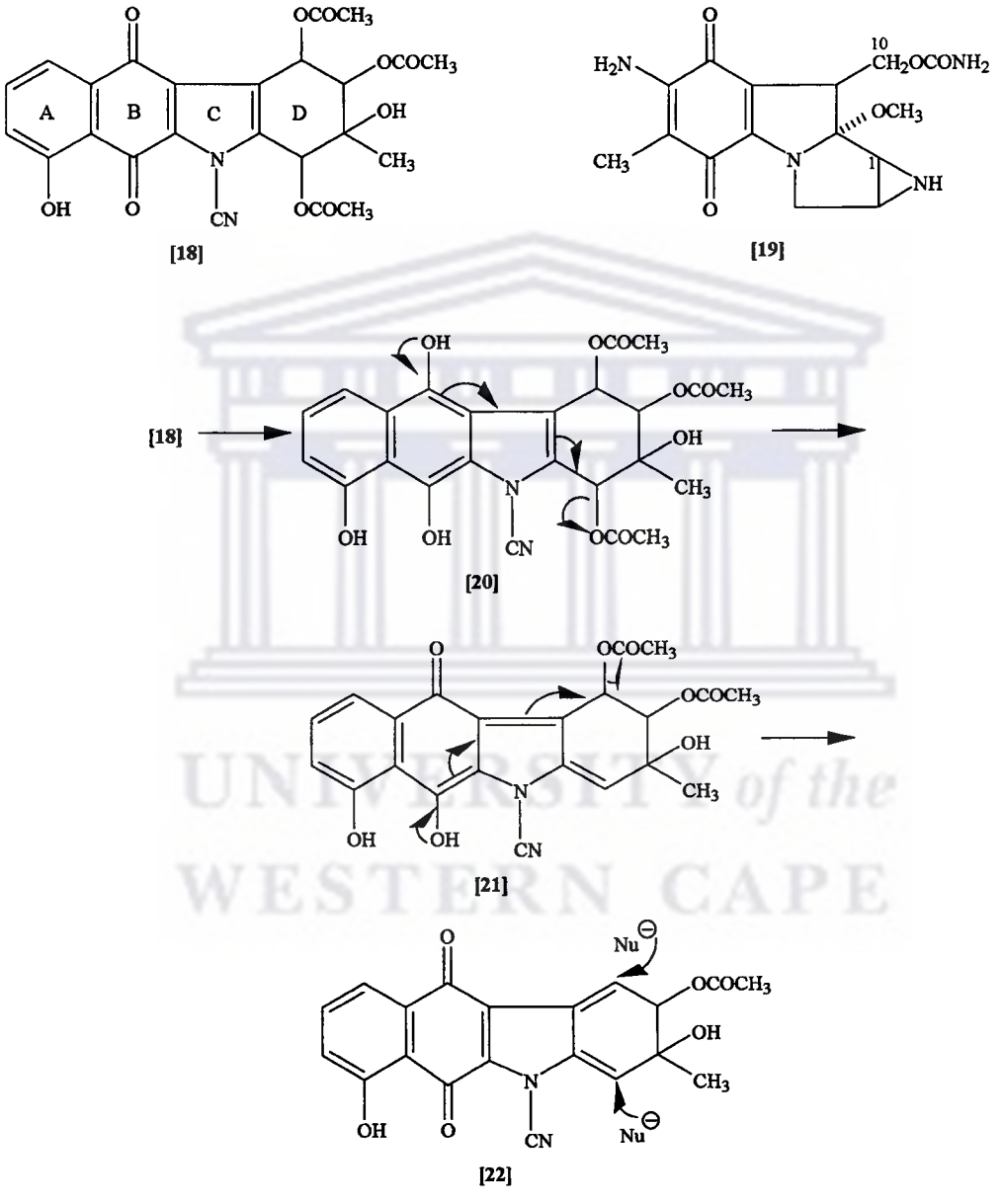


Scheme 1

Subsequent loss of HX would give the vinylogous quinone methide **16**, which then functions as a potent alkylating agent *via* a Michael addition reaction.

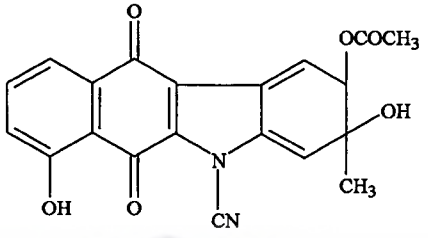
Kinamycin C **18** is an indole quinone, has shown marked antibiotic activity. There are close structural relationships between kinamycin C **18** and mitoycin C **19**.

Kinamycin C **18** has potential leaving groups, ($OCOCH_3$) at positions analogous to position 1 and 10 of mitomycin C **19**. Thus it may also function as a bioreductive alkylating agent as outlined in Scheme 2 (model 2)[2].

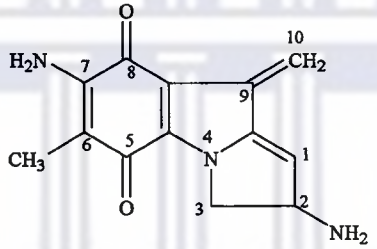


Scheme 2

The proposed active forms of kinamycin C and mitomycin C, respectively **22** and **24**, further suggests that simple alkenyl- and dienyl-substituted quinones may function directly as alkylating agents (Michael acceptors) and thus show biological activity.



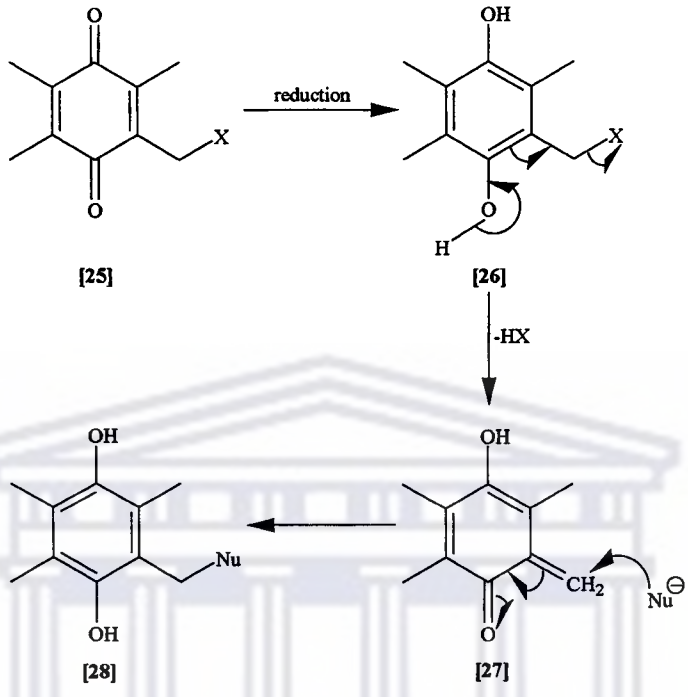
[23]



[24]

Model 3 – Simple quinone methides

Sartorelli, Lin, and co-workers [11-14] suggested a simple quinone methide model. They have shown that certain simple quinones, which are substituted with one or more $-CH_2X$ groups present marked antineoplastic activity. Based on the obtained results they proposed that simple quinones such as **25** may function as alkylating agents according to the mechanism illustrated in Scheme 3.

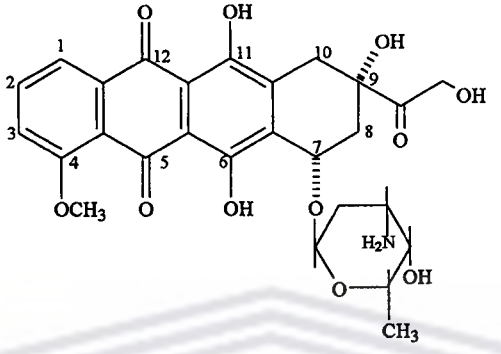


Scheme 3

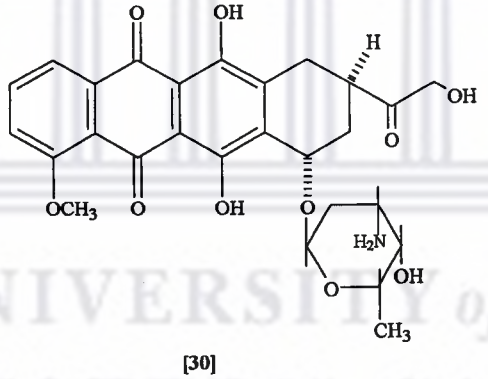
According with this model the simple quinone methides **27** are the key alkylating agents generated *in vivo*.

The two anthracyclines, adriamycin **29** and daunorubicin **30** are a major class of natural products that show marked anticancer activity. Adriamycin has the widest spectrum of clinical activity of any known compound[15]. Clinical evaluations have shown it to have significant activity against various tumors including leukemia, lung cancer, breast cancer, sarcoma, lymphoma and neuroblastoma[16]. Adriamycin **29** is a hydroquinone, which is the penultimate precursor to the quinone methide. Direct elimination of the

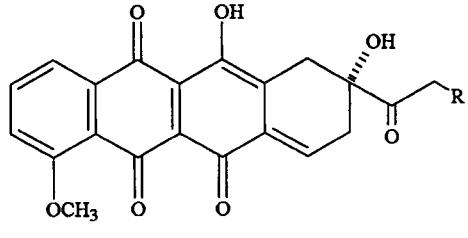
sugar moiety would give **31**, which would function as a reactive Michael acceptor (model 3).



[29]

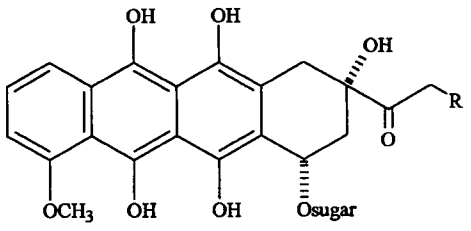


[30]



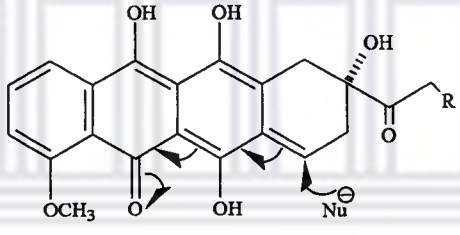
[31]

A mechanism that is even more in accord with the bioreductive alkylation concept would involve *in vivo* reduction of the quinone nucleus in adriamycin to give **32**.



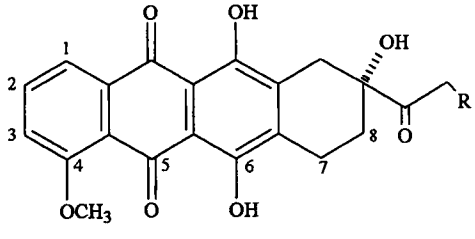
[32]

Elimination of the sugar group could then proceed to give the quinone methide **33**, ideally set up to undergo a Michael addition with any nucleophile *viz.* bacterial agent.



[33]

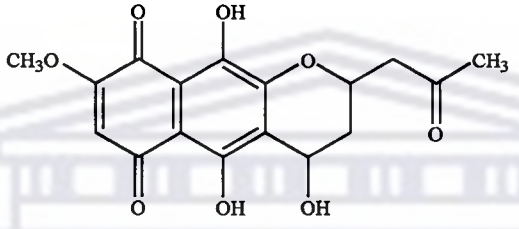
Reduction of daunorubicin **30** under mild conditions ($Na_2S_2O_4$) results in its quantitative conversion to 7-deoxydaunomycinone **34**, a tautomer of quinone methide **33**.



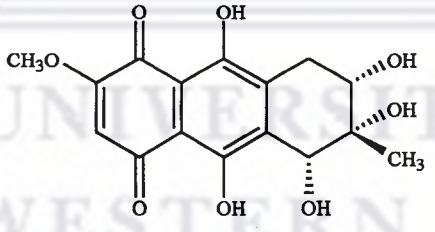
[34]

Such a transformation demonstrates that the sugar group at C-7 is exceptionally inclined to be eliminated from the fully reduced natural product.

Adriamycin has structural similarities to a number a naturally occurring and biologically active naphthazirins whose mode of action could also be one of bioreductive quinone methide formation[4]. Some examples are erythrostominone **35**[17] and bostricyn **36**, which are antibiotics.



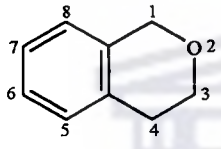
[35]



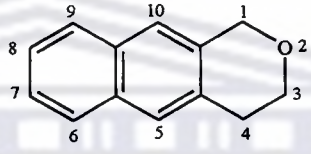
[36]

1.3. Synthetic protocols that have been employed in the synthesis of benzoisochromanquinones

The benzo[c]pyran (or isochroman) ring system is an intergral subunit of a variety of dihydronaphthopyranquinones which show biological activity. Numbering of the benzo[c]pyran and dihydronaphthopyran[2,3-c]pyran ring systems are outlined below.



benzo [*c*]pyran

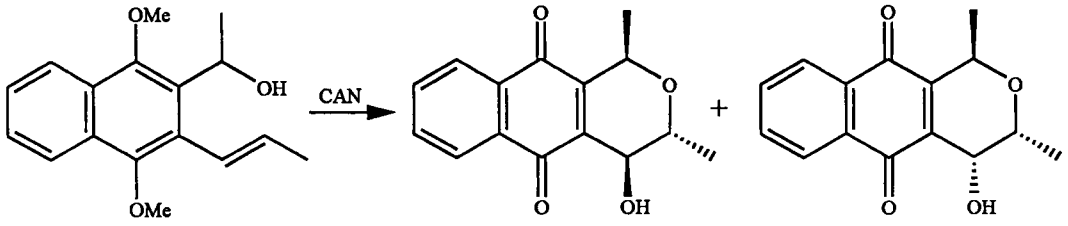


dihydronaphtho [2,3-*c*]pyran

The literature review presented below relates to the syntheses of a wide spectrum of intermediates, which undergo cyclisation to form the dihydropyran ring.

1.3.1. Cerium(IV) Ammonium Nitrate Mediated Cyclisations

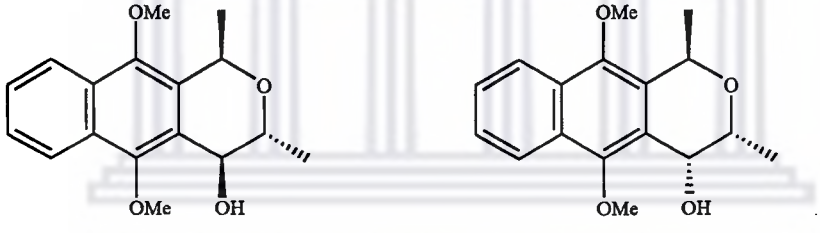
In 1981 Giles[18] and co-workers reported a convenient synthesis of the naphtho[2,3-c]-pyran ring system which is contained in a variety of naturally occurring quinones. Using cerium(IV) ammonium nitrate (CAN), the naphthalene dimethyl ether **37**, underwent oxidative cyclisation to afford two naphthopyran quinones **38** (20%) and **39** (59%) (Scheme 4).



[37] [38] [39]

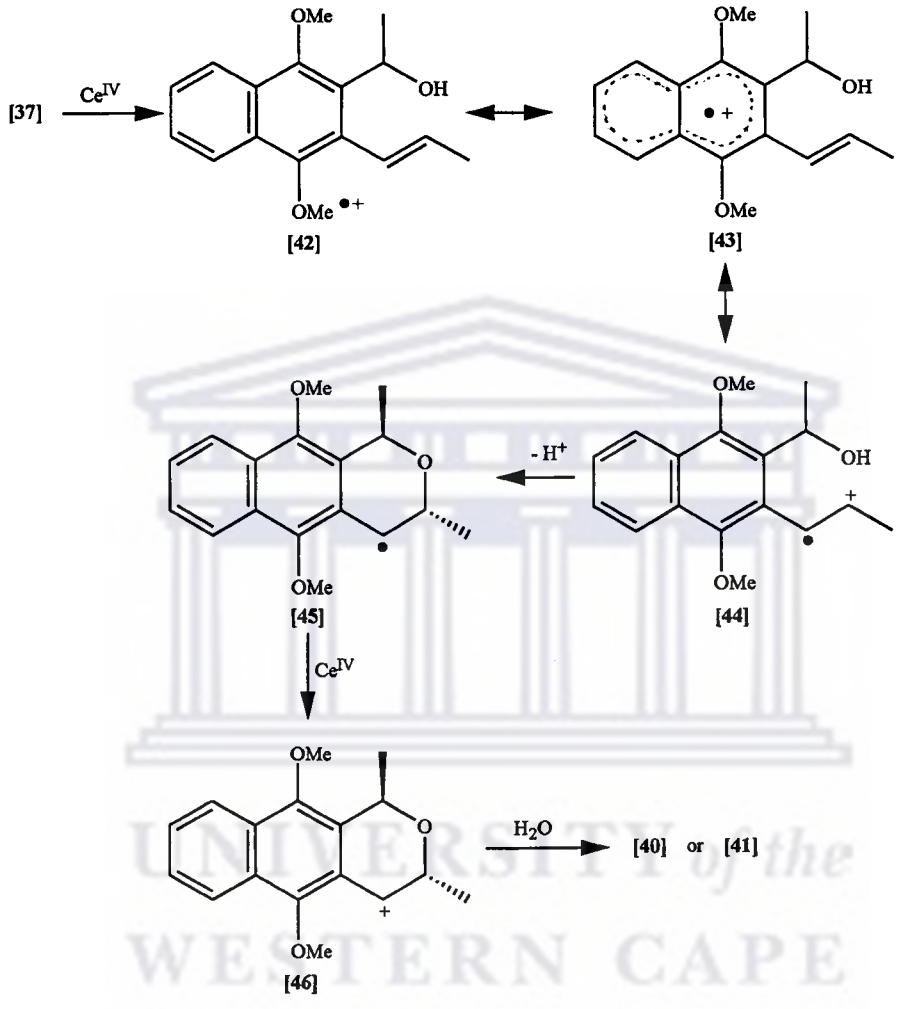
Scheme 4

The authors later showed that cyclisation preceded oxidation[19], since when **37** was treated with 2 mol equivalents of CAN the two naphthopyran intermediates **40** and **41** were isolated.



[40] [41]

A mechanism consistent with the experimental observations was also later proposed by the authors[20] as outlined in Scheme 5.



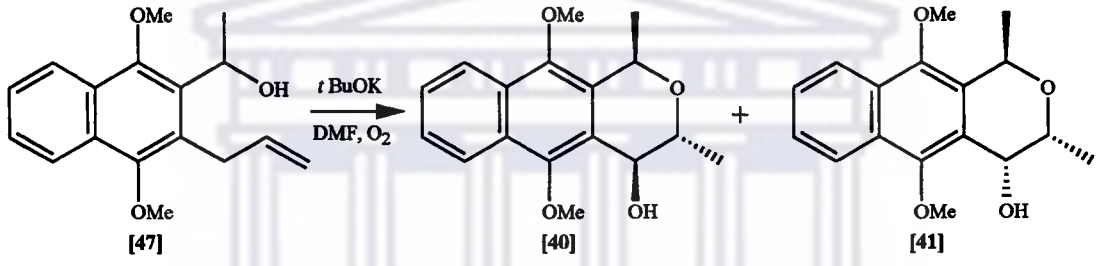
Scheme 5

The results indicated that for the cerium promoted-oxidative cyclisation of **37**, the methoxy group *ortho* to the alkenyl group plays a key role. A resonance stabilized radical cation (**42** ↔ **43** ↔ **44**) is formed by oxidation of **37** at the methoxy group *ortho* to the alkenyl substituent with cerium(IV) (1mol equiv.). Ring closure and loss of a proton give rise to a benzylic radical **45** which undergoes oxidation with a second

cerium ion to give the benzylic carbonium ion **46**; this then undergoes nucleophilic attack by the water present to give the products **40** and **41** [20].

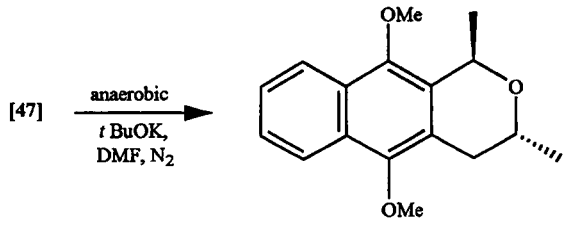
1.3.2. Potassium tert-Butoxide Mediated Cyclisations

In an alternate synthetic method Giles *et al.*[21] cyclized 2-(alk-2-enyl)-3-(1-hydroxyalkyl)-1,4-dimethoxynaphthalene **47** to the same 4-hydroxy derivatives **40** and **41**, using potassium tert-butoxide in dimethylformamide in the presence of pure oxygen[21] (Scheme 6).



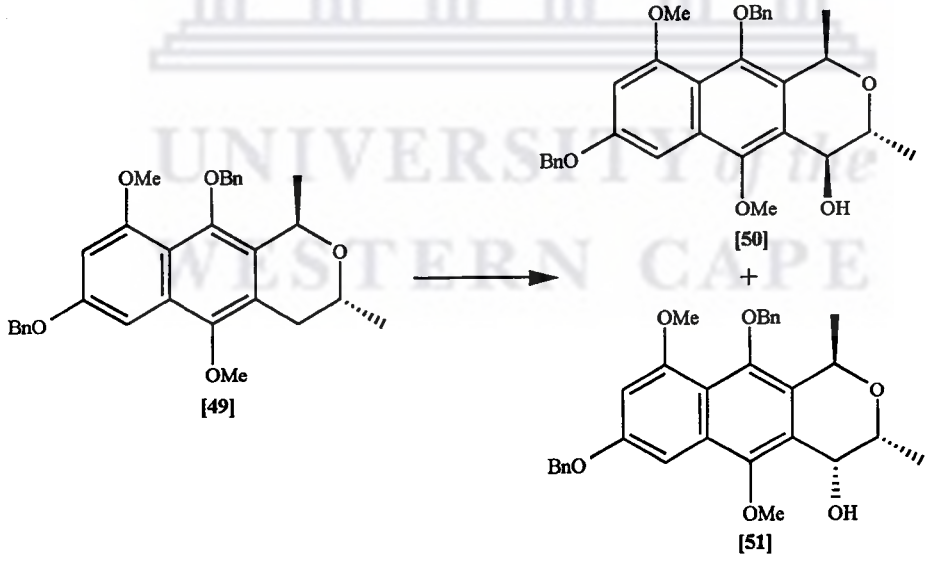
Scheme 6

On the other hand anaerobic base-catalyzed cyclisation of **47** gave the naphthopyran **48** in which the methyl groups in the pyran ring are stereospecifically *trans* (Scheme 7). Thus compound **47**, when treated with potassium *tert*-butoxide in dimethylformamide at 60 °C for 15 minutes under nitrogen, gave pyran **48** (100%) free of the corresponding *cis*-isomer. Treating compound **47** for a longer time and in the presence of air afforded the hydroxylated derivative **40** (28%) together with minor amounts of the epimer **41** (7%) (Scheme 6).



Scheme 7

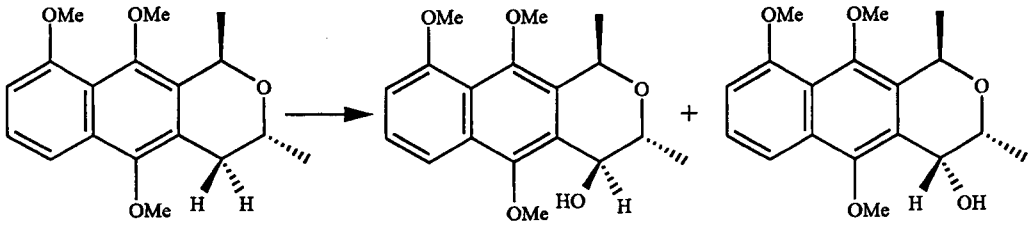
Giles *et al.*[22] improved the yields of the 4-hydroxynaphthopyrans by changing the solvent. This major achievement was established when *bis*-benzyloxynaphthopyran **49** was dissolved in dry dimethyl sulphoxide through which dry oxygen was bubbled during the reaction and then treated with 4 mole equivalents of potassium *tert*-butoxide. The *bis*-benzyloxynaphthopyran **49** afforded the hydroxylated products **50** (60%) and **51** (24%) (Scheme 8).



Scheme 8

In 1996 Green reported a high yielding synthesis of racemic hongconin **4**[23]. Quantitative C-4 – hydroxylation was achieved by treating the naphthopyran **52** with 7

mol equivalents of potassium *tert*-butoxide in dimethylformamide while bubbling oxygen through the medium at 60 °C. In this way the epimeric mixture of 4 – hydroxynaphthopyrans **53** and **54** were produced in the ratio 4 : 1 (Scheme 9).



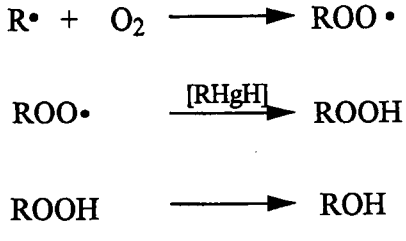
[52] [53] [54]

Scheme 9

Treatment of the epimeric mixture of alcohols **53** and **54** with either pyridinium chlorochromate dispersed on Celite or pyridinium dichromate dispersed on alumina, followed by silver(II) oxide in nitric acid oxidation produced hongconin **4** in 63% yield for the last two steps.

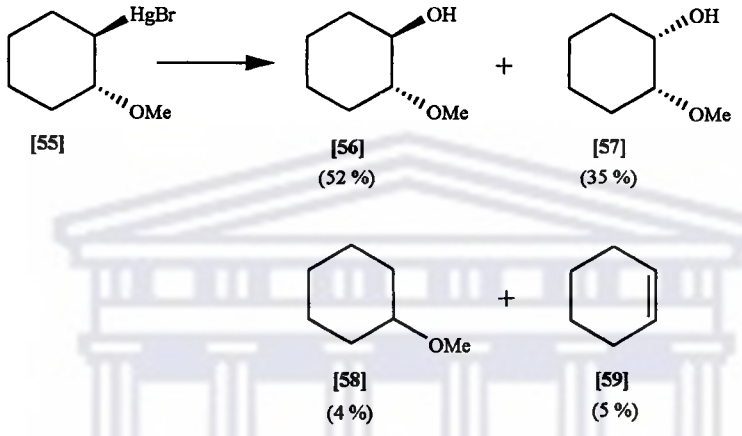
1.3.3. Reductive Mercury(II) Mediated Oxidative Cyclisation

Hill and Whitesides[24] demonstrated that the efficient trapping of radical intermediates with oxygen provides a useful method for forming carbon- oxygen bonds (Scheme 10).



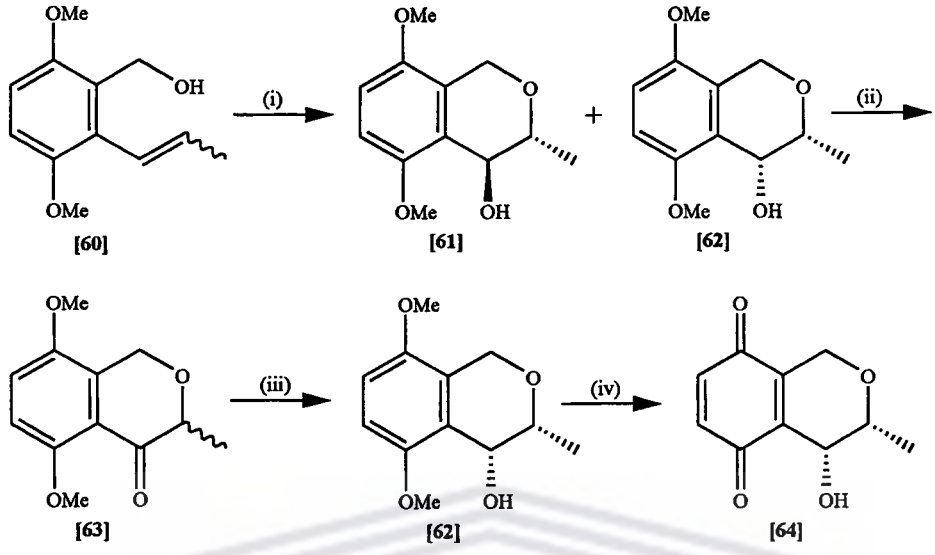
Scheme 10

They showed that when a solution of mercurial **55** in dimethylformamide was added to a solution of sodium borohydride (also in dimethylformamide) through which oxygen was rapidly passed, a diastereomeric mixture of β-alkoxy alcohols **56** and **57** together with trace amounts of **58** and **59** were obtained (Scheme 11).



Scheme 11

In their synthesis towards substituted 4-hydroxybenzo[c]pyranquinones, de Koning[25] and co-workers used the Hill and Whitesides' method [24] to form the carbon – oxygen bond at C-4 of the pyran ring. They treated alcohol **60** with mercury(II) acetate and sodium borohydride in the presence of oxygen to afford a diastereomeric mixture of products **61** and **62** in a reported 86 % yield. The *cis*-isomer was exclusively obtained by initially oxidizing the isomeric mixture to the racemic ketone **63,** followed by reduction with lithium aluminium hydride in ether to give the diastereomerically pure dimethoxybenzo[c]pyran **62**. Oxidation of **62** with silver(II) oxide [26] afforded the quinone **64** in 89% yield (Scheme 12).



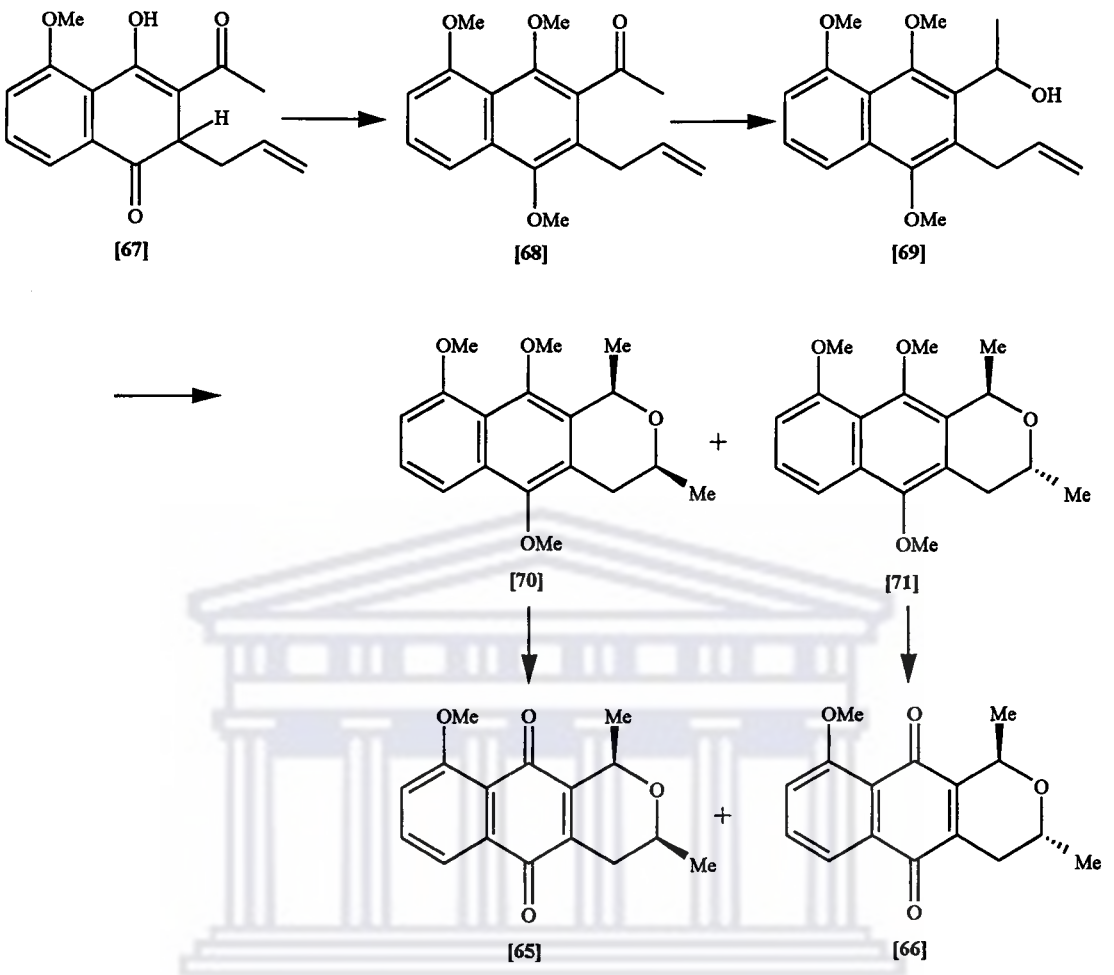
(i) $Hg(OAc)_2$, O_2, $NaBH_4$, DMF, 86 % ; (ii) PCC, CH_2Cl_2, 74 %;

(iii) $LiAlH_4$, Et_2O, 80 %; (iv) AgO, HNO_3, 89 %.

Scheme 12

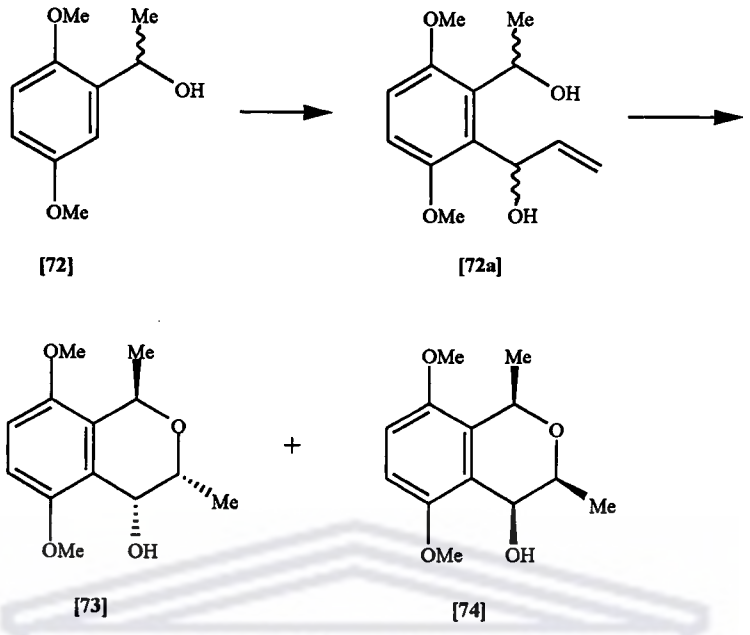
1.3.4. Reductive Mercury(II) Mediated Cyclisation

In the synthesis towards (±) eleutherin **65** and (±) isoeleutherin **66**, Uno [27,28] started with the allylated product **67** which was directly converted to the trimethoxynaphthalene **68** in 92% yield by treatment with methyl iodide and potassium carbonate in boiling acetone. Reduction of ketone **68** with lithium aluminium hydride in ether produced alcohol **69** in 98% yield. Intramolecular oxymercuration and subsequent reduction with sodium borohydride gave a mixture of two diastereomeric naphthopyrans (**70** : **71** = ca. 1 : 1, combined yield was 93%). Separation by column chromatography gave the pure *cis* and *trans* isomers **70** (42%) and **71** (47%). Each isomer (**70** or **71**) was separately oxidized by cerium(IV) ammonium nitrate to afford (±) eleutherin **65** (90%) and (±) isoeleutherin **66** (89%). The overall yields of **65** and **66** were 38% and 34% from **67** respectively (Scheme 13).



Scheme 13

Kraus *et al.*[29] used a mercury-mediated cyclisation during their synthesis of racemic hongconin **4**. They started from racemic alcohol **72,** which was converted to the dianion with 2 equivalents of n-butyllithium. After reaction with acrolein at –78 °C, followed by acidification, an inseparable mixture of diols **72a** was isolated in 41% yield. The mixture of diols was treated with mercuric acetate in aqueous tetrahydrofuran according to the method of Maruyama [30] and then reduced with sodium borohydride to give a 5 : 1 ratio of alcohols **73** and **74** in 59% isolated yield (Scheme 14).

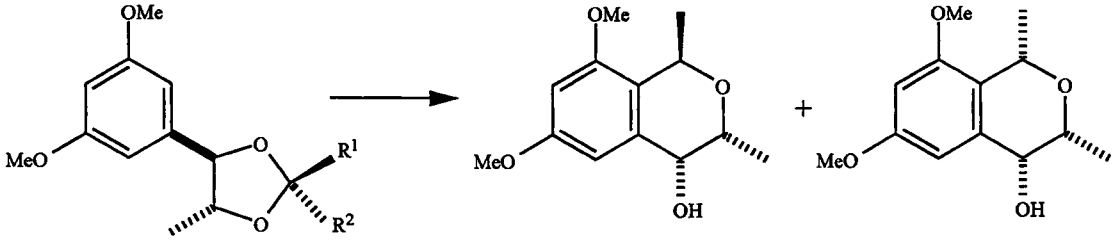


Scheme 14

1.3.5. Titanium(IV) Mediated Isomerisations

Giles [31,32] showed that diastereomeric mixtures of phenyl-and naphthyl dioxolanes are stereoselectively isomerised with titanium tetrachloride in methylene chloride at –78 °C to yield benzo- and naphthopyrans.

Thus treatment of a mixture of 4-(3',5'–dimethoxyphenyl)-2, 5–dimethyl-1, 3-dioxolanes, **75** and **76** with 2 mol equivalents of titanium tetrachloride in dichloromethane at –78 °C for 30 minutes lead to the isolation of two isochromane isomers **77** and **78** in yields of 10% and 73% respectively [33] (Scheme 15).



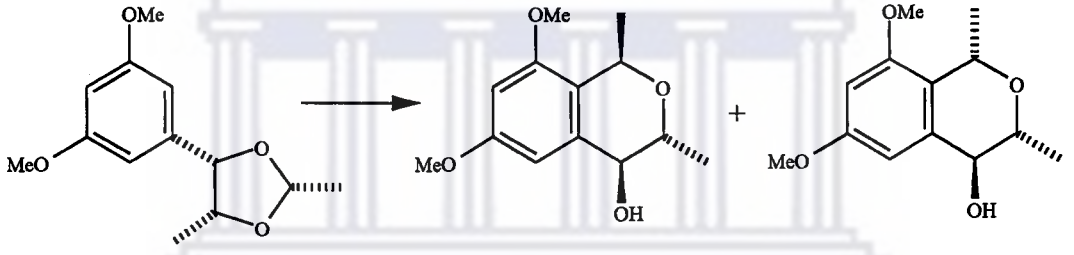
[75] $R^1 = Me, R^2 = H$

[76] $R^1 = H, R^2 = Me$

[77] [78]

Scheme 15

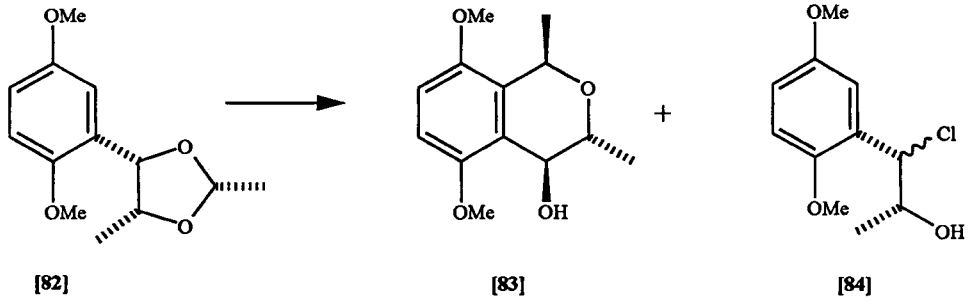
The all *cis*–dioxolane **79** under the same reaction conditions lead to the isolation of isochromanes **80** and **81** in 70% and 17% yield respectively (Scheme 16).



[79] [80] [81]

Scheme 16

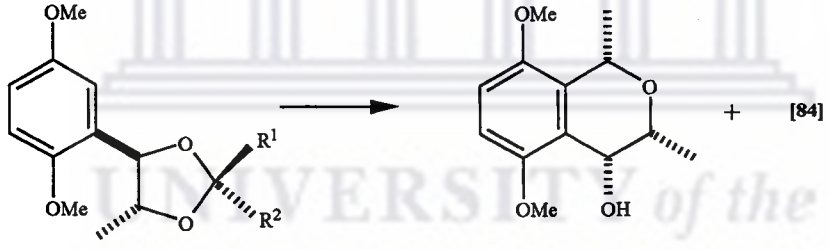
Further investigation into the stereoselective isomerisation of 4 - (2',5' –dimethoxyphenyl)-2, 5 –dimethyl -1, 3-dioxolanes, showed that treatment of the all *cis*- dioxolane **82** with 1 equivalent of titanium tetrachloride in dichloromethane at –78 °C for 30 minutes gave aside from starting material (20%) the isochromane **83** (18%) and a diastereomeric mixture (1 : 1) of chlorohydrins **84** (45%) [34] (Scheme 17).



[82] [83] [84]

Scheme 17

Treatment of the 2:1 mixture of 4,5 –*trans* –dioxolanes **85** and **86** under the same reaction conditions, afforded a new isochroman **87** as the sole product of isomerisation together with the diastereomeric mixture of chlorohydrins **84** in yields of 45% and 31% respectively (Scheme 18).

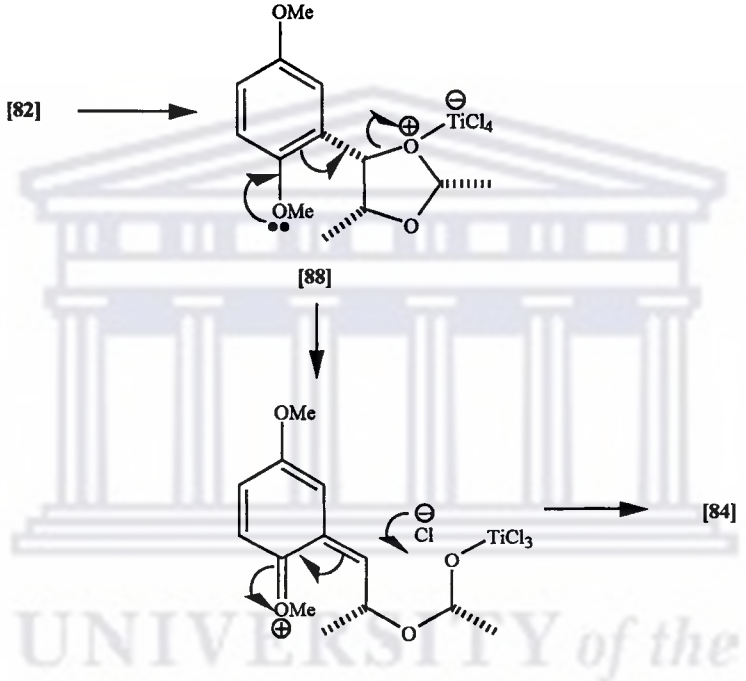


[85] R^1 = Me, R^2 = H
[86] R^1 = H, R^2 = Me

[87]

Scheme 18

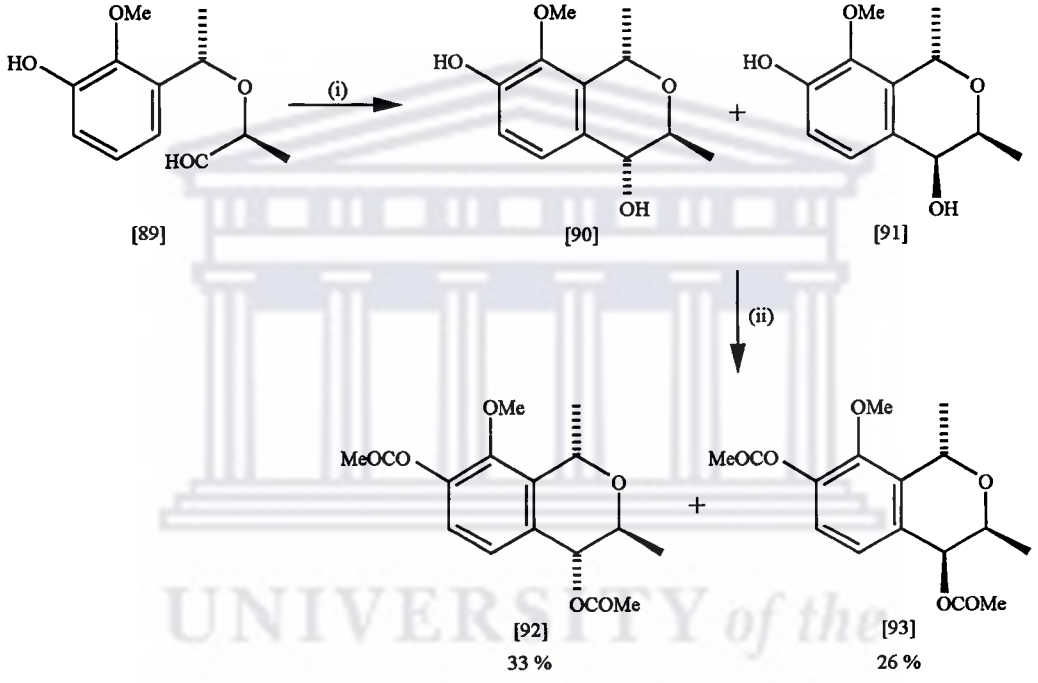
The authors rationalized that the relatively low yields of the isochromanes **83** and **87** derived from **82**, **85** and **86**, in comparison with those from their 3,5-dimethoxy isomers [33], are ascribed to the influence of the 2' -methoxy substituent, being *ortho* to the dioxolane ring. This group promotes the alternative C-4 – O-3 bond cleavage upon reaction with the Lewis acid (shown for intermediate **88** from dioxolane **82** in Scheme 19), with formation of the chlorohydrin **84** [34].



Scheme 19

1.3.6. Intramolecular Cyclisation of Tethered Lactaldehydes

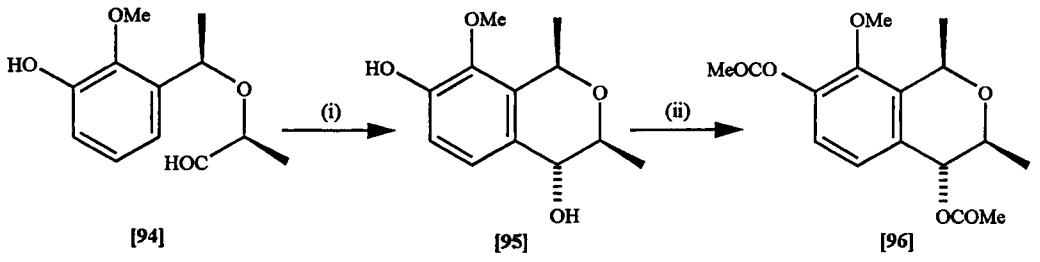
Giles and co-workers [35] showed that intramolecular cyclisation of an asymmetric phenolic aldehyde **89** occurs under mild conditions of chromatography over silica gel, to afford an epimeric mixture of asymmetric *trans*-1, 3-dimethylisochroman-4-ols **90** and **91**. The latter diols were unstable and thus converted into their diacetates **92** and **93** in 33% and 26% yield respectively (Scheme 20).



(i) column chromatography on silica gel with 5 – 50 % ethyl acetate / hexane / trace triethylamine as eluent; (ii) dry pyridine, acetic anhydride, 20 hrs. at room temperature

Scheme 20

The corresponding *cis*–1,3-dimethylisochroman-4-ol **95** was similarly obtained from aldehyde **94**. The diol **95** was converted into the diacetate **96** in 77% yield (Scheme 21).



[94] [95] [96]

Scheme 21

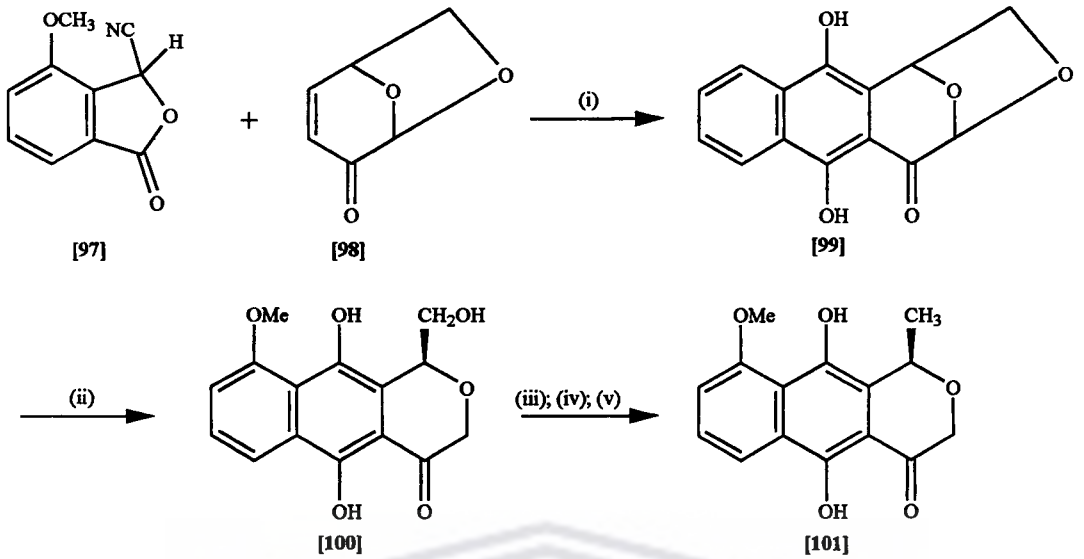
1.3.7. Annelation Reactions Using Phthalides and Pre-formed Lactones

In 1985, Freskos and Swenton were the first to report an annelation strategy for the preparation of a chiral naphthopyran ring system which is central to the naphtho [2,3-c]pyran-5,10-quinone type antibiotics [36].

The reaction of the anion of 3-cyano-4-methoxy-3-H-isobenzofuran-1-one **97** with levoglucosenone **98** produced a stable, crystalline, chiral naphthohydroquinone **99** (65%). Reductive ring opening of **99** using a zinc-copper couple in tetrahydrofuran produced the primary alcohol **100** which was transformed into the desired chiral compound **101** (60%) (Scheme 22).

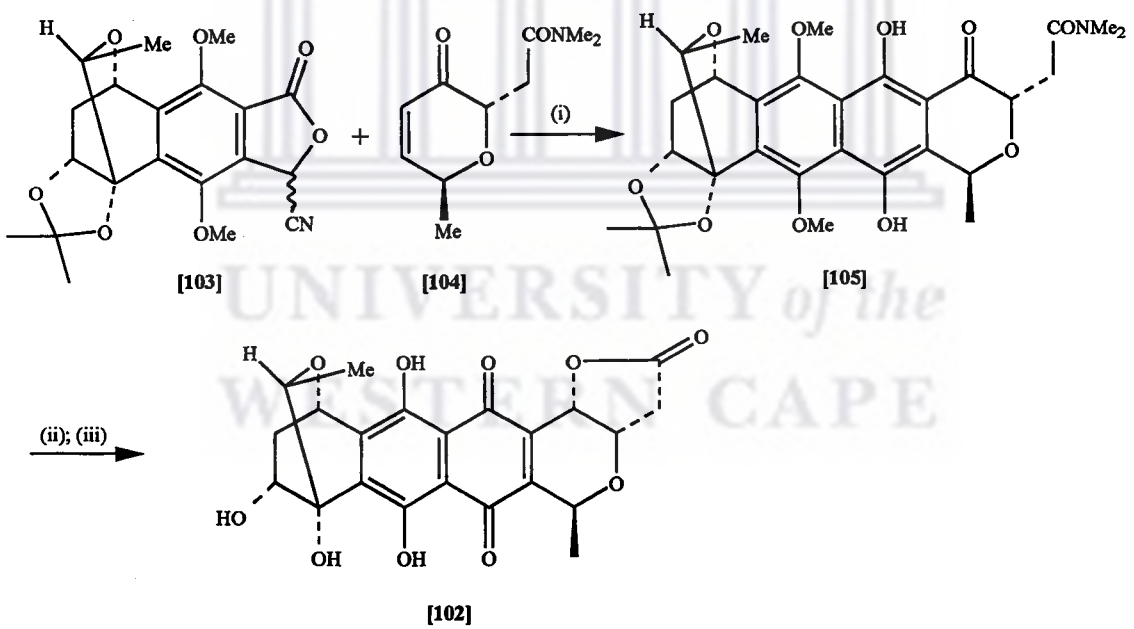
Yoshi et al. [37] described a stereo-controlled synthesis of optically active natural granaticin **102**, which employs benzannulation between the pentacyclic phthalide **103** and a dihydropyran **104**, both having the correct absolute stereochemistry. Lactonization of the resulting product **105** and oxidative O – demethylation produced optically active granaticin **102** in 62% yield (Scheme 23).

This method of annelation of a pre-formed pyranone and a phththalide has also been used for the enantioselective synthesis of (-) hongconin **106** [38,39], (+) hongconin **107** and medermycin **108** [40].



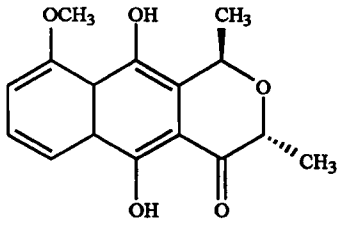
(i) $MeSOCH_2Li$; (ii) Zn – Cu couple; (iii) $MeSO_2Cl$; (iv) NaI; (v) Zn – Cu couple

Scheme 22

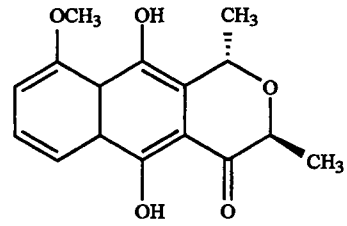


(i) $MeSOCH_2Li$; (ii) excess of 2-methoxypropene, camphorsulphonic acid, THF, room temperature; (iii) cerium(IV) ammonium nitrate, MeCN, then $AlCl_3$ (6 equiv.), Et_2S (24 equiv.), CH_2Cl_2, room temperature.

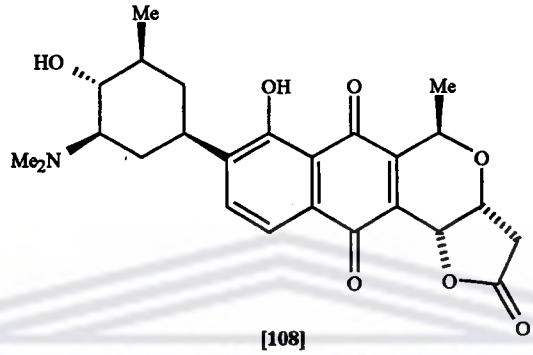
Scheme 23



[106]



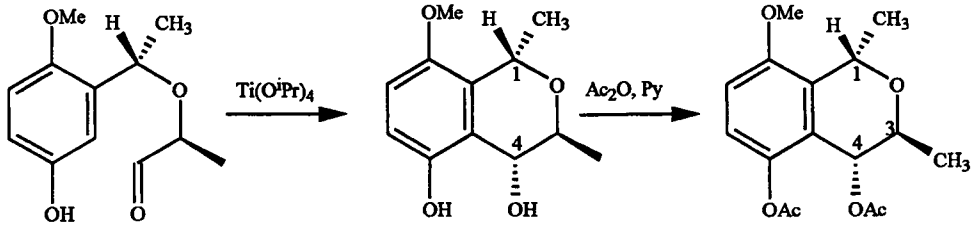
[107]



[108]

1.3.8. Titanium Tetraisopropoxide Mediated Cyclisation

Giles and Joll [41] described the first chiral synthesis of 4-acetoxybenzo[c]pyran **111** related to the aphid pigments. They treated an optically pure phenol **109**, bearing a tethered aldehydic side chain derived from (S)-ethyl lactate with titanium tetraisopropoxide in dichloromethane under ultrasonic irradiation. The formed unstable diol **110** was then immediately converted to the diacetate **111** in an overall yield of 71% from **109** (Scheme 24).

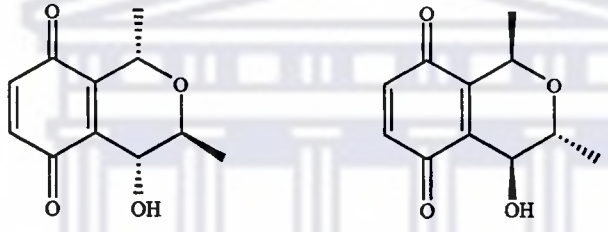


[109] [110] [111]

Scheme 24

Some intramolecular reactions between metal phenolates and chiral aldehydes have shown that the process is highly diastereoselective (d.e's of at least 90%), with the choice of the metal determining the mode of addition (*syn* or *anti*) during the carbon-carbon formation [42,43]. The triisopropoxytitanium phenolate, with toluene as solvent, afforded the product of *anti* addition from **109**, whereas the use of a bromomagnesium phenolate in dichloromethane furnished the *syn* addition product.

This method was used by Giles and Joll [44] towards the asymmetric synthesis of the enantiomer **112** of the benzopyranquinone **113**.

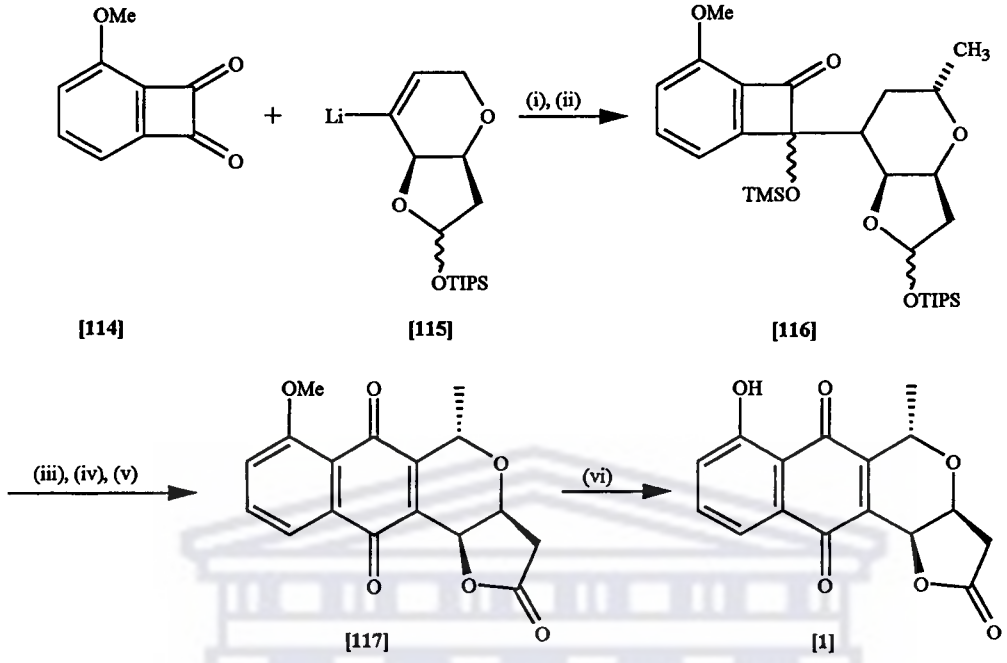


[112] [113]

1.3.9. Thermal Ring Expansions

Moore et al. [45] reported the chiral synthesis of (-) nanaomycin D **1**, which is based upon the thermal ring expansion of 4-alkenyl-4-hydroxycyclobutenones to hydroquinones [46,47]. They started with 3-methoxybenzocyclobutenedione **114** which was converted to the adduct **116** upon treatment with the lithium reagent **115**, in tetrahydrofuran at –78 °C, followed by a trimethylsilyl chloride quench. Thermolysis of adduct **116** in refluxing *p*-xylene follwed by hydrolysis and oxidation gave 9-*O*-methylnanaomycin D **117**. Demethylation with aluminium trichloride gave the natural product **1** (Scheme 25).

This method was also used to synthesize racemic nanaomycin D **1** and deoxyfrenolicin **7** [48,49].



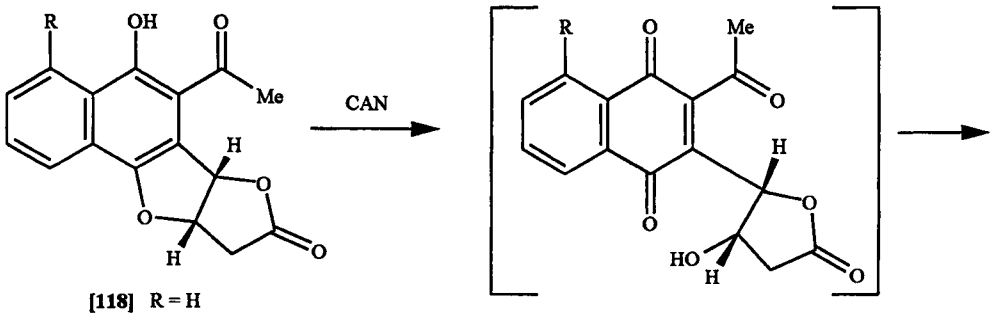
(i) THF, -78 °C; (ii) TMSCl, (iii) Δ, p-xylene; (iv) HCl; (v) PCC; (vi) $AlCl_3$

Scheme 25

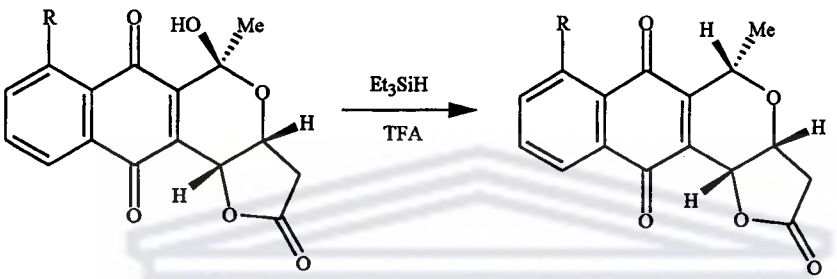
1.3.10. Cyclisation of the Dihydropyran Ring by ring-cleavage of a Furonaphthalene with Cerium(IV) ammonium nitrate

Brimble *et al.*[50] reported that furo[3,2-b]naphtho[2,1-d]furan-8(9H)-ones **118** and **119** undergo oxidation with cerium ammonium nitrate to give rearranged hemiketals **120** and **121** respectively. Reduction of these hemiketals with triethyl silylhydride afforded pyranonaphthoquinones with a fused γ–lactone **122, 123**. The furonaphthofuran ring systems **118** and **119** are formed *via* the uncatalyzed addition of 2-trimethylsilyloxyfuran to 1,4-benzoquinones (Scheme 26).

This method was also used to synthesize the griseusin A **124** ring system[51], 5-epi-7-deoxykalafungin **125**[52], 5-epi-7-O-methylkalafungin **126**[52], 5-epi-arizonin B1 **127** [53], 5-epi-arizonin C1 **128**[53], arizonin C1 **10**[54], and an actinorhodin monomer **129**[55].

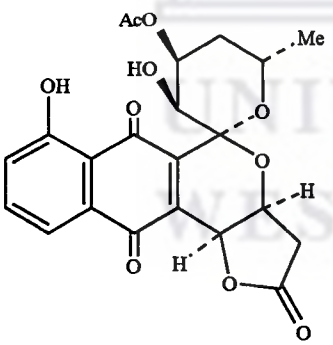


[118] R = H
[119] R = OMe

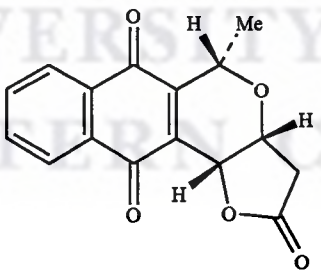


[120] R = H; 72 %
[121] R = OMe; 76 %
[122] R = H; 92 %
[123] R = OMe; 95 %

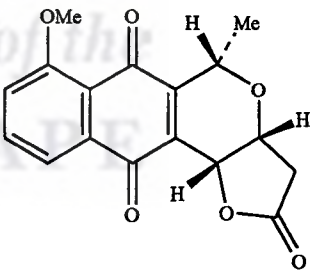
Scheme 26



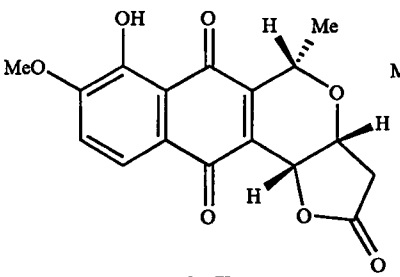
[124]



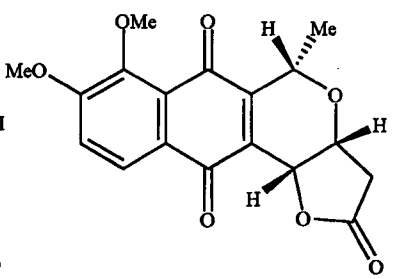
[125]



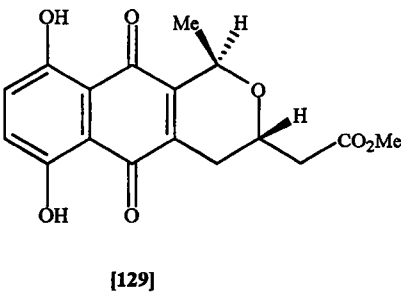
[126]



[127]



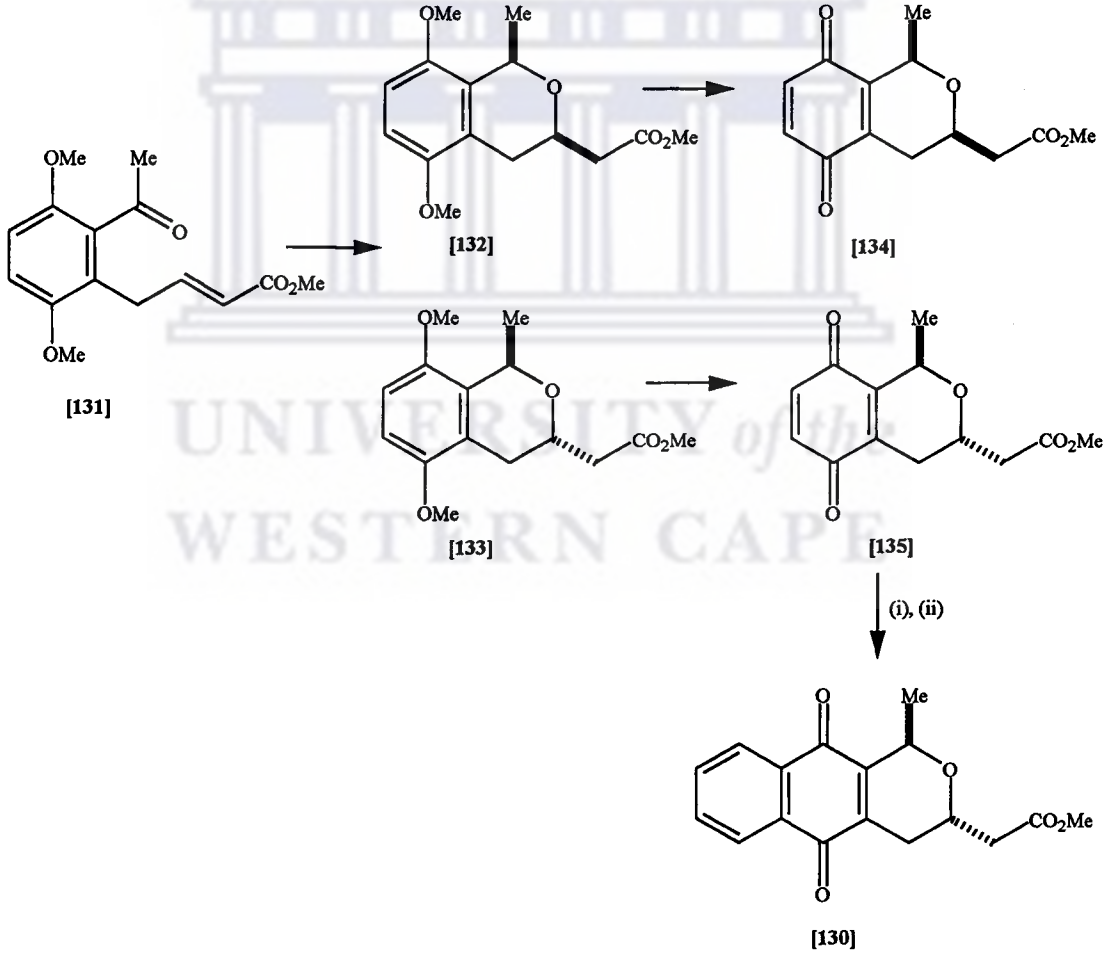
[128]



[129]

1.3.11. Reductive cyclisation with sodium borohydride

In 1981, Yoshii *et al.*[56] reported the synthesis of 9-deoxynanaomycin A methyl ester **130**. Here a conjugated ester **131** was reduced with sodium borohydride in methanol to produce a mixture of cis- and trans- isochromans, **132** and **133** (in a ratio 1 : 3.5). The isochromanes were oxidatively demethylated with cerium(IV) ammonium nitrate to afford the corresponding quinones **134** and **135**. Compound **135** was treated with 1-acetoxybuta-1,3-diene in toluene followed by treatment with sodium carbonate in aqueous ethanol to form the deoxynanaomycin A methyl ester **131** in 78% yield (Scheme 27).



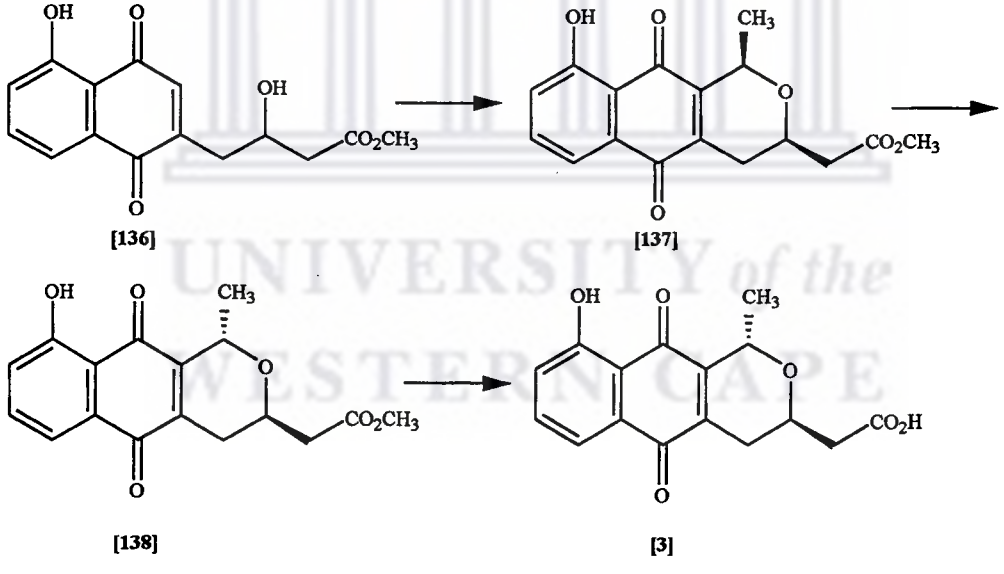
(i) 1-acetoxybuta-1,3-diene in toluene, (ii) Na_2CO_3 in aq. Ethanol

Scheme 27

Racemic nanaomycin A **3** [57] was also synthesised *via* this method.

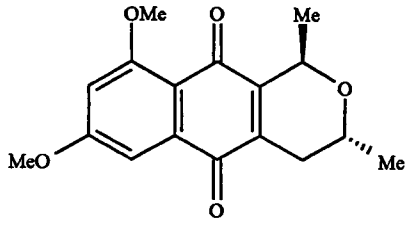
1.3.12. Cyclisation using acetaldehyde followed by acid-catalyzed dehydration

An efficient synthetic route to racemic nanaomycin A **3** was reported by Yoshii *et al.*[58]. The dihydropyran ring formation was achieved according to the method of Li [59,60]. Compound **136** was reacted with zinc and hydrochloric acid in tetrahydrofuran for 5 minutes to which an excess of acetaldehyde was added. Heating was continued at 60 ° C for 4 hours. Oxidation with silver(I) oxide resulted in the formation of pyranojuglone **137** (the *cis*-isomer of nanaomycin A methyl ester) in 51% yield. Isomerisation of **137** to the *trans*-isomer **138** was effected with sulphuric acid and the latter ester **138** was saponified [59,61] to afford (±) nanaomycin A **3** in 66% yield (Scheme 28).

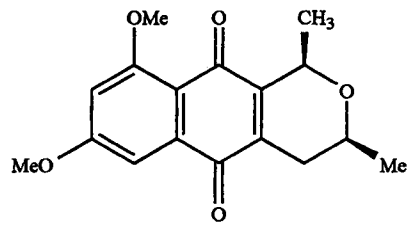


Scheme 28

This method of dihydropyran ring formation was also used by Cameron *et al.*[62] in their synthesis of (±) deoxyquinone A dimethyl ether **139** and its epimer (±)-7-methoxyeleutherin **140**.



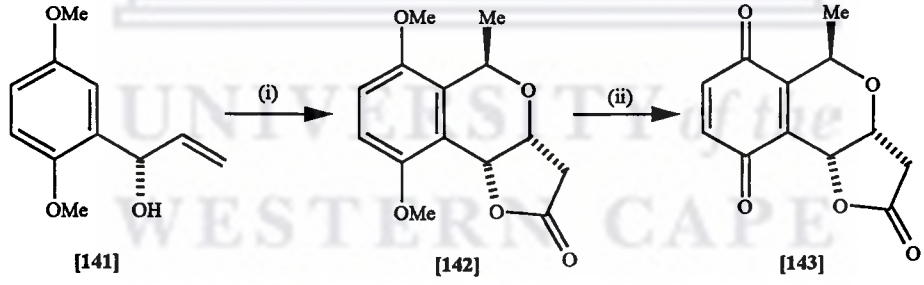
[139]



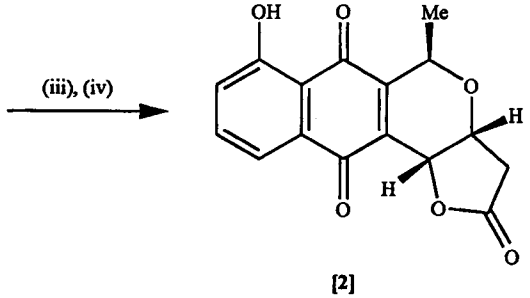
[140]

1.3.13. Palladium(II) Mediated Cyclisations

In the synthesis of kalafungin **2**, Kraus *et al.*[63] cyclised the diol **141** with palladium acetate and cupric chloride under an atmosphere of carbon monoxide to provide the lactone **142** in 61% yield. Oxidation using standard Rapoport[26] conditions (AgO, nitric acid) generated the benzoquinone **143** in 91% yield. Quinone **143** was treated with 1-[(trimethylsilyl)oxy]-1,3-butadiene in methylene chloride, followed by Jones oxidation to provide racemic **2** in 63% yield from **142** (Scheme 29).



[141] [142] [143]

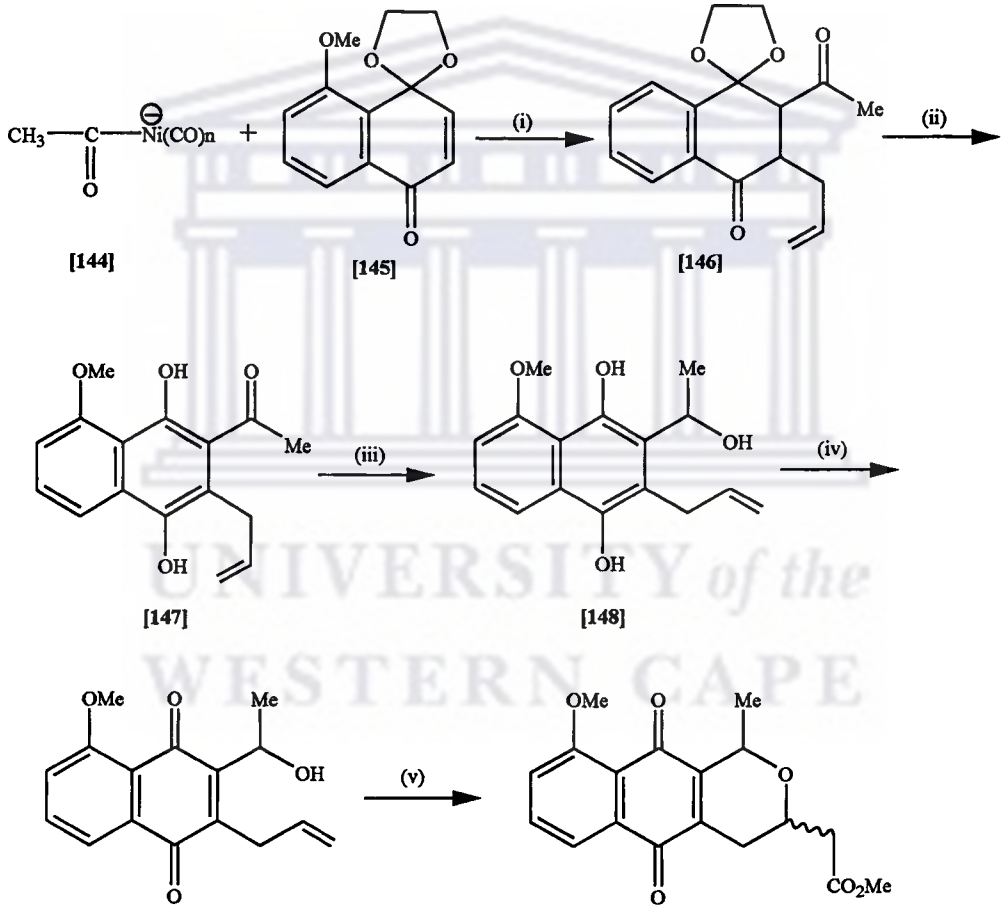


[2]

(i) $Pd(OAc)_2$ (30 %), $CuCl_2$ (2.5 eq.), CO, THF; (ii) AgO, HNO_3 (6N), THF, 1hr.
(iii) 1-[(trimethylsilyl)oxy]-1,3-butadiene, CH_2Cl_2, -78 °C; (iv) Jones oxidation

Scheme 29

In the synthesis of nanaomycin A **3**, the conjugate addition of an acylate-nickel complex **144** to an appropriate naphthoquinone monoketal **145** followed by trapping with an alkyl halide was used by Semmelhack [64,65]. The key intermediate **149** was treated with palladium dichloride, excess cupric chloride and carbon monoxide in methanol to afford the pyran ester isomers **150** and **151** in the ratio 3 : 2 in 66% yield. Previous work[59,61] had described the equilibration between **150** and **151,** and the deprotection of the methoxy and ester groups to eventually produce (+) nanaomycin A **3** (Scheme 30).



(i) allyl iodide; (ii) HCl (6 M), dioxane, argon, (iii) $NaBH_4$, (iv) DDQ;

(v) $PdCl_2$, $CuCl_2$, CO, MeOH

Scheme 30

SECTION 2. AIMS

1. To devise a general protocol for the synthesis of chiral *ortho*-alkenyl hydroxyethyl dialkoxy benzene systems.

2. To establish the most favourable conditions for the cyclisation of these systems to the corresponding chiral isochromans and 4-hydroxyisochromans without the loss of chirality.

3. To convert the chiral isochromans into the corresponding quinones for biological evaluation.

SECTION 3. EXPERIMENTAL – GENERAL PROCEDURES

Purification of Solvents

All solvents used for reactions and preparative chromatography were distilled prior to use. Tetrahydrofuran and diethyl ether were dried in sodium using the sodium benzophenone ketyl radical as indicator. Dimethylformamide, tetrahydrofuran, diethyl ether and toluene were stored over molecular sieves (4A). Other reagents obtained from commercial sources were used without further purification.

Chromatographic Separations

Preparative column chromatography was carried out on dry-packed columns using Merck silica gel 60 (particle size 0.2 - 0.5 mm) as the adsorbent and Merck silica gel 60 (0.063 – 0.2 mm) as the stationary phase. Mixtures of ethyl acetate and hexane were used as the eluant.

Physical and Spectroscopic Data

All melting points were obtained on a FISCHER-JOHNS melting point apparatus and are uncorrected.

^{1}H-nmr (nuclear magnetic resonance) spectra were recorded on VARIAN 200 spectrometer. Spectra were recorded in deuterated chloroform ($CDCl_3$) and chemical shifts are reported in parts per million downfield from tetramethylsilane, the internal standard; coupling constants are given in Hertz. Splitting patterns are designated as "s", "d", "t", "q", "m", "bs" and "sept", these symbols indicate "singlet", "doublet", "triplet", "quartet", "multiplet", "broad singlet" and "septet".

^{13}C-nmr (nuclear magnetic resonance) spectra were recorded on VARIAN 200 spectrometer. Spectra were recorded in deuterated chloroform ($CDCl_3$) and chemical

shifts are reported in parts per million relative to the central signal of deuterated chloroform, taken as δ 77.0.

^{19}F-nmr (nuclear magnetic resonance) spectra were recorded at the Department of Chemistry, University of Cape Town, on a VARIAN 200 spectrometer.

Infrared spectra were recorded on a PERKIN ELMER FT-IT spectrometer PARAGON 2000. Oil samples were recorded as thin films between sodium chloride plates, while solid samples were recorded as potassium bromide pellets.

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

Optical rotations were measured on a PERKIN ELMER-Polarimeter 141 at 21 °C at the sodium D line.

Elemental analyses were performed on both oil and solid samples where possible on a CARLO ERBA 1500 NA analyzer.

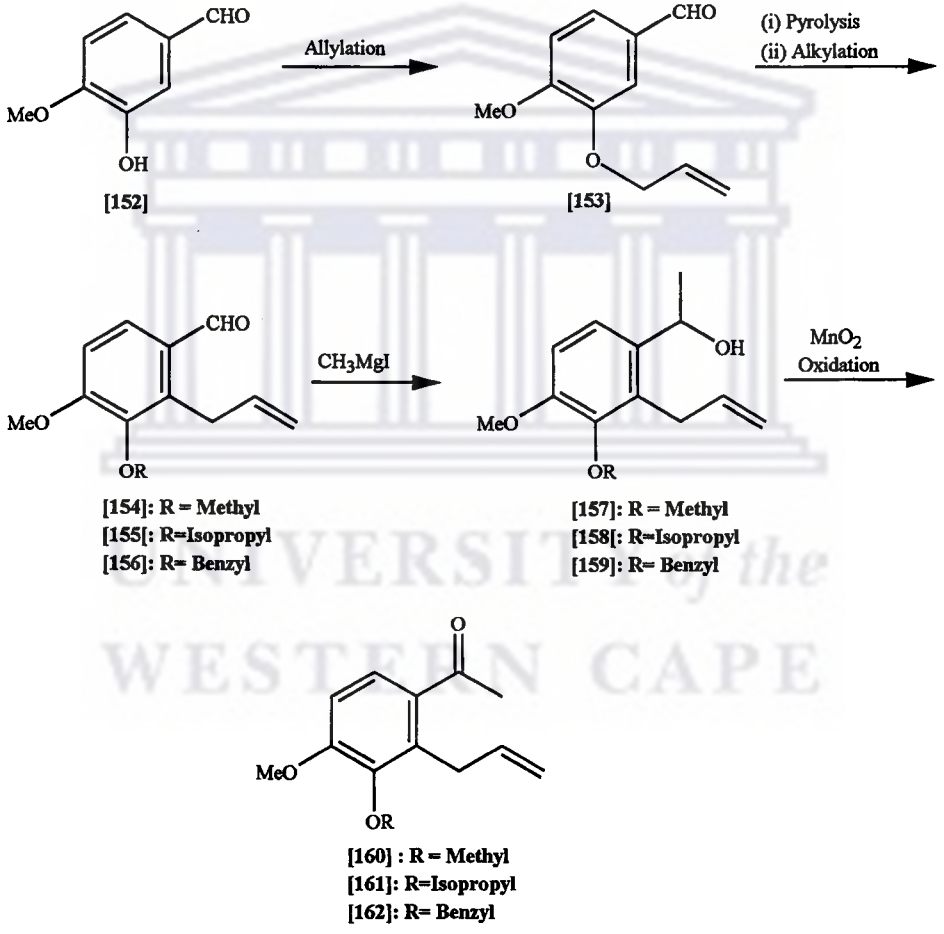
Other General Procedures

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

SECTION 4. RESULTS AND DISCUSSION

4.1. The Synthesis of 2-Alkenyl-3,4-dialkoxylated acetophenones

The synthesis of 2-alkenyl-3,4-dialkoxy acetophenones **160, 161** and **162** were envisaged as outlined in Scheme 31. These compounds were prepared as the precursors for the chiral reduction of the ketone functionality to the corresponding (*R*)-alcohols (Scheme 31).



Scheme 31

The synthesis commenced with the allylation of 3-hydroxy-4-methoxybenzaldehyde **152**. Compound **152** was heated with potassium carbonate and allyl bromide in

dimethylformamide at 80 °C for 18 hours under nitrogen to give the allylated product **153** in 91% yield. The allylated product **153** was pyrolysed at 180 °C for 12 hours during which the allyl group migrates to the sterically disfavoured *ortho*-position [66, 67, 68]. After addition of the appropriate allyl halide and potassium carbonate, the reaction mixture was heated (80 °C) under nitrogen in dimethylformamide for 24 hours to afford the ortho-allylated benzaldehydes **154** (77%), **155** (89%) and **156** (77%). These compounds were treated with methyl magnesium iodide to yield the corresponding secondary alcohols **157** (93%), **158** (80%) and **159** (89%) which were oxidized to the desired acetophenones **160** (57%), **161** (60%) and **162** (57%) using 10 mass equivalents of manganese dioxide in boiling benzene.

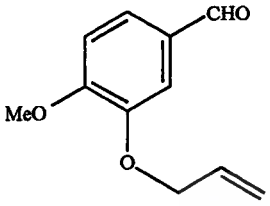
The tetrasubstituted benzaldehydes **154**, **155** and **156** are typified by the *ortho* coupled pair of aromatic hydrogens and the concommitant disappearance of the single proton signal at δ 7.40 in the ^{1}H-nmr spectra of **153**. Also, the shift in the methylene signal of the allyl group from δ 4.66 in the precursor **153** to δ 3.85 in the product **154** clearly demonstrates the migration of the allyl group to the *ortho* position.

The appearance of the methyl doublet at δ 1.46 with *J* 6.4 Hz in the ^{1}H-nmr spectrum of **157**, clearly demonstrates that the carbonyl group has undergone reduction which is corroborated by the strong O-H stretching frequency at ν_{max} 3404 cm^{-1} in the infrared spectrum. The strong carbonyl adsorption band at ν_{max} 1684 cm^{-1} in the infrared spectrum together with the appearance of the singlet at δ 2.52 for the methyl group of the acetyl side chain in the ^{1}H-nmr spectrum was sufficient evidence to support the oxidation of alcohol **157** to the corresponding ketone **160**.

4.1.1. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

4-Methoxy-3-prop-2'-enyloxybenzaldehyde (153)



[153]

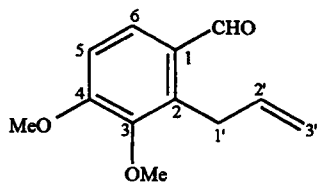
3-Hydroxy-4-methoxybenzaldehyde **152** (20.89 g, 0.137 mol) was dissolved in dry dimethylformamide (150 ml). Allyl bromide (48.4 g, 0.4 mol, 34 ml) and potassium carbonate (55.2 g, 0.4 mol) were then added. The mixture was stirred vigorously at 80 °C (oil bath) under nitrogen for 18 hours. The cooled mixture was filtered and the filtrate diluted with water (1.2 L). The resulting aqueous solution was then extracted with diethyl ether (4 × 250 ml). The organic layer was dried over magnesium sulphate, filtered and the solvent removed by rotary evaporation. The residue was purified by column chromatography using initially (5:95) and later (1:4) ethyl acetate - hexane as eluant. The product was obtained as a pale yellow oil (24 g, 91%).

153 ν_{max} 1686 cm^{-1} (C=O); δ_H 3.96 (3H, s, ArOCH_3), 4.66 (2H, m, OCH_2CH=CH_2), 5.40 (2H, m, CH_2CH=CH_2), 6.10 (1H, m, CH_2CH=CH_2), 6.97 (1H, d, *J* 8.2 Hz, 5-H), 7.40 (1H, d, *J* 1.8 Hz, 2-H), 7.46 (1H, dd, *J* 8.2 and 1.8 Hz, 6-H), 9.82 (1H, s, CHO); δ_C 55.1 (ArOCH_3), 69.7 (ArOCH_2), 110.6 (C-5), 110.8 (C-3'), 118.6 (C-2'), 126.8 (C-6), 130.0 (C-1), 132.5 (C-2), 148.5 (C-3), 154.8 (C-4), 191 (C=O); MS (EI): *m/z* (%): 192 (M^+, 100), 177 (13), 163 (24), 151 (29), 133 (14), 95 (33), 77 (27).

Found: C, 68.62 %; H, 6.11 %.

Calculated for $C_{11}H_{12}O_3$: C, 68.72%; H, 6.31%; *M* 192.23.

3,4-Dimethoxy-2-prop-2'-enylbenzaldehyde (154)



[154]

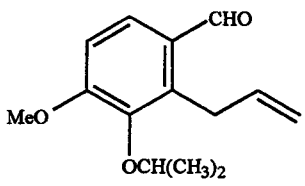
4-Methoxy-3-prop-2'-enyloxybenzaldehyde **153** (8.01 g, 0.0417 mol) was pyrolyzed at 180 °C under nitrogen for 12 hours. After cooling the intermediate product was dissolved in dimethylformamide (80 ml). Methyl iodide (23.7 g, 0.166 mol, 10.4 ml) and potassium carbonate (23 g, 0.166 mol) were added. The reaction mixture was vigorously stirred and heated (80 °C) in an oil bath for 24 hours under nitrogen. The reaction mixture was cooled, filtered and the filter cake washed with dimethylformamide (2 × 30 ml). The filtrate was transferred to a separating funnel with water (600 ml) and the aqueous layer was extracted with diethyl ether (4 × 150 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as a yellow oil in (6.64 g, 77 %).

154 ν_{max} 1686 cm^{-1} (C=O); δ_H 3.81 (3H, s, ArOC*H*$_3$), 3.86 (2H, dt, *J* 5.8 and 1.8 Hz C*H*$_2$CH=CH$_2$), 3.93 (3H, s, ArOC*H*$_3$), 4.91 (1H, dq, *J* 17.4 and 1.8 Hz, *trans*-CH$_2$CH=C*H*$_2$), 5.01 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-CH$_2$CH=C*H*$_2$), 6.00 (1H, m, CH$_2$C*H*=CH$_2$), 6.92 (1H, d, *J* 8.6 Hz, 5-H), 7.64 (1H, d, *J* 8.6 Hz, 6-H), 10.05 (1H, s, C*H*O); δ_C 28.7 (*C*H$_2$CH=CH) 55.8 (ArO*C*H$_3$), 61.0 (ArO*C*H$_3$), 110.0 (C-5), 115.8 (C-3'), 128.1 (C-1)[a], 129.2 (C-6), 136.3 (C-2)[a], 137.3 (C-2'), 147.4 (C-3)[b], 157.7 (C-4)[b], 191.1 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 206 (M^+, 32) 191 (100), 175 (35), 163 (10), 147 (13), 103 (10), 91 (10).

Found: C, 69.72%; H, 6.61%.

Calculated for $C_{12}H_{14}O_3$: C, 69.87%; H, 6.86%; *M* 206.26.

3-Isoproyloxy-4-methoxy-2-prop-2'-enylbenzaldehyde (155)



[155]

4-Methoxy-3-prop-2'-enyloxybenzaldehyde **153** (8.01 g, 0.0417 mol) was pyrolyzed at 180 °C under nitrogen for 12 hours. After cooling the intermediate product was dissolved in dimethylformamide (80 ml). Isopropyl bromide (20.5 g, 0.166 mol, 15.8 ml) and potassium carbonate (23 g, 0.166 mol) were added and the reaction mixture was stirred and heated at (80 °C) for 24 hours under nitrogen. The reaction mixture was cooled, filtered and the filter cake washed with dimethylformamide (2 × 30 ml). The filtrate was transferred to a separating funnel with water (600 ml) and the aqueous layer was extracted with diethyl ether (4 × 150 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as a yellow oil in (7.16 g, 90 %).

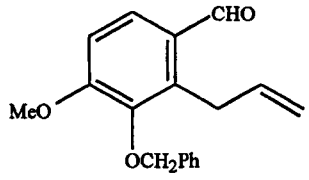
155 ν_{max} 1686 cm^{-1} (C=O); δ_H 1.28 [6H, d, *J* 6.2 Hz $OCH(CH_3)_2$], 3.88 (2H, dt, *J* 5.8 and 1.6 Hz, $CH_2CH=CH_2$), 3.90 (3H, s, $ArOCH_3$), 4.56 [1H, sept, *J* 6.2 Hz, $OCH(CH_3)_2$], 4.88 (1H, dq, *J* 17.2 and 1.6 Hz, *trans*-$CH_2CH=CH_2$), 5.02 (1H, dq, *J* 10.2 and 1.6 Hz, *cis*-$CH_2CH=CH_2$), 6.00 (1H, m, $CH_2CH=CH_2$), 6.90 (1H, d, *J* 8.6 Hz, 5-H), 7.61 (1H, d, *J* 8.6 Hz, 6-H), 10.07 (1H, s, CHO); δ_C 22.5 [2×($OCH(CH_3)_2$)], 29.0 ($CH_2CH=CH_2$), 55.7 ($ArOCH_3$), 75.0 ($OCH(CH_3)_2$), 109.7 (C-5), 115.7 (C-3'), 128.2 (C-6), 128.2 (C-1)[a], 136.6 (C-2)[a], 137.3 (C-2'), 145.1 (C-3)[b], 157.8 (C-4)[b], 191.3 (CHO). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 234 (M^+, 19), 219 (18), 192 (39), 177 (100), 159 (20), 131 (18), 103 (103).

Found: C, 71.66%; H, 7.74%.

Calculated for $C_{14}H_{18}O_3$: C, 71.76%; H, 7.76%; *M* 234.32.

3-Benzyloxy-4-methoxy-2-prop-2'-enylbenzaldehyde (156)

4-Methoxy-3-prop-2'-enyloxybenzaldehyde **153** (8.01 g, 0.0417 mol) was pyrolyzed at 180 °C under nitrogen for 12 hours. After cooling the intermediate product was dissolved in dimethylformamide (80 ml). Benzyl bromide (28.4 g, 0.166 mol, 19.8 ml) and potassium carbonate (23 g, 0.166 mol) were added. The reaction mixture was stirred and heated at (80 °C) for 24 hours under nitrogen. The reaction mixture was cooled, filtered and the filter cake washed with dimethylformamide (2 × 30 ml). The filtrate was transferred to a separating funnel with water (600 ml) and the aqueous layer was extracted with diethyl ether (4 × 150 ml). The residue obtained upon work-up was purified by column chromatography using initially (1:9) then later (1:4) ethyl acetate - hexane as eluant. The product obtained was a yellow oil (9.05 g, 77%).



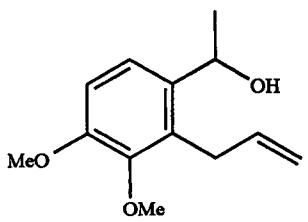
[156]

156 ν_{max} 1686 cm^{-1} (C=O); δ_H 3.85 (2H, dt, *J* 5.6 and 1.8 Hz, $CH_2CH=CH_2$), 3.97 (3H, s, $ArOCH_3$), 4.89 (1H, dq, *J* 17.6 and 1.8 Hz, *trans*-$CH_2CH=CH_2$), 4.98 (2H, s, OCH_2Ph), 5.02 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-$CH_2CH=CH_2$), 6.00 (1H, m, $CH_2CH=CH_2$), 6.96 (1H, d, *J* 8.6 Hz, 5-H), 7.37 (5H, m, Ph*H*'s), 7.67 (1H, d, *J* 8.6 Hz, 6-H), 10.06 (1H, s, C*H*O); δ_C 28.9 ($CH_2CH=CH_2$), 56.0 ($ArOCH_3$), 75.0 (OCH_2Ph), 110.0 (C-5), 115.9 (C-2'), 128.2 (×2 aryl), 128.6 (×2 aryl), 129.2 (C-6), 136.7 (aryl), 137.3 (×2, C-2' and aryl), 137.5 (C-1)[a], 140.7 (C-2)[a], 146.2 (C-3)[b], 157.8 (C-4)[b], 191.2 (CHO). Assignments with the same superscripts may be interchanged. MS (EI) *m/z* (%): 282 (M^+, 2), 264 (17), 191 (100), 177 (43), 163 (17), 103 (11), 91 (95), 65 (12).

Found: C, 76.66%; H, 6.33%.

Calculated for $C_{18}H_{18}O_3$: C, 76.56%; H, 6.44%; *M* 282.36.

3,4-Dimethoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (157)



[157]

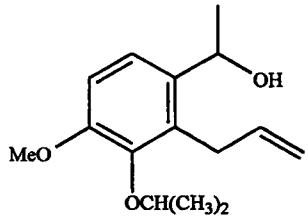
3,4-Dimethoxy-2-prop-2'-enylbenzaldehyde **154** (4.12 g, 20 mmol) was dissolved in dried diethyl ether (40 ml) and dripped into a freshly prepared solution of methyl magnesium iodide in dried diethyl ether [from magnesium turnings (730 mg, 30 mmol) and methyl iodide (4.26 g, 30 mmol, 1.88 ml) in 40 ml dried diethyl ether]. The solution was stirred for 40 minutes, then treated with a saturated solution of ammonium chloride to dissolve the magnesium salts. The resulting solution was extracted with diethyl ether (3 × 80ml). The residue obtained upon work-up was purified by column chromatography using initially (1:4) then later (2:3) ethyl acetate - hexane as eluant. The product obtained was a yellow oil (4.14 g, 93%).

157 ν_{max} 3404 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.4 Hz, CH_3CHOH), 1.58 (1H, bs, D_2O exchangeable, CH_3CHOH), 3.52 (2H, ddt, *J* 13.0, 5.6 and 2.0 Hz, $CH_2CH=CH_2$), 3.80 (3H, s, $ArOCH_3$), 3.86 (3H, s, $ArOCH_3$), 4.90 (1H, dq, *J* 17.0 and 2.0 Hz, *trans*-$CH_2CH=CH_2$), 5.03 (1H, dq, *J* 10.2 and 2.0 Hz, *cis*-$CH_2CH=CH_2$), 5.06 (1H, q, *J* 6.4 Hz, CH_3CHOH), 6.00 (1H, m, $CH_2CH=CH_2$), 6.86 (1H, d, *J* 8.2 Hz, 5-H), 7.24 (1H, d, *J* 8.2 Hz, 6-H); δ_C 24.3 (CH_3CHOH), 29.7 ($CH_2CH=CH_2$), 55.7 (Ar-OCH_3), 60.9 ($ArOCH_3$), 66.2 (CH_3CHOH), 110.8 (C-5), 115.3 (C-3'), 121.0 (C-6), 130.7 (C-2)[a], 137.2 (C-1)[a], 137.9 (C-2'), 147.1 (C-3)[b], 152.1 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 23), 207 (100), 189 (55), 174 (41), 158 (16).

Found: C, 70.03%; H, 8.12%.

Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

3-Isopropyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (158)



[158]

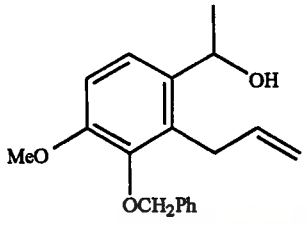
3-Isopropyloxy-4-methoxy-2-prop-2'-enylbenzaldehyde **155** (4.68 g, 20 mmol) was dissolved in dried diethyl ether (40 ml) and dripped into a freshly prepared solution of methyl magnesium iodide in dried diethyl ether [from magnesium turnings (730 mg, 30 mmol) and methyl iodide (4.26 g, 30 mmol, 1.88 ml) in 40 ml dried diethyl ether]. The solution was stirred for 40 minutes, then treated with a saturated solution of ammonium chloride to dissolve the magnesium salts. The resulting solution was extracted with diethyl ether (3 × 80ml). The residue obtained upon work-up was purified by column chromatography using initially (1:4) then later (2:3) ethyl acetate - hexane as eluant. The product was obtained as a yellow oil (4.01 g, 80%).

158 ν_{max} 3396 cm^{-1} (O-H); δ_H 1.24 [3H, d, *J* 6.2 Hz, $CH(CH_3)_2$], 1.27 [3H, d, *J* 6.2 Hz, $CH(CH_3)_2$], 1.44 (3H, d, *J* 6.4 Hz, CH_3CHOH), 1.75 (1H, bs, D_2O exchangeable, CH_3CHOH), 3.54 (2H, ddt, *J* 16.4, 5.8 and 1.8 Hz, $CH_2CH=CH_2$), 3.82 (3H, s, $ArOCH_3$), 4.49 [1H, sept, *J* 6.2 Hz, $OCH(CH_3)_2$], 4.95 (1H, dq, *J* 17.2 and 1.8 Hz, *trans*-$CH_2CH=CH_2$), 5.00 (1H, dq, *J* 10.4 and 1.8 Hz, *cis*-$CH_2CH=CH_2$), 5.08 (1H, q, *J* 6.4 Hz, CH_3CHOH), 5.95 (1H, m, $CH_2CH=CH_2$), 6.83 (1H, d, *J* 8.6 Hz, 5-H), 7.22 (1H, d, *J* 8.6 Hz, 6-H); δ_C 22.6 [2×($CH(CH_3)_2$)], 24.3 (CH_3CHOH), 30.2 ($CH_2CH=CH_2$), 55.7 ($ArOCH_3$), 66.1 (CH_3CHOH), 74.7 [$CH(CH_3)_2$], 110.7 (C-5), 115.1 (C-3'), 120.4 (C-6), 131.1 (C-2)[a], 137.3 (C-1)[a], 137.9 (C-2'), 144.8 (C-3)[b], 152.1 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 250 (M^+, 35), 208 (16), 193 (100), 175 (38), 165 (19), 143 (66), 133 (15), 115 (24).

Found: C, 71.76%; H, 8.92%.

Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.87%; *M* 250.37.

3-Benzyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (159)



[159]

3-Benzyloxy-4-methoxy-2-prop-2'-enylbenzaldehyde **156** (2.82 g, 10 mmol) was dissolved in dried diethyl ether (20 ml) and dripped into a freshly prepared solution of methyl magnesium iodide in dried diethyl ether (from magnesium turnings (365 mg, 15 mmol) and methyl iodide (2.13 g, 15 mmol, 0.94 ml) in 20 ml dried diethyl ether]. The solution was stirred for 40 minutes, then treated with a saturated solution of ammonium chloride to dissolve the magnesium salts. The resulting solution was extracted with diethyl ether (3 × 40 ml). The residue obtained upon work-up was purified by column chromatography using initially (1:4) then later (2:3) ethyl acetate - hexane as eluant. The product was obtained as yellow oil (2.63 g, 88%).

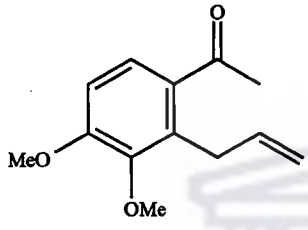
159 ν_{max} 3384 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.4 Hz, CH_3CHOH), 1.68 (1H, bs, D_2O exchangeable, CH_3CHOH), 3.51 (2H, ddt, *J* 14.2, 5.8 and 1.8 Hz, $CH_2CH=CH_2$), 3.88 (3H, s, $ArOCH_3$), 4.88 (1H, dq, *J* 17.2 and 1.8 Hz, *trans*-$CH_2CH=CH_2$), 4.98 (2H, s, OCH_2Ph), 5.03 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-$CH_2CH=CH_2$), 5.06 (1H, q, *J* 6.4 Hz, CH_3CHOH), 5.97 (1H, m, $CH_2CH=CH_2$), 6.91 (1H, d, *J* 8.6 Hz, 5-H), 7.31 (1H, d, J 8.6 Hz, 6-H), 7.40 (5H, m, Ph*H*'s); δ_C 24.3 (CH_3CHOH), 29.9 ($CH_2CH=CH_2$), 55.8 ($ArOCH_3$), 66.2 (CH_3CHOH), 74.8 (CH_2Ph), 110.9 (5-C), 115.3 (C-3'), 121.1 (C-6), 127.9 (aryl), 128.1 (×2, aryl), 128.5 (×2, aryl), 131.0 (aryl), 137.9 (C-2'), 137.3 (C-1)[a], 138.1 (C-2)[a], 145.0 (C-3)[b] and 152.2 (C-4)[b]. Assignments with the same superscripts

may be interchanged. MS (EI): *m/z* (%): 298 (M^+, 79), 283 (43), 265 (35), 202 (56), 189 (84), 175 (52), 161 (43), 131 (33), 91 (100).

Found: C, 76.30%; H, 7.53%.

Calculated for $C_{19}H_{22}O_3$: C, 76.47%; H, 7.45%; *M* 298.41.

Acetyl-3,4-dimethoxy-2-prop-2'-enylbenzene (160)



[160]

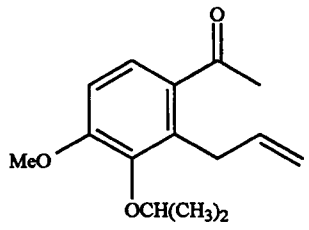
3,4-Dimethoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene **157** (2.16 g, 9.3 mmol) was dissolved in dry benzene (150ml) and activated manganese dioxide (21.6 g, 10 mass equiv.) was added. The reaction mixture was stirred at reflux under nitrogen for 40 minutes. The fine manganese dioxide particles were removed by filtration through a celite plug. The solvent was evaporated off and the residue purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as bright yellow oil (1.22 g, 57%).

160 ν_{max} 1684 cm^{-1} (C=O); δ_H 2.52 (3H, s, CH_3CO), 3.76 (2H, dt, *J* 6.0 and 1.8 Hz, $CH_2CH{=}CH_2$), 3.80 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 4.94 (1H, dq, *J* 17.0 and 1.8 Hz, *trans*-$CH_2CH{=}CH_2$), 4.95 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-$CH_2CH{=}CH_2$), 6.00 (1H, m, $CH_2CH{=}CH_2$), 6.80 (1H, d, *J* 8.8 Hz, 5-H), 7.50 (1H, d, *J* 8.8 Hz, 6-H); δ_C 29.6 (CH_3CO), 30.4 ($CH_2CH{=}CH_2$), 55.8 ($ArOCH_3$), 60.9 ($ArOCH_3$), 109.1 (C-5), 114.9 (C-3'), 126.8 (C-6), 131.5 (C-2)[a], 135.0 (C-1)[a], 137.8 (C-2') 148.0 (C-3)[b], 155.7 (C-4)[b], 200.5 (*C*HO). Assignments with the same superscripts can be interchanged. MS (EI): *m/z* (%): 220 (M^+, 4), 205 (100), 190 (45), 174 (13), 161 (10).

Found: C, 70.92%; H, 7.23%.

Calculated for $C_{13}H_{16}O_3$: C, 70.87%; H, 7.34%; *M* 220.29

Acetyl-3-isopropyloxy-4-methoxy-2-prop-2'-enylbenzene (161)



[161]

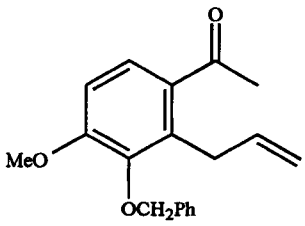
3-Isopropyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene **158** (2.25 g, 9.0 mmol) was dissolved in dry benzene (150 ml) and activated manganese dioxide (22.5 g, 10 mass equiv.) was added. The reaction mixture was stirred at reflux under nitrogen for 40 minutes. The fine manganese dioxide particles were removed by filtration through a celite plug. The solvent was evaporated off and the residue purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as bright yellow oil (1.34 g, 60%).

161 ν_{max} 1688 cm^{-1} (C=O); δ_H 1.27 [6H, d, *J* 6.4 Hz, CH(C*H*$_3$)$_2$], 2.51 (3H, s, C*H*$_3$CO), 3.80 (2H, dt, *J* 6.0 and 1.8 Hz, C*H*$_2$CH=CH$_2$), 3.87 (3H, s, ArOC*H*$_3$), 4.50 [1H, sept, *J* 6.4 Hz, OC*H*(CH$_3$)$_2$], 4.93 (1H, dq, *J* 17.0 and 1.8 Hz, *trans*-CH$_2$CH=C*H*$_2$), 4.95 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-CH$_2$CH=C*H*$_2$), 5.91 (1H, m, CH$_2$C*H*=CH$_2$), 6.78 (1H, d, *J* 8.8 Hz, 5-H), 7.44 (1H, d, *J* 8.8 Hz, 6-H); δ_C 22.6 [2×(CH(*C*H$_3$)$_2$], 29.7 (*C*H$_3$CO), 30.6 (*C*H$_2$CH=CH$_2$), 55.7 (ArO*C*H$_3$), 75.0 [O*C*H(CH$_3$)$_2$], 108.8 (C-5), 114.9 (C-3'), 126.0 (C-6), 131.9 (C-2)[a], 135.2 (C-1)[a], 137.6 (C-2'), 145.6 (C-3)[b], 155.7 (C-4)[b], 201.0 (*C*HO). Assignments with the same superscripts can be interchanged. MS (EI): *m/z* (%): 248 (M^+, 6), 206 (21), 191 (100), 159 (52), 131 (13).

Found: C, 72.44%; H, 8.21%.

Calculated for $C_{15}H_{20}O_3$: C, 72.54%; H, 8.13%; *M* 248.35.

Acetyl-3-benzyloxy-4-methoxy-2-prop-2'-enylbenzene (162)



[162]

3-Benzyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene **159** (2.55 g, 8.6 mmol) was dissolved in dry benzene (200 ml) and activated manganese dioxide (25.5 g, 10 mass equiv.) was added. The reaction mixture was stirred at reflux under nitrogen for 40 minutes. The fine manganese dioxide particles were removed by filtration through a celite plug. The solvent was evaporated off and the residue purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as a yellow-brown oil (1.45 g, 57%).

162 ν_{max} 1684 cm^{-1} (C=O); δ_H 2.54 (3H, s, CH_3CO), 3.78 (2H, dt, *J* 5.8 and 1.6 Hz, $CH_2CH=CH_2$), 3.93 (3H, s, $ArOCH_3$), 4.93 (1H, dq, *J* 18.6 and 1.8 Hz, *trans*-$CH_2CH=CH_2$), 4.95 (1H, dq, *J* 8.6 and 1.8 Hz, *cis*-$CH_2CH=CH_2$), 4.96 (2H, s, OCH_2Ph), 5.98 (1H, m, $CH_2CH=CH_2$), 6.85 (1H, d, *J* 8.6 Hz, 5-H), 7.41 (5H, m, Ph*H*'s), 7.53 (1H, d, *J* 8.6 Hz, 6-H); δ_C 29.6 (CH_3CO), 30.6 ($CH_2CH=CH_2$), 55.8 ($ArOCH_3$), 78.4 (CH_2Ph), 109.1 (C-5), 115.0 (C-3'), 127.0 (C-6), 128.1 (×3, aryl), 128.6 (×2, aryl), 131.7 (aryl), 137.8 (C-2'), 135.3 (C-1)[a], 146.8 (C-2)[a], 147.1 (C-3)[b] and 155.8 (C-4)[b] and 200.6 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 296 (M^+, 4), 278 (57), 263 (41), 249 (12), 231 (21), 205 (69), 191 (63), 177 (41), 163 (30), 91 (100), 65 (12), 43 (19).

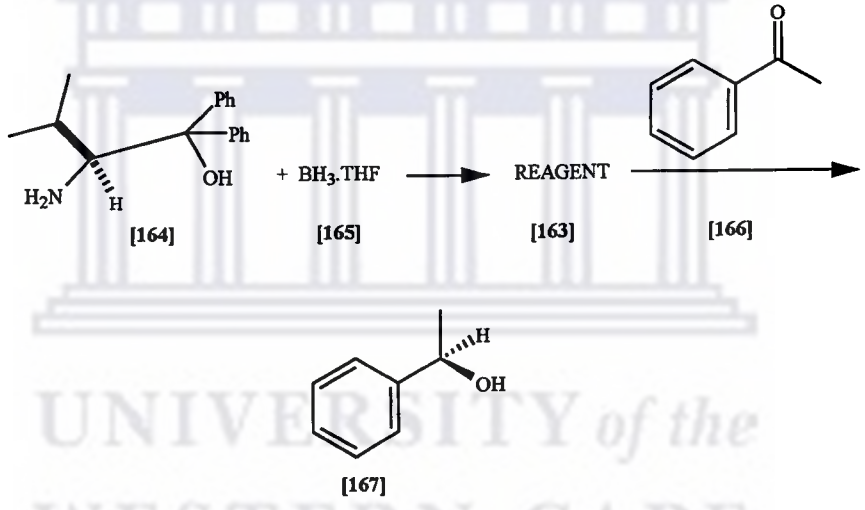
Found: C, 76.91%; H, 6.65%.

Calculated for $C_{19}H_{22}O_3$: C, 76.99%; H, 6.82%; *M* 296.39.

4.2. Chiral Reduction of ketones using Corey-Bakshi-Shibata catalyst

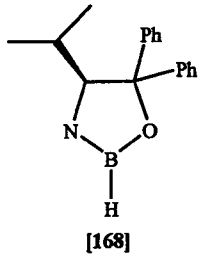
4.2.1. Literature Precedents

In 1983, Itsuno *et al*, reported that ketones, in the presence of a reagent **163** prepared from (*S*)-valinol **164** and borane **165** were asymmetrically reduced to afford the corresponding (*R*)-alcohols in high optical (94 - 100% enantiomeric excess) and chemical (100%) yields [69,70,71]. The authors showed that (*S*)-valinol **164** together with two equivalents of BH_3.THF at –78 °C to 0 °C, over several hours converted acetophenone **166** into (R)-1-phenylethanol **167** with 94% enantiomeric excess [69,71] (Scheme 32).

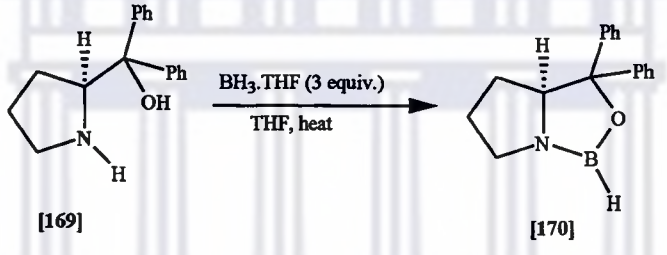


Scheme 32

The identity of reagent **163** and the mechanism for the chiral reduction was not known until 1987, when Corey and co-workers[72] identified reagent **163** as the oxazaborolidine **168**.



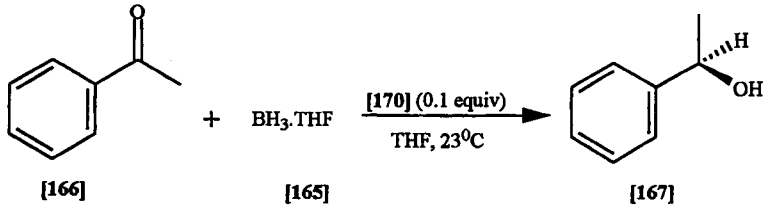
Solutions of **168** alone did not reduce acetophenone **166**, even after several hours at 23 °C. However, mixtures of **168** and BH_3.THF **165** (0.6 to 0.2 mol equiv) effected complete reduction of acetophenone **166** in less than one minute to afford (*R*)-1-phenylethanol **167** (97% ee). In the absence of **168** acetophenone **166** was reduced very slowly with BH_3.THF **165** at 23 °C to the expected racemic mixture of alcohols[72]. The authors[72] proceeded to develop a better catalyst termed the Corey-Bakshi-Shibata catalyst (CBS-catalyst) **170** by heating, at reflux (*S*)-(-)-2-(diphenylhydroxymethyl)pyrrolidine **169** with three equivalents of BH_3.THF **165** in tetrahydrofuran under a closed argon-borane atmosphere (Scheme 33).



[169] [170]

Scheme 33

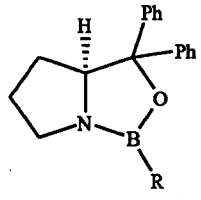
The CBS-catalyst **170** (0.1 equiv) in tetrahydrfuran and BH_3.THF **165** (1.2 equiv) reduced acetophenone **166** at 23 °C to (*R*)-1-phenylethanol **167** with 97% enantiomeric excess, in quantitative yield (Scheme 34).



[166] [165] [167]

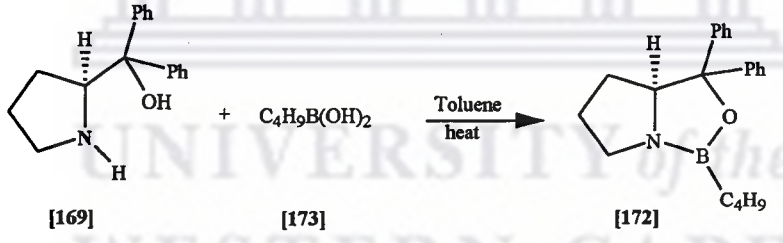
Scheme 34

In contrast to the CBS-catalyst **170**, which is air and moisture sensitive, the more robust boron-methylated **171**[73,74] and boron-butylated **172**[75] oxazaborolidine catalysts were prepared. The advantages of these catalysts are that they can be stored in closed containers at room temperature and weighed or transferred in air.



[171] R = Methyl
[172] R = Butyl

The boron-butylated oxazaborolidine **172** was prepared by heating at reflux (*S*)-(-)-2-(diphenylhydroxymethyl)pyrrolidine **169** and n-butylboronic acid **173** in toluene under nitrogen using a Dean-Stark trap or a Soxhlet apparatus containing 4 A molecular sieves in a thimble to remove water (Scheme 35).

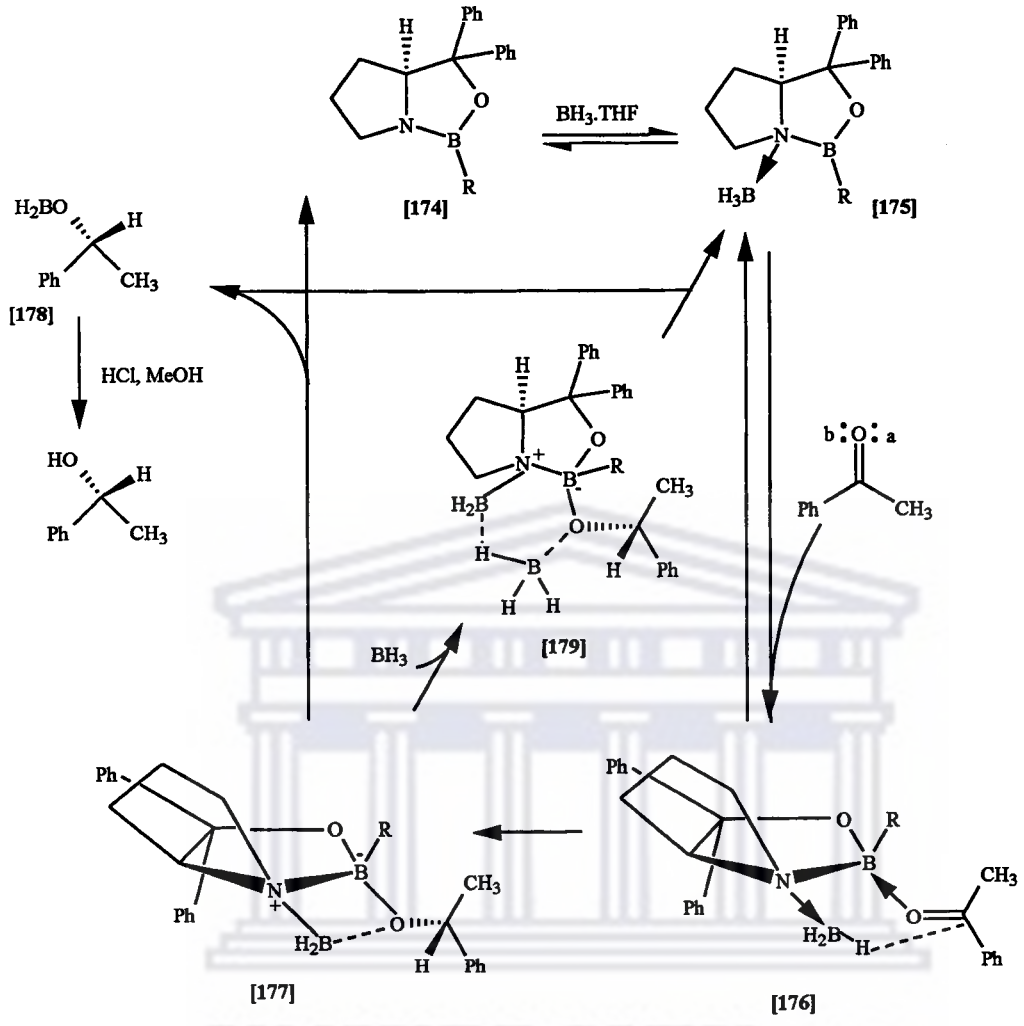


[169] [173] [172]

Scheme 35

Mechanistic Rationale

Corey *et al.* also proposed a mechanism for the asymmetric reduction reaction[72,76] as outlined in (Scheme 36).



Scheme 36

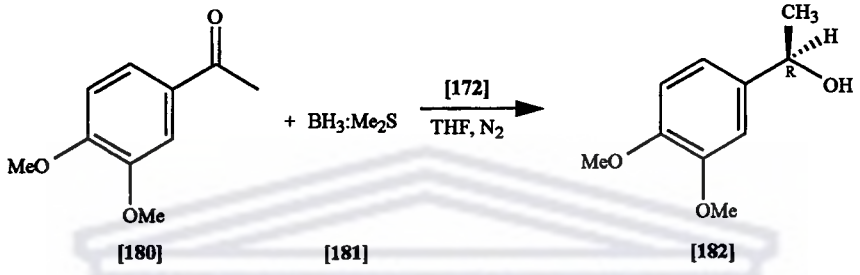
The initial step in the pathway is the rapid (and probably reversible) coordination of BH_3 to the Lewis basic nitrogen atom on the α face of oxazaborolidine **174** to form the *cis*-fused oxazaborolidine•BH_3 complex **175**[72,77,78]. The coordination of the electrophilic BH_3 to the nitrogen atom of **174** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The strongly Lewis acidic complex **175** then readily binds to the ketonic substrate, for

example acetophenone, at the more sterically accessible electron pair (*a* in the case of acetophenone) and *cis* to the vicinal BH_3 group (→ **176**). This manner of binding minimizes unfavourable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for stereoelectronically favorable, face-selective hydride transfer via a six-membered transition state to form the reduction product **177**. Thus the rate enhancement for the oxazaborolidine-catalyzed reduction is due to the activation of the stoichiometric reducing agent BH_3 by coordination with the Lewis basic nitrogen atom of **174** with simultaneous intensification of the Lewis acidity of the boron atom in the heterocycle for coordination to the ketone. This leads to subsequent enthalpically and entropically favorable face-selective intramolecular hydride transfer[79,80,81,82]. Dissociation of the reduction product from **177** to regenerate the oxazaborolidine catalyst may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of **177** to regenerate **174** and form the boronate **178** by cyclo-elimination; [83] or 2) by the addition of BH_3 to **177** to form a six-membered BH_3-bridged species **179**, which decomposes to produce the catalyst-BH_3 complex **175** and boronate **178**[84,85]. The facile disproportionation of **178** to afford dialkoxyborane $(RO)_2BH$ and BH_3 allows the efficient use of the three hydrogen atoms of the stoichiometric reductant[86,87].

We selected the CBS-catalyst for our reductions since literature data has shown that the CBS reduction process results in excellent enatioselectivities, near quantitative yields, and short reaction times[76]. Furthermore, a product whose absolute configuration can be predicted from the relative effective steric bulk of the two carbonyl appendages is obtained, since coordination of the electrophilic boron ring **175** with the ketonic oxygen is *anti* to the larger carbonyl appendage[72,76].

4.2.2. Chiral Reduction of 2-Alkenyl-3,4-dialkoxylated Acetophenones

As a preliminary experiment, 3,4-dimethoxyacetophenone **180** (in tetrahydrofuran) and boron-dimethylsulphide **181** (in tetrahydrofuran) were added simultaneously to the CBS-catalyst **172** (in tetrahydrofuran) over 15 minutes and stirred under nitrogen to afford the (*R*)-alcohol **182** in 90% yield (Scheme 37).

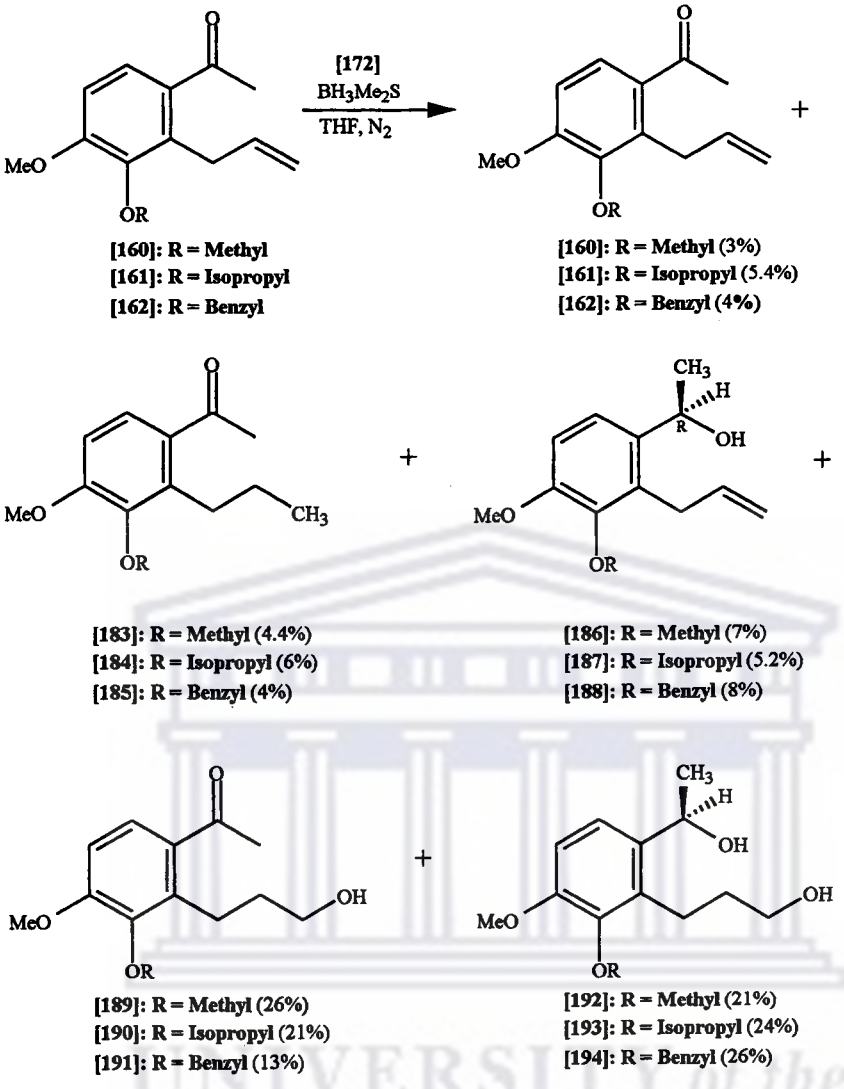


[180] [181] [182]

Scheme 37

The enantiomeric excess of **182** was determined using the europium shift reagent to afford a value greater than 97% (see Section 4.3.2.).

When ketones **160, 161** and **162** were subjected to reduction using the Corey-Bakshi-Shibata catalyst **172**, under same reaction conditions, some starting material together with an array of products were obtained (Scheme 38).



Scheme 38

Assignment of the structure **183** to the molecule is based on the microanalysis and mass spectrum, which both support the molecular formula $C_{13}H_{18}O_3$. A strong band at 1688 cm^{-1} in the infrared spectrum confirms the conjugated ketonic function and in which the ^{1}H-nmr spectrum the following signals are also conclusive. A triplet at δ 0.98 (*J* 7.4 Hz) is ascribed to the 3'-methyl group of the propyl side chain which is coupled to the

2'-methylene protons appearing as a multiplet at δ 1.55 and these in turn show connectivity to a 2-proton multiplet at δ 2.90 of the 1'-methylene group.

The main spectral evidence for the keto-alcohol **189** which was not obtained in a highly pure form is *inter alia* ascribed to a strong ν_{max} at 3348 cm^{-1} due to the O-H group and a strong ν_{max} at 1680 cm^{-1} due to the ketone C=O in the infrared spectrum. A 3-proton singlet at δ 2.56 is ascribed to the acetyl group while a 2-proton triplet at δ 3.54 with ^3J 6.0 Hz is ascribed to the H-3' while a 2-proton triplet at δ 3.03 with ^3J 6.2 Hz is ascribed to the benzylic H-1'. A multiplet at δ 1.81 is ascribed to the H-2'.

In the case of the diol **192**, the main spectral evidence for assigning the structure was *inter alia* a strong broad peak at ν_{max} at 3350 cm^{-1} for the O-H in the infrared spectrum. A 3-proton doublet at δ 1.49 (^3J 6.4 Hz) connected to a 1-proton quartet at δ 5.10 (^3J 6.4 Hz) as demonstrated in the ^{1}H-nmr and COSY spectra confirmed the presence of the hydroxyethyl side chain. The following two proton signals which appear in the ^{1}H-nmr spectrum corroborated the 3-propanol side chain as well namely, a triplet at δ 3.54 with ^3J 6.1 Hz for H-3', a multiplet at δ 2.82 for H-1' and a multiplet at δ 1.81 for H-2'.

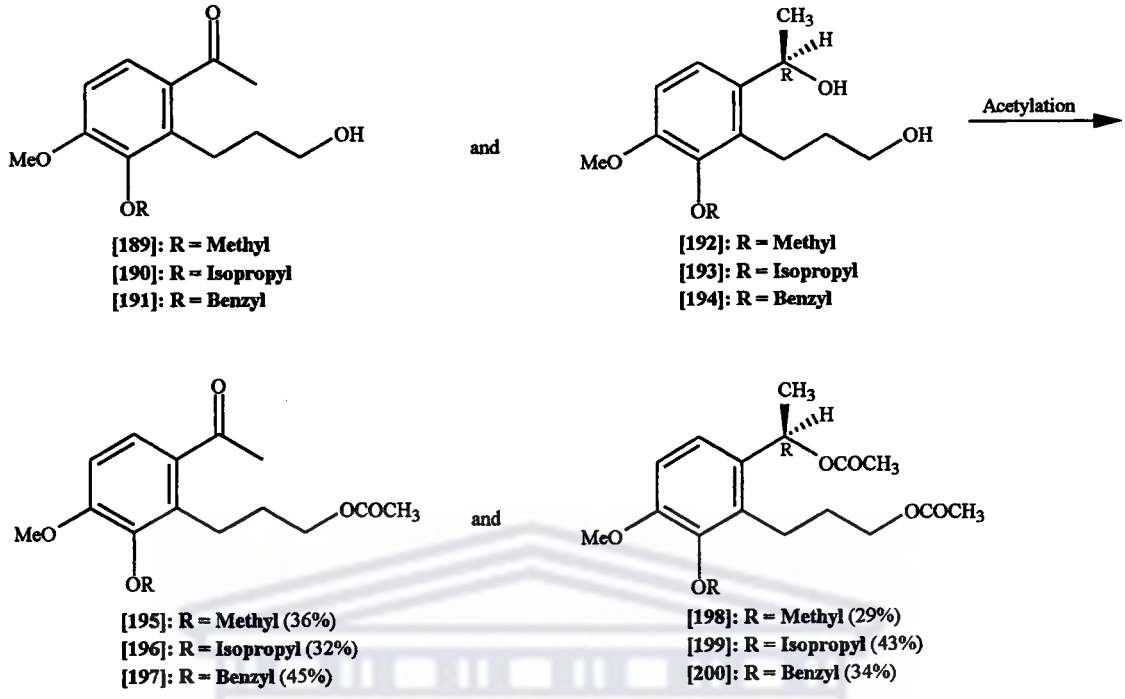
Since the keto-alcohol **190** and the diol **193** were obtained as a mixture, very difficult to separate, the yield for these two molecules is based on the relative integration of signals in the ^{1}H-nmr spectrum. Evidence for the two molecules is based on *inter alia* the following signals in the ^{1}H-nmr spectrum. For keto-alcohol **190** a 3-proton signal at δ 2.56 for the acetyl methyl group, a 2-proton triplet at δ 3.46 with ^3J 6.2 Hz for H-3', a 2-proton triplet at δ 3.10 with ^3J 6.2 Hz for H-1' and a 2-proton multiplet at δ 1.83 for H-2' would suffice to establish effective hydration of the terminal olefinic bond.

In the case of diol **193** evidence pointing to the structure is the following: a 3-proton doublet at δ 1.45 with ^3J 6.4 Hz for the methyl group of the hydroxyethyl side chain

supported by a 1-proton quartet at δ 5.15 with ^{3}J 6.4 Hz, a 2-proton triplet at δ 3.43 with ^{3}J 6.0 Hz for H-3', a multiplet δ 2.83 for H-1' and a 2-proton multiplet at δ 1.75 for H-2' thus also establishing the salient features of the assigned structure.

Assignment of the structures **191** to the keto-alcohol and **194** to the diol are also based entirely on the ^{1}H-nmr spectra as these molecules were difficult to separate completely. Thus the assignment for the structure **191** to the keto-alcohol is based on *inter alia* the following signals in the ^{1}H-nmr spectrum. A singlet at δ 2.57 for the acetyl methyl group, a 2-proton triplet at δ 3.48 with ^{3}J 6.0 Hz for H-3', a 2-proton triplet at δ 3.03 with ^{3}J 6.02 Hz for H-1' and a multiplet at δ 1.83 for H-2', while assignment of the diol structure 194 is based on a 3-proton doublet at δ 1.49 with ^{3}J 6.4 Hz for the methyl group of the hydroxyethyl side chain supported by a 1-proton quartet at δ 5.10 with ^{3}J 6.4 Hz, a 2-proton triplet at δ 3.47 with ^{3}J 6.0 Hz for H-3', a multiplet at δ 2.79 for H-1' and a 2- proton multiplet at δ 1.81 for H-2'.

The later eluting alcohols **189** - **194** were characterized as their acetates by reacting them with an acetylating reagent of acetic anhydride and pyridine (ratio 2:1) for 24 hours at room temperature to afford the acetates **195** – **200** (Scheme 39).



[189]: R = Methyl
[190]: R = Isopropyl
[191]: R = Benzyl

[192]: R = Methyl
[193]: R = Isopropyl
[194]: R = Benzyl

[195]: R = Methyl (36%)
[196]: R = Isopropyl (32%)
[197]: R = Benzyl (45%)

[198]: R = Methyl (29%)
[199]: R = Isopropyl (43%)
[200]: R = Benzyl (34%)

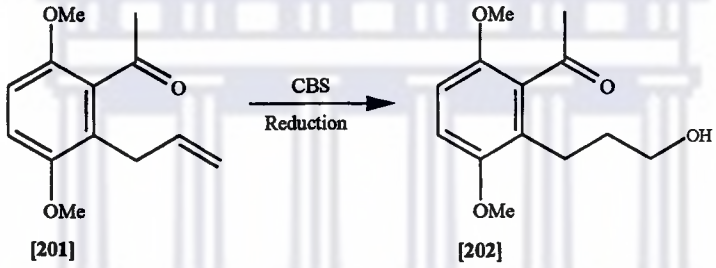
Scheme 39

The presence of two separate carbonyl stretching frequencies in the infrared spectrum, *viz.* at 1742 cm^{-1} for the ester and the other at 1688 cm^{-1} for the conjugated ketone supported the keto ester structure **195** assigned to the molecule. Both methyl singlet signals were observed in the ^{1}H-nmr spectrum with the acyl methyl signal at δ 2.06 while the acetyl methyl appeared at δ 2.54. The propan-3-ol acetate side chain was evident by the three sets of 2-proton signals at δ 1.86, 3.00 and 4.13. The latter signal being a clearly defined triplet with typical ^3J coupling of 6.8 Hz.

The diacetate structure assigned to isolate **198** was based on the following spectral evidence. A strong carbonyl band at 1752 cm^{-1} is typical of the ester carbonyl group in the infrared spectrum. The methyl doublet at δ 1.51 with ^3J 6.6 Hz together with the expected quartet at δ 6.02 in the ^{1}H-nmr spectrum confirms the 1-acetoxyethyl side chain. The presence of two acetate groups is evident by the two methyl singlets at δ 2.04

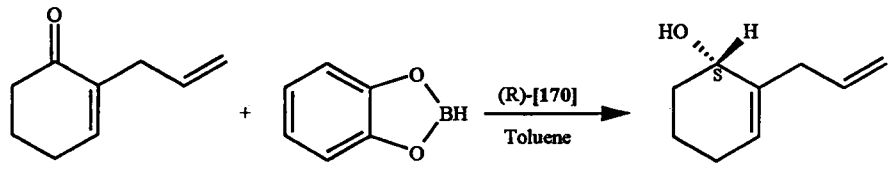
and 2.08 supported by the presence of two ester carbonyl groups at δ 170.5 and 171.5 in the ^{13}C-nmr spectrum. The lowfield triplet at δ 4.13 is typical of a methylene group adjacent to an acetate.

The desired (*R*)-alcohols **186**, **187** and **188** were obtained in unacceptable yields. This result was similar to that reported by Giles and Green[88]. The authors demonstrated that the CBS catalyzed chiral reduction of ketone **201** yielded the alcohol **202** only (Scheme 40). They attributed the result to the severe steric phenomena at the carbonyl carbon, which inhibits the delivery of the hydride to the S*i* face of the ketone and since the only other active site is the olefin, it becomes the favoured site for attack.



Scheme 40

The very poor chiral reduction we were able to effect was not suitable for our multi-step syntheses towards chiral isochroman quinones and hence an alternate strategy was sought. Overman *et al.*[89] showed that enantioselective reduction of 2-allylcyclohex-2-en-1-one **203** with catechol-borane **204** as reducing agent in the presence of the (*R*)-oxazaborolidine catalyst (R)-**170**, provided the corresponding (*S*)-cyclohexenol **205** in 93% yield and enantiomeric excess greater than 96% (scheme 41). The use of catechol-borane as reducing agent in our synthesis led to a dark brown residue which could not be isolated nor characterized.



[203] [204] [205]

Scheme 41

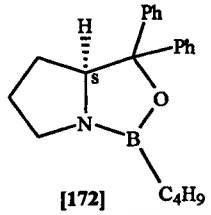
Stone [90] reported that the selectivity increases with increasing temperature until an optimal range is reached (30-50 °C) where the selectivity begins to decrease. Varying the temperature in our synthesis led to no improvement in our results.

The fraction isolated in 7% yield was assigned the structure of the expected chiral alcohol **186** since all its spectral data were identical to the racemic alcohol **157** synthesized earlier. Due to the very low yields of all the expected chiral alcohols **186**, **187** and **188**, their enantiomeric excesses were not measured by conversion to the Mosher esters. Instead, an alternative route to the chiral alcohols was sought.

4.2.3. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

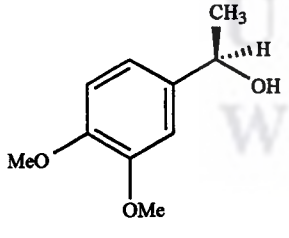
Preparation of Corey-Bakshi-Shibata (CBS) Catalyst (172)[75]



[172]

To a solution of (*S*)-(-)-2-(diphenylhydroxymethyl)pyrrolidine (500 mg, 1.98 mmoles) in (20 ml) of toluene was added n-butylboronic acid (221 mg, 2.17 mmoles) and the mixture was heated under reflux under nitrogen using either a Dean-Stark trap or Soxhlet apparatus containing 4A molecular sieves in a thimble to remove water. After 12 hours the reaction mixture was concentrated in vacuo and the residue of **172** was dissolved in toluene to give a 0.5 M toluene solution which was stored under dry nitrogen at 4 °C.

(*R*)-3,4-Dimethoxy-1-(1'-hydroxyethyl)-benzene (182)



[182]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst (0.3 ml, 0.15 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide (BH_3Me_2S.THF) in tetrahydrofuran (1 ml, 1mmol) was added dropwise to the CBS catalyst. 3,4-Dimethoxyacetophenone **180** (1.80 g, 10 mmol) in dried tetrahydrofuran (5 ml) was added simultaneously with additional BH_3Me_2S.THF (6 ml, 6 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (2 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml). The residue obtained upon work-up was purified by column chromatography using ethyl

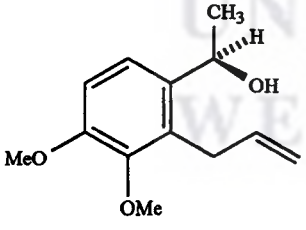
acetate - hexane (3:7) as eluant. The product was obtained as a colourless oil (1.71 g, 94%).

182 ν_{max} 3416 cm^{-1} (O-H); δ_H 1.47 (3H, d, *J* 6.4Hz, CH_3CHOH), 1.82 (1H, bs, D_2O exchangeable, CH_3CHOH), 3.87 (3H, s, $ArOCH_3$), 3.89 (3H, s, $ArOCH_3$), 5.88 (1H, q, *J* 6.4 Hz, CH_3CHOH), 6.87 (3H, m, Ar-*H*'s); δ_C 25.1 (CH_3CHOH), 55.9 ($ArOCH_3$), 56.0 ($ArOCH_3$), 70.3 (CH_3CHOH), 108.8 (C-5), 111.1 (C-2), 117.7 (C-6), 138.7 (C-1), 148.5 (C-3)[a] and 149.2 (C-4)[a]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 183 (M^+, 11), 182 (55), 167 (72), 139 (100), 124 (28). $[\alpha]_D$ = +29.8° (c = 1075, CH_2Cl_2), enatiomeric excess: ^{1}H-nmr (Mosher esters) 79% and europium shift reagent 97%.

Found: C, 66.01%; H, 7.68%

Calculated for $C_{10}H_{14}O_3$: C, 66.07%; H, 7.72%; *M* 183.14.

(*R*)-3,4-Dimethoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (186)



[186]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst reagent (0.136 ml, 0.07 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide in tetrahydrofuran (BH_3Me_2S.THF) (0.45 ml, 0.45 mmol) was added dropwise to the CBS reagent. Acetyl-3,4-dimethoxy-2-prop-2'-enylbenzene **160** (1.00 g, 4.55 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (2.72 ml, 2.72 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant.

Five compounds eluted in the order: starting material **160** (28 mg, 3%), ketone **183** (44 mg, 4.4%), **186** (70 mg, 7%), **189** (280 mg, 26%), **192** (230 mg, 21%). Further elution with methanol gave a polymeric material.

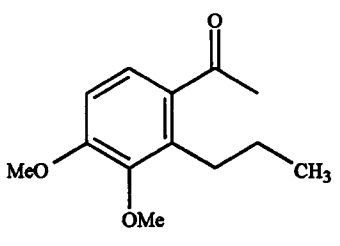
Preparation of mono-and di-acetates (195, 196, 197, 198, 199 and 200)

The sample was added to 15 ml of an acetylating mixture (acetic anhydride:pyridine; ratio 2:1), and stirred for 24 hours at room temperature. The reaction mixture was poured onto ice slurry (150 ml) and stirred for 1hour. Diethyl ether (50 ml) was added and the solution transferred to a separating funnel and extracted with ether. The aqueous phase was washed with hydrochloric acid (1M), followed by washing with a saturated sodium hydrogen carbonate until the solution was neutralized. The organic phase was extracted with dichloromethane (3 × 40 ml), dried over magnesium sulphate, filtered and the solvent evaporated to a residue. The residue was purified by preparative thin layer chromatography to afford the product.

189 and **192** were converted to their acetates **195** (120 mg, 36 %) and **198** (90 mg, 29 %) for full characterization purposes. All the products were oils.

1-Acetyl-3,4-dimethoxy-2-propylbenzene (183)

183 ν_{max} 1688 cm^{-1} (C=O); δ_H 0.98 (3H, t, *J* 7.4 Hz, 3'-H), 1.55 (2H, m, 2'-H), 2.54 (3H, s, CH_3CO), 2.90 (2H, m, 1'-H), 3.81 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 6.78 (1H, d, *J* 8.8 Hz, 5-H), 7.48 (1H, d, *J* 8.8 Hz, 6-H); δ_C 14.6 (C-3'), 24.6, (C-2'), 28.6 (CH_3CO), 29.8 (C-1'), 55.8 ($Ar-OCH_3$),



[183]

60.9(ArO*C*H$_3$), 108.6 (C-5), 126.8 (C-6), 131.5 (C-1)[a], 138.4 (C-2)[a], 147.8 (C-3)[b], 155.5 (C-4)[b], 200.7 (C=O). Assignments with the same superscripts can be interchanged. MS (EI): *m/z* (%): 222 (M^+, 15), 207 (100), 176 (14).

Found: C, 70.15%; H, 8.27%.

Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

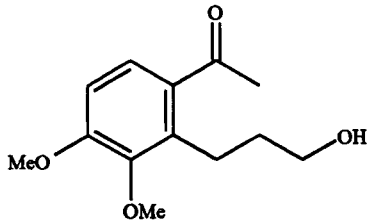
186 ν_{max} 3404 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.4 Hz, C*H*$_3$CHOH), 1.58 (1H, bs, D_2O exchangeable, CH$_3$CHO*H*), 3.52 (2H, ddt, *J* 13.0, 5.6 and 2.0 Hz, C*H*$_2$CH=CH$_2$), 3.80 (3H, s, ArOC*H*$_3$), 3.86 (3H, s, ArOC*H*$_3$), 4.90 (1H, dq, *J* 17.0 and 2.0 Hz, *trans*-CH$_2$CH=C*H*$_2$), 5.03 (1H, dq, *J* 10.2 and 2.0 Hz, *cis*-CH$_2$CH=C*H*$_2$), 5.06 (1H, q, *J* 6.4 Hz, CH$_3$C*H*OH), 6.00 (1H, m, CH$_2$C*H*=CH$_2$), 6.86 (1H, d, *J* 8.8 Hz, 5-H), 7.24 (1H, d, *J* 8.8 Hz, 6-H); δ_C 24.3 (*C*H$_3$CHOH), 29.7 (*C*H$_2$CH=CH$_2$), 55.7 (ArO*C*H$_3$), 60.9 (ArO*C*H$_3$), 66.2 (CH$_3$*C*HOH), 110.8 (C-5), 115.3 (C-3'), 121.0 (C-6), 130.7 (C-2)[a], 137.2 (C-1)[a], 137.9 (C-2'), 147.1 (C-3)[b], 152.1 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 23), 207 (100), 189 (55), 174 (41), 158 (16).

Found: C, 70.12%; H, 8.20%.

Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

1-Acetyl-2-(3'-hydroxypropyl)-3,4-dimethoxybenzene (189)

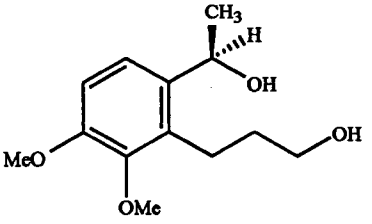
189 ν_{max} 3348 cm^{-1} (O-H) and 1680 cm^{-1} (C=O); δ_H 1.81 (2H, m, 2'-H), 2.56 (3H,s, C*H*$_3$CO), 3.03 (2H, t, *J* 6.2 Hz, 1'-H), 3.54 (2H, t, *J* 6.0 Hz, 3'-H), 3.83 (3H, s, ArOC*H*$_3$), 3.92 (3H, s, ArOC*H*$_3$), 6.82 (1H, d, *J* 8.8 Hz, 5-H), 7.50 (1H, d, *J* 8.8 Hz, 6-H).



[189]

1-(1'-Hydroxyethyl)-2-(3'-hydroxypropyl)-3,4-dimethoxybenzene (192)

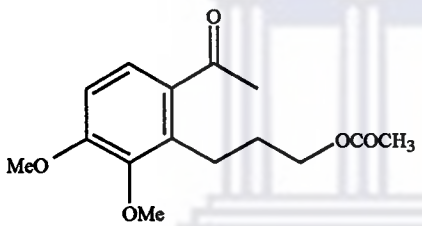
192 ν_{max} 3350 cm^{-1} (O-H); δ_H 1.49 (3H, d, J 6.4 Hz, CH_3CHOH), 1.81 (2H, m, 2'-H), 2.82 (2H, m, 1'-H), 3.54 (2H, t, *J* 6.1 Hz, 3'-H), 3.83 (3H, s, $ArOCH_3$), 3.92 (3H, s, $ArOCH_3$), 5.10 (1H, q, *J* 6.4 Hz, CH_3CHOH), 6.80 (1H, d, *J* 8.8 Hz, 5-H), 7.24 (1H, d, *J* 8.8 Hz, 6-H).



[192]

2-(3'-Acetoxypropyl)-1-acetyl-3,4-dimethoxybenzene (195)

195 ν_{max} 1688 cm^{-1} (C=O) for ketone and 1742 cm^{-1} (C=O) for ester; δ_H 1.86 (2H, m, 2'-H), 2.06 (3H, s, CH_3CO), 2.54 (3H, s, CH_3OCO), 3.00 (2H, m, 1'-H), 3.81 (3H, s, $ArOCH_3$), 3.91 (3H, s, $ArOCH_3$), 4.13 (2H, t, *J* 6.8 Hz, 3'-H), 6.80 (1H, d, *J* 8.6 Hz, 5-H), 7.53 (1H, d, *J* 8.6 Hz, 6-H); δ_C 21.0 (CH_3CO), 23.3 ($OCOCH_3$), 29.6 (C-1')[a], 29.8 (C-2')[a], 55.8 ($ArOCH_3$), 60.8 ($ArOCH_3$), 64.8 (C-3'), 108.9 (C-5), 127.2 (C-6), 131.1 (C-1)[b], 137.3 (C-2)[b], 147.9 (C-3)[c], 155.7 (C-4)[c], 171.5 ($OCOCH_3$), 200.2 (CH_3COAr). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 280 (M^+, 17), 220 (22), 205 (48), 192 (100), 177 (42).

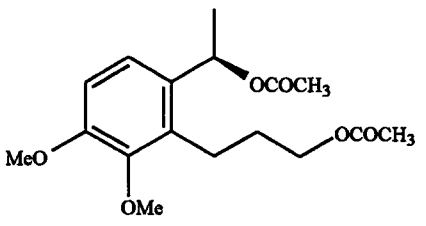


[195]

Found: C, 64.12%; H, 7.11%.

Calculated for $C_{15}H_{20}O_5$: C, 64.26%; H, 7.21%; *M* 280.35.

1-(1'-Acetoxyethyl)-2-(3'-acetoxypropyl)-3,4-dimethoxybenzene (198)



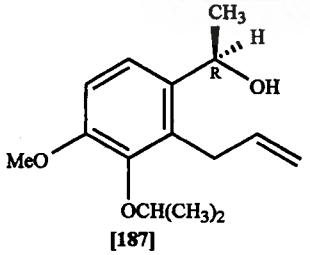
[198]

198 ν_{max} 1752 cm^{-1} (C=O); δ_H 1.51 (3H, d, *J* 6.6 Hz, CH_3CH), 1.75 (2H, m, 2'-H), 2.04 (3H, s, CH_3OCO), 2.08 (3H, s, CH_3OCO), 2.75 (2H, m, 1'-H), 3.82 (3H, s, $ArOCH_3$), 3.85 (3H, s, $ArOCH_3$), 4.13 (2H, t, *J* 6.4 Hz, 3'-H), 6.02 (1H, q, *J* 6.6 Hz, CH_3CH), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.15 (1H, d, *J* 8.6 Hz, 6-H); δ_C 21.0 ($OCOCH_3$)[a], 21.4 ($OCOCH_3$)[a], 22.2 ($ArCCH_3$), 22.7 (C-2'), 29.7 (C-1'), 55.7 ($ArOCH_3$), 60.7 ($ArOCH_3$), 64.4 (C-3'), 68.9 (ArCOAc), 110.6 (C-5), 121.8 (C-6), 132.9 (C-1)[b], 133.3 (C-2)[b], 147.1 (C-3)[c], 152.3 (C-4)[c], 170.5 ($OCOCH_3$), 171.5 ($OCOCH_3$). Assignments with the same superscripts can be interchanged. MS (EI): *m/z* (%): 264 [M^+ - 60, 65], 204 (26), 189 (100), 174 (38), 158 (12), 129 (13).

Found: C, 62.89%; H, 7.38%.

Calculated for $C_{17}H_{24}O_6$: C, 62.94%; H, 7.47; *M* 324.41.

(*R*)-3-Isopropyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (187)

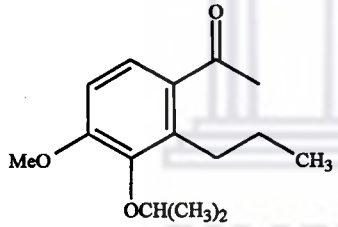


[187]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst reagent (0.122 ml, 0.061 mmol) in 0.5M toluene under nitrogen. 1 M Borane dimethyl sulphide in tetrahydrofuran (BH_3Me_2S.THF) (0.407 ml, 0.407 mmol) was added dropwise to the CBS reagent. Acetyl-3-isopropyloxy-4-methoxy-2-prop-2'-enylbenzene **161** (1.01 g, 4.07 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (2.44 ml, 2.44 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes.

The reaction mixture was extracted with dichloromethane (4 × 40 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. Five compounds eluted in the order: starting material **161** (54mg, 5.4%), ketone **184** (60 mg, 6%), **187** (53 mg, 5.2%), mono-ol **190** (220 mg, 21%) and diol **193** (247 mg, 23%). Further elution with methanol gave a polymeric material. Compounds **190** and **193** were converted to their acetates **196** (93 mg, 32%) and **199** (130 mg, 43%) for the purposes of full characterization. All products were obtained as oils.

1-Acetyl-3-isopropyloxy-2-propyl-4-methoxybenzene (184)



[184]

184 ν_{max} 1686 cm^{-1} (C=O); δ_H 0.93 (3H, t, *J* 7.4 Hz, 3'-H), 1.26 [6H, d, *J* 6.0 Hz, OCH(C*H*$_3$)$_2$], 1.52 (2H, m, 2'-H), 2.52 (3H, s, C*H*$_3$CO), 2.92 (2H, m, 1'-H), 3.85 (3H, s, ArOC*H*$_3$), 4.46 [1H, sept, *J* 6.0 Hz, OC*H*(CH$_3$)$_2$], 6.71 (1H, d, *J* 8.6 Hz, 5-H), 7.42 (1H, d, *J* 8.6 Hz, 6-H); δ_C 12.6 (C-3'), 20.6 [2 × CH$_3$(*C*H$_3$)$_2$], 22.1 (*C*H$_3$CO), 27.0 (C-2'), 27.8 (C-1'), 53.6 (ArO*C*H$_3$), 72.9 [*C*H(CH$_3$)$_2$], 106.3 (C-5), 124.2 (C-6), 129.7 (C-1)[a], 136.8 (C-2)[a], 143.5 (C-3)[b], 153.6 (C-4)[b], 199.1 (C=O). Assignments with the same superscripts can be interchanged. MS (EI): *m/z* (%): 250 (M^+, 15), 208 (17), 193 (100).

Found: C, 71.83%; H, 8.78%.

Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.88%; *M* 250.37.

187 ν_{max} 3396 cm^{-1} (O-H); δ_H 1.24 [3H, d, *J* 6.2 Hz, CH(C*H*$_3$)$_2$], 1.27 [3H, d, *J* 6.2 Hz, CH(C*H*$_3$)$_2$], 1.44 (3H, d, *J* 6.4 Hz, C*H*$_3$CHOH), 1.75 (1H, bs, D_2O exchangeable, CH$_3$CHO*H*), 3.54 (2H, ddt, *J* 16.4, 5.8 and 1.8 Hz, C*H*$_2$CH=CH$_2$), 3.82 (3H, s,

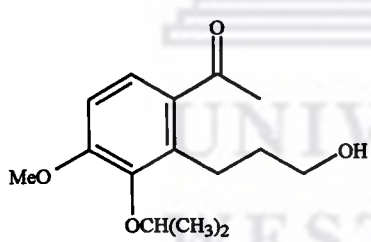
ArOCH_3), 4.49 [1H, sept, J 6.2 Hz, OCH(CH$_3$)$_2$], 4.95 (1H, dq, J 17.2 and 1.8 Hz, *trans*-CH$_2$CH=CH_2), 5.00 (1H, dq, J 10.4 and 1.8 Hz, *cis*-CH$_2$CH=CH_2), 5.08 (1H, q, J 6.4 Hz, CH$_3$CHOH), 5.95 (1H, m, CH$_2$CH=CH$_2$), 6.83 (1H, d, J 8.6 Hz, 5-H), 7.22 (1H, d, J 8.6 Hz, 6-H); δ_C 22.6 [2×(CH(*C*H$_3$)$_2$)], 24.3 (*C*H$_3$CHOH), 30.2 (*C*H$_2$CH=CH$_2$), 55.7 (ArO*C*H$_3$), 66.1 (CH$_3$*C*HOH), 74.7 (*C*H(CH$_3$)$_2$), 110.7 (C-5), 115.1 (C-3'), 120.4 (C-6), 131.1 (C-2)[a], 137.3 (C-1)[a], 137.9 (C-2'), 144.8 (C-3)[b], 152.1 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 250 (M^+, 35), 208 (16), 193 (100), 175 (38), 165 (19), 143 (66), 133 (15), 115 (24).

Found: C, 71.76%; H, 8.92%.

Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.87%; M 250.37.

1-Acetyl-2-(3'-hydroxypropyl)-3-isopropyloxy-4-methoxybenzene (190)

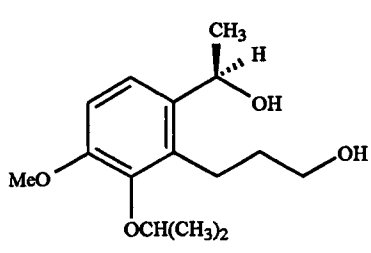
190 δ_H 1.28 [6H, d, J 6.2 Hz, CH(CH_3)$_2$], 1.83 (2H, m, 2'-H), 2.56 (3H, s, CH_3CO), 3.10 (2H, t, J 6.2 Hz, 1'-H), 3.46 (2H, t, J 6.2 Hz, 3'-H) 3.89 (3H, s, ArOCH_3), 4.50 [1H, m, CH(CH$_3$)$_2$], 6.80 (1H, d, J 8.6 Hz, 5-H), 7.54 (1H, d, J 8.6 Hz, 6-H).



[190]

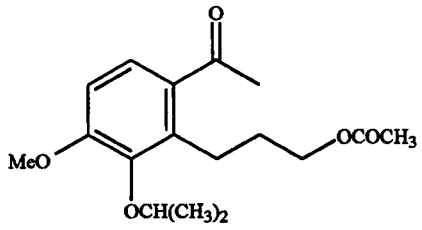
1-(1'-Hydroxyethyl)-2-(3'-hydroxypropyl)-3-isopropyloxy-4-methoxybenzene (193)

193 δ_H 1.25 [6H, d, J 6.2 Hz, CH(CH_3)$_2$], 1.45 (3H, d, J 6.4 Hz, CH_3CHOH), 1.75 (2H, m, 2'-H), 2.83 (2H, t, J 6.2 Hz, 1'-H), 3.43 (2H, t, J 6.0 Hz, 3'-H) 3.81 (3H, s, ArOCH_3), 4.50 [1H, m, CH(CH$_3$)$_2$], 6.79 (1H, d, J 8.6 Hz, 5-H), 7.21 (1H, d, J 8.6 Hz, 6-H).



[193]

2-(3'-Acetoxypropyl)-1-acetyl-3-isopropyloxy-4-methoxybenzene (196)



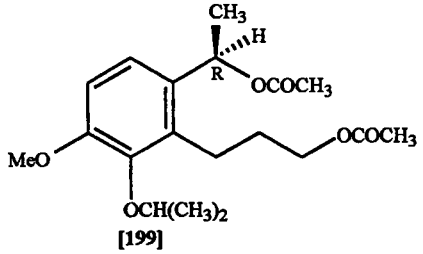
[196]

196 ν_{max} 1688 cm^{-1} (C=O) for ketone and 1734 cm^{-1} (C=O) for ester; δ_H 1.27 [6H, d, *J* 6.2 Hz, OCH(CH_3)$_2$], 1.89 (2H, m, 2'-H), 2.06 (3H, s, CH_3OCO), 2.55 (3H, s, CH_3CO), 3.08 (2H, t, *J* 8.5 Hz, 1'-H), 3.88 (3H, s, ArOCH_3), 4.10 (2H, t, *J* 6.8 Hz, 3'-H), 4.56 [1H, sept, *J* 6.2 Hz, OC*H*(CH_3)$_2$], 6.77 (1H, d, *J* 8.8 Hz, 5-H), 7.49 (1H, d, *J* 8.8 Hz, 6-H); δ_C 21.2 (ArCOCH_3), 22.7 [2 × CH(CH_3)$_2$], 23.8 (OCOCH_3), 29.5 (C-1')[a], 29.7 (C-2')[a], 55.7 (Ar-OCH_3), 64.9 (C-3'), 74.8 (*C*H(CH_3)$_2$), 108.7 (C-5), 126.5 (C-6), 131.2 (C-1)[b], 137.6 (C-2)[b], 145.5 (C-3)[c], 155.6 (C-4)[c], 171.4 (O*C*OCH$_3$), 200.3 (Ar*C*OCH$_3$). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 308 (M^+, 9), 266 (29), 206 (100), 191 (100), 178 (50), 163 (20).

Found: C, 66.27%; H, 7.77%.

Calculated for $C_{17}H_{24}O_5$: C, 66.20%; H, 7.86%; *M* 308.41.

1-(1'-Acetoxyethyl)-2-(3'-acetoxypropyl)-3-isopropyloxy-4-methoxybenzene (199)



[199]

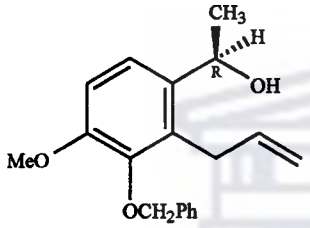
199 ν_{max} 1766 cm^{-1} (C=O); δ_H 1.27 [6H, d, *J* 6.2 Hz, OCH(CH_3)$_2$], 1.51 (3H, d, *J* 6.6 Hz, CH_3CHOAc), 1.86 (2H, m, 2'-H), 2.05 (3H, s, CH_3OCO), 2.08 (3H, s, CH_3OCO), 2.80 (2H, m, 1'-H), 3.82 (3H, s, ArOCH_3), 4.12 (2H, t, *J* 6.4 Hz, 3'-H), 4.52 [1H, sept, *J* 6.2 Hz, OC*H*(CH_3)$_2$], 6.08 (1H, q, *J* 6.6 Hz, CH_3C*H*OAc), 6.80 (1H, d, *J* 8.6 Hz, 5-H), 7.12 (1H, d, *J* 8.6 Hz, 6-H); δ_C 21.1 [CH(*C*H$_3$)$_2$], 21.5 [2×CH(*C*H$_3$)$_2$] , 22.3 (*C*H$_3$OCO), 22.8 (*C*H$_3$OCO), 23.3 (*C*H$_3$), 29.3 (C-2'), 55.7 (ArO*C*H$_3$), 64.6 (C-3'), 69.1 [*C*H(OAc)], 74.5 [*C*H(CH$_3$)$_2$], 110.4 (C-5),

121.2 (C-6), 132.8 (C-1)[a], 133.8 (C-2)[a], 144.8 (C-3)[b], 152.2 (C-4)[b], 170.4 (C=O), 171.4 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 352 (M^+, 7), 292 (11), 250 (35), 190 (100), 175 (26), 143 (16).

Found: C, 64.61%; H, 8.10%.

Calculated for $C_{19}H_{28}O_6$: C, 64.74%; H, 8.02%: *M* 352.47.

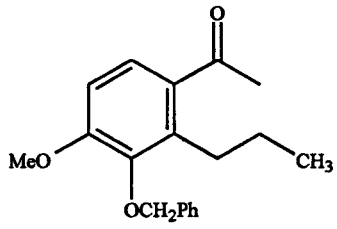
(*R*)-3-Benzyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-2'-enylbenzene (188)



[188]

In an oven dried three necked flask was introduced the Corey Bakshi Shibata (CBS) catalyst reagent (0.1 ml, 0.05 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide (BH_3Me_2S.THF) in tetrahydrofuran (0.33 ml, 0.33 mmol) was added dropwise to the CBS reagent. Acetyl-3-benzyloxy-4-methoxy-2-prop-2'-enylbenzene **162** (1.00 g, 3.3 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (1.99 ml, 1.99 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. Five compounds eluted in the order: starting material **162** (40 mg, 4%), ketone **185** (40 mg, 4%), **188** (83 mg, 8%), mono-ol **191** (140 mg, 13%) and diol **194** (280 mg, 26%). Further elution with methanol gave a polymeric material. The alcohols **191** and **194** were converted to their acetates **197** (71 mg, 45%) and **200** (130 mg, 34%) for the purposes of full characterization. All the products were oils.

1-Acetyl-3-benzyloxy-2-propyl-4-methoxybenzene (185)



[185]

185 ν_{max} 1677 cm^{-1} (C=O); δ_H 0.95 (3H, t, *J* 7.4 Hz, 3'-H), 1.54 (2H, m, 2'-H), 2.56 (3H, s, C*H*$_3$CO), 2.92 (2H, t, *J* 8.8 Hz, 1'-H), 3.93 (3H, s, ArOC*H*$_3$), 4.98 (2H, s, OC*H*$_2$Ph), 6.81 (1H, d, *J* 8.6 Hz, 5-H), 7.41 (5H, m, Ph*H*'s), 7.49 (1H, d, *J* 8.6 Hz, 6-H); δ_C 14.5 (C-3'), 24.5 (ArCOC*H*$_3$), 28.9 (C-2'), 29.7 (C-1'), 55.7 (ArOC*H*$_3$), 74.8 (OC*H*$_2$Ph), 108.6 (C-5), 127.0 (C-6), 127.9 (×3, aryl), 128.5 (×2, aryl), 137.9 (aryl), 131.4 (C-1)[a], 138.6 (C-2)[a], 146.7 (C-3)[b], 155.6 (C-4)[b] and 200.6 (ArCOCH$_3$). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 298 (M^+, 31), 256 (100), 207 (54), 191 (33), 178 (37), 191 (33), 178 (37), 157 (19), 91 (100).

Found: C, 76.39%; H, 7.55%.

Calculated for $C_{19}H_{22}O_3$: C, 76.47%; H, 7.45%; *M* 298.41.

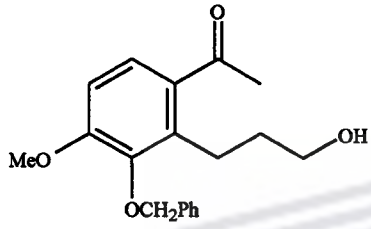
188 ν_{max} 3384 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.4 Hz, *CH*$_3$CHOH), 1.68 (1H, bs, D_2O exchangeable, CH$_3$CHO*H*), 3.51 (2H, ddt, *J* 14.2, 5.8 and 1.8 Hz, C*H*$_2$CH=CH$_2$), 3.88 (3H, s, ArOC*H*$_3$), 4.88 (1H, dq, *J* 17.2 and 1.8 Hz, *trans*-CH$_2$CH=C*H*$_2$), 4.98 (2H, s, OC*H*$_2$Ph), 5.03 (1H, dq, *J* 10.2 and 1.8 Hz, *cis*-CH$_2$CH=C*H*$_2$), 5.06 (1H, q, *J* 6.4 Hz, CH$_3$C*H*OH), 5.97 (1H, m, CH$_2$C*H*=CH$_2$), 6.91 (1H, d, *J* 8.6 Hz, 5-H), 7.31 (1H, d, *J* 8.6 Hz, 6-H), 7.40 (5H, m, Ph*H*'s); δ_C 24.3 (*C*H$_3$CHOH), 29.9 (*C*H$_2$CH=CH$_2$), 55.8 (ArO*C*H$_3$), 66.2 (CH$_3$*C*HOH), 74.8 (*C*H$_2$Ph), 110.9 (5-C), 115.3 (C-3'), 121.1 (C-6), 127.9 (aryl), 128.1 (×2, aryl), 128.5 (×2, aryl), 131.0 (aryl), 137.9 (C-2'), 137.3 (C-1)[a], 138.1 (C-2)[a], 145.0 (C-3)[b] and 152.2 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 298 (M^+, 79), 283 (43), 265 (35), 202 (56), 189 (84), 175 (52), 161 (43), 131 (33), 91 (100).

Found: C, 76.30%; H, 7.53%.

Calculated for $C_{19}H_{22}O_3$: C, 76.47%; H, 7.45%; *M* 298.41.

1-Acetyl-2-(3'-hydroxypropyl)-3-benzyloxy-4-methoxybenzene (191)

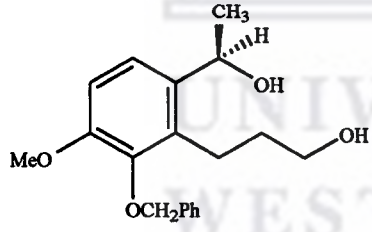
191 δ_H 1.83 (2H, m, 2'-H), 2.57 (3H, s, C*H*$_3$CO), 3.03 (2H, t, *J* 6.0 Hz, 1'-H), 3.48 (2H, t, *J* 6.0 Hz, 3'-H), 3.95 (3H, s, ArOC*H*$_3$), 4.98 (2H, s, OC*H*$_2$Ph), 6.85 (1H, d, *J* 8.6 Hz, 5-H), 7.39 (5H, m, Ph*H*'s), 7.55 (1H, d, *J* 8.6 Hz, 6-H).



[191]

1-(1'-Hydroxyethyl)-2-(3'-hydroxypropyl)-3-benzyloxy-4-methoxybenzene (194)

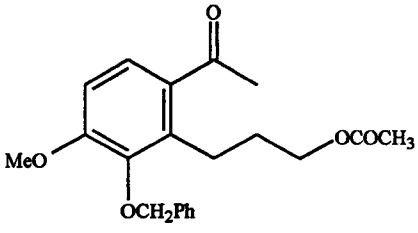
194 δ_H 1.49 (3H, d *J* 6.4 Hz, C*H*$_3$CHOH), 1.81 (2H, m, 2'-H), 2.79 (2H, m, 1'-H), 3.47 (2H, t, *J* 6.0 Hz, 3'-H), 3.89 (3H, s, ArOC*H*$_3$), 4.98 (2H, s, OC*H*$_2$Ph), 5.10 (1H, q, *J* 6.4 Hz, CH$_3$C*H*OH), 6.87 (1H, d, *J* 8.8 Hz, 5-H), 7.28 (1H, d, *J* 8.8 Hz, 6-H), 7.41 (5H, m, Ph*H*'s).



[194]

2-(3'-Acetoxypropyl)-1-acetyl-3-benzyloxy-4-methoxybenzene (197)

197 ν_{max} 1684 cm^{-1} (C=O) for ketone and 1750 cm^{-1} (C=O) for ester; δ_H 1.89 (2H, m, 2'-H), 1.96 (3H, s, C*H*$_3$OCO), 2.55 (3H, s, C*H*$_3$CO), 3.08 (2H, t, *J* 7.8 Hz, 1'-H), 3.93 (3H, s, ArOC*H*$_3$), 4.08 (2H, t, *J* 6.6 Hz, 3'-H), 4.97 (2H, s, OC*H*$_2$Ph), 6.84 (1H, d, *J* 8.6 Hz, 5-H), 7.39



[197]

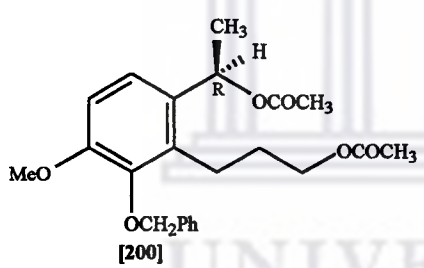
(5H, m, Ph*H*'s), 7.56 (1H, d, *J* 8.6 Hz, 6-H); δ_C 20.9 (*C*H_3CO), 23.6 (*C*H_3COO), 29.5 (C-2'), 29.7 (C-1'), 55.8 (ArO*C*H_3), 64.7 (*C*H_2OAc), 74.6 (O*C*H_2Ph), 108.9 (C-5), 127.4 (C-6), 128.0 (×3, aryl), 128.5 (×2, aryl), 135.7 (aryl), 131.1 (C-1)[a], 137.7 (C-2)[a], 146.7 (C-3)[b], 155.7 (C-4)[b], 171.4 (O*C*OCH$_3$) and 200.1 (Ar*C*OCH$_3$). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 296 [M^+-60, (1)], 206 (100), 191 (41), 91 (27).

Found: C, 70.68%; H, 6.74%.

Calculated for $C_{21}H_{24}O_5$: C, 70.76%; H, 6.80%; *M* 356.45.

1-(1'-Acetoxyethyl)-2-(3'-acetoxypropyl)-3-benzyloxy-4-methoxybenzene (200)

200 ν_{max} 1734 cm^{-1} (C=O); δ_H 1.52 (3H, d, *J* 6.6 Hz, C*H*$_3$CHOAc), 1.86 (2H, m, 2'-H), 2.00 (3H, s, C*H*$_3$COO), 2.06 (3H, s, C*H*$_3$COO), 2.75 (2H, m, 1'-H), 3.88 (3H, s, ArOC*H*$_3$), 4.06 (2H, t, *J* 7.0 Hz, 3'-H), 5.01 (2H, s, C*H*$_2$Ph), 6.08 (1H, q, *J* 6.6 Hz, CH$_3$C*H*OAc), 6.85 (1H, d, *J* 8.6 Hz, 5-H), 7.11 (1H, d, *J* 8.6 Hz, 6-H), 7.39 (5H, m, Ph*H*'s); δ_C 20.9 (*C*H$_3$CHOAc), 21.4 (*C*H$_3$OCO), 22.1 (*C*H$_3$OCO), 23.0 (C-2'), 29.6 (C-1'), 55.7 (ArO*C*H$_3$), 64.3 (*C*HOAc), 68.9 (C-3'), 74.7 (O*C*H$_2$Ph), 110.6 (5-C), 121.9 (C-6), 127.9 (×3, aryl), 128.5, (×2, aryl), 133.5 (aryl), 132.9 (C-1)[a], 138.1 (C-2)[a], 145.0 (C-3)[b] and 152.4 (C-4)[b], 170.4 and 171.4 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 340 [M^+-60, (7)], 190 (100), 175 (13), 91 (15).



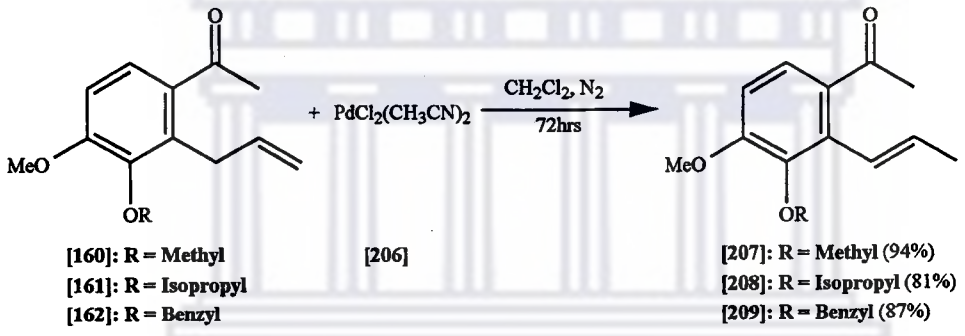
[200]

Found: C, 79.47%; H, 7.78%.

Calculated for $C_{23}H_{28}O_6$: C, 79.50%; H, 7.93%; *M* 400.51.

4.3. Synthesis of 1-alkenyl-3,4-dialkoxylated acetophenones

Owing to the low yields of the (*R*)-alcohols **186**, **187** and **188** obtained during the CBS catalyzed reduction of the ketone precusors **160**, **161** and **162**, we embarked upon a strategy to conjugate the double bond[91] in the alkenyl group from the C-2' atom to the C-1' atom by reacting the ketones **160**, **161** and **162** with *bis*-(acetonitrile)dichloro palladium(II) **206** in dichloromethane at 35 °C under nitrogen for 72 hours to afford the corresponding conjugated side chain ketones **207** (94%), **208** (81%) and **209** (87%) (Scheme 42).

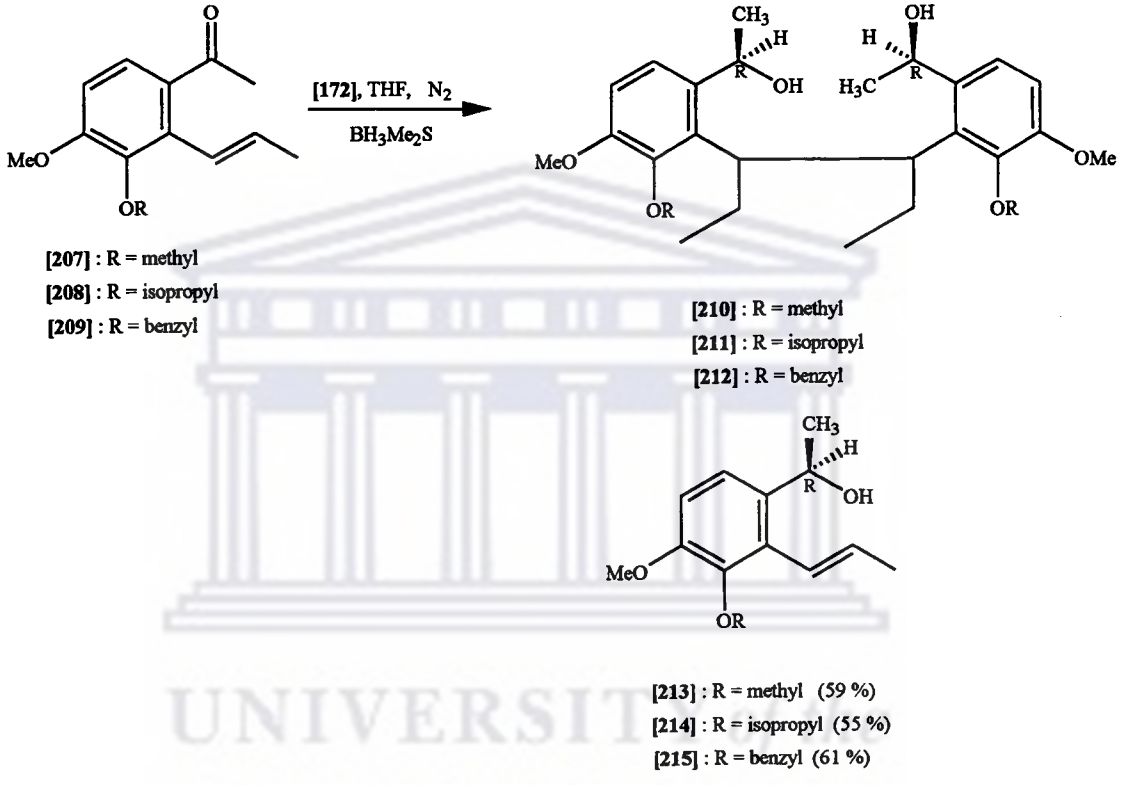


Scheme 42

Clear evidence for conjugation of the prop-2'-enyl side chain to the *trans*-prop-1'-enyl isomer is evident from the ^{1}H-nmr spectrum in which the 3'-H appeared as a doublet of a doublet in the region δ 1.86 – 1.90 with ^{3}J 6.6 – 6.8 Hz and ^{4}J 1.8 Hz from long range coupling to 1'-H. A doublet of a quartet in the region of δ 5.80 – 5.90 with ^{3}J 16.0 and 6.6 Hz confirmed the *trans* nature of the olefinic side chain for 2'-H. The more deshielded 1'-H appeared as a doublet of quartets in the region of δ 6.70 with ^{3}J 16.0 Hz and ^{4}J 1.8 Hz. In the ^{13}C-nmr spectra the C'-3 appeared in the expected region of δ 30.6.

4.3.1. Chiral reduction of 1-alkenyl-3,4-dialkoxylated acetophenones

The conjugated ketones were subjected to enantioselective reduction using the CBS-catalyst **172** and borane-dimethyl sulphide **181** as the reducing agent to afford firstly the dimers **210**, **211** and **212** followed by the (*R*)-alcohols **213** (59%), **214** (55%) and **215** (61%) (Scheme 43).



Scheme 43

During the reductive process in which the ketone moiety is chirally reduced it would appear that the CBS catalyst was also capable of causing the benzylic positions to undergo a novel C-C bond formation a precedent which we were not able to find in the literature. A possible reason could be ascribed to the proximity of the benzylic positions in an intermediate complex between the CBS catalyst and the alcohol in which hydride transfer to the C-2 of the side chain occurs with concomitant loss of the catalyst and

C-C bond formation. A number of variations including lower temperature, dilution versus concentration of reagents, speed at which BH_3 and ketone were simultaneously introduced, were attempted but without any significant reduction in the formation of the dimer. In each of the three cases of reduction, the same dimeric material was isolated as illustrated in the experimental section. Since all the analytical data is so similar except for the 3-alkoxy group a representative discussion of the reasons for making the assignments will be confined to the 3,4-dimethoxy case **210**.

The mass spectra for the three dimeric products of the series were not useful since they did not indicate molecular ions. The fragmentation patterns proved rather complicated and thus will not be discussed since more useful analytical data was obtained from the other analytical techniques available. Microanalysis had values, which are acceptable for the proposed molecular formula $C_{26}H_{38}O_6$. A very prominent band in the infrared spectrum at 3434 cm^{-1} confirmed the presence of the –OH group.

The two tethered side chains are evident from a pair of triplets at δ 1.04 and δ 1.08 each integrating for three protons and with a ^3J 7.2 Hz in the ^{1}H-nmr spectrum. The two methyl groups of the reduced hydroxy ethyl side chain each appeared as 3-proton doublets at δ 1.52 and δ 1.63 with ^3J 6.6 Hz. Interestingly the two methine protons of the newly formed C-C bond appeared as 1-proton multiplets at δ 2.68 and δ 2.48. A COSY spectrum of the dimer clearly demonstrated the connection of each of these methine protons with the adjacent methylene protons at δ 1.7 – 1.9 which in turn were connected to the triplets at δ 1.04 and δ 1.08. A sharp series of four peaks in the region of δ 3.9 accounts for the four methoxy groups while two broad signals at δ 4.28 and δ 4.38 both D_2O exchangeable are assigned to the two OH groups of the hydroxyethane side chain. A 2-proton quartet at δ 5.20 with ^3J 6.6 Hz is assigned to the two methine protons of the hydroxyethyl side chain and this is confirmed by the clear connectivity

shown in the COSY spectrum to the methyl doublets at δ 1.52 and δ 1.63. Finally the aryl *ortho* hydrogens appeared as a multiplet at δ 6.75 integrating for three protons with a separate doublet at δ 6.93 with *J* 8.8 Hz integrating for one proton. The ^{13}C-nmr spectrum showed a total of 26 C-atoms some overlapping while others, especially in the aromatic region being just slightly different (see Section 4.3.3.). The ^{1}H-nmr and ^{13}C-nmr patterns are similar for all three dimers of the series leading to the conclusion that a similar mechanism is involved during the CBS catalyzed chiral reduction of the *ortho*-1'-alkenyl aryl ketones.

In the ^{1}H-nmr spectra of the series of chiral alcohols **213**, **214** and **215** the methyl group of the hydroxyethyl side chain appeared as a doublet in the region of δ 1.45 with ^{3}J 6.2 Hz while the methine proton of this same side chain appeared as a quartet in the expected region of δ 5.15 with ^{3}J 6.2 Hz. The position of the OH, which is concentration dependent varied from δ 1.60 – 1.90. Confirmation of this reduction was also evident by the disappearance of the C=O peak of the ketone precursors at δ 203 and replaced by the benzylic peak at δ 66.4 in the ^{13}C-nmr spectra.

4.3.2. Determination of the Enatiomeric Excess Values

The enatiomeric excess value (*ee* %) can be defined by the expression:

$$ee(\%) = \frac{S1 - S2}{S1 + S2} \times 100$$

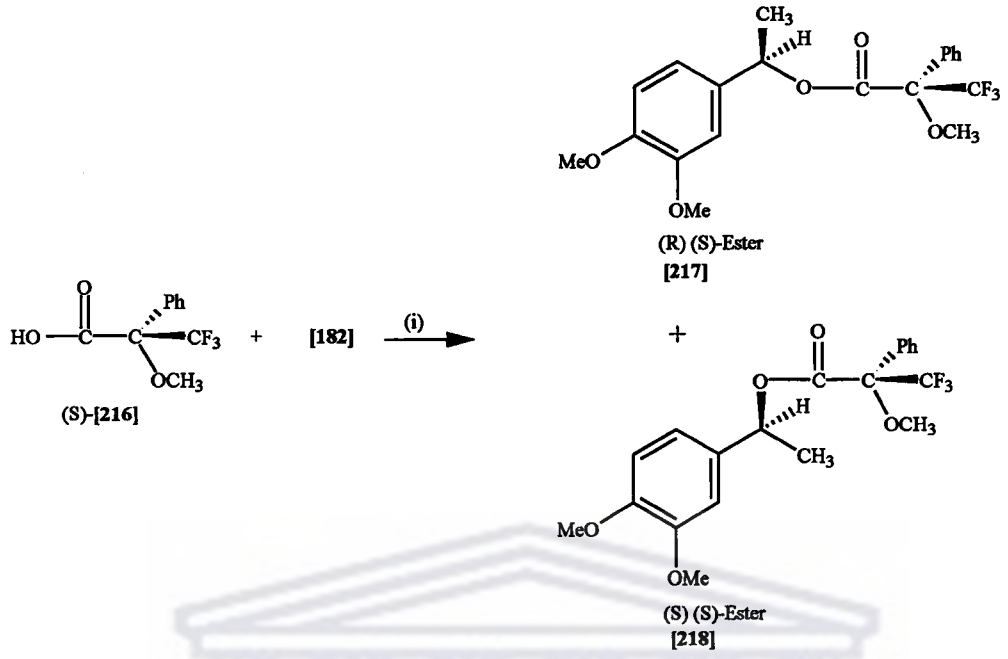
where, S1 is the integration of the signal of the major enantiomer and S2 is the integration of the signal of the minor enantiomer. The enatiomeric excess value (*ee* %) gives an indication of the optical purity of the product isolated.

Mosher[92,93] *et al* reported that α-methoxy-α-trifluoromethylphenylacetic acid (MPTA) reacts *via* its acid chloride with chiral alcohols to give a mixture of diastereomeric esters

whose nuclear magnetic resonance spectra can be used for quantitative analysis of the enantiomeric composition of the chiral alcohol from which it is made. The advantage of this reagent is that there is generally excellent separation of both proton and fluorine nuclear magnetic resonance signals of the diastereomers. Furthermore, the presence of the trifluoromethyl group permits the use of fluorine nuclear magnetic resonance spectra, which occurs in an uncongested region of the spectrum[94].

Another method that may be used for determining the enantiomeric excess is the addition of a chiral shift reagent such as Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate].

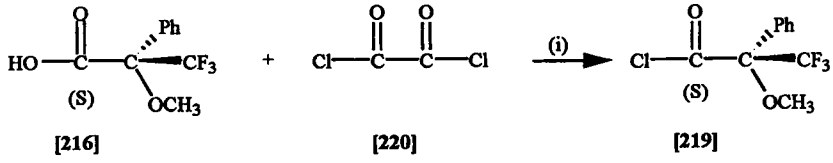
In the determination of the enantiomeric excess the (*R*)-alcohol **182**, the Mosher esters were prepared by dissolving **182** in dichloromethane to which (*S*)-MPTA **216** (4.0 mass equiv), 4-dimethylaminopyridine (0.4 mass equiv) and dicyclohexylcarbodiimide (4.0 mass equiv) were added. The reaction mixture was stirred at room temperature for 15 hours (Scheme 44). The Mosher esters **217** and **218** were purified by preparative thin layer chromatography using acetone – hexane (1:9) as eluant.



Scheme 44

In the determination of the enantiomeric excess value for the (*R*)-alcohols (**213-215**) the direct reaction of the (*R*)-alcohols with (*S*)-MPTA **216** in the presence of 4-dimethylaminopyridine and dicyclohexylcarbodiimide was unsuccessful, since hydrolysis of the Mosher esters back to the (*R*)-alcohols occurred during the chromatographic purification. In alternative approach the (*S*)-MPTA **216** was first converted to the more active (*S*)-MPTA-chloride **219** and in turn reacted with the (*R*)-alcohol to give the Mosher esters.

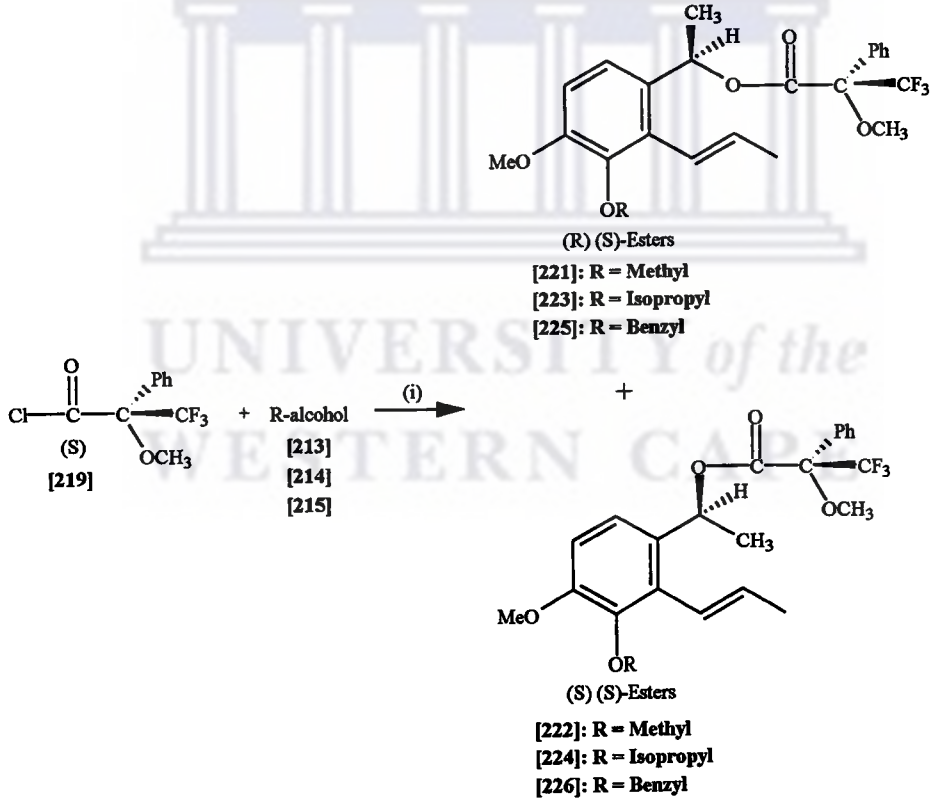
Thus (*S*)-MPTA **216** was reacted with oxalyl chloride **220** (1.2 mmol) and a catalytic amount of dimethylformamide (0.1mmol) to give the (*S*)-MPTA-chloride **219**[95,96] (Scheme 45).



(i) dimethylformamide, dichloromethane, room temp., 4 hours.

Scheme 45

The (*R*)-alcohols (**213**, **214** and **215**) were then reacted with (*S*)-MPTA-chloride **220** (1.1 mmol), 4-dimethylaminopyridine (1.0 mmol) and triethylamine (3 mmol) in dry dichloromethane (3 ml) to yield the diastereomeric esters **221** to **226** (Scheme 46) which were analyzed by proton and fluorine nuclear magnetic resonance spectroscopy.



(i) 4-dimethylaminopyridine, triethylamine, dry dichloromethane

Scheme 46

The first method for determining the enantiomeric excess value was the addition of Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] to the alcohols **182, 213, 214** and **215**, and was effected in progressive amounts until a separation of peaks of selected protons was sufficient as to allow for their sepatate integration. In all cases, peaks underwent a very strong deshielding migration and individual molecules will be illustrated separately as to which proton peaks were chosen. For compound **182**, the chromatographed material was treated with Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] and whilst all peaks experienced very strong deshielding namely, the CH_3 doublet at δ 1.48 was deshielded to δ 2.42 and the methine quartet at δ 4.85 was deshielded to δ 6.50. No splitting of these signals was observed even when the concentration of Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] was in the order of 25%. Although the CBS reduction of similar systems has been reported to proceed with >97% ee [76], one would have to synthesize the alternate enantiomer and mix the two in say a 2:3 ratio and again subject to the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] reagent examine the ^{1}H-nmr spectra.

For compound **213**, the addition of Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] effected a deshielding influence on all peaks and it was found that the 6-H moved from δ 7.26 to δ 8.11 and the enantiomeric 6-H appeared at δ 8.02 separate from the former which allowed the enantiomeric excess to be determined as 71% by comparing the relative integrations of the two peaks.

For compound **214**, the addition of Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] again had a strong

deshielding effect on all proton signals and in this instance the signal that could be clearly identified for the two enantiomers was the one due to 5-H which shifted from δ 6.82 to δ 6.97 and δ 7.00 which allowed the enantiomeric excess to be calculated as 75%.

For compound **215**, the addition of Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] again had a strong deshielding effect on all proton signals. In this instance 6-H was deshielded from δ 7.28 to the enantiomeric doublet at δ 8.01and δ 8.09 which allowed the calculation of the enantiomeric excess to be made as 74%.

In the case of the Mosher esters the signals that were sufficiently separate for a comparative integration analysis were in all cases due to the OCH_3 group of the Mosher ester. Although other signals of the alcohol showed a splitting, they were not sufficiently separated to allow for unambiguous integrational assignments.

For compound **182**, the OCH_3 signals appeared at δ 3.47 and δ 3.57 which translated into an enantiomeric excess value of 79% which was much lower than the 97% as determined by the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method.

For compound **213**, the OCH_3 signals appeared at δ 3.46 and δ 3.55 and allowed for a calculation of an enantiomeric excess value of 64% which was in fair agreement to the 71% determined by the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method.

For compound **214**, the OCH_3 signals appeared at δ 3.47 and δ 3.54 which translated into an enantiomeric excess value of 60% as compared to 75% determined by the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method.

For compound **215**, the comparable OCH_3 signals appeared at δ 3.48 and δ 3.56 which translated into an enantiomeric excess value of 53% as compared to 74% determined by the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method.

A further determination of the enantiomeric excess values for the Mosher esters was done by ^{19}F-nmr spectroscopy in which the two ^{19}F signals for the enantiomers were separate and integrated to afford the following enantiomeric excess values.

For molecule **213** the signals were at δ 80.62 and δ 80.77 and gave an enantiomeric excess value of 80% in better agreement to the value obtained by the Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method.

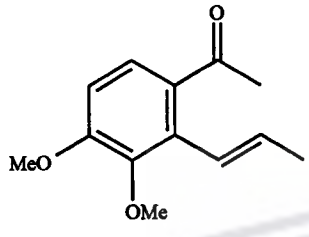
For molecule **214** the relevant signals in the ^{19}F-nmr spectrum appeared at δ 80.62 and δ 80.77 giving an enantiomeric excess value of 55%. For molecule **215** the relevant signals in the ^{19}F-nmr spectrum appeared at δ 80.63 and δ 80.77 giving an enantiomeric excess value of 55%. It is believed that is values are lower due to the time the samples were in the nuclear magnetic resonance tubes and thus some hydrolysis could have occurred.

The Europium *tris*[3-heptafluoropropylhydromethoxymethylene-(+)-camphorate] addition method gave values which were consisted and was advantageous since no additional sample preparation was required.

4.3.3. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

Acetyl-3,4-dimethoxy-2-prop-1'-enylbenzene (207)



[207]

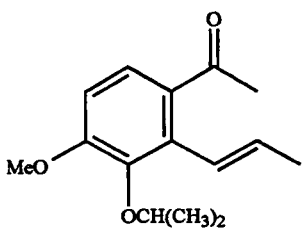
Acetyl-3,4-dimethoxy-2-prop-2'-enylbenzene **160** (1.00 g, 4.45 mmol) was dissolved in dry dichloromethane (50 ml) and palladium chloride *bis*-acetonitrile (100 mg) was added. The reaction mixture was stirred at reflux under nitrogen for 72hours. The palladium chloride *bis*-acetonitrile was removed by filtering the reaction mixture through a silica gel plug. The filtrate was evaporated to a residue and the residue purified by column chromatography using ethyl acetate – hexane (1:9) as eluant. The product was obtained as a bright yellow oil (0.94g, 94%).

207 ν_{max} 1684 cm^{-1} (C=O); δ_H 1.90 (3H, dd, *J* 6.6 and 1.8 Hz, CH=CHC*H*$_3$), 2.41 (3H, s, ArCOC*H*$_3$), 3.75 (3H, s, ArOC*H*$_3$), 3.89 (3H,s, ArOC*H*$_3$), 5.85 (1H, dq, *J* 16.0 and 6.6 Hz, CH=C*H*CH$_3$), 6.73 (1H, dq, *J* 16.0 and 1.8 Hz, C*H*=CHCH$_3$), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.25 (1H, d, *J* 8.6 Hz, 6-H); δ_C 19.3 (C-3'), 30.6 (*C*H$_3$CO), 55.9 (ArO*C*H$_3$) 60.3 (ArO*C*H$_3$), 110.0 (C-2'), 124.7 (C-6)[a], 124.8 (C-5)[a], 132.4 (C-2)[b], 133.4 (C-1'), 133.8 (C-1)[b], 146.5 (C-3)[c], 154.9 (C-4)[c] and 203.4 (CH$_3$*C*O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 220 (M^+, 13), 205 (100), 190 (16), 161 (20).

Found: C, 70.76%; H, 7.44%.

Calculated for $C_{13}H_{16}O_3$: C, 70.88%; H, 7.34%; *M* 220.29.

Acetyl-3-isopropyloxy-4-methoxy-2-prop-1'-enylbenzene (208)



[208]

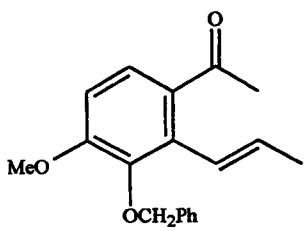
Acetyl-3-isopropyloxy-4-methoxy-2-prop-2'-enylbenzene **161** (2.00 g, 8.07 mmol) was dissolved in dry dichloromethane (100 ml) and palladium chloride *bis*-acetonitrile (200 mg) was added. The reaction mixture was stirred at reflux under nitrogen for 72 hours. The palladium chloride *bis*-acetonitrile was removed by filtering the reaction mixture through a silica gel plug. The filtrate was evaporated to a residue and the residue purified by column chromatography using ethyl acetate – hexane (1:9) as eluant. The product was obtained as a bright yellow oil (0.81g; 81%).

208 ν_{max} 1694 cm^{-1} (C=O); δ_H 1.23 [6H, d, *J* 6.2 Hz, $CH(CH_3)_2$], 1.88 (3H, dd, *J* 6.6 and 1.8 Hz, $CH{=}CHCH_3$), 2.34 (3H, s, $ArCOCH_3$), 3.86 (3H, s, $ArOCH_3$), 4.38 [1H, m, $OCH(CH_3)_2$], 5.82 (1H, dq, *J* 16.0 and 6.6 Hz, $CH{=}CHCH_3$), 6.72 (1H, dq, *J* 16.0 and 1.8 Hz, $CH{=}CHCH_3$), 6.82 (1H, d, *J* 8.8 Hz, 5-H), 7.18 (1H, d, *J* 8.8 Hz, 6-H); δ_C 19.2 (CH_3CO), 22.6 [2×$CH(CH_3)_2$], 30.7 (C-3'), 55.9 ($ArOCH_3$), 75.5 [$CH(CH_3)_2$], 110.0 (C-2'), 124.3 (C-6)[a], 125.7 (C-5)[a], 125.9 (C-1)[b], 128.8 (C-2)[b], 133.1 (C-1'), 144.6 (C-3)[c], 155.9 (C-4)[c], 203.9 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 248 (M^+, 17), 233 (42), 205 (15), 191 (100), 176 (24), 163 (13).

Found: C, 72.43%; H, 8.17%.

Calculated for $C_{15}H_{20}O_3$: C, 72.54%; H, 8.13%; *M* 248.35.

Acetyl-3-benzyloxy-4-methoxy-2-prop-1'-enylbenzene (209)



[209]

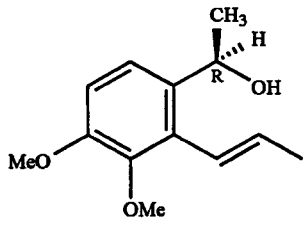
Acetyl-3-benzyloxy-4-methoxy-2-prop-2'-enylbenzene **162** (1.00 g, 3.38 mmol) was dissolved in dry dichloromethane (50 ml) and palladium chloride *bis*-acetonitrile (100 mg, 10 mol%) was added. The reaction mixture was stirred at reflux under nitrogen for 72 hours. The palladium chloride *bis*-acetonitrile was removed by filtering the reaction mixture through a silica gel plug. The filtrate was evaporated to a residue and the residue purified by column chromatography using ethyl acetate – hexane (1:9) as eluant. The product was obtained as a bright yellow oil (0.87 g, 87%).

209 ν_{max} 1684 cm^{-1} (C=O); δ_H 1.84 (3H, dd, *J* 6.6 and 1.8 Hz, CH=CHC*H*$_3$), 2.40 (3H, s, ArCOC*H*$_3$), 3.90 (3H, s, ArOC*H*$_3$), 4.89 (2H, s, OC*H*$_2$Ph), 5.82 (1H, dq, *J* 16.0 and 6.6 Hz, CH=C*H*CH$_3$), 6.63 (1H, dq, *J* 16.0 and 1.8 Hz, C*H*=CHCH$_3$), 6.84 (1H, d, *J* 8.6 Hz, 5-H), 7.28 (1H, d, *J* 8.6 Hz, 6-H), 7.37 (5H, m, Ph*H*'s); δ_C 19.2 (C-3'), 30.6 (ArCO*C*H$_3$), 56.0 (ArO*C*H$_3$), 74.0 (O*C*H-Ph), 110.1 (C-2'), 125.1 (C-6)[a], 128.1 (C-5)[a], 128.4 (×3, aryl), 128.5 (×2, aryl), 133.0 (C-2)[b], 133.5 (C-1'), 133.8 (C-1)[b], 137.5 (aryl), 145.3 (C-3)[c], 155.1 (C-4)[c] and 203.3 (Ar*C*OCH$_3$). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 296 (M^+, 4), 205 (100), 190 (13), 178 (11), 163 (55), 91 (28), 43 (15).

Found: C, 76.78%; H, 6.93%.

Calculated for $C_{19}H_{22}O_3$: C, 76.99%; H, 6.82%; *M* 296.39.

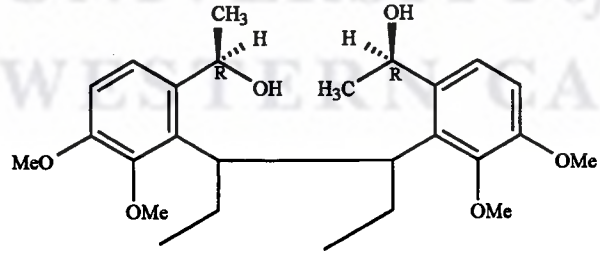
(*R*)-3,4-Dimethoxy-1-(1'-hydroxyethyl)-2-prop-1'-enylbenzene (213)



[213]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst reagent (0.136 ml, 0.07 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide in tetrahydrofuran (BH_3Me_2S.THF) (0.45 ml, 0.45 mmol) was added dropwise to the CBS reagent. Acetyl-3,4-dimethoxy-2-prop-1'-enylbenzene (1.00 g, 4.55 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (2.72 ml, 2.72 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml), dried over magnesium sulphate and filtered. The filtrate was evaporated to a residue and was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant.

The first compound to elute was assigned the dimeric structure **210** and was obtained as a thick oil (0.3g, 18%).



[210]

210 ν_{max} 3434 cm^{-1} (O-H); δ_H 1.04 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.08 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.52 [3H, d, *J* 6.6 Hz, $CH(OH)CH_3$], 1.63 [3H, d, *J* 6.6 Hz, $CH(OH)CH_3$], 1.82 (4H, overlapping multiplet, $CHCH_2CH_3$), 2.43 (1H, m, $CHCH_2CH_3$), 2.62 (1H, m, $CHCH_2CH_3$), 3.82, 3.84, 3.85 and 3.86 (each 3H, s, $ArOCH_3$), 4.28 and 4.38 [each 1H, bs, D_2O exchangeable, $CH(OH)CH_3$], 5.20 [2H, q, *J* 6.6 Hz, $CH(OH)CH_3$], 6.75 (3H,

m, both 5-H's and one of the 6-H's), 6.93 (1H, d, *J* 8.8 Hz, 6-H); δ_C 14.1, 14.3, 22.5, 23.8, 27.3, 27.6, 55.6, 55.7, 60.5, 60.7, 70.1 (×2), 73.9 (×2), 109.3, 110.2, 119.3, 120.4, 133.1, 133.4, 133.6, 134.8, 146.8, 147.4, 154.4 and 152.0; MS (EI): *m/z* (%): 269 (13), 91 (100).

Found: C, 69.97%; H, 8.62%.

Calculated for $C_{26}H_{38}O_6$: C, 69.91%; H, 8.59%; *M* (446.64).

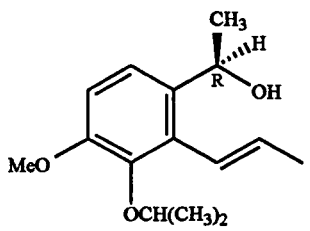
Further elution gave the product **213**; as a pale yellow oil (0.59 g, 59%) in yield.

213 ν_{max} 3407 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.4 Hz, C*H*$_3$CHOH), 1.64 (1H, bs, D_2O exchangeable, CH$_3$CHO*H*), 1.92 (3H, dd, *J* 6.4 and 1.8 Hz, CH=CHC*H*$_3$), 3.72 (3H, s, ArOC*H*$_3$), 3.86 (3H, s, ArOC*H*$_3$), 5.13 (1H, q, *J* 6.4 Hz, CH$_3$C*H*OH), 6.00 (1H, m, CH=C*H*CH$_3$), 6.42 (1H, dq, *J* 16.0 and 1.8 Hz, C*H*=CHCH$_3$), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.26 (1H, d, *J* 8.6 Hz, 6-H); δ_C 19.4 (C-3'), 24.4 (*C*H$_3$CHOH), 55.9 (ArOCH$_3$), 60.2 (ArO*C*H$_3$), 66.4 (CH$_3$*C*HOH), 111.0 (C-2'), 120.7 (C-6), 123.5 (C-5), 131.2 (C-2)[a], 132.3 (C-1'), 136.7 (C-1)[a], 146.5 (C-3)[b], 151.5 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 11), 207 (100), 189 (15), 176 (15), 164 (13); $[\alpha]_D$ = +32.2° (c = 0.785, CH_2Cl_2); enantiomeric excess: ^{1}H-nmr (Mosher esters) 64%, ^{19}F-nmr (Mosher esters) 80% and europium shift reagent 71%.

Found: C, 70.16%; H, 8.13%.

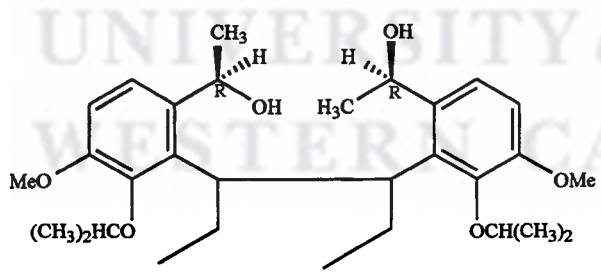
Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

(*R*)-3-Isopropyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-1'-enylbenzene (214)



[214]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst reagent (0.122 ml, 0.061 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide in tetrahydrofuran (BH_3Me_2S.THF) (0.407 ml, 0.407 mmol) was added dropwise to the CBS reagent. Acetyl-3-Isopropyloxy-4-methoxy-2-prop-1'-enylbenzene (1.01 g, 4.07 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (2.44 ml, 2.44 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate - hexane (1:4) as eluant. The first compound to elute was assigned the dimeric structure **211** as was obtained as a thick oil (0.42 g, 21%).



[211]

211 ν_{max} 3428 cm^{-1} (O-H); δ_H 0.97 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.04 (3H, t, *J* 7.2 Hz, CH_2CH_3), 1.20 [6H, d, *J* 6.4 Hz, $OCH(CH_3)_2$], 1.37 [6H, d, *J* 6.4 Hz, $OCH(CH_3)_2$], 1.51 [3H, d, *J* 6.8 Hz, $CH(OH)CH_3$], 1.63 [3H, d, *J* 6.8 Hz, $CH(OH)CH_3$], 1.80 (4H, overlapping multiplet, $CHCH_2CH_3$), 2.52 (1H, m, $CHCH_2CH_3$), 2.70 (1H, m, $CHCH_2CH_3$), 3.82 and 3.83 (each 3H, s, $ArOCH_3$), 4.30 and 4.39 [each 1H, bs, D_2O

exchangeable, CH(O*H*)CH_3], 4.52 [2H, m, OC*H*$(CH_3)_2$] 5.20 [2H, q, *J* 6.8 Hz, C*H*(OH)CH_3], 6.73 (3H, m, both 5-H's and one of the 6-H's) and 6.88 (1H, d, *J* 8.8 Hz, 6-H); δ_C 14.0, 14.4, 21.1, 22.2, 22.3, 22.9, 23.0, 23.3, 26.7, 27.8, 55.5, 55.6, 70.2 (×2), 74.0 (×2), 74.1, 74.4, 109.0, 110.0, 118.7, 119.8, 133.1, 133.5, 133.6, 135.4, 144.6, 145.1, 151.4 and 152.1; MS (EI): *m/z* (%): 482 (23), 467 (17), 235 (18), 206 (100), 191 (25).

Found: C, 71.53%; H, 9.17%.

Calculated for $C_{30}H_{46}O_6$: C, 71.66%; H, 9.24%; *M* (502.76).

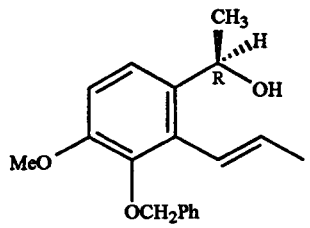
Further elution gave the product **214**; as a pale yellow oil (0.56 g, 55%) in yield.

214 ν_{max} 3400 cm^{-1} (O-H); δ_H 1.22 [6H, d, *J* 6.2 Hz, OCH(C*H*$_3)_2$], 1.45 (3H, d, *J* 6.2 Hz, C*H*$_3$CHOH), 1.66 (1H, bs, D_2O exchangeable, CH_3CHO*H*), 1.91 (3H, dd, *J* 6.4 and 1.6 Hz, CH=CHC*H*$_3$), 3.82 (3H, s, ArOC*H*$_3$), 4.29 [1H, sept, *J* 6.2 Hz, OC*H*$(CH_3)_2$], 5.13 (1H, q, *J* 6.4 Hz, CH_3C*H*OH), 5.98 (1H, dq, *J* 16.0 and 6.4 Hz, CH=C*H*CH_3), 6.41 (1H, dq, *J* 16.0 and 1.8 Hz, C*H*=$CHCH_3$), 6.82 (1H, d, *J* 8.6 Hz, 5-H), 7.26 (1H, d, *J* 8.6 Hz, 6-H); δ_C 19.2 (C-3'), 22.6 [2×CH(*C*$H_3)_2$], 24.0 (*C*H_3CHOH), 55.2 (ArO*C*H_3), 66.5 (CH_3*C*HOH), 75.4 (*C*H$(CH_3)_2$), 110.8 (C-2'), 120.2 (C-6), 124.5 (C-5), 132.0 (C-2)[a], 132.2 (C-1'), 136.5 (C-1)[a], 144.6 (C-3)[b], 152.5 (C-4)[b]. Assignments with the same superscripts may be interchanged. (EI): *m/z* (%): 250 (M^+, 19), 208 (18), 193 (100), 175 (26), 165 (21); 143 (27), 133, (19), 115 (11); $[\alpha]_D$ = +28.3° (c = 0.755, CH_2Cl_2); enantiomeric excess: ^{1}H-nmr (Mosher esters) 60%, ^{19}F-nmr (Mosher esters) 55% and europium shift reagent 75%.

Found: C, 71.86%; H, 8.89%.

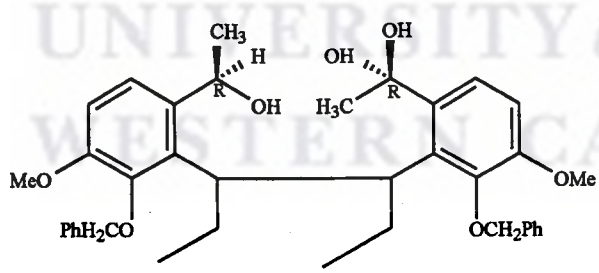
Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.87%; *M* 250.37.

(*R*)-3-Benzyloxy-4-methoxy-1-(1'-hydroxyethyl)-2-prop-1'-enylbenzene (215)



[215]

In an oven dried three necked flask was introduced the Corey-Bakshi-Shibata (CBS) catalyst reagent (0.1 ml, 0.05 mmol) in 0.5 M toluene under nitrogen. 1 M Borane dimethyl sulphide (BH_3Me_2S.THF) in tetrahydrofuran (0.33 ml, 0.33 mmol) was added dropwise to the CBS reagent. Acetyl-3-benzyloxy-4-methoxy-2-prop-1'-enylbenzene (0.98 g, 3.31 mmol) in dried tetrahydrofuran (2 ml) was added simultaneously with additional BH_3Me_2S.THF (1.99 ml, 1.99 mmol) and the reaction mixture left to stir for 30 minutes. Methanol (1 ml) was then added and stirring was continued for a further 10 minutes. The reaction mixture was extracted with dichloromethane (4 × 40 ml) and the residue obtained was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The first compound to elute was assigned the dimeric structure **212** and was obtained as a thick oil (0.37 g, 19%).



[212]

212 ν_{max} 3407 cm^{-1} (O-H); δ_H 0.97 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.02 (3H, t, *J* 7.4 Hz, CH_2CH_3), 1.53 [3H, d, *J* 6.6 Hz, $CH(OH)CH_3$], 1.64 [3H, d, *J* 6.6 Hz, $CH(OH)CH_3$], 1.64 (4H, overlapping multiplet, $CHCH_2CH_3$), 2.44 (1H, m, $CHCH_2CH_3$), 2.60 (1H, m, $CHCH_2CH_3$), 3.88 and 3.89 (each 3H, s, $ArOCH_3$), 4.38 and 4.40 [each 1H, bs, D_2O exchangeable, $CH(OH)CH_3$], 5.10 [6H, m, CH_2Ph and $CH(OH)CH_3$], 6.80 (3H, m, both

5-H's and one of the 6-H's), 6.95 (1H, d, *J* 8.8 Hz, 6-H), 7.40 (10H, m, aryl ring); δ_C 14.1, 14.4, 21.5, 24.0, 27.4, 28.0, 55.9, 56.0, 70.1 (×2), 74.0, 74.6, 74.8, (×2), 109.5, 110.4, 119.6, 120.7, 127.8 (×4), 128.5 (×4), 128.6 (×2), 133.5, 133.7 (×2), 133.9, 135.2, 138.2, 145.9, 146.5, 151.6 and 152.2; MS (EI): *m/z* (%): 538 (22), 436 (14), 221 (18), 193 (14), 192 (100), 177 (18).

Found: C, 76.10%; H, 7.69%.

Calculated for $C_{38}H_{46}O_6$: C, 76.21%; H, 7.76%; *M* (598.84).

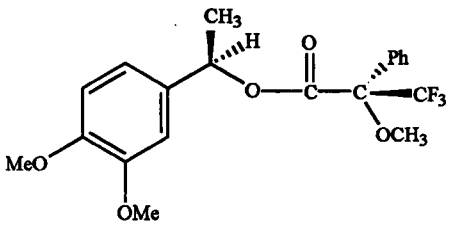
Further elution gave the product **215**; as a pale yellow oil (0.61g, 61%) in yield.

215 ν_{max} 3396 cm^{-1} (O-H); δ_H 1.46 (3H, d, *J* 6.2 Hz, C*H*$_3$CHOH), 1.89 (3H, dd, *J* 6.6 and 1.8 Hz, CH=CHC*H*$_3$), 3.87 (3H, s, ArOC*H*$_3$), 4.88 (2H, s, OC*H*$_2$Ph), 5.11 (1H, q, *J* 6.4 Hz, CH$_3$C*H*OH), 5.97 (1H, dq, *J* 16.0 and 6.4 Hz, CH=C*H*CH$_3$), 6.39 (1H, dq, *J* 16.0 and 1.8 Hz, C*H*=CHCH$_3$), 6.87 (1H, d, *J* 8.4 Hz, 5-H), 7.32 (1H, d, *J* 8.4 Hz, 6-H), 7.38 (5H, m, Ph*H*'s); δ_C 19.2 (C-3'), 24.4 (*C*H$_3$CO), 56.0 (ArO*C*H$_3$), 66.5 (*C*HOH), 74.6 (O*C*H$_2$Ph), 111.1 (C-2'), 120.8 (C-6), 123.7 (C-5), 128.3 (×3, aryl), 128.4 (×2, aryl), 131.1 (C-2)[a], 132.4 (C-1'), 136.7 (C-1)[a], 138.0 (aryl), 145.5 (C-3)[b], 152.1 (C-4)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 298 (M^+, 22), 296 (44), 281 (27), 267 (33), 256 (74); 207 (52), 191, (36), 178 (41), 161 (19), 145 (13), 91 (100); $[\alpha]_D$ = +21.9°, (c = 0.755, CH_2Cl_2); enantiomeric excess: ^{1}H-nmr (Mosher esters) 53%, ^{19}F-nmr (Mosher esters) 55% and europium shift reagent 74%.

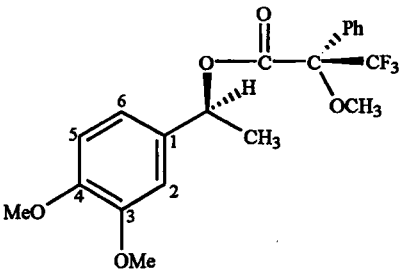
Found: C, 76.51%; H, 7.36%.

Calculated for $C_{19}H_{22}O_3$: C, 76.47%; H, 7.45%; *M* 298.41.

Preparation of Mosher Esters (217 and 218)



(R) (S)-Ester
[217]

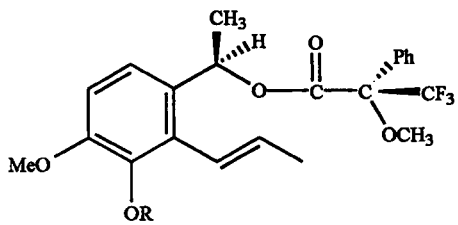


(S) (S)-Ester
[218]

The (*R*)-alcohol **182** (50 mg, 0.275 mmol) was dissolved in dichloromethane (2 ml) to which (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (200 mg), 4-dimethylaminopyridine (20 mg, 0.164 mmol) and dicyclohexylcarbodiimide (200 mg, 0.969 mmol) were added. The reaction mixture was stirred under nitrogen for 15 hours. The residue obtained after work-up was purified by preparative thin layer chromatography using acetone – hexane (1:9) as eluant to afford the product as an oil.

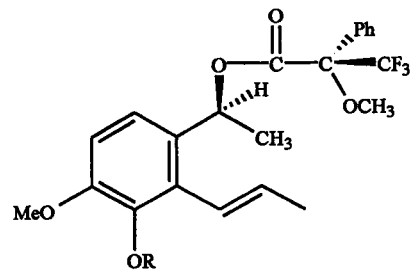
217 and **218** δ_H 1.63 (3H, d, *J* 6.6 Hz, C*H*$_3$CH), 3.47 and 3.57 (3H, q, *J* 1.2 Hz, OC*H*$_3$ of Mosher ester enantiomers), 3.72 and 3.86 (3H, s, ArOC*H*$_3$), 6.06 (1H, q, *J* 6.6 Hz, CH$_3$C*H*), 6.71 (1H, d, *J* 1.8 Hz, 2-H), 6.79 (1H, d, *J* 8.2 Hz, 5-H), 6.87 (1H, dd, *J* 8.2 and 1.8 Hz, 6-H), 7.35 (5H, m, Ph*H*'s).

Preparation of Mosher Esters (221-226)



(R) (S)-Esters

[221]: R = Methyl
[223]: R = Isopropyl
[225]: R = Benzyl



(S) (S)-Esters

[222]: R = Methyl
[224]: R = Isopropyl
[226]: R = Benzyl

(*S*)-α-methoxy-α-trifluoromethylphenylacetic acid (100 mg, 0.427 mmol) was converted to the acid chloride, using oxalyl chloride (1.2 equiv, 0.512 mmol) and catalytic amount of dimethylformamide (0.1 equiv, 0.0427 mmol) by stirring in dichloromethane (3 ml) at room temperature for 4 hours followed by distillation under vacuum.

To the alcohol (40 mg) in dry dichloromethane (2 ml) was added 4-dimethylaminopyridine (1 equiv), triethylamine (3 equiv) and (*S*)-MPTA-chloride (1.1 equiv). The mixture was stirred overnight at room temperature until completion of the esterification as judged by thin layer chromatography. The residue obtained after work-up was purified by preparative thin layer chromatography using ethyl acetate – hexane (1:4) as eluant to afford the product as an oil.

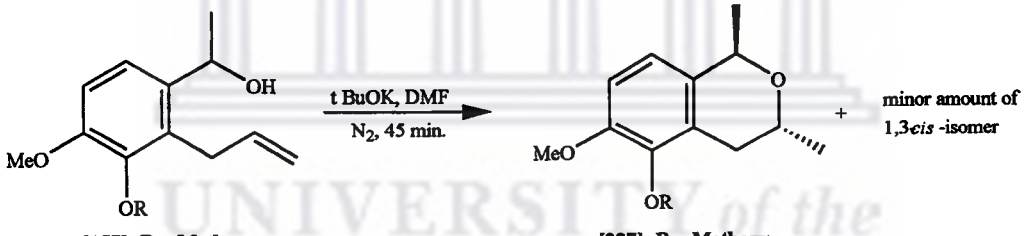
221 and **222** δ_H 1.57 (3H, d, *J* 6.6 Hz, C*H*$_3$CH), 1.93 (3H, dd, *J* 6.6 and 1.8 Hz, 3'-H), 3.46 and 3.55 (3H, q, *J* 1.4 Hz, OC*H*$_3$ of Mosher ester enantiomers), 3.72 and 3.86 (3H, s, ArOC*H*$_3$), 5.92 (1H, dq, *J* 16.0 and 6.6 Hz, *trans*-2'-H), 6.29 (1H, q, *J* 6.6 Hz, CH$_3$C*H*), 6.43 (1H, dq, *J* 16.0 and 1.8 Hz, *trans*-1'-H), 6.92 (1H, d, *J* 8.6 Hz, 5-H), 7.15 (1H, d, *J* 8.6 Hz, 6-H), 7.38 (5H, m, Ph*H*'s).

223 and **224** δ_H 1.24 [6H, d, *J* 6.4 Hz, CH(C*H*$_3$)$_2$], 1.56 (3H, d, *J* 6.6 Hz, C*H*$_3$CH), 1.93 (3H, dd, *J* 6.6 and 1.8 Hz, 3'-H), 3.47 and 3.54 (3H, q, *J* 1.6 Hz, OC*H*$_3$ of Mosher ester enantiomers), 3.81 and 3.82 (3H, s, ArOC*H*$_3$), 4.32 [1H, m, C*H*(CH$_3$)$_2$], 5.91 (1H, dq, *J* 15.8 and 6.6 Hz, *trans*-2'-H), 6.35 (1H, q, *J* 6.6 Hz, CH$_3$C*H*), 6.42 (1H, dq, *J* 15.8 and 1.8 Hz, *trans*-1'-H), 6.69 (1H, d, *J* 8.6 Hz, 5-H), 6.86 (1H, d, *J* 8.6 Hz, 6-H), 7.36 (5H, m, Ph*H*'s).

225 and **226** 1.57 (3H, d, *J* 6.6 Hz, C*H*$_3$CH), 1.88 (3H, dd, *J* 6.6 and 1.8 Hz, 3'-H), 3.48 and 3.56 (3H, q, *J* 1.2 Hz, OC*H*$_3$ of Mosher ester enantiomers), 3.85 and 3.87 (3H, s, ArOC*H*$_3$), 4.88 (2H, s, C*H*$_2$Ph), 5.90 (1H, dq, *J* 16.0 and 6.6 Hz, *trans*-2'-H), 6.30 (1H, q, *J* 6.6 Hz, CH$_3$C*H*), 6.41 (1H, dq, *J* 16.0 and 1.8 Hz, *trans*-1'-H), 6.73 (1H, d, *J* 8.8 Hz, 5-H), 6.93 (1H, d, *J* 8.8 Hz, 6-H), 7.41 (5H, m, Ph*H*'s).

4.4. Metal Mediated Cyclisation of the *(R)*-1(1'-hydroxyethyl)-2-(prop-2'-enyl)-4-methoxybenzenes into their corresponding Isochromans

The various intramolecular cyclisation methods of precursors leading to formation of the benzo[c]pyran ring systems have been discussed in the literature section. Of particular interest were the cyclisation methods in which potassium tertiary butoxide[21] and mercuric acetate[30] were used. In order to test the validity of the cyclisation method with potassium tertiary butoxide, the racemic alcohols **157**, **158** and **159** were selected and treated as follows. To a heated solution of 1 equivalent of racemic alcohol dissolved in dry dimethylformamide was added 4 equivalents of potassium tertiary butoxide. The reaction mixture was heated at 80 °C under nitrogen for 45 minutes to afford mainly the racemic *trans*-pyrans **227** (96%), **228** (90%) and **229** (77%) after chromatography (Scheme 47).



[157]: R = Methoxy
[158]: R = Isopropyl
[159]: R = Benzyl

[227]: R = Methoxy
[228]: R = Isopropyl
[229]: R = Benzyl

Scheme 47

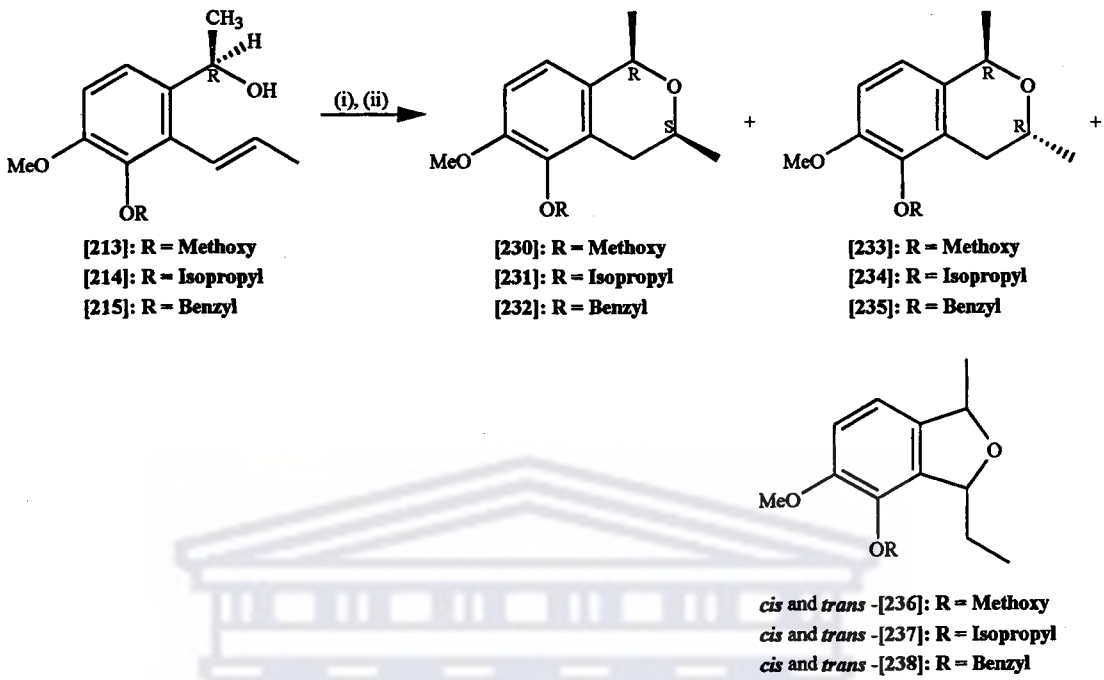
The assignment of the 1,3-*trans* configuration is based on the position of the chemical shift of the 3-H in the ^{1}H-nmr spectrum. In the three molecules synthesized the 3-H appeared as a multiplet in the region of δ 3.98 - δ 4.00. These results are in accordance with the results of the Giles group mentioned earlier[21].

As a result of the very poor yields of the (*R*)-alcohols **186**, **187** and **188** obtained from the reduction of the ketone precursors **160**, **161** and **162** discussed earlier in Chapter 2 we introduced an alteration in the steric environment about the ketonic group by vitue of conjugation of the double bond in the propenyl side chain. Thus reduction of the ketones **207**, **208** and **209** using BH_3 and the Corey-Bakshi-Shibata catalyst was far more successful in affording much more reasonable yields of the (*R*)-alcohols **213**, **214** and **215** and this has been discussed in Section 4.3.1.

Although intramolecular cyclisation of the racemic alcohols **157**, **158** and **159** into the corresponding benzopyrans **227**, **228** and **229** occur in high yield using the powerful base, potassium *tertiary*-butoxide in dimethylformamide, it was not considered to be a viable method for the conversion of the corresponding chiral alcohols **213**, **214** and **215** into chiral isochromans. The possibility exists in our view that the benzylic 1-H might be prone to attack by the powerful basic tertiary-butoxide anion and lead to racemisation and thus the mercuric acetate method[30] was choosen.

It is known that this method provides both the 1,3-*cis*- as well as the 1,3-*trans*-dimethyl benzopyran products[27,28,29,30] but we were confident that these diastereomers could be separated chromatographically if not at the isochroman oxidation level, then at the isochromanquinone oxidation level.

The (*R*)-alcohol (1 mol equiv) was dissolved in a solution of tetrahydrofuran-water (ratio 1:1) to which mecuric acetate (1 mol equiv) was added and the reaction mixture was stirred at room temperature for one hour. Two portions of sodium hydroxide solution were added at hourly intervals, followed by the addition of sodium borohydride (22.0 mol equiv) to give an inseparable mixture of *cis*- and *trans*- chiral pyrans (Scheme 48).



[213]: R = Methoxy
[214]: R = Isopropyl
[215]: R = Benzyl

[230]: R = Methoxy
[231]: R = Isopropyl
[232]: R = Benzyl

[233]: R = Methoxy
[234]: R = Isopropyl
[235]: R = Benzyl

***cis* and *trans* -[236]: R = Methoxy**
***cis* and *trans* -[237]: R = Isopropyl**
***cis* and *trans* -[238]: R = Benzyl**

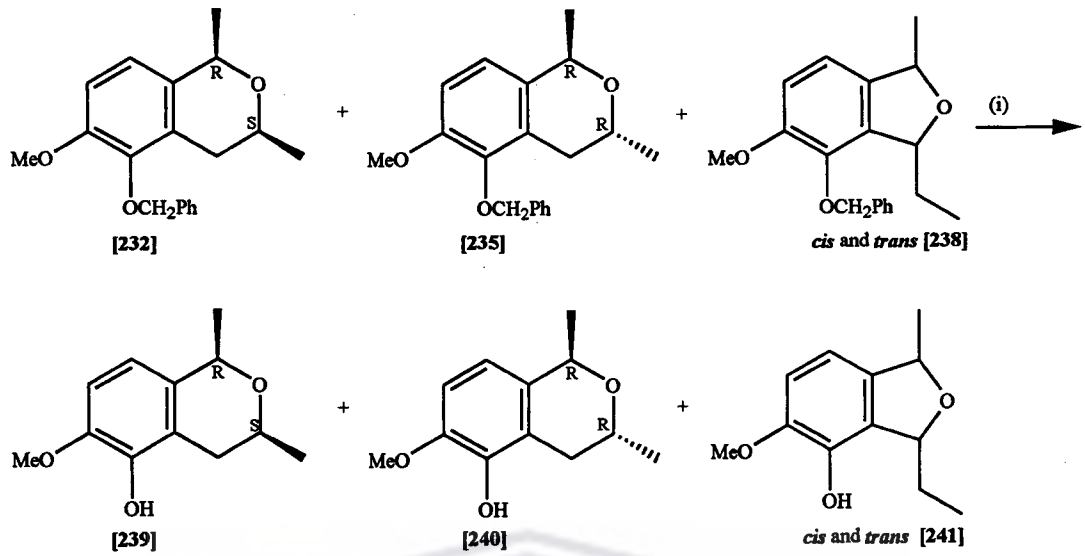
(i) THF/ H_2O, $Hg(OAc)_2$; (ii) NaOH (3M), $NaBH_4$.

Scheme 48

The GC-MS demonstrated a profile of four peaks, two small ones eluting before the two major ones. It was also most interesting to note that from the fragmentation patterns of the four products, each pair was similar and each compound has the same molecular mass and consequently same molecular formula which in turn suggested that all four compounds were isomers of each other. As it turned out, the earlier fractions were due to the *cis*-**238** and *trans*-**238** benzofurans while latter major fractions are due to the two isochromans **232** and **235**. The ^{1}H-nmr spectrum of the mixture of the chiral isochromans **232** and **235** separated from the benzofurans were in accordance with their structures but will not be discussed at this stage since it was decided to separate the isomers at the quinone oxidation level (Section 4.5.).

Thus the mixture of the isochromans **232, 235** and benzofurans (*cis*- and *trans*-) **238** were debenzylated *via* catalytic hydrogenolysis in ethyl acetate using 5% palladium on charcoal to afford a mixture comprising the two major 5-hydroxyisochromans **239, 240** and the hydroxybenzofurans (*cis*- and *trans*-) in 97% yield. A small portion of the product was plated to obtain a pure quantity of the chiral phenol **240** for spectral analysis.

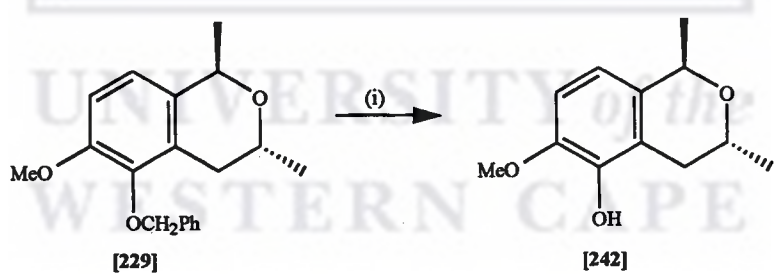
A strong ν_{max} at 3472 cm^{-1} confirmed the presence of the phenolic OH group in the infrared spectrum. In the ^{1}H-nmr spectrum the 3-proton doublet at δ 1.33 with ^3J 6.2 Hz is assigned to 3-CH_3 while the 3-proton doublet at δ 1.49 with ^3J 6.6 Hz is assigned to the 1-CH_3 which is confirmed by being coupled to the 1-H which appeared as a quartet at δ 4.99 with ^3J 6.6 Hz. A doublet of a doublet at δ 2.42 with ^2J 16.8 and ^3J 10.0 Hz is assigned to the pseudoaxial 4-H while a doublet of a doublet at δ 2.85 with ^2J 16.8 and ^3J 3.6 Hz is assigned to the pseudoequatorial 4-H. A multiplet at δ 4.12 is assigned to 3-H again indicating the *trans* 1,3-relationship of the methyl groups of the pyran ring and a 3-proton singlet at δ 3.87 is assigned to the CH_3O group. Finally the 5-OH group appeared as a single peak at δ 5.69 being D_2O exchangeable while the two *ortho* coupled aromatic protons 7-H and 8-H appeared as doublets at δ 6.54 and δ 6.73 with ^3J 8.4 Hz respectively.



(i) ethyl acetate, 5% palladium on charcoal, 2-3 drops HCl (conc.)

Scheme 49

Similarly the racemic *trans*-benzyl pyran **229** was also de-benzylated under similar reaction conditions to afford the racemic *trans*-phenol **242** (96%) (Scheme 50).



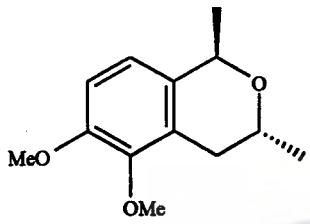
(i) ethyl acetate, 5% palladium on charcoal, 2-3 drops HCl (conc.)

Scheme 50

4.4.1. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

trans-3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[c]pyran (227)



[227]

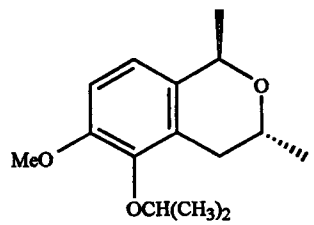
In an oven dried two-necked flask 3,4-dimethoxy-1-(1-hydroxyethyl)-2-prop-2'-enylbenzene **157** (500 mg, 2.25 mmol) and dry dimethylformamide (50 ml) were combined. Under nitrogen atmosphere potassium tertiary butoxide (1.01 g, 9.01 mmol) was added and the reaction mixture heated at 70-80 °C for 45 minutes. Water (200 ml) and diethyl ether (100 ml) were added and the reaction mixture extracted with diethyl ether (4 × 100 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate - hexane (1.5:8.5) as eluant. The product (*trans* isomer) was obtained as a colorless oil (482 mg, 96%).

227 ν_{max} 1274 cm^{-1} (C-O); δ_H 1.33 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.49 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.42 (1H, dd, *J* 16.8 and 9.9 Hz, 4-H_a), 2.91 (1H, dd, *J* 16.8 and 3.6 Hz, 4-H_e), 3.81 (3H, s, ArOCH_3), 3.95 (3H, s, ArOCH_3), 4.00 (1H, m, 3-H), 5.00 (1H, q, *J* 6.6 Hz, 1-H), 6.75 (1H, d, *J* 8.4 Hz, 7-H), 6.78 (1H, d, *J* 8.4 Hz, 8-H); δ_C 21.6 (3-CH_3), 22.4 (1-CH_3), 30.5 (C-4), 55.9 (ArOCH$_3$), 60.2 (ArOCH$_3$), 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-8a)[a], 132.4 (C-4a)[a], 146.2 (C-6)[b], 150.6 (C-5)[b]. Assignments with the same superscripts may be interchaged. MS (EI): *m/z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16).

Found: C, 70.14%; H, 8.21%.

Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

***trans*-3,4-Dihydro-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (228)**



[228]

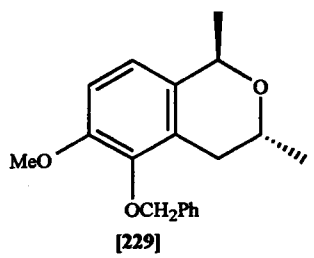
In an oven dried two-necked flask 3-isopropyloxy-4-methoxy-1-(1-hydroxyethyl)-2-prop-2'-enylbenzene **158** (500 mg, 2.00 mmol) and dry dimethylformamide (50 ml) were combined. Under a nitrogen atmosphere potassium tertiary butoxide (897 mg, 8.0 mmol) was added and the reaction mixture heated at 70-80 °C for 45 minutes. Water (200 ml) and diethyl ether (100 ml) were added and the reaction mixture extracted with diethyl ether (4 × 100 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1.5:8.5) as eluant. The product (*trans* isomer) was obtained as a colorless oil (450 mg, 90%).

228 ν_{max} 1262 cm^{-1} (C-O); δ_H 1.25 [6H, d, *J* 6.2 Hz, $CH(CH_3)_2$], 1.29 (3H, d, *J* 6.2, 3-CH_3), 1.48 (3H, d, *J* 6.6, 1-CH_3), 2.42 (1H, dd, *J* 16.4 and 9.4 Hz, 4-H_a), 2.91 (1H, dd, *J* 16.4 and 3.4 Hz, 4-H_e), 3.81 (3H, s, $ArOCH_3$), 3.98 (1H, m, 3-H), 4.49 [1H, sept, *J* 6.2 Hz, $CH(CH_3)_2$], 5.00 (1H, q, *J* 6.6 Hz, 1-H), 6.72 (1H, d, *J* 8.4 Hz, 7-H), 6.76 (1H, d, *J* 8.4 Hz, 8-H); δ_C 21.5 (CH_3), 22.5 (CH_3), 22.8 [×2, $CH(CH_3)_2$], 31.4 (C-4), 55.9 ($ArOCH_3$), 63.8, (C-3), 70.2 (C-1), 74.4 [$CH(CH_3)_2$], 110.4 (C-7), 120.1 (C-8), 128.5 (C-8a)[a], 132.4 (C-4a)[a], 144.1 (C-6)[b], 150.8 (C-5)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13).

Found: C, 70.14%; H, 8.21%.

Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.88%; *M* 250.37.

***trans*-3,4-dihydro-5-benzyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (229)**



[229]

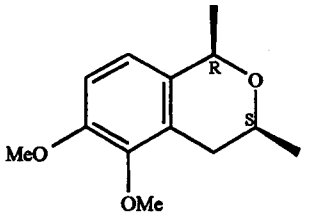
In an oven dried two-necked flask 3-benzyloxy-4-methoxy-1-(1-hydroxyethyl)-2-prop-2'-enylbenzene **159** (500 mg, 1.68 mmol) and dry dimethylformamide (50 ml) were combined. Under a nitrogen atmosphere potassium tertiary butoxide (753 mg, 6.71 mmol) was added and the reaction mixture heated at 70-80 °C for 45 minutes. Water (200 ml) and diethyl ether (100 ml) were added to the reaction mixture and extracted with diethyl ether (4 × 100 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1.5:8.5) as eluant. The product (*trans* isomer) was obtained as a white solid (384 mg; 77%).

229 melting point 84-87 °C (from hexane – ethyl acetate); ν_{max} 1274 cm^{-1} (C-O); δ_H 1.26 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.48 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.31 (1H, dd, *J* 16.8 and 9.6 Hz, 4-H_a), 2.82 (1H, dd, *J* 16.8 and 3.4 Hz, 4-H_e), 3.87 (3H, s, ArOCH_3), 3.98 (1H, m, 3-H), 4.97 (1H, q, *J* 6.6 Hz, 1-H), 4.99 (2H, s, OCH_2Ph), 6.76 (1H, d, *J* 8.8 Hz, 7-H), 6.82 (1H, d, *J* 8.8 Hz, 8-H), 7.38 (5H, m, Ph*H*'s); δ_C 21.4 (3-*C*H_3), 22.5 (1-*C*H_3), 30.8 (C-4), 56.0 (ArO*C*H_3), 63.6 (C-3), 70.2 (C-1), 74.3 (O*C*H_2Ph), 110.5 (C-7), 120.8 (C-8), 127.9 (aryl), 128.0 (×2, aryl), 128.2 (×2, aryl), 128.4 (aryl), 132.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], 150.7 (C-6)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14) 177.(20), 163 (53), 135 (17), 91 (100).

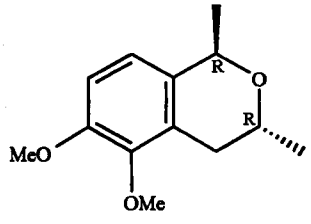
Found: C, 76.41%; H, 7.32%.

Calculated: C, 76.47%; H, 7.45%. $C_{19}H_{22}O_3$ (298.41).

(1*R*,3*S*)-3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[c]pyran (230) and **(1*R*,3*R*)-3,4-dihydro-5,6-dimethoxy-1,3-dimethylbenzo[c]pyran (233)**



[230]



[233]

The (*R*)-methoxy alcohol **213** (520 mg, 2.34 mmol) was dissolved in tetrahydrofuran (17 ml) and water (17 ml). Mercuric acetate (746 mg, 2.34 mmol) was added and the reaction stirred for 1 hour. Sodium hydroxide solution (17 ml × 3 M) was added and the reaction stirred for another hour. A further portion of sodium hydroxide solution (17 ml × 3 M) and sodium borohydride (1.95 g, 51.5 mmol) were added and the reaction mixture was then allowed to stir for another hour. The reaction mixture was extracted with ethyl acetate (3 × 50 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate - hexane (1:4) as eluant. The product (pale yellow oil) was obtained as a mixture of isomers (330 mg, 64%). An aliquot of the product mixture was separated by preparative thin layer chromatography using ethyl acetate – hexane (1:9) for full characterization purposes. The first band eluted comprised of the mixture of benzofurans **236** followed by the chiral *cis*-isomer **230** and lastly the chiral *trans*-isomer **233** all being oils.

230 ν_{max} 1274 cm^{-1} (C-O); δ_H 1.39 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.52 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.51 (1H, dd, *J* 17.0 and 10.6 Hz, 4-H_a), 2.88 (1H, dd, *J* 17.0 and 3.4 Hz, 4-H_e), 3.75 (1H, m, 3-H), 3.81 (3H, s, ArOCH_3), 3.85 (3H, s, ArOCH_3), 4.91 (1H, q, *J* 6.2 Hz, 1-H), 6.76 (1H, d, *J* 8.4 Hz, 7-H), 6.83 (1H, d, *J* 8.4 Hz, 8-H);

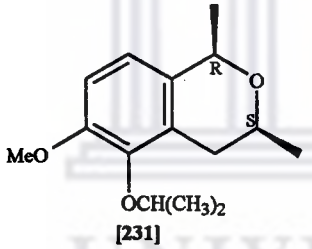
δ_C 21.6 (3-*C*H$_3$), 22.4 (1-*C*H$_3$), 30.5 (C-4), 55.9 (ArO*C*H$_3$), 60.2 (ArO*C*H$_3$), 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-8a)[a], 132.4 (C-4a)[a], 146.2 (C-6)[b], 150.6 (C-5)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16).

Found: C, 70.14%; H, 8.21%.

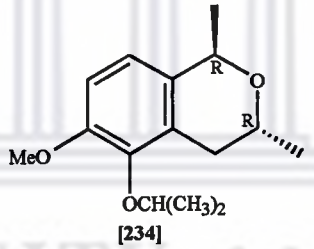
Calculated for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.18%; *M* 222.31.

The spectra of **233** were identical in all respects to the racemic *trans*-isomer **227**.

(1*R*,3*S*)-3,4-Dihydro-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (231) and **(1*R*,3*R*)-3,4-dihydro-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (234)**



[231]



[234]

The (*R*)-isopropyl alcohol **214** (404 mg, 1.62 mmol) was dissolved in tetrahydrofuran (19 ml) and water (19 ml). Mercuric acetate (516 mg, 1.62 mmol) was added and the reaction stirred for 1 hour. Sodium hydroxide solution (11.5 ml × 3 M) was added and the reaction stirred for another hour. A further portion of sodium hydroxide solution (11.5 ml × 3 M) and sodium borohydride (1.350 g, 35.7 mmol) were added and the reaction mixture was then allowed to stir for another hour. The reaction mixture was extracted with ethyl acetate (3 × 50 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product (pale yellow oil) was obtained as a mixture of isomers (220 mg, 55%). An

aliquot of the product mixture was separated by preparative thin layer chromatography using ethyl acetate – hexane (1:9) for full characterization purposes. The fisrt band eluted contained the mixture of hydroxypyrans **237** followed by the chiral *cis*-isomer **231** and lastly the chiral *trans*-isomer **234** all being oils.

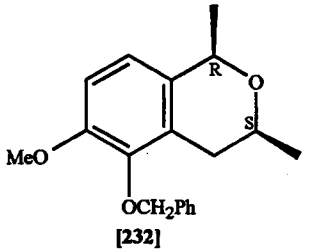
231 ν_{max} 1262 cm^{-1} (C-O); δ_H 1.26 [6H, d, *J* 6.2 Hz, $CH(CH_3)_2$], 1.34 (3H, d, *J* 6.2, 3-CH_3), 1.47 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.40 (1H, dd, *J* 16.4 and 9.8 Hz, 4-H_a), 2.89 (1H, dd, *J* 16.4 and 3.2 Hz, 4-H_e), 3.71 (1H, m, 3-H), 3.81 (3H, s, $ArOCH_3$), 4.47 [1H, sept, *J* 6.2 Hz, $CH(CH_3)_2$], 4.77 (1H, q, *J* 6.2 Hz, 1-H), 6.73 (1H, d, *J* 8.4 Hz, 7-H), 6.75 (1H, d, *J* 8.4 Hz, 8-H); δ_C 21.5 (3-CH_3), 22.5 (1-CH_3), 22.7 [×2, $CH(CH_3)_2$], 31.4 (C-4), 55.9 ($ArOCH_3$), 66.3, (C-3), 70.2 (C-1), 74.4 [$CH(CH_3)_2$], 110.7 (C-7), 120.1 (C-8), 128.5 (C-8a)[a], 132.4 (C-4a)[a], 144.1 (C-6)[b], 150.8 (C-5)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13).

Found: C, 70.24%; H, 8.41%.

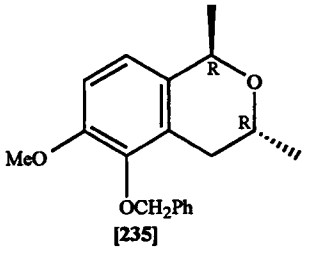
Calculated for $C_{15}H_{22}O_3$: C, 71.95%; H, 8.88%; *M* 250.37.

The spectra of **234** were identical in all respects to the racemic *trans*-isomer **228**.

(1*R*,3*S*)- 5-Benzyloxy-3,4-Dihydro-6-methoxy-1,3-dimethylbenzo[c]pyran (232) and **(1*R*,3*R*)- 5-Benzyloxy-3,4-dihydro-6-methoxy-1,3-dimethylbenzo[c]pyran (235)**



[232]



[235]

The (*R*)-benzyl alcohol **215** (375 mg, 1.258 mmol) was dissolved in tetrahydrofuran (15 ml) and water (15 ml). Mercuric acetate (401 mg, 1.258 mmol) was added and the reaction stirred for 1 hour. Sodium hydroxide solution (9 ml × 3 M) was added and the reaction stirred for another hour. A further portion of sodium hydroxide solution (9 ml × 3 M) and sodium borohydride (1.048 g, 27.7 mmol) were added and the reaction mixture was then allowed to stir for another hour. The reaction mixture was extracted with ethyl acetate (3 × 50 ml) and the residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product (yellow oil) was obtained as a mixture of isomers (233 mg, 62%). An aliquot of the product mixture was separated by preparative thin layer chromatography using ethyl acetate – hexane (1:9) for full characterization purposes. Again the first band to elute contained the mixture of benzofurans **238** followed by the chiral *cis*-isomer **232** and lastly the chiral *trans*-isomer **235** all being oils.

232 ν_{max} 1269 cm^{-1} (C-O); δ_H 1.32 (3H, d, *J* 6.2 Hz, 3-C*H*$_3$), 1.46 (3H, d, *J* 6.2 Hz, 1-C*H*$_3$), 2.30 (1H, dd, *J* 16.8 and 11.0 Hz, 4-H$_a$), 2.85 (1H, dd, *J* 16.8 and 3.2 Hz, 4-H$_e$), 3.75 (1H, m, 3-H), 3.87 (3H, s, ArOC*H*$_3$), 4.78 (1H, q, *J* 6.2 Hz, 1-H), 4.99 (2H, s, OC*H*$_2$Ph), 6.78 (1H, d, *J* 8.8 Hz, 7-H), 6.80 (1H, d, *J* 8.8 Hz, 8-H), 7.38 (5H, m, Ph*H*'s); δ_C 21.3 (3-*C*H$_3$), 22.5 (1-*C*H$_3$), 30.8 (C-4), 56.0 (ArO*C*H$_3$), 63.6 (C-3), 70.2 (C-1), 74.3 (O*C*H$_2$Ph), 110.7 (C-7), 120.8 (C-8), 127.9 (aryl), 128.2 (×2, aryl), 128.3 (×2, aryl), 128.4 (aryl), 134.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], 150.7 (C-6)[b]. Assignments with the same superscripts may be interchanged.

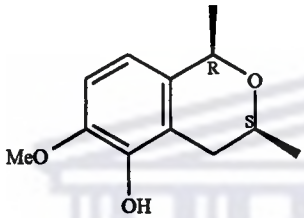
MS (EI): *m/z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14) 177 (20), 163 (53), 135 (17), 91 (100).

Found: C, 76.61%; H, 7.52%.

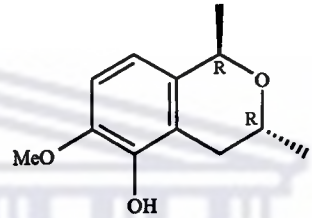
Calculated for $C_{19}H_{22}O_3$: C, 76.47%; H, 7.45%; *M* 298.41.

The spectra of **235** were identical in all respects to the racemic *trans*-isomer **229**.

(1*R*,3*R*)-3,4-Dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (239) and (1*R*,3*S*)-3,4-dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (240)



[239]



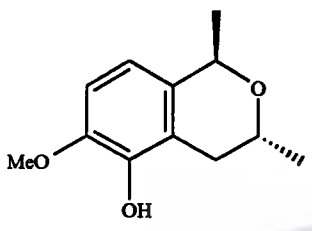
[240]

The isomeric mixture of benzyl chiral pyrans **232** and **235** and furan **238** (988 mg, 3.32 mmol) was dissolved in ethyl acetate (40 ml) containing 5% palladium on charcoal (100 mg) and 3 drops concentrated hydrochloric acid (10 M) were added. The reaction mixture was stirred for 15 hours under flow of hydrogen. The reaction mixture was filtered and the solvent evaporated to afford the crude product as a red oil (670 mg, 97%).

239 and **240** δ_H 1.30-1.54 (12H, pairs of doublets, *J* 6.2-6.6 Hz, 1- and 3-CH_3), 2.40 (2H, overlapping dd, *J* 17.0 and 10.0 Hz, pseudoaxial 4-H), 2.82 (2H, overlapping dd, *J* 17.0 and 3.8 Hz, pseudoequatorial 4-H), 3.86 and 3.87 (6H, each s, ArOCH_3), 3.90 and 4.12 (2H, m, 3-H of *cis* and *trans* isomers), 4.80 and 5.00 (2H, each q, *J* 7.6 Hz, 1-H), 5.78 (2H, br s, D_2O exchangeable, 5-O*H*), 6.65 (4H, overlapping pairs of doublets, *J* 8.4 Hz, 7- and 8-H).

A small portion was plated and eluted with ethyl acetate – hexane (1:5) which allowed the isolation of a small amount of pure **240** that had a ^{1}H-nmr spectrum identical to the racemic material **242**.

Racemic-*trans*-3,4-dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (242)



[242]

The racemic-*trans* pyran **229** (123 mg, 0.413 mmol) was dissolved in ethyl acetate (15 ml) to which 5% palladium on charcoal (15 mg) was added followed by 2 drops of concentrated hydrochloric acid (10 M). The reaction mixture was stirred for 24 hours under flow of hydrogen. The residue obtained upon work-up was purified by column chromatography using ethyl acetate - hexane (1:4) as the eluant. The product was obtained as a red oil (82 mg, 96%).

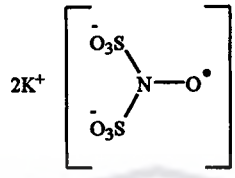
242 ν_{max} 3472 cm^{-1} (O-H); δ_H 1.33 (3H, d, *J* 6.2 Hz, 3-C*H*$_3$), 1.49 (3H, d, *J* 6.6 Hz, 1-C*H*$_3$), 2.42 (1H, dd, *J* 16.8 and 10.0 Hz, 4-H$_a$), 2.85 (1H, dd, *J* 16.6 and 3.6 Hz, 4-H$_e$), 3.87 (3H, s, ArOC*H*$_3$), 4.12 (1H, m, 3-H), 4.99 (1H, q, *J* 6.6 Hz, 1-H), 5.69 (1H, bs, D_2O exchangeable, 5-O*H*), 6.54 (1H, d, *J* 8.4 Hz, H-7), 6.73 (1H, d, *J* 8.4 Hz, H-8); δ_C 21.7 (3-*C*H$_3$), 22.6 (1-*C*H$_3$), 30.2 (C-4), 56.3 (ArO*C*H$_3$), 63.4 (C-2), 70.6 (C-1), 108.6 (C-7), 116.3 (C-8), 120.1 (C-4a)[a], 133.1 (C-8a)[a], 143.3 (C-5)[b], 144.4 (C-6)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 208 (M^+, 22), 193 (100), 161 (11), 143 (25) 133 (20).

Found: C, 69.28%; H, 7.44 %.

Calculated for $C_{12}H_{16}O_3$: C, 69.20%; H, 7.56%; *M* 208.28.

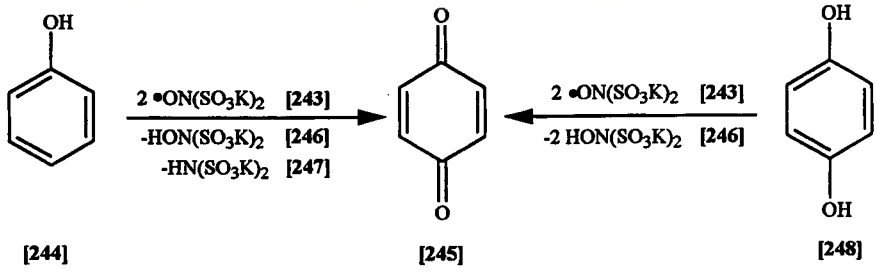
4.5. Oxidation of Phenolic Pyrans to their corresponding Quinones

Fremy was the first to prepare potassium nitrosodisulphate commonly known as Fremy's salt **243**[97]. Hantzsch and Semple[98] showed that solutions of **243,** which are purple in colour contain monomeric nitrosodisulphonate ions; the yellow solid of **243**, however is made up of dimeric species.



[243]

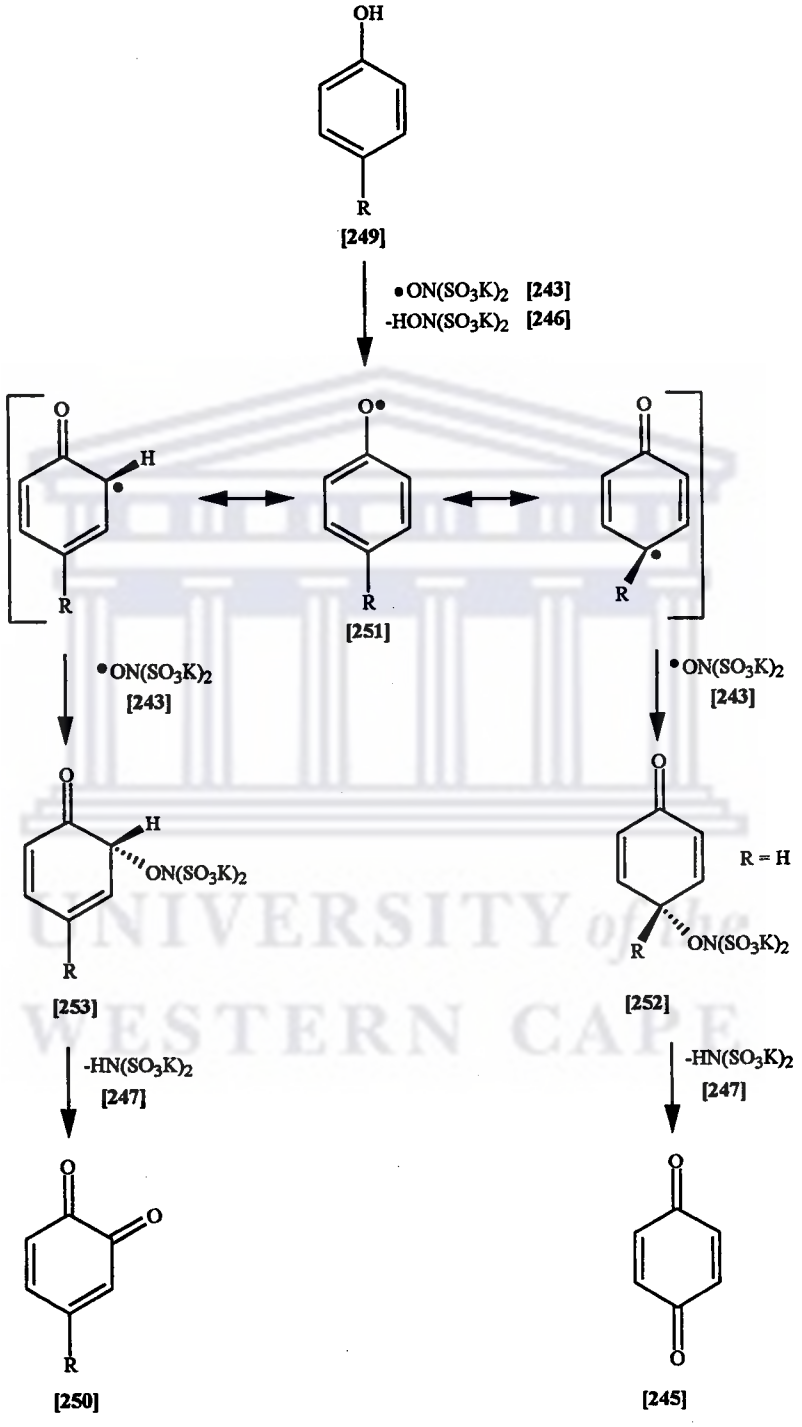
The overall stoichiometry of the oxidation of phenols with Fremy's salt has been shown[99] to involve the reaction of 1equivalent of phenol **244** with 2 equivalents of **243** to give 1 equivalent of benzoquinone **245**, 1 equivalent of dipotassium hydroxyimidodisulfate **246**, and 1 equivalent of dipotassium imidobissulfate **247**. The oxidation of hydroquinones also results in the formation of benzoquinones, but the stoichiometry is different. For example[99], 1 equivalent of hydroquinone **248** reacts with 2 equivalents of **243** to give 1 equivalent of benzoquinone **245** and 2 equivalents of dipotassium hydroxyimidodosulfate **246** (Scheme 51).



[244] [245] [248]

Scheme 51

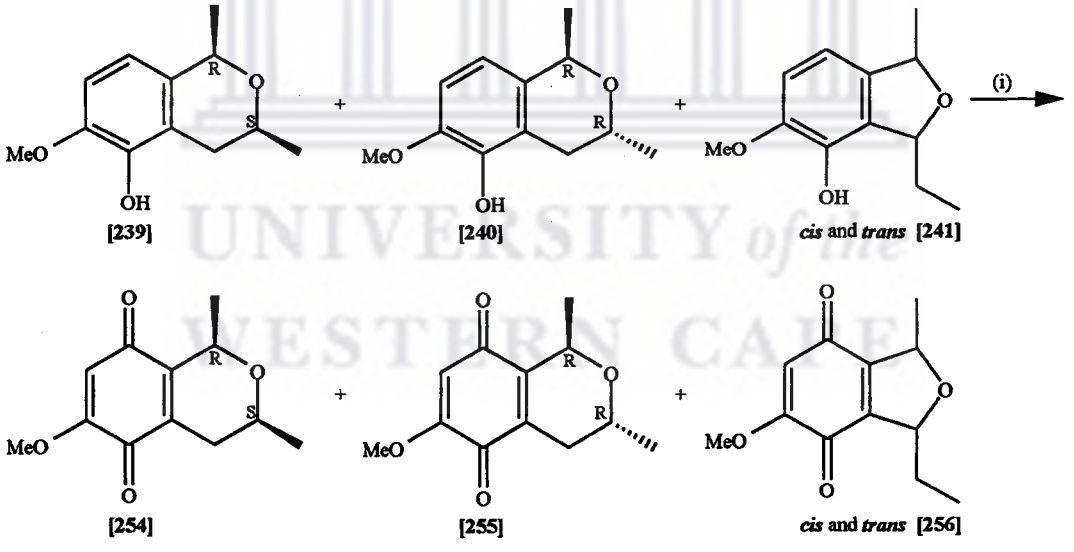
A general mechanistic interpretation, consistent with the observed stoichiometry, was suggested[99] for Fremy's radical oxidation of phenols and is depicted in Scheme 52.



Scheme 52

Hydrogen abstraction from **249** by **243** results in the formation of dipotassium hydroxyimidobissulfate **246** and the resonance stablized radical **251**. This can react with a second equivalent of **243** to give either of the cyclohexadienone intermediates **252** or **253**, depending on the nature of R, followed by loss of the elements of dipotassium imidobissulfate **247** to give the benzoquinones **245** or **250**[99,100].

The chiral phenolic pyrans **239** and **240** and hydroxybenzofurans **241** were oxidized to their corresponding chiral isochromanquinones **254** and **255** and benzofuranquinones **256** by dissolving them in methanol and then adding this solution to an aqueous buffered solution of 2 mol equivalents of Fremy's salt **243**. The reaction mixture was stirred at room temperature for 1 hour, quenched with water and extracted with dichloromethane to afford a product mixture (Scheme 53).



(i) Fremy's salt in aqueous buffer solution; room temp; 1 hour.

Scheme 53

Separation of the product mixture was achieved by radial chromatography using ethyl acetate – hexane (1:9) as eluant. The furan **256** (6%) eluted first followed very closely by the *cis*- and *trans*- chiral isochromanquinones in **254** (26%) and **255** (28%). The specific rotation of the *cis*- and *trans*- chiral isochromanquinones were +97° and -14° and their enantiomeric excesses 48% and 69% respectively, as determined by the Europium shift reagent.

The mass spectrum of **256** indicated that it was an isomer of the expected isochromanquinone **255**, due to its mass also being 222 and having a molecular formula $C_{12}H_{14}O_4$. The infrared spectrum showed strong absorption at ν_{max} 1665 cm^{-1} typical of the quinone system.

The ^{1}H-nmr spectrum had the following features. The ethyl side chain at C-3 of the furan ring for quinone **256** was quite evident since the 2'-H's appeared as a triplet at δ 0.93 with ^3J 7.2 Hz while a 2-proton multiplet is observed at δ 1.71 for the 1'-H. The signal for the methine proton 3-H overlapped with the methine signal for 1-H at δ 5.26. A COSY spectrum clearly indicated that both methine protons 1- and 3-H are indeed present at δ 5.26 and the assignment is made due to firstly a cross peak with the 1-CH_3 doublet at δ 1.47 with ^3J 6.2 Hz, and a further cross peak with 1'-H peak at δ 1.71. This latter peak also had the expected cross peak with the 2'-H triplet at δ 0.93. Finally the 5-OCH_3 group appeared as a singlet at δ 3.83 while 6-H appeared as a singlet at δ 5.84.

In the ^{13}C-nmr spectrum the 2'-CH_3 of the side chain appeared at δ 9.2 while the 1-CH_3 appeared at the δ 21.0 and the 1'-CH_2 appeared at δ 27.4.

The next quinone to elute was assigned the *cis* 1,3-dimethyl structure **254** and is based on the following ^{1}H-nmr spectral data.

A doublet at δ 1.33 with ^3J 6.2 Hz is assigned to 3-CH_3 while a doublet at δ 1.48 with ^3J 6.6 Hz is assigned to 1-CH_3. The pseudoaxial 4-H appeared as a ddd at δ 2.13 with ^2J

18.4 Hz while coupling to the pseudoaxial 3-H is observed as 10.0 Hz and finally long range coupling to the pseudoaxial 1-H is 4.0 Hz. On the other hand, the pseudoequatorial 4-H appeared as a doublet of a triplet at δ 2.61 with ^2J 18.4 Hz and further coupling of 2.8 Hz with the pseudoaxial 3-H. A multiplet at δ 3.53 is assigned to 3-H while 1-H appeared as a multiplet at δ 4.69. The OCH_3 appeared as a singlet at δ 3.80 while the quinone 7-H appeared as a singlet at δ 5.83. Upon the addition of about 10 mol percent Europium shift reagent to the compound all the signals experienced a deshielding effect and notable among these was the 1-CH_3 doublet which was deshielded from δ 1.48 to δ 2.10 where it showed separation of the signals, the 6-OCH_3 signal which was shifted from δ 3.80 to δ 4.37 where two signals were decernable but the most dramatic was the quinone 7-H singlet which was deshielded from δ 5.83 to δ 7.00 where two different signals were clearly evident and from the relative integrations the enantiomeric excess was calculated to be 48%.

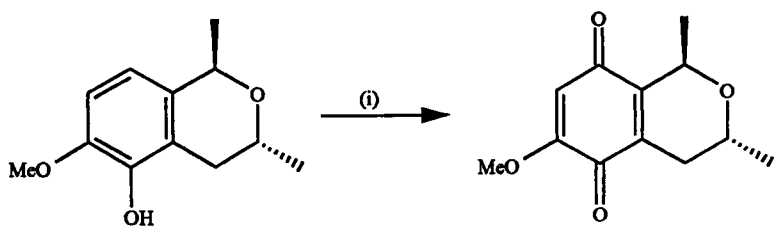
Further elution from the chromatotron afforded the *trans* pyran quinone **255** the structure of which is also based on the ^{1}H-nmr spectrum. In this case a doublet at δ 1.31 with ^3J 6.2 Hz is assigned to 3-CH_3 while a doublet at δ 1.46 with ^3J 7.0 Hz is assigned to 1-CH_3. The pseudoaxial 4-H appeared as a ddd at δ 2.12 with ^2J 19.0 Hz while coupling to the pseudoaxial 3-H is 10.0 Hz and long range coupling to the pseudoaxial 1-H is 2.2 Hz. In contrast to the *cis* 1,3- dimethyl isomer **254**, the pseudoequatorial 4-H appeared as a doublet of a doublet at δ 2.60 with ^2J 19.0 Hz and coupling to the adjacent pseudoaxial 3-H was observed to be 3.2 Hz. This is a consequence of the smaller dihedral angle between the two protons in question. The 6-OCH_3 signal appeared as a singlet at δ 3.81 while the 3-H appeared as a multiplet at δ 3.95 typical for the *trans* disubstituted pyran ring[51]. The 1-H appeared as a dq at δ 4.85 with ^3J of 7.0 Hz and a similar long range coupling of 2.2 Hz to the pseudoaxial 4-H. The quinoid 7-H appeared

as a singlet at δ 5.84. Upon the addition of approximately 10 mol percent of the Europium shift reagent the signal was significantly separated into two peaks of the enantiomers appearing at δ 6.59 and δ 6.53 and from their relative integrals the enantiomeric excess was calculated to be 69%. It is further interesting to note the C-signals in the ^{13}C-nmr spectra of the two diastereoisomers which is presented in a tabular format.

^{13}C-nmr signals for the *cis* and *trans* chiral isochromanquinones **254** and **255** in ppm.

C-atom	254	255
1-CH_3	21.3	21.5
3-CH_3	21.1	19.9
C-4	29.9	29.3
OCH_3	56.3	56.3
C-3	68.8	62.7
C-1	69.9	67.2
C-7	107.8	107.4
4a/8a	138.3	137.4
8a/4a	144.8	144.7
C-6	158.3	158.5
C-5/C-8	181.3	181.4
C-8/C-5	186.5	186.0

Next, the racemic *trans*- phenolic pyran **242** was oxidized with Fremy's salt in a similar manner to afford the bright yellow solid racemic *trans*- isochromanquinone **257** in 51% yield (Scheme 54).



[242] [257]

(i) Fremy's salt in aqueous buffer solution; room temp; 1 hour.

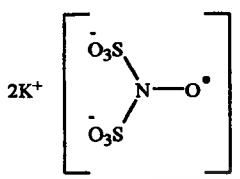
Scheme 54

The ^{1}H-nmr spectrum of the racemic quinone **257** was very similar to the chiral isomer **255** with one exception *viz* the multiplicity of the pseudoequatorial 4-H which appeared as a ddd at δ 2.61 with couplings of 19.0 Hz to the pseudo 4-H, a coupling of 3.6 Hz to the pseudoaxial 3-H and a very minor coupling of 0.6 Hz to the pseudoequatorial 1-H. The comparable signal for the chiral isomer **255** appeared as a dd at δ 2.60 with ^{2}J of 19.0 Hz and ^{3}J of 3.2 Hz with the pseudoaxial 3-H. This small difference could in part be due to the purity of the products more than the racemic versus chiral nature.

4.5.1. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

Preparation of Fremy's Salt (243)



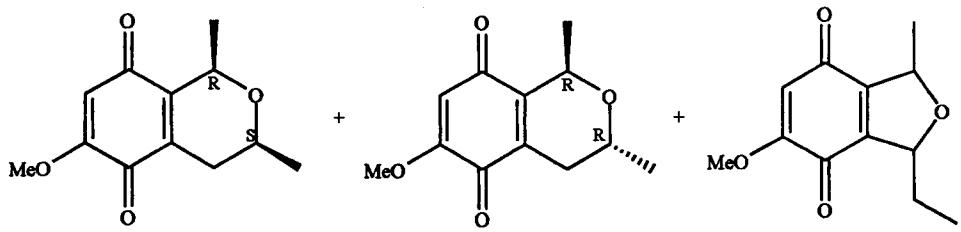
[243]

Sodium nitrite (5 M, 100 ml) was placed in a 1-liter beaker and cooled in an ice bath. Chopped ice (200 g) was added and the solution stirred steadily as a freshly prepared sodium bisulphite solution (100 ml, 35% w/v) was added, followed by glacial acetic acid (20 ml). A momentary darkening of the reaction mixture was observed, indicating that the reaction was complete. After the addition of concentrated ammonia (25 ml, sp gr 0.88), the mixture was again cooled in an ice bath, and fresh ice added. *Important* it is necessary to keep ice present in the reaction mixture throughout the next stage. Ice-cold 0.2 M potassium permanganate (400 ml) is now added dropwise with continued stirring, during approximately 1 hour. The precipitated manganese dioxode is removed by gravity filtration (Whatman No. 5, 24 cm), using two or more funnels in parallel to reduce the time required. The filtrate is allowed to come to room temperature as filtration proceeds but any unfiltered suspension is kept in an ice bath.

A portion of the filtrate (10-15 ml) is treated with an equal volume of saturated potassium chloride solution to precipitate some Fremy's salt for seeding the main batch. The bulk of the filtrate is stirred steadily, while saturated potassium chloride (250 ml) is added dropwise over a period of about 45 minutes. Small portions of the previously prepared suspension are added from time to time during this period until the solid persists in the bulk solution. Precipitation is complete by stirring the bulk cooled in ice for a further 45 minutes.

The orange solid is collected on a Buchner funnel but is not sucked dry. It is washed with ammoniacal saturated potassium chloride solution (containing *ca.* 5% v/v 0.88 ammonium hydroxide), and finally with acetone. Only after the whole washing process is all the liquid sucked away, but even air is not drawn through. The solid is spread on a watch glass and the acetone allowed to evaporate for 10-15 minutes. Finally, the orange crystals are stored in a dessicator over calcium oxide, in the presence of ammonium carbonate in a separate dish to provide an ammoniacal atmosphere. Under these conditions even this relatively crude material is stable for several months (crude yield, based on bisulphite, 81-82%).

(1*R*,3*S*)-6-Methoxy-1,3-dimethyl-5,8-dioxybenzo[c]pyran (254) and **(1*R*,3*R*)-6-methoxy-1,3-dimethyl-5,8-dioxybenzo[c]pyran (255)**



[254] [255] *cis* and *trans* [256]

To 12 ml of buffered aqueous solution (78.8 ml of 0.2 M Na_2HPO_4 and 171.2 ml of 0.2 M NaH_2PO_4) containing Fremy's salt (0.773 g, 1.44 mmol), a methanolic solution (0.82 ml) of the phenolic mixture of **239**, **240** and **241** (150 mg, 0.72 mmol) was added in one portion. The original violet colour of Fremy's salt rapidly changed to brown. Stirring was continued for 1 hour. Water (20 ml) was added to the reaction mixture which was then extracted with (3 × 30 ml) of dichloromethane. The residue obtained upon work-up was separated into its components by radial chromatography using ethyl acetate – hexane (1:9) as eluant to afford firstly the furan **256** (9mg, 6%) as a bright yellow oil.

256 ν_{max} 1665 cm^{-1} (C=O) δ_H 0.93 (3H, t, *J* 7.2 Hz, 2'-CH_3), 1.47 (3H, d, *J* 6.2 Hz, 1-CH_3), 1.71 (2H, m, 1'-CH_2), 3.83 (3H, s, ArOCH_3), 5.26 (2H, m, overlapping 1-H and 3-H), 5.84 (1H, s, 6-H); δ_C 9.2 (2'-*C*H_3), 21.0 (1-*C*H_3), 27.4 (1'-*C*H_2), 56.8 (Ar*O*CH_3), 79.8 (C-3), 83.8 (C-1), 107.6 (C-6), 142.9 (C-3a)[a], 148.3 (C-7a)[a], 159.7 (C-5), 178.7 (C=O)[b] and 183.9 (C=O)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 15), 193 (100), 165 (26).

Found: C, 64.74%; H, 6.47%.

Calculated for $C_{12}H_{14}O_4$: C, 64.84%; H, 6.36%; *M* 222.26.

The next product to be isolated from the chromatotron was quinone **254** (42mg, 26%) as bright yellow crystals, m.p. 100 – 103 °C (from hexane – ethyl acetate). ν_{max} 1680 and 1666 cm^{-1} (C=O); δ_H 1.33 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.48 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.13 (1H, ddd, *J* 18.4, 10.0 and 4.0 Hz, pseudoaxial 4-H), 2.61 (1H, dt, *J* 18.4 and 2.8 Hz, pseudoequatorial 4-H), 3.53 (1H, m, 3-H), 3.80 (3H, s, ArOCH_3), 4.69 (1H, m, 1-H), 5.83 (1H, s, 7-H); δ_C 21.1 (3-*C*H_3), 21.3 (1-*C*H_3), 29.9 (C-4), 56.3 (ArO*C*H_3), 68.8 (C-3), 69.9 (C-1), 107.8 (C-7), 138.3 (C-8a)[a], 144.8 (C-4a)[a], 158.3 (C-6), 181.3 (C-5)[b], 186.5 (C-8)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37) 165 (28) 151 (26), 119 (13), 91 (14); $[\alpha]_D$ = +97° (c = 0.545, CH_2Cl_2); enantiomeric excess (europium shift reagent 48%).

Found: C, 64.62%; H, 6.48%.

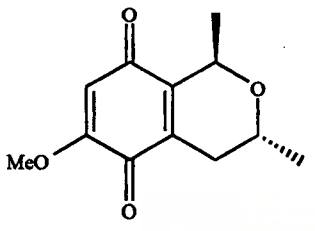
Calculated for $C_{12}H_{14}O_4$: C, 64.84%; H, 6.36%; *M* 222.26.

The final product to elute from the chromatotron was the *trans* quinone **255** (44mg, 28%) as a bright yellow solid, m.p. 104 – 106 °C (from hexane – ethyl acetate). ν_{max} 1680 and 1665 cm^{-1} (C=O); δ_H 1.31 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.46 (3H, d, *J* 7.0 Hz, 1-CH_3), 2.12 (1H, ddd, *J* 19.0, 10.0 and 2.2 Hz, pseudoaxial 4-H), 2.60 (1H, dd, *J* 19.0 and 3.2 Hz, pseudoequatorial 4-H), 3.81 (3H, s, ArOCH_3), 3.95 (1H, m, 3-H), 4.85 (1H, dq, *J* 7.0 and 2.2 Hz, 1-H), 5.85 (1H, s, 7-H); δ_C 19.9 (3-*C*H_3), 21.5 (1-*C*H_3), 29.3 (C-4), 56.3 (ArO*C*H_3), 62.7 (C-3), 67.2 (C-1), 107.4 (C-7), 137.4 (C-8a)[a], 144.7 (C-4a)[a], 158.5 (C-6), 181.4 (C-5)[b], 186.0 (C-8)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37) 165 (28) 151 (26), 119 (13), 91 (14). $[\alpha]_D$ = -14° (c = 0.720, CH_2Cl_2); enantiomeric excess (europium shift reagent 69%).

Found: C, 64.89%; H, 6.41%.

Calculated for $C_{12}H_{14}O_4$: C, 64.84%; H, 6.36%; *M* 222.26.

Racemic *trans*-6- Methoxyisochromanquinone (257)



[257]

To 4.7ml of buffered aqueous solution (78.8 ml of 0.2 M Na_2HPO_4 and 171.2 ml of 0.2 M NaH_2PO_4) containing Fremy's salt (0.200 g, 0.56 mmol), a methanolic solution (0.4 ml) of the phenol **242** (58 mg, 0.28 mmol) was added in one portion. The original violet colour of Fremy's salt rapidly changed to brown. Stirring was continued for 1 hour. Water (10 ml) was added to the reaction mixture which was then extracted with dichloromethane (3 × 30 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant. The product was obtained as a bright yellow solid (32mg, 51%), m.p. 134 – 136 °C (from hexane – ethyl acetate). ν_{max} 1680 and 1655 cm^{-1} (C=O); δ_H 1.30 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.45 (3H, d, *J* 7.0 Hz, 1-CH_3), 2.11 (1H, ddd, *J* 19.0, 10.2 and 2.2 Hz, pseudoaxial 4-H), 2.61 (1H, ddd, *J* 19.0, 3.6 and 0.6 Hz, pseudoequatorial 4-H), 3.80 (3H, s, ArOCH_3), 3.92 (1H, m, 3-H), 4.83 (1H, dq, *J* 7.0 and 2.2 Hz, 1-H), 5.84 (1H, s, 7-H); δ_C 19.9 (3-CH_3), 21.5 (1-CH_3), 29.3 (C-4), 56.3 (ArOCH_3), 62.7 (C-3), 67.2 (C-1), 107.4 (C-7), 137.4 (C-8a)[a], 144.7 (C-4a)[a], 158.5 (C-6), 181.4 (C=O), 186.0 (C=O). Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37) 165 (28) 151 (26), 119 (13), 91 (14).

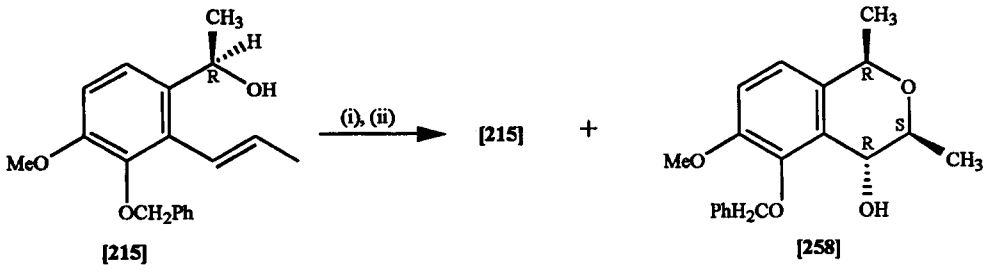
Found: C, 64.81%; H, 6.42%.

Calculated for $C_{12}H_{14}O_4$: C, 64.84%; H, 6.36%; *M* 222.26.

4.6. The Synthesis of 4-Hydroxy-benzo[c]pyrans

de Koning *et al.* [25,101] reported that a hydroxyl group can be introduced at the C-4 position of the benzo[c]pyran ring to give the 4-hydroxyisochroman-4-ol in which the key step involved was an oxidative mercury mediated ring closure reaction of an *ortho* alkenyl hydroxymethyl aryl precursor. Their synthesis was based on Hill and Whitesides' method[24], which demonstrated that the trapping of radical intermediates with oxygen was an efficient method for forming carbon-oxygen bonds.

In an attempt to synthesize chiral 4-hydroxyisochroman-4-ols we used de Koning's protocol[101]. The (*R*)-alcohol **215** was dissolved in dry tetrahydrofuran and mercuric acetate (1.33 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes after which time sodium bromide (1.33 mmol) in hot methanol (10 ml) was added and the reaction mixture stirred for an additional 30 minutes. Removal of the solvents by rotary evaporation at 40 °C gave a residue which was dissolved in dimethylformamide and this was dripped into a slurry of sodium borohydride (2.22 mmol) in dimethylformamide (15 ml) into which dry oxygen had previously been bubbled for 15 minutes and the passage of oxygen was continued in this manner for an additional 3 hours (Scheme 55). Upon work-up and purification the major product obtained was the *cis* 4-hydroxyisochroman-4-ol **258** (20 mg, 7%) and starting material **215**.

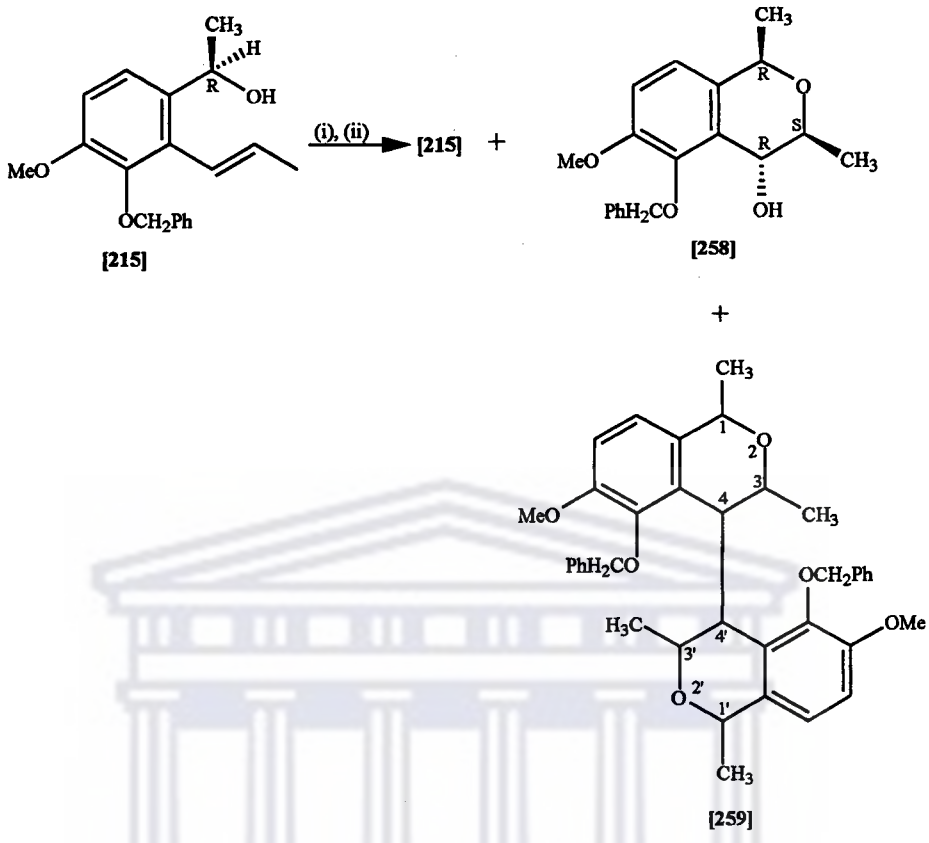


[215] [258]

(i) THF, $Hg(OAc)_2$, NaBr; (ii) DMF, O_2, $NaBH_4$.

Scheme 55

In an attempt to increase the yield of the desired product **258** the reaction was performed over a longer period and the products obtained were a dimer **259** (11%), starting material **215** and the *cis* 4-hydroxyisochroman-4-ol **258** (7%) (Scheme 56). Owing to the low yield of the 4-hydroxyisochroman-4-ol **258** an alternate method was sought.



(i) THF, $Hg(OAc)_2$, NaBr; (ii) DMF, O_2, $NaBH_4$

Scheme 56

Evidence for the dimeric material **259** is based upon the mass spectrum which showed a molecular ion at 594: calculated for $C_{38}H_{42}O_6$: 594. Elemental analysis supported the molecular formula.

In the ^{1}H-nmr spectrum four pairs of 3-proton doublets appeared as the first sign of a dimer. Doublets at δ 1.28 and δ 1.35 both with ^3J 6.2 Hz are assigned the two 3-CH_3-groups of the pyran ring while doublets at δ 1.50 and δ 1.51 each with ^3J 6.6 Hz are assigned the two 1-CH_3-groups. The assignments are corroborated in the COSY spectrum which showed very clear cross-peaks between the 3-CH_3 signals and the 3-H signals at δ 3.98 and δ 4.28 while the 1-CH_3 signals had a strong connectivity with the

1-H quartets at δ 4.90. The two 3-H signals *viz* at δ 3.98 and δ 4.28 are significantly different due to their juxtaposition to different anisotropic effects of the aryl ring systems in their close proximity compared to the 1-H. Both these signals have a common connectivity to a 2-proton multiplet at δ 2.87 which has been assigned to the 4-H protons of the new C-C bond. Interestingly the 6-methoxy signals overlap exactly to give a 6-proton singlet at δ 3.90 whereas the methylene protons of the two benzyl groups appear as two separate double doublet signals, the one pair being at δ 4.76 and δ 4.89 with ^{2}J 11.0 Hz each and the other pair at δ 5.34 and δ 5.44 with ^{2}J 11.0 Hz as well. The four aromatic protons due to 7- and 8-H appeared as a multiplet at δ 6.80 while the two aryl ring protons appeared as a sharp 10-proton multiplet at δ 7.40.

It was quite evident from the ^{13}C-nmr spectrum that the molecule was a dimer with the two halves of the dimer very similar but yet slightly different *viz* most of the peaks appeared as very closely spaced singlets for the same C-atom. For example the C-1 and C-3 methyl group appeared at δ 21.7, 22.0, 22.3 and 23.8 while the two methoxy group carbons appeared at δ 55.95 and 56.03.

The next synthesis based on Maruyama's[30] method of ring closure, and thus the (*R*)-alcohols **214** and **215** were dissolved in tetrahydrofuran-water (ratio 1:1) to which mercuric acetate was added and the reaction mixture stirred for 1 hour. Sodium hydroxide (3 M) was added followed by the addition of sodium bromide after another hour. Dry oxygen was rapidly bubbled through the reaction mixture for an hour after which sodium hydroxide (3 M) and sodium borohydride were added. Stirring and bubbling oxygen through the reaction mixture was continued for a further 4 hours. Upon work-up and brief chromatographic purification the products that were obtained turned out to be mixtures of *cis* 1,3- and *trans* 1,3-dimethyl-4-hydroxyisochroman-4-ols. Thus the (*R*)-alcohols **214** and **215** afforded isomeric mixtures of the 4-hydroxyisochroman-

4-ols (**261** and **262**; 40%) and (**258** and **260**; 63%) respectfully under the new synthetic protocol.

Sufficient amounts of one of the two isomers were obtained absolutely pure by careful preparative layer chromatography to allow a comprehensive spectral analysis. In both instances it transpired that the (*R*, *S*, *R*)-isomers **258** and **261** were isolated in chirally pure form.

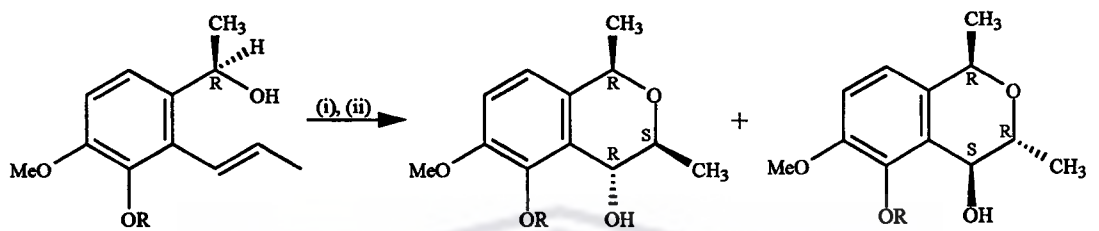
For enantiomer **261** the hydroxy group was evident in the infrared spectrum by a strong ν_{max} at 3506 cm^{-1}. In the ^{1}H-nmr spectrum a doublet at δ 1.24 with ^3J 6.2 Hz is assigned to the 3-CH_3 while the doublet at δ 1.43 with ^3J 5.8 Hz is assigned to the 1-CH_3. The *cis* 1,3-dimethyl stereochemistry of the pyran ring is apparent from the position of the well defined doublet of a quartet at δ 3.80[51]. Coupling of 6.2 Hz in the quartet clearly establishes the 3-H relative to the 3-CH_3 group while the doublet of 8.0 Hz allows for the assignment of the 4-H as being pseudoaxial and consequently the 4-OH is then pseudoequatorial. The remainder of the signals are described in the experimental section. Addition of the Europium shift reagent as before to the sample in the nuclear magnetic resonance tube in increasing amounts and up to approximately 25 mol % caused tremendous deshielding of all the proton signals but even at this concentration it was not possible to detect the separation of any signals. In the absence of an alternate enantiomer it is not possible to establish unequivocally what the ee value is. It had an $[\alpha]_D$ = +30.5° (c = 1.11 in dichloromethane).

The next isolated fraction could not be purified sufficiently to measure the specific rotation due to the presence (^{1}H-nmr) of **261** but was assigned the structure **262** based largely on the ^{1}H-nmr spectrum which had *inter alia* the following signals. A quintet at δ 3.96 with ^3J 6.6 Hz is assigned to the 3-H and due to the position of the signal, the relative arrangement of the 1,3-dimethyl groups in the pyran ring is *trans*[51]. The 4-OH

appeared as a doublet at δ 4.10 with ^3J 3.0 Hz and is D_2O exchangeable while the 4-H appeared as a doublet of a doublet at δ 4.58 with a large coupling to the *trans* 3-H of 6.6 Hz and a smaller coupling of 3.0 Hz to the 4-OH. This effectively implies that the 4-OH group is pseudoequatorial and hence the structural assignment as **262**.

In a similar manner the benzyl analogue **258** was obtained in a chirally pure form from careful preparative layer chromatography of a small portion of the mixture of **258** and **260** and had the following spectral characteristics. A strong ν_{max} at 3539 cm^{-1} in the infrared spectrum is indicative of the hydroxy group. In the ^{1}H-nmr spectrum, the following signals were pertinent in the assignment of the structure **258**. Doublets at δ 1.42 with ^3J 5.8 Hz and δ 1.49 with ^3J 6.6 Hz are assigned to the 3-CH_3 and 1-CH_3 groups respectively. A doublet of quartets at δ 3.59 is assigned to the 3-H and again the *cis* 1,3-dimethyl nature of the pyran ring is apparent. Coupling between 3-H and the 3-CH_3 group is shown by J 5.8 Hz in the quartets while trans coupling to the 4-H of J 8.8 Hz indicates that the 4-OH is pseudoequatorial as found for the isopropoxy analogue **261**. The sharp doublet at δ 4.14 with ^3J 1.6 Hz and being D_2O exchangeable is assigned to the pseudoequatorial 4-OH while a doublet of a doublet at δ 4.46 with ^3J 8.8 and 1.6 Hz is assigned to the pseudoaxial 4-H. Addition of Europium shift reagent even up to a maximum of 25 mol %, although inducing very strong deshielding in all the signals did not show any of the signals to split and thus again it is assumed that the molecule is chirally pure. The measured $[\alpha]_D$ was +27.0° (c = 0.69 in dichloromethane). The alternative diastereoisomer **260** was isolated and from the ^{1}H-nmr spectrum the structure could be assigned. The following signals were used to make the assignment. A D_2O exchangeable doublet at δ 2.02 with ^3J 8.2 Hz is assigned to the pseudoequatorial 4-OH. In this isomer the *trans* 1,3-dimethylpyran configuration is confirmed by 3-H appearing as a multiplet at δ 3.90. A broad doublet at δ 4.50 with $^3J \approx 8.0$ Hz showed a

cross-peak to both the multiplet at δ 3.90 and the doublet at δ 2.02 in the COSY spectrum and is assigned to the pseudoaxial 4-H. The large coupling of 8 Hz supported the assignment of the 4-OH as being pseudoequatorial as found in the isopropoxy analogue **262**. This is shown in Scheme 57.



[215]: R = Benzyl
[214]: R = Isopropyl

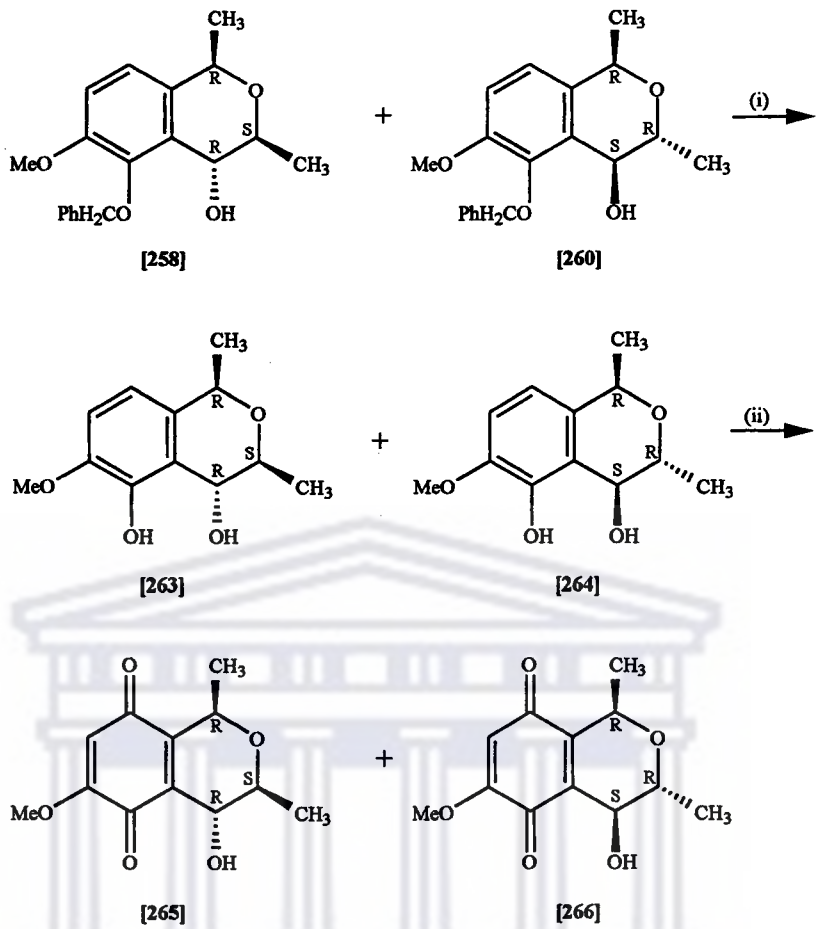
[258]: R = Benzyl
[261]: R = Isopropyl

[260]: R = Benzyl
[262]: R = Isopropyl

(i) THF, $Hg(OAc)_2$, NaBr; (ii) DMF, O_2, $NaBH_4$

Scheme 57

It was considered possible to effect a more efficient separation of the diastereoisomers **258** and **260** at the quinone oxidation level and consequently the mixture comprising the latter two 4-hydroxypyrans was transformed further. Thus the isomeric mixture of 4-hydroxyisochroman-4-ols **258** and **260** was debenzylated to give the isochroman-diols **263** and **264** which were oxidized with Fremy's salt described earlier to afford the isomeric mixture of *cis*- and *trans*- 4-hydroxyisochromanquinones **265** and **266** respectively (Scheme 58).



(i) Ethyl acetate, 5% Pd on Carbon, HCl (conc), H_2; (ii) Fremy's Salt

Scheme 58

Efforts were directed to purify only one isomer of the diastereoisomers for the purposes of full characterisation and biological evaluation. To this end isomer **265** was purified sufficiently for this purpose and efforts to purify isomer **266** were abandoned since the activity was anticipated to be similar to **265**.

Assignment of the stereochemistry as *cis* 1,3-dimethyl and the pseudoequatorial position of the 4-OH is based not only on the structures of the precursors but also on the ^{1}H-nmr spectrum which had *inter alia* the following signals. A D_2O exchangeable sharp doublet at δ 3.42 with ^3J 2.6 Hz for the pseudoequatorial 4-OH; a multiplet at δ 3.82 for

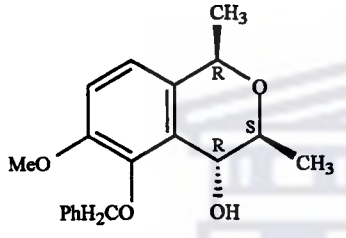
the 3-H which coincided with the signal of the 6-OCH_3 at δ 3.82; a ddd at δ 4.34 with ^3J coupling of 7.8 Hz to the *trans* 3-H, further ^3J coupling of 2.6 Hz to the 4-OH and finally long range ^5J coupling of 1.0 Hz with the pseudoequatorial 1-H assigned to the pseudoaxial 4-H; a doublet of quartets at δ 4.77 with ^3J of 7.0 Hz to the 1-CH_3 and long range coupling of 1.0 Hz to the pseudoaxial 4-H assigned to 1-H and finally 7-H appeared as a singlet at δ 5.88. The Europium shift reagent was added in increasing quantities to the solution of quinone **265** and even at levels of 30 mol % there was no separation of any of the very sharp signals due to the 1- and 3-CH_3 nor the 7-H which would indicate that the enantiomeric excess value of the quinone with a measured $[\alpha]_D$ = -69° (c = 1.28 in dichloromethane) is in the region of 97%.

4.6.1. Experimental

The experimental conditions are described in the Experimental – General Procedures, (Section 3).

Method A

(1*R*,3*S*,4*R*)- 5-benzyloxy-3,4-Dihydro-4-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (258)

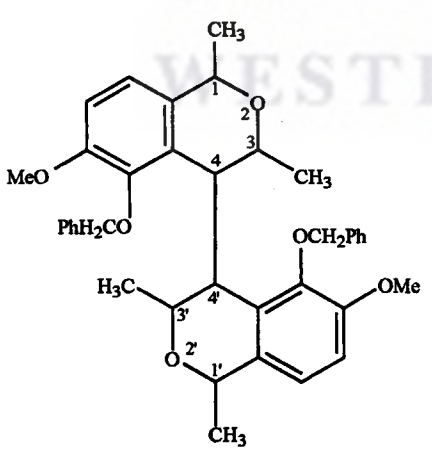


[258]

The (*R*)-alcohol **215** (280 mg, 0.939 mmol) in tetrahydrofuran (25 ml) was treated with mercuric acetate (399 mg, 1.25 mmol) at 25 °C and stirred for 30 minutes, after which time sodium bromide (128.6 mg, 1.25 mmol) in hot methanol (10 ml) was added and stirring was continued for an additional 30 minutes. Removal of solvents by rotary evaporation at 40 °C gave a residue which was dissolved in dimethylformamide (25 ml) and this was dripped into a slurry of sodium borohydride (71 mg, 1.88 mmol) in dimethylformamide (12 ml) into which dry oxygen had previously been bubbled for 5 minutes and the passage of oxygen in this manner was continued for an additional 3 hours after addition. Removal of the solvent at 50 °C under reduced pressure afforded a grey semisolid which was mixed with water (40 ml) and the resulting suspension was extracted with dichloromethane and the residue obtained was purified by column chromatography using ethyl acetate – hexane (3:7) as eluant to yield the *cis*- 4-hydroxyisochroman-4-ol **258** (20 mg, 7%).

Method B

The (*R*)-alcohol **215** (280 mg, 0.939 mmol) in tetrahydrofuran (25 ml) was treated with mercuric acetate (399 mg, 1.25 mmol) at 25 °C and stirred for 2 hours, after which time sodium bromide (128.6 mg, 1.25 mmol) in hot methanol (10 ml) was added and stirring was continued for an additional 2 hours. Removal of the solvents by rotary evaporation at 40 °C gave a residue which was dissolved in dimethylformamide (25 ml) and this was dripped into a slurry of sodium borohydride (71 mg, 1.88 mmol) in dimethylformamide (12 ml) into which dry oxygen had previously been bubbled for 30 minutes and the passage of oxygen in this manner was continued for an additional 12 hours after addition. Removal of the solvent at 50 °C under reduced pressure afforded a grey semisolid which was mixed with water (40 ml) and the resulting suspension was extracted with dichloromethane and the residue obtained was purified by column chromatography using ethyl acetate – hexane (3:7) as eluant to yield the dimer **259** (60 mg, 11%) the *cis*- 4-hydroxyisochroman-4-ol (20 mg, 7%) and starting material **215**.



[259]

259 melting point 171-174 °C with decomposition; δ_H 1.23 (3H, d, *J* 6.2 Hz, 3-C*H*$_3$), 1.35 (3H, d, *J* 6.2 Hz, 3-C*H*$_3$), 1.50 (3H, d, *J* 6.6 Hz, 1-C*H*$_3$), 1.51 (3H, d, *J* 6.6 Hz, 1-C*H*$_3$), 2.87 (2H, m, 4- and 4'-H), 3.90 (6H, s, ArOC*H*$_3$), 3.98 (1H, q, *J* 6.0 Hz, 3-H), 4.28 (1H, q, *J* 6.0 Hz, 3-H), 4.76 and 4.89 (2H, dd, *J* 11.0 Hz each, OC*H*$_2$Ph), 4.90 (2H, m, 1- and 1'-H), 5.34 and 5.44 (2H, dd, *J* 11.0 Hz each, OC*H*$_2$Ph), 6.80 (2H, m, 7- and 8-H), 7.40 (10H, m, aryl *H*'s); δ_C 21.7, 22.0, 22.3, 23.8, 27.4, 55.95, 56.03, 67.1, 69.6, 73.2, 73.5, 110.0, 110.4, 120.5, 121.2, 128.78 (×2), 128.9 (×2), 129.0 (×2), 129.1 (×2), 129.8 (×2), 131.0, 131.8

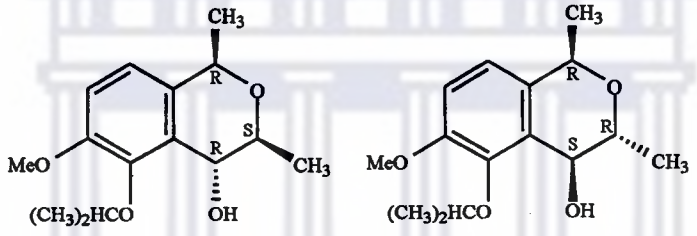
(×2), 133.1 (×2), 136.9 (×2), 137.1 (×2), 143.6 (×2), 150.7 and 151.0; MS (EI): *m/z* (%): 594 (M^+, 1), 297 (90), 269 (23), 205 (92), 191 (80), 163 (47), 117 (58), 91 (100).

Found: C, 76.68%; H, 7.27%.

Calculated for $C_{38}H_{42}O_6$: C, 76.73%; H, 7.1%; *M* 594.80.

Method C

(1*R*,3*S*,4*R*)-3,4-Dihydro-4-hydroxy-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (261) and **(1*R*,3*R*,4*S*)-3,4-dihydro-4-hydroxy-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[c]pyran (262)**



[261] [262]

The (*R*)-isopropyloxy alcohol **214** (250 mg, 1.00 mmol) was dissolved in tetrahydrofuran (30 ml) and water (30 ml). Mercuric acetate (319 mg, 1.00 mmol) was added and the reaction mixture stirred for 1 hour. Sodium hydroxide solution (7.2 ml × 3 M) was added and the reaction mixture stirred for another 1hour. Sodium bromide (102.9 mg, 1.00 mmol) was added to the reaction mixture and stirring was continued for another 1 hour. The reaction mixture was then oxygenated by bubbling oxygen rapidly through the solution for an hour after which, sodium hydroxide (7.2 ml × 3 M) and sodium borohydride (719 mg, 19.01 mmol) were added. The reaction mixture was stirred under the bubbling oxygen atmosphere for 4 hours until the solution was no longer grey in colour. The aqueous phase was extracted with ethyl acetate and the residue obtained from work-up was purified by column chromatography using initially

(1.5:8.5), then later (3:7) ethyl acetate - hexane as eluant. The product was obtained as a pale yellow oily mixture of *cis*- and *trans*-isomers (107 mg, 40%). An aliquot of the product mix was separated by preparative thin layer chromatography for full characterization purposes using (1:9) ethyl acetate - hexane as eluant.

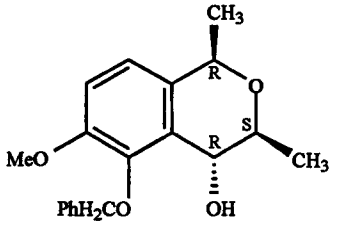
261 ν_{max} 3506 cm^{-1} (O-H); δ_H 1.24 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.43 (3H, d, *J* 5.8 Hz, 1-CH_3), 1.48 [6H, d, *J* 6.6 Hz, CH(CH_3)$_2$], 3.80 (1H, dq, *J* 8.0 and 6.2 Hz, 3-H), 3.84 (3H, s, ArOCH_3), 4.70 (4H, m, 1-, 4- and CH_2Ph), 6.80 (1H, d, *J* 7.8 Hz, 7-H) and 6.83 (1H, d, *J* 7.8 Hz, 8-H); δ_C 19.1, 21.7, 22.5, 23.2, 55.9 (ArOCH_3), 70.7, 72.9, 75.2, 75.7, 112.0 (C-7), 119.5 (C-8), 131.8, 133.5, 144.7 and 150.9; MS (EI): *m/z* (%): 266 (M^+, 9), 249 (11), 222 (64), 191 (100), 180 (60), 163 (22), 133 (27); $[\alpha]_D$ = +30.5° (c = 1.110, CH_2Cl_2); enantiomeric excess (europium shift reagent): >99%.

Found: C, 67.58%; H, 8.27%.

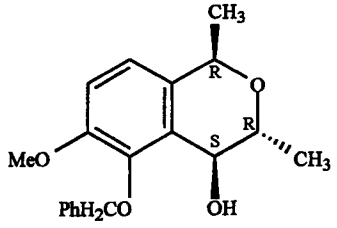
Calculated for $C_{15}H_{22}O_4$: C, 67.63%; H, 8.34%; *M* 266.37.

262 ν_{max} 3510 cm^{-1} (O-H); δ_H 1.22 (3H, d, *J* 6.0 Hz, 3-CH_3), 1.34 [3H, d, *J* 6.6 Hz, CH(CH_3)$_2$], 1.42 (3H, d, *J* 6.2 Hz, 1-CH_3), 1.53 [3H, d, *J* 7.0 Hz, CH(CH_3)$_2$], 3.83 (3H, s, ArOCH_3), 3.96 (1H, quintet, *J* 6.6 Hz, 3-H), 4.10 (1H, d, *J* 3.0 Hz, 4-O*H*, D_2O exchangeable), 4.58 (1H, dd, *J* 6.6 and 3.0 Hz, 4-H), 4.69 [1H, m, C*H*(CH$_3$)$_2$], 4.89 (1H, q, *J* 6.6 Hz, 1-H), 6.72 (1H, d, *J* 8.2 Hz, 7-H) and 6.84 (1H, d, *J* 8.2 Hz, 8-H); δ_C 17.8, 21.9, 22.4, 23.2, 55.0 (ArOCH_3), 68.7, 69.2, 69.4, 75.4, 112.4 (C-7), 120.2 (C-8),130.3, 132.6, 145.2 and 150.8; MS (EI): *m/z* (%): 266 (M^+, 9), 249 (11), 222 (64), 191 (100), 180 (60), 163 (22), 133 (27). Sample could not be isolated in a sufficiently pure form for optical measurements.

(1*R*,3*S*,4*R*)-5-Benzyloxy-3,4-Dihydro-4-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (258) and **(1*R*,3*R*,4*S*)- 5-Benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-dimethylbenzo[c]pyran (260)**



[258]



[260]

The (*R*)-benzyl alcohol **215** (793 mg, 2.66 mmol) was dissolved in tetrahydrofuran (40 ml) and water (40 ml). Mercuric acetate (931 mg, 2.93 mmol) was added and the reaction mixture stirred for 1 hour. Sodium hydroxide solution (19 ml × 3 M) was added and the reaction mixture stirred for a further 1 hour. Sodium bromide (301.5 mg, 2.93 mmol) was added to the reaction mixture and stirring was continued for another 1 hour. The reaction mixture was oxygenated by bubbling oxygen rapidly through the solution for 1 hour after which, sodium hydroxide (19 ml × 3 M) and sodium borohydride (2.22 g, 55.7 mmol) were added. The reaction mixture was stirred under the bubbling oxygen atmosphere for 4 hours until the solution was no longer grey in colour. The aqueous phase was extracted with ethyl acetate (3 × 40 ml), the residue obtained upon work-up was purified by column chromatography using initially (1.5:8.5) then later (3:7) ethyl acetate in hexane as eluant. The product was obtained as a pale yellow oily mixture of *cis*- and *trans*-isomers (525 mg, 63%). An aliquot of the product mixture was separated by preparative thin layer chromatography for characterization purposes using ethyl acetate – hexane (1:9) as eluant.

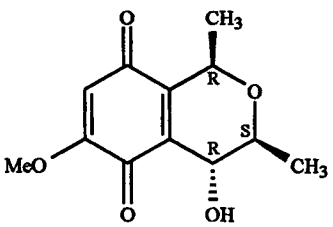
258 ν_{max} 3539 cm^{-1} (O-H); δ_H 1.42 (3H, d, *J* 5.8 Hz, 3-C*H*$_3$), 1.49 (3H, d, *J* 6.6 Hz, 1-C*H*$_3$), 3.59 (1H, dq, *J* 8.8 and 5.8 Hz, 3-H), 3.90 (3H, s, ArOC*H*$_3$), 4.14 (1H, d, *J* 1.6 Hz, 4-O*H*, D_2O exchangeable), 4.46 (1H, dd, *J* 8.8 and 1.6 Hz, 4-H), 4.75 (1H, q, *J* 6.6 Hz, 1-H), 4.98 (1H, d, *J* 10.6 Hz, C*H*$_2$Ph), 5.24 (1H, d, *J* 10.6 Hz, C*H*$_2$Ph), 6.84 (1H, d, *J* 8.1 Hz, 7-H), 6.90 (1H, d, *J* 8.1 Hz, 8-H) and 7.40 (5-H, m, Ph*H*'s); δ_C 19.2, 21.5, 56.0 (ArO*C*H$_3$), 70.0, 72.8, 75.2, 75.4, 112.1 (C-7), 120.0 (C-8), 128.1, 128.6 (×2), 128.7 (×2), 131.5, 133.7, 137.0, 145.9 and 150.9; MS (EI): *m/z* (%): 314 (M^+, 2), 206 (44), 191 (100), 179 (28) 164 (31) 149 (13), 91 (27); $[\alpha]_D$ = +27° (c = 0.690, CH_2Cl_2); enantiomeric excess (europium shift reagent): >99%.

Found: C, 72.41%; H, 7.15%.

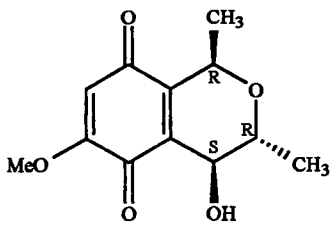
Calculated for $C_{19}H_{22}O_4$: C, 72.58%; H, 7.07%; *M* 314.41.

260 ν_{max} 3539 cm^{-1} (O-H); δ_H 1.34 (3H, d, *J* 6.6 Hz, 3-C*H*$_3$), 1.46 (3H, d, *J* 6.6 Hz, 1-C*H*$_3$), 2.02 (1H, d, *J* 8.2 Hz, 4-O*H*, D_2O exchangeable), 3.90 (3H, s, ArOC*H*$_3$), 3.90 (1H, m, 3-H), 4.50 (1H, bd, *J* 8.0 Hz, 4-H), 5.04 (1H, q, *J* 6.6 Hz, 1-H), 5.07 (1H, d, *J* 10.6 Hz, C*H*$_2$Ph), 5.20 (1H, d, *J* 10.6 Hz, C*H*$_2$Ph), 6.78 (1H, d, J 8.0 Hz, 7-H), 6.89 (1H, d, *J* 8.0 Hz, 8-H), 7.39 (3H, m, 3'-,4'-and 5'-H of aryl ring) and 7.44 (2-H, m, 1'- and 5'-H of aryl ring); δ_C 17.0, 21.4, 56.2 (O*C*H$_3$), 63.5, 66.7, 70.9, 75.5, 113.5 (C-7), 121.1 (C-8), 128.2, 128.5 (×4), 13.6, 131.9, 137.8, 146.0 and 151.1; MS (EI): *m/z* (%): 314 (M^+, 2), 206 (44), 191 (100), 179 (28) 164 (31) 149 (13), 91 (27). Sample could not be isolated in a sufficiently pure form for optical measurements.

(1*R*,3*S*,4*R*)-3,4-Dihydro-4-methoxy-1,3-dimethyl-5,8-dioxybenzo[c]pyran (265) and **(1*R*,3*R*,4*S*)-3,4-dihydro-4-methoxy-1,3-dimethyl-5,8-dioxybenzo[c]pyran (266)**



[265]



[266]

A mixture of *cis*- and *trans*- hydroxypyrans **258** and **260** (206 mg, 0.656 mmol) was dissolved in ethyl acetate (25 ml) to which palladium on charcoal (21mg) and two drops of concentrated hydrochloric acid (10 M) was added. The reaction mixture was stirred under hydrogen and monitored by thin layer chromatography until the starting material was consumed (after 15 hours). The reaction mixture was filtered and the ethyl acetate evaporated to give a dark red residue.

The residue was dissolved in methanol (3 ml) and added to 10ml of a buffered aqueous solution (78.8 ml of 0.2 M Na_2HPO_4 and 171.2 ml of 0.2 M NaH_2PO_4) of Fremy's salt (0.988 g, 1.84 mmol). The reaction mixture was stirring for 1 hour (rapid colour change from violet to brown). Water (40 ml) was added to the reaction mixture which was then extracted with dichloromethane (3 × 30 ml). The residue obtained upon work-up was purified by column chromatography using ethyl acetate – hexane (1:4) as eluant to afford the bright yellow *cis*-isomer (41 mg, 26%) as an oil from the initial pyranquinone mixture.

265 ν_{max} 3494 cm^{-1} (O-H) and 1672 cm^{-1} (C=O); δ_H 1.36 (3H, d, *J* 6.2 Hz, 3-CH_3), 1.52 (3H, d, *J* 7.0 Hz, 1-CH_3), 3.42 (1H, d, *J* 2.6 Hz D_2O exchangeable, 4-OH), 3.82 (3H, s, ArOCH_3), 3.82 (1H, m, 3-H), 4.34 (1H, ddd, *J* 7.8, 2.6 and 1.0 Hz, pseudoaxial 4-H),

4.77 (1H, dq, *J* 7.0 and 1.0 Hz, 1-H), 5.88 (1H, s, 6-H); δ_C 18.5 (3-*C*H$_3$), 19.2 (1-*C*H$_3$), 56.5 (ArO*C*H$_3$), 67.1 (C-3), 67.6 (C-1), 107.8 (C-7), 116.2 (C-4), 137.1 (C-8a)[a], 146.1 (C-4a)[a], 158.8 (C-6), 183.0 (C-8)[b], 185.8 (C-5)[b]. Assignments with the same superscripts may be interchanged. MS (EI): *m/z* (%): 239 [M^++1, 1], 194 (81), 166 (100), 151 (84), 123 (13), 109 (15), 69 (12); $[\alpha]_D$ = - 69° (c = 1.280, CH_2Cl_2); enantiomeric excess (Europium shift reagent) > 98%.

Found: C, 60.56%; H, 5.82%.

Calculated for $C_{12}H_{14}O_5$: C, 60.49%; H, 5.93%; *M* 238.26.

4.7. Conclusions

It has been demonstrated that starting from a 3,4-dialkoxylated-1-(1'-hydroxyethyl)-2-prop-1'-enylbenzene precursor in which a preconceived chiral centre *viz* C-1 of the to be formed pyran ring system is incorporated and followed by a mercury(II) mediated ring closure protocol, chirality could be induced at C-3 of the pyran ring. No doubt, the fact that the 3-methyl group of the pyran ring prefers the equatorially less sterically demanding position played a major role in this process.

In one instance, the chiral 6- methoxyisochromanquinone was prepared and evaluated spectroscopically .

Persuant to our future goals, a hydroxyl group was successfully introduced at position 4 of the pyran ring by altering the conditions of the mercury(II) mediated cyclisation of the chiral alcohol precursors and in one instance the chiral 4-hydroxy-6-methoxyisochromanquinone was prepared and evaluated spectroscopically.

This method would have greater merit as a useful synthetic protocol if the initial chiral reduction of the acetyl orthoalkenyl precursor could furnish a cleaner reduction product of higher enantiomeric excess value.

4.8. *In Vitro* Antimicrobial Screening Activity of Synthetic Compounds

Compounds **254**, **255**, **257**, **265**, **266** and **267** were screened for antimicrobial activity and specificity against Gram positive and Gram negative organisms employing the Bauer-Kirby method[102].

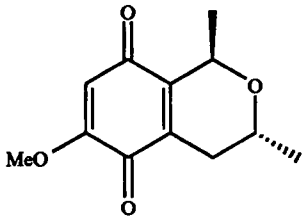
4.8.1. General Methodology

Filter paper discs[102] with a diameter of 10 mm were impregnated with the compounds dissolved in triple distilled dichloromethane. The discs were dried under reduced pressure and placed onto the surface of nutrient agar plates inoculated with the test organisms. The plates were incubated at 37 °C for 24 hours and the diameter of the zones of inhibition (including that of the impregnated discs) was measured. Inhibition of microbial growth was indicated by a clear zone around the disc. All determinations were done in duplicate. Except in cases where only a limited amount of test-compound was available, the discs were impregnated to contain 2.81, 1.40 and 0.70 μmol of compound.

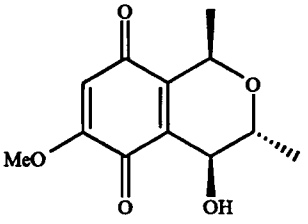
It is important for the reader who is less familiar with the subject to note that antibiotics diffuse through agar gels at different rates so that zone sizes alone produced are not always directly comparable and can thus not be related to relative activities of the compounds under investigation in an unambiguous way.

The following organisms were obtained from the South African Bureau of standards (SABS) in Pretoria for experimental work.

Inhibition Activity of Compounds [257] and [267] against SABS Organisms



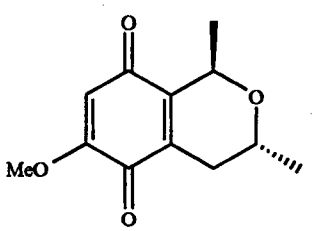
racemic -[257]



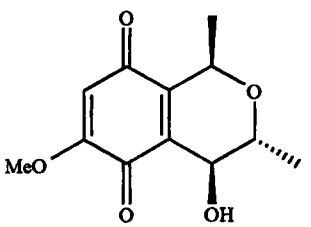
racemic -[267]

Gram Positive Organism and SABS culture number	Dose in µmol	Zone of inhibition in mm	
		[257]	[267]
Staphylococcus aureus SATCC Sta 53	2.81	26	35
	1.40	25	32
	0.70	23	28
Bacillus Subtilus SATCC Bac 96	2.81	20	32
	1.40	20	32
	0.70	19	28
Candida albicans fungus	2.81	17	30
	1.40	16	30
	0.70	13	28
Gram Negative Organism and SABS culture number			
Psuedomonas auroginosa SATCC Pse 2	2.81	0	5
	1.40	0	0
	0.70	0	0
Proteus mirabilis SATCC Pre 1	2.81	0	28
	1.40	0	28
	0.70	0	25
Eschericia coli SATCC Esc 25	2.81	0	5
	1.40	0	0
	0.70	0	0

Inhibition Activity of Compounds [255] and [266] against SABS Organisms



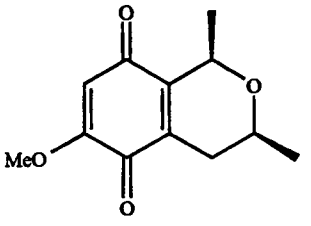
chiral -[255]



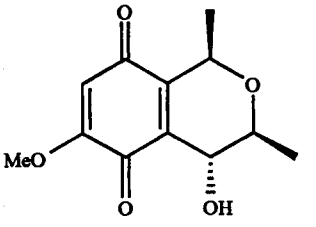
chiral -[266]

Gram Positive Organism and SABS culture number	Dose in µmol	Zone of inhibition in mm	
		[255]	[266]
Staphylococcus aureus SATCC Sta 53	2.81	21	35
	1.40	21	35
	0.70	21	30
Bacillus Subtilus SATCC Bac 96	2.81	22	35
	1.40	23	35
	0.70	20	30
Candida albicans fungus	2.81	18	35
	1.40	14	35
	0.70	13	33
Gram Negative Organism and SABS culture number			
Psuedomonas auroginosa SATCC Pse 2	2.81	0	5
	1.40	0	0
	0.70	0	0
Proteus mirabilis SATCC Pre 1	2.81	0	30
	1.40	0	28
	0.70	0	25
Eschericia coli SATCC Esc 25	2.81	0	5
	1.40	0	0
	0.70	0	0

Inhibition Activity of Compounds [254] and [265] against SABS Organisms



chiral -[254]



chiral -[265]

Gram Positive Organism and SABS culture number	Dose in µmol	Zone of inhibition in mm	
		[254]	[265]
Staphylococcus aureus SATCC Sta 53	2.81	26	35
	1.40	25	35
	0.70	20	30
Bacillus Subtilus SATCC Bac 96	2.81	26	35
	1.40	28	35
	0.70	21	30
Candida albicans fungus	2.81	20	35
	1.40	15	35
	0.70	15	33
Gram Negative Organism and SABS culture number			
Psuedomonas auroginosa SATCC Pse 2	2.81	0	5
	1.40	0	0
	0.70	0	0
Proteus mirabilis SATCC Pre 1	2.81	0	30
	1.40	0	28
	0.70	0	25
Eschericia coli SATCC Esc 25	2.81	0	5
	1.40	0	0
	0.70	0	0

4.8.2. Conclusions

These results are somewhat disappointing since it would appear that there is only a very modest improvement in the inhibitory activity by the chiral isochromans **254** and **255** relative to the racemic mixture **257** at lower dose levels.

On the other hand a similar response was not observed for the two chiral 4-hydroxyisochromanols **265** and **266** relative to the racemic mixture **267**. This could in part be due to the nature of the inhibition measurement which is not entirely indicative of by what factor molecules are more active than others. Further *in vivo* testing would be necessary to determine this.

However, the one noticeable improvement in inhibitory activity is clearly evident in the systems containing the 4-OH group over those not having them as found earlier[103].

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