UNIVERSITY OF SOUTHAMPTON

# A STUDY TOWARDS THE TOTAL SYNTHESIS OF THE PSEUDOPTEROSINS.

by

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Faculty of Science
Department of Chemistry

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

# A Synthetic Approach Towards The Pseudopterosins

By

Graham E. M. Sibley

A synthetic approach to the Pseudopterosins, a family of marine natural products which display potent anti-inflammatory and analgesic agents, is described. The approach presented to the pseudopterosins aglycone utilises a tetrahydrofuran derivative and a sequential Friedel-Crafts alkylation reaction. The stereochemistry of the precursor is controlled by iodo-lactonisation and etherification reactions with kinetic and thermodynamic control of the respective cyclisations. The subsequent cyclisation of the precursor appears to heavily dependant upon the nature of the side chain in the C-1 position and treatment of the precursor with boron trifluoride dietherate afforded the desired phenalene nucleus in excellent yield.

## Contents

## Preface

The research described in this thesis was carried out at the University of Southampton between October 1996 and October 1999. No part of this thesis has previously been submitted for a degree at this or any other university except where specific acknowledgement has been made

## Acknowledgements

I would like to thank Dr. David Harrowven for his advice and support over the last three years. In addition to this I would like to thank my friends and colleges at Southampton, in particular the members of my group both past and present.

My special thanks are also extended to the excellent technical support at Southampton; Mrs Joan Street for NMR and Dr. J. Langley for mass spectroscopy.

**Abbreviations.**

| | |
|---|---|
| Ac | acetate |
| AIBN | azo-*iso*-butyronitrile |
| Amu | atomic mass units |
| APCI | atomspheric pressure chemical ionisation |
| Approx. | approximately |
| Bn | benzyl |
| Bu | butyl |
| Cat. | Catalytic |
| CI | chemical ionisation |
| COSY | correlation spectroscopy |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicyclo[5.4.0]unde-7-ene |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DHP | 3,4-dihydro-2H-pyran |
| DIBAL-H | di-*iso*-butylaluminium hydride |
| DMAD | dimethyl acetylenedicarboxylate |
| DMAP | 4-dimethylaminopyridine |
| DMF | N,N-dimethylforamide |
| DMS | dimethylsulfide |
| DMSO | dimethylsulfoxide |
| EI | electron impact |
| eq. | equivalents |
| ES | electrospray |
| Et | ethyl |
| EVL | ethoxyvinyllithium |
| FT | Fourier transform |
| hr | hours |

| | |
|---|---|
| HMDS | 1,1,1,3,3,3-hexamethyldisilazane |
| HMPA | hexamethylphosphoramide |
| HMPT | hexamethylphosphorous triamide |
| IR | infra red |
| LAH | lithium aluminium hydride |
| LDA | lithium di-*iso*-propylamide |
| LHMDS | lithium hexamethyldisilylamide |
| lit. | literature |
| *m*-CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| Min | minutes |
| m.p. | melting point |
| Ms | methanesulfonyl |
| NBS | N-bromosuccinimide |
| NMO | 4-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| n.O.e | nuclear Overhauser effect |
| NSAID | non-steroidal anti-inflammatory drug |
| *P.* | *Pseudopterogorgia* |
| PCC | pyridinium chorochromate |
| Ph | phenyl |
| Piv | pivaloyl |
| PL | phospholipase |
| PPA | polyphosphoric acid |
| Ps. | Pseudopterosin |
| psi | pounds per square inch |
| py | pyridine |
| Red-Al | sodium bis(2-methoxyethoxy)aluminium hydride |
| RT | room temperature |
| sia | siamyl |
| TBAF | tetrabutylammonium fluoride |

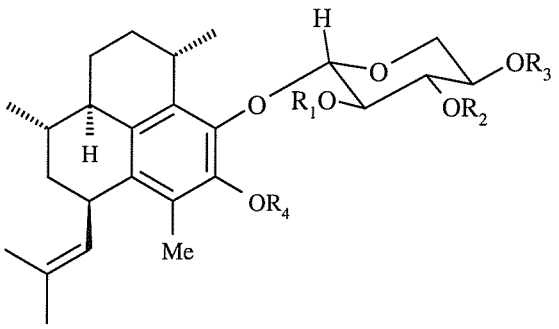
| | |
|---|---|
| TBS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| tlc | thin layer chromatography |
| TMEDA | N,N,N´,N´-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Ts | *para*-toluene sulfonyl |
| UV | ultra violet |
| Vis | visible |
| X | halide |
| xs. | excess |

*Chapter One*

# Introduction to the Pseudopterosins

## 1.1 Discovery of the Pseudopterosins

Marine organisms have attracted intense interest from physical scientists in recent years due to the chemical diversity and biomedical potential of the natural products found in marine invertebrates. For example, extensive studies of sea whips of the genus *Pseudopterogorgia* led to the discovery of many novel terpenoids[1-3] and secosterols.[4] Of these the species *Pseudopterogorgia elisabetha*, found in the shallow waters off the Bahamas, has attracted greatest attention. Prompted by the discovery of potent anti-inflammatory activity in crude extracts of these sea whips four tricyclic diterpene pentosides referred to as pseudopterosins A-D (**1-4**) were shown to be the bioactive principles. The structure of these four pseudopterosins was determined with the aid of X-ray crystallographic analysis of pseudopterosin C. The structures of pseudopterosins A, B and D were subsequently determined by spectral analysis and by derivitisation; each being related by chemical interconversions (Figure 1).[5,6]




**1 Ps A** : $R_1=R_2=R_3=R_4=H$
**2 Ps B** : $R_1=Ac, R_2=R_3=R_4=H$
**3 Ps C** : $R_2=Ac, R_1=R_3=R_4=H$
**4 Ps D** : $R_3=Ac, R_1=R_2=R_4=H$

**Figure 1**

Potential biomedical applications of the pseudopterosins became apparent with the discovery that they exhibited anti-inflammatory and analgesic properties,[6] with potencies upto fifty times greater than indomethacin, the industry standard. Pseudopterosin A-D were, however, acutely toxic in the range of 50 mg/kg in mice.

This discovery fuelled further studies of *P. elisabethae*. These resulted in the isolation of six new pseudopterosins (E-J) **5-10** (Figure 2) and the methylated aglycone **11a** (Figure 3).[7]

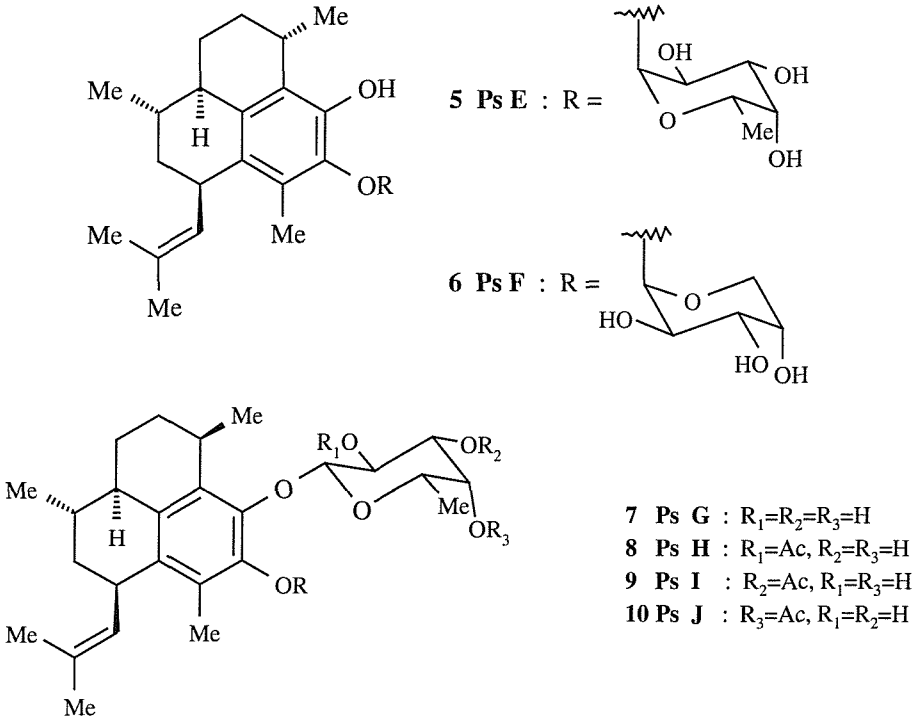



**Figure 2**

These new pseudopterosins displayed similar anti-inflammatory characteristics to the earlier pseudopterosins A-D. Superior anti-inflammatory activity was observed with the pseudopterosin E, the most potent compound, and with an absence of toxic effects in a dose in excess of 300 mg/kg in mice. A further collection from the Bahamas revealed two further pseudopterosins, K and L **12-13** (Figure 3).

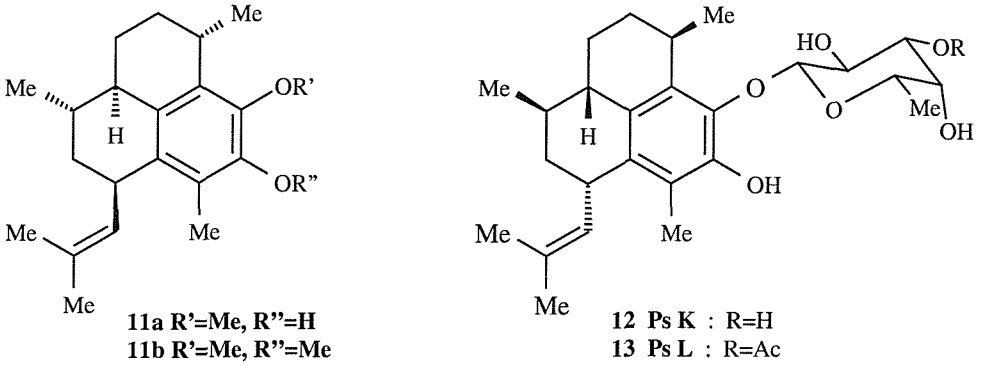
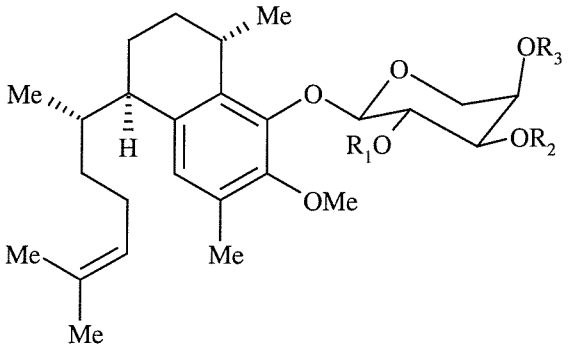
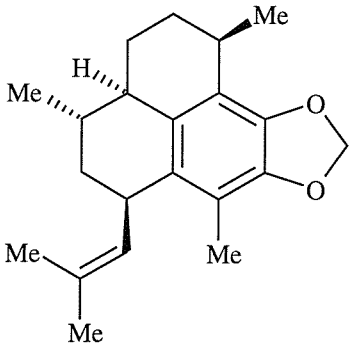



**Figure 3**

## 1.2 The *Seco*-Pseudopterosins and Helioporins

The *seco*-pseudopterosins (A-D) **14-17**, are related to pseudopterosin A by bond cleavage between C1-C12. Derived from Caribbean sea whips of the genus *Pseudopterogorgia*, they were discovered in the Florida Keys[8] and shown to display similar anti-inflammatory and analgesic properties to the pseudopterosins. Comprehensive spectral analysis and chemical transformations were utilised to determine the structures of the *seco*-pseudopterosins, which were found to be arabinose glycosides possessing aglycones of the serrulatane class of diterpenoids (Figure 4).




**14 seco Ps A** : $R_1=R_2=R_3=H$
**15 seco Ps B** : $R_1=Ac, R_2=R_3=H$
**16 seco Ps C** : $R_2=Ac, R_1=R_3=H$
**17 seco Ps D** : $R_3=Ac, R_2=R_3=H$

**18** Helioporin E

**Figure 4**

The helioporins are a group of bioactive diterpenes isolated from the blue coral *Heliopora coerulea* which share a benzodioxole substruture.[9] These metabolites exhibit antiviral and cytotoxic properties. The structure of helioporin E **18** proposed in the isolation paper was closely related to the aglycone of pseudopterosins G-J (Figure 4). However, total synthesis has shown the original stereochemical assignment to be incorrect.[10]

## 1.3 Biological Activity

Pharmacological interest in the pseudopterosins stems from the anti-inflammatory and analgesic properties which these illicit.[11] Inflammation is an extremely painful affliction, which effects both the young and old. It is reported to be the result of increased blood flow or a build up in body fluids in infected areas.[12]

Inflammation is thought to be initiated by the release of the enzyme phospholipase $A_2$ ($PLA_2$) which catalyses the hydrolysis of membrane phospholipid esters at the sn-2 position.[13] This in turn induces the biosynthesis of arachidonic acid which leads to excessive production of plasma constituents such as thromboxanes, eicosonoids and leukotrienes.

Knowledge of the biochemical processes which result in inflammation, has lead to the development of anti-inflammatory drugs. These have two primary modes of action. In general, steroidal drugs inhibit the enzyme phospholipase $A_2$ ($PLA_2$) and thus prevent the biosynthesis of arachidonic acid while non steroidal drugs are believed to interrupt the arachidonic bio-pathway, preventing the formation of other substrates.

The pseudopterosins appear to have a novel mechanism of pharmacological action, which is distinct from that of the cyclo-oxygenase inhibiting anti-inflammatory agents, in that they affect both the cyclo-oxygenase and lipoxygenase pathways. Of particular significance is the fact that the pseudopterosins do not act as prostoglandin $H_2$ synthase inhibitors.

## 1.4 Nomenclature

The numbering system used by Fenical to describe the pseudopterosins and the *seco*-pseudopterosins is shown in Figure 5. Within the body of the thesis this nomenclature has been used to aid in the description of the stereogenic centers. Within the experimental section systematic naming and numbering is used.

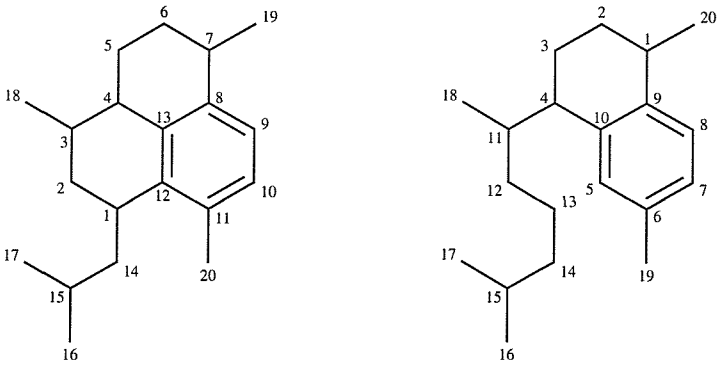


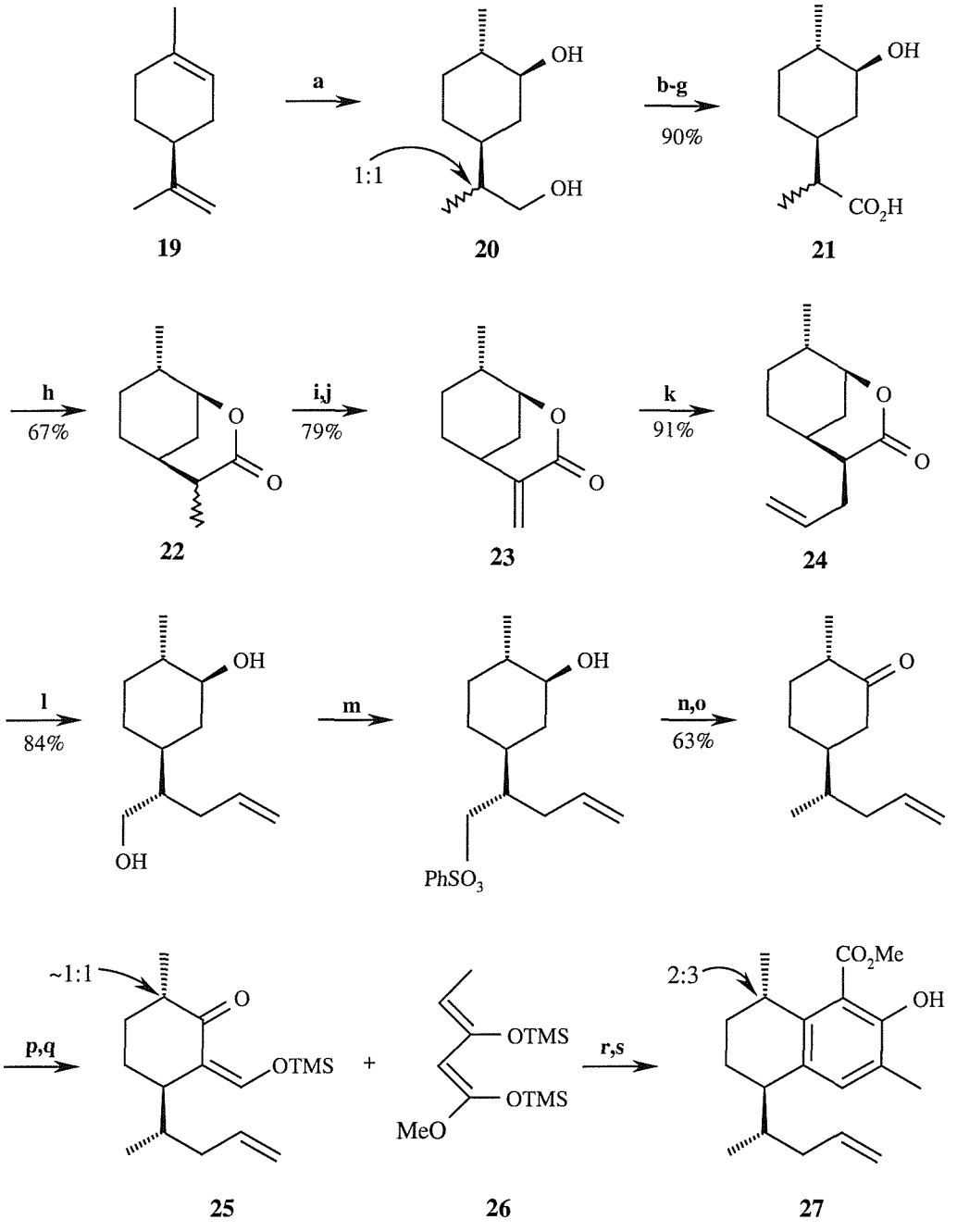
**Figure 5**

## 1.5 Total Synthesis and Approaches to the Pseudopterosins

### (I) The Broka Synthesis.

The first reported total synthesis of pseudopterosin A in an optically active form was outlined by Broka *et al.*[14] This route also allowed for the preparation of the related *seco*-pseudopterosins and is outlined in Scheme 1 & 2.

The starting point of the synthesis was the readily available *S*-(-)-limonine **19** which, upon treatment with thexylborane in accordance to the procedure of Brown,[15] afforded the epimeric mixture of diols **20** (1:1). These were converted by a routine sequence into the hydroxy acids **21** and lactones **22**. Selenation followed by oxidation gave the α-methylene lactose **23** as a single diastereoisomer. The C-3 stereochemistry was then established by treatment with vinylmagnesium bromide, copper (I) iodide and trimethylsilyl chloride giving **24** as a single stereoisomer on aqueous workup. Conversion to the silylated hydroxymethylene derivative **25** by standard experimental procedures, led to some loss of stereochemical integrety at the C-6 position. The aromatic nucleus was then established by reaction of **25** with diene **26** to give a mixture of phenols **27** in a 2:3 ratio of diastereoisomers.[16]

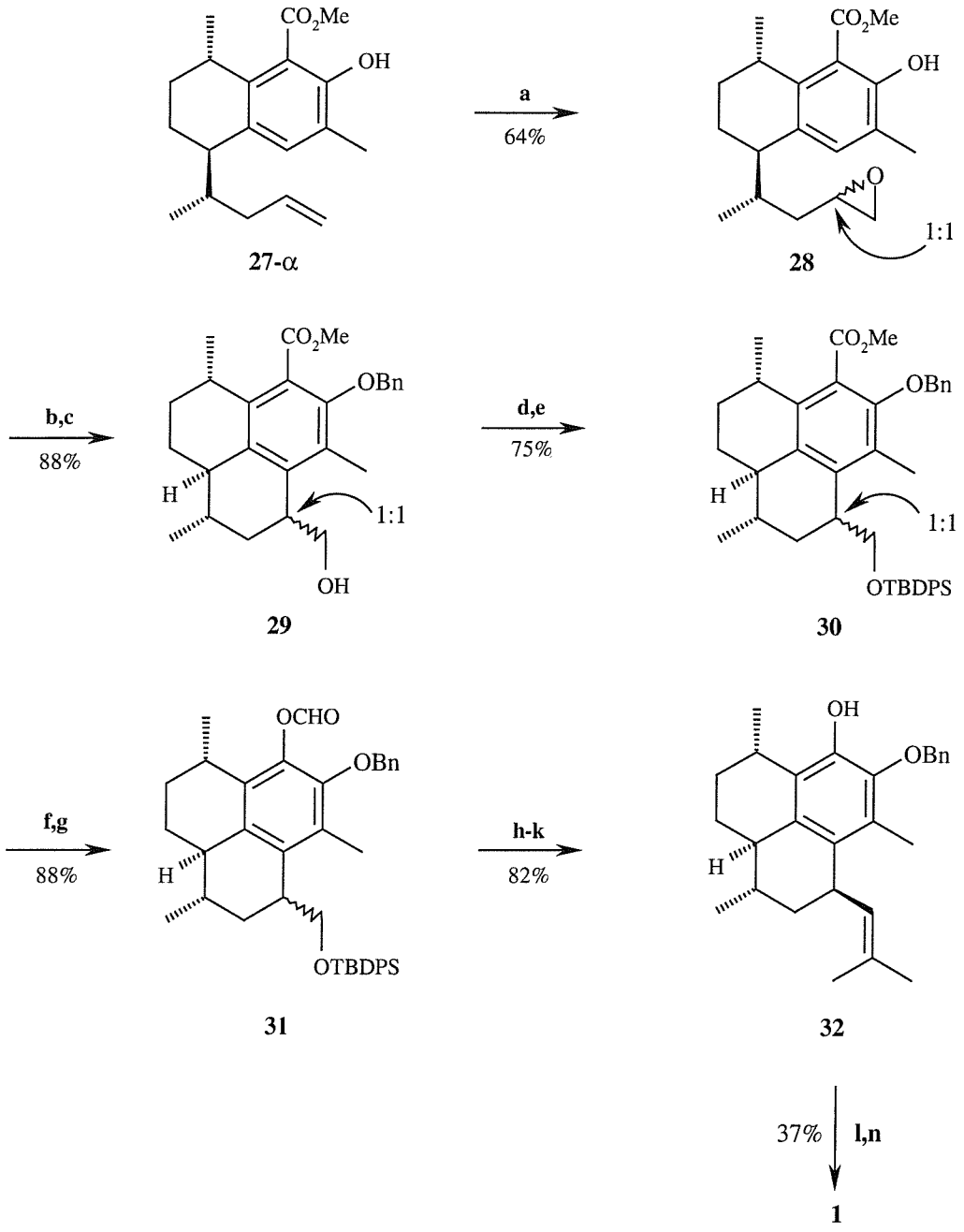



**Reagents & Conditions: a.** thexylborane, $H_2O_2$, NaOH; **b.** Piv-Cl, pyr; **c.** DHP, cat. PPTS, DCM; **d.** aq. KOH; **e.** PCC, NaOAc, DCM; **f.** $NaClO_2$, aq. *t*-BuOH; **g.** AcOH-$H_2O$; **h.** *p*-TsOH, Tol, reflux; **i.** LDA, PhSeCl, HMPA; **j.** $H_2O_2$; **k.** vinylmagnesium bromide, CuI-DMSO, TMSCl, THF, –40°C; **l.** LAH, THF; **m.** $PhSO_2Cl$, $NEt_3$, DMAP, DCM; **n.** $LiBHEt_3$, THF; **o.** PCC, DCM; **p.** $HCO_2Et$, NaH, dioxane; **q.** TMSCl, $NEt_3$, hexane; **r.** $TiCl_4$, DCM, –78°C; **s.** NaOMe, MeOH.

**Scheme 1**

The ring closure of the desired isomer **27-α** was achieved via peracid oxidation of **27** to a mixture of epoxides **28**. This was followed by intramolecular Friedel-Crafts alkylation utilising $SnCl_4$ and subsequent benzylation of the phenolic hydroxy group giving **29**. The primary alcohol was then silylated and the ester reduced by DIBAL giving **30** (1:1 mixture). The benzylic alcohol was next converted to a formyl ester by sequential oxidation, first to the aldehyde with PCC and then by Baeyer-Villiger oxidation to **31**.

The next objective was the introduction of an *iso*-butylene side chain. This was achieved by the transformation of the silyl ether into an aldehyde and treatment with the dianion of *iso*-butric acid. This gave a β-hydroxy acid and resulted in cleavage of the formate ester. Decarboxylative dehydration then gave **32**, which was converted to the pseudopterosin A aglycone using standard procedures as shown in Scheme 2.




**Reagents & Conditions: a.** *m*-CPBA; **b.** $SnCl_4$, DCM; **c.** BnBr, DMSO, $K_2CO_3$; **d.** (*t*-Bu)$Ph_2SiCl$, imidazole, DMF; **e.** DIBAL, DCM; **f.** PCC, DCM; **g.** *m*-CPBA; **h.** TBAF, AcOH, THF; **i.** Swern; **j.** $Me_2CLiCO_2Li$, THF; **k.** $Me_2NCH(OR)_2$; **l.** 1α-bromo-2,3,4-triacetyl-*D*-xylose (8 eq.), AgOTf (8 eq.), tetramethylurea, $CH_2Cl_2$, 20°C, 51%; **m.** KOH, MeOH; **n.** Li/$NH_3$, THF, 73%.

## Scheme 2

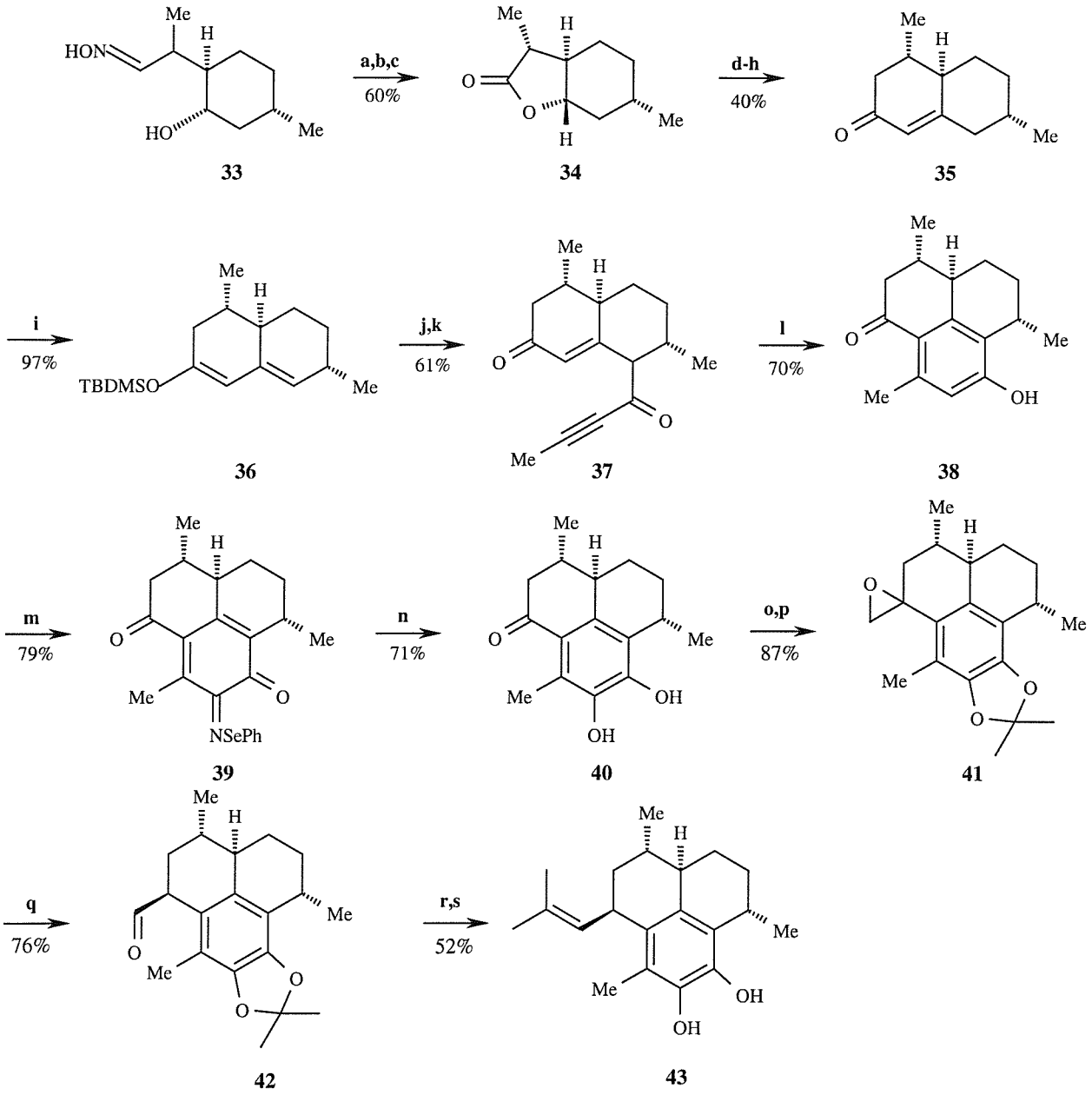
## (II) The Corey Synthesis.

The synthetic strategy adopted by Corey[17] utilised (1*S*,2*R*,5*S*)-(+)-menthol as the readily available starting material which was converted to the oxime **33**. This in turn was converted to α-lactone **34** by a sequence of three steps followed by a further five steps to give the octalone **35** which displayed the correct stereochemistry at the C-3, C-4 and the C-7 positions.

The reaction of the enone **35** with potassium hydride in THF-HMPA with *tert*-butyldimethylsilyl chloride gave the enol ether **36**, which was sequentially transformed to the diketone **37** in two steps. Construction of the tricyclic nucleus was achieved by the reaction of **37** with potassium hydride in THF and resulted in formation of the desired phenol **38**. This was then *ortho*-hydroxylated by oxidation with benzene selenic anhydride and hexamethyldisilazane, forming the N-(phenylselenyl)-o-quinone imine **39** which was hydrolysed and reduced to give the catechol **40**.

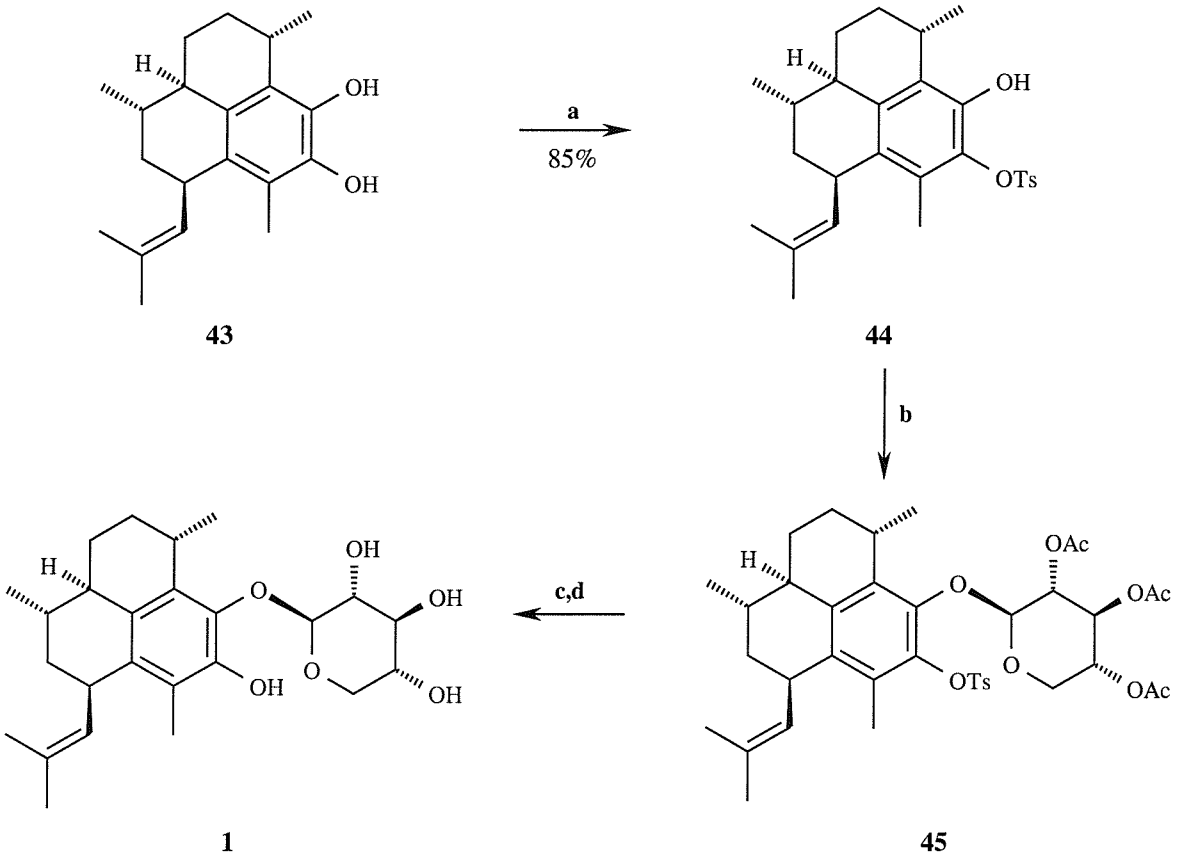
In order to complete the synthesis of the aglycone an *iso*-butyl substituent needed to be introduced at C-1. This was achieved by the initial protection of the catechol moiety as an *iso*-propylidene group. The ketone was then transformed into epoxide **41**, which rearranged to aldehyde **42** on exposure to boron trifluoride etherate. A Wittig reaction and deprotection of the *iso*-propylidene group gave pseudopterosin A aglycone **43** (Scheme 3).

To allow the pseudopterosin aglycone **43** to be carried through to pseudopterosin A and E, a means of distinguishing the two phenolic hydroxy groups was required. This was accomplished by mono-tosylation to afford selectively the C-10 tosylate **44**. Pseudopterosin A **1** was then prepared by reaction with 2,3,4-triacetyl-α-D-xylopyranosyl bromide giving **45** and subsequent deprotection of the hydroxyl groups as shown in Scheme 4.




**Reagents & Conditions: a.** $NaHSO_3$, 50°C, 4 hr, $H_2O$; **b.** $Br_2$, $H_2O$, $CaCO_3$, 23°C, 1½ hr; **c.** LDA, THF, 0°C, 2 hr, aq. $NH_4Cl$; **d.** DIBAL, $CH_2Cl_2$, -78°C, 2 hr; **e.** $Ph_3P{=}C(CH_3)SEt$, DMSO, 23°C, 24 hr; **f.** Swern; **g.** $HgCl_2$, MeCN-$H_2O$, 50°C, 1 hr; **h.** NaOMe, MeOH, 23°C, 12 hr; **i.** KH, TBDMSCl, THF-HMPA, 12 hr; **j.** 2-butynal, TMS-Otf, $CH_2Cl_2$, -78°C; **k.** PCC, $CH_2Cl_2$, 23°C, 3 hr; **l.** KH, THF, 23°C, 24 hr; **m.** $C_6H_6$-$[C_6H_5Se(O)]_2O$, HMDS; aq. AcOH, cat. $HClO_4$, 23°C, 2 hr; **n.** aq. $NaHSO_3$; **o.** $(CH_3)_2C(OCH_3)_2$, PPTS, $CHCl_3$, 70°C, 12 hr; **p.** $(CH_3)_3S^+Cl^-$; KH; **q.** $BF_3.Et_2O$; **r.** $(CH_3)_2C{=}PPh_3$; **s.** 10% HCl.

## Scheme 3

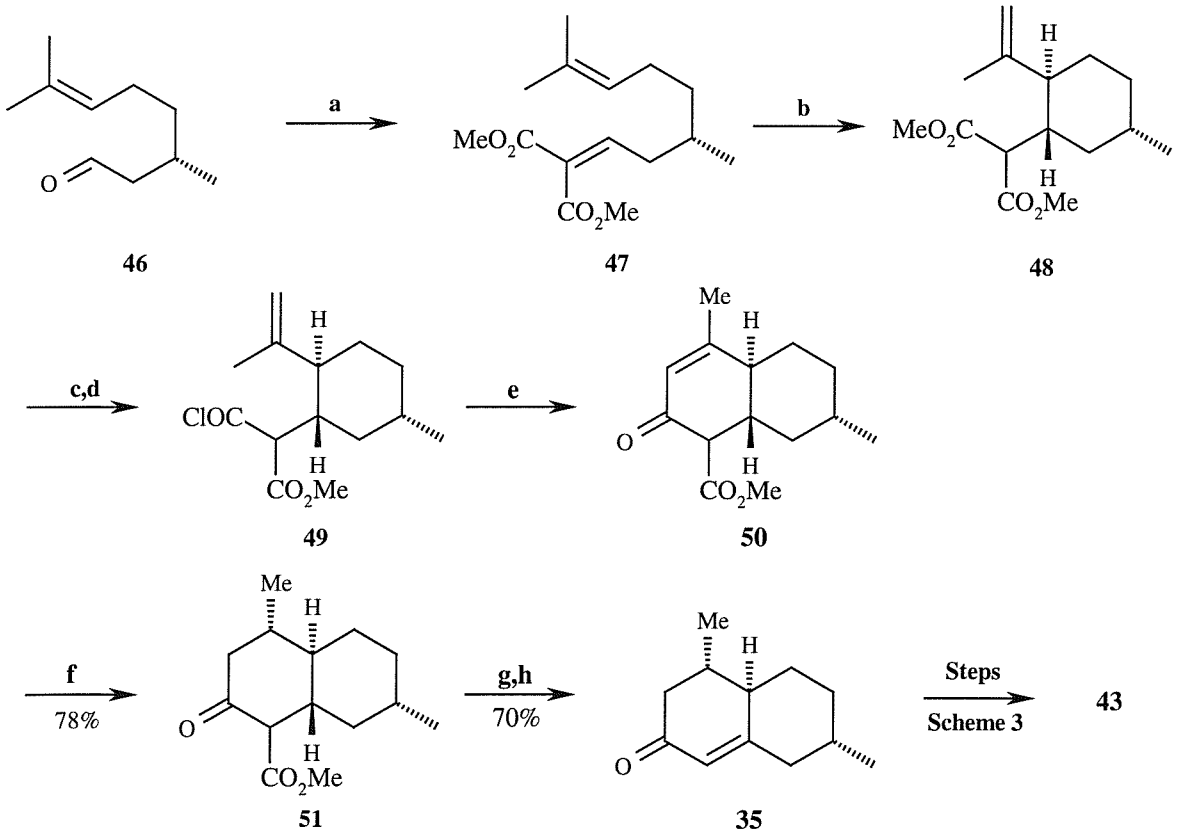



**Reagents & Conditions: a.** TsCl, $Et_3N$, DCM, −30°C to 23°C, 2 hr; **b.** NaH, $CH_3CN$, 23°C, 2,3,4-triacetyl-α-D-xylopyranosyl bromide; **c.** KOH, MeOH-$H_2O$, 23°C, 1 hr; **d.** 6% NaHg, MeOH, 54% overall from **44**.

## Scheme 4

## (III) Corey's Second Synthesis.

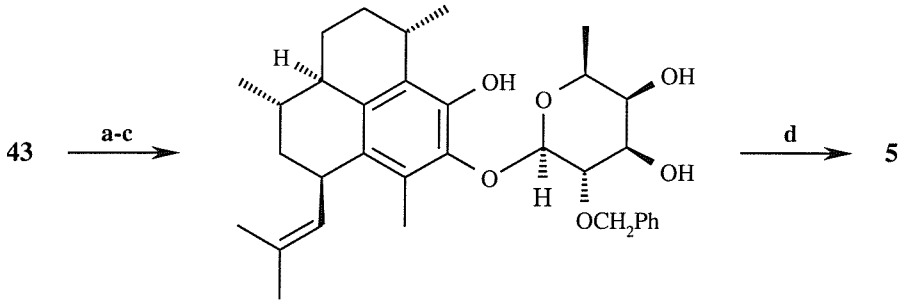
Later, Corey improved upon the early stages of the synthesis, producing the key intermediate **35** in eight steps from (*S*)-citronellal **46**.[18] The reaction of (*S*)-citronellal **46** with dimethyl malonate gave the unsaturated malonic ester **47**, which in turn was treated with ferric chloride giving the diester **48** with good diastereoselectivity. The corresponding acid chloride **49** was then formed by initial conversion to the monoacid and then reaction with oxalyl chloride and DMF. Treatment of the acid chloride **49** with ethylaluminium dichloride afforded the β-keto ester **50** which was then transformed by a dissolving metal reduction into the saturated keto ester **51**. Subsequent bromination, dehydrobromination and decarboxylation gave the enone **35** (Scheme 5). This was then transformed to the catechol **43** by the synthetic sequence outlined previously (Scheme 3).




**Reagents & Conditions: a.** $CH_2(CO_2Me)_2$, $H^+$, 23°C, 12 hr; **b.** $FeCl_3$, $CH_2Cl_2$, −78°C, 3 hr, 89% overall from **46**; **c.** LiOH, MeOH; **d.** $(COCl)_2$, DMF; **e.** 3 eq. $EtAlCl_3$, $CH_2Cl_2$, -30°C to 23°C, 24 hr, 72% overall from **48**; **f.** Li, $NH_3$-THF, −78°C; **g.** NaH, THF, $Br_2$, 3 hr; **h.** LiCl, Δ, 6 hr.

**Scheme 5**

Corey additionally described a method of synthesising pseudopterosin E from the aglycone. Details of this are presented in Scheme 6.

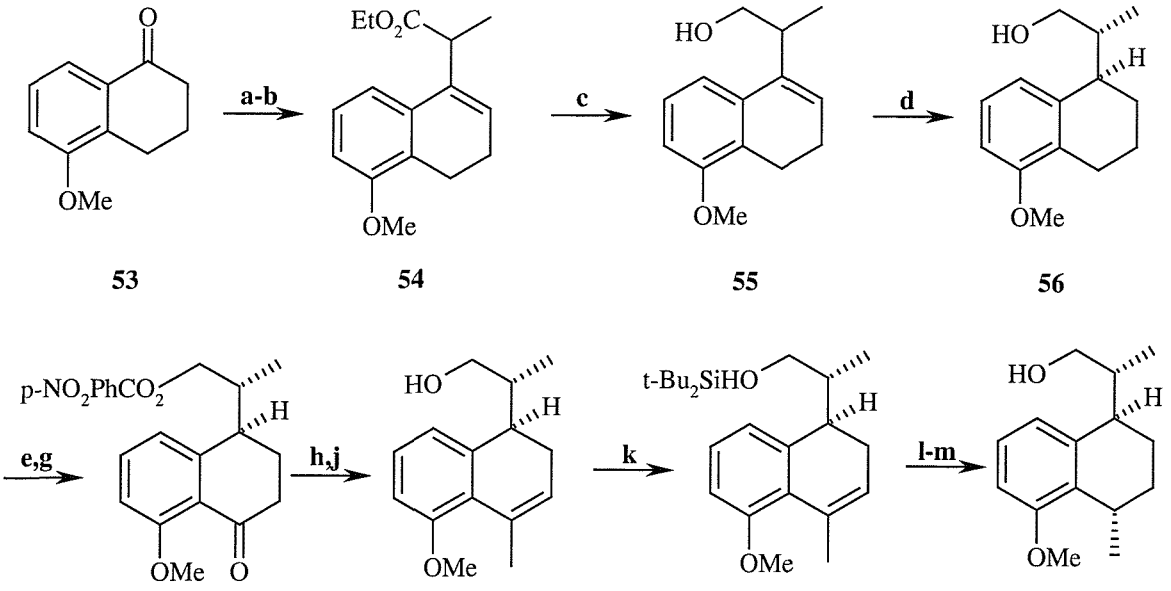



**Reagents & Conditions:** **a.** 2 eq. *n*-BuLi, THF; **b.** 2-*O*-Benzyl-3,4-di-*O*-*p*-methoxybenzoyl fucopyranosyl bromide, 23°C; **c.** LiOH, THF-$CH_3OH$; **d.** Li, liquid $NH_3$, THF, −40°C, 53% overall from **43**.

**Scheme 6**

## (IV) The McCombie Synthesis

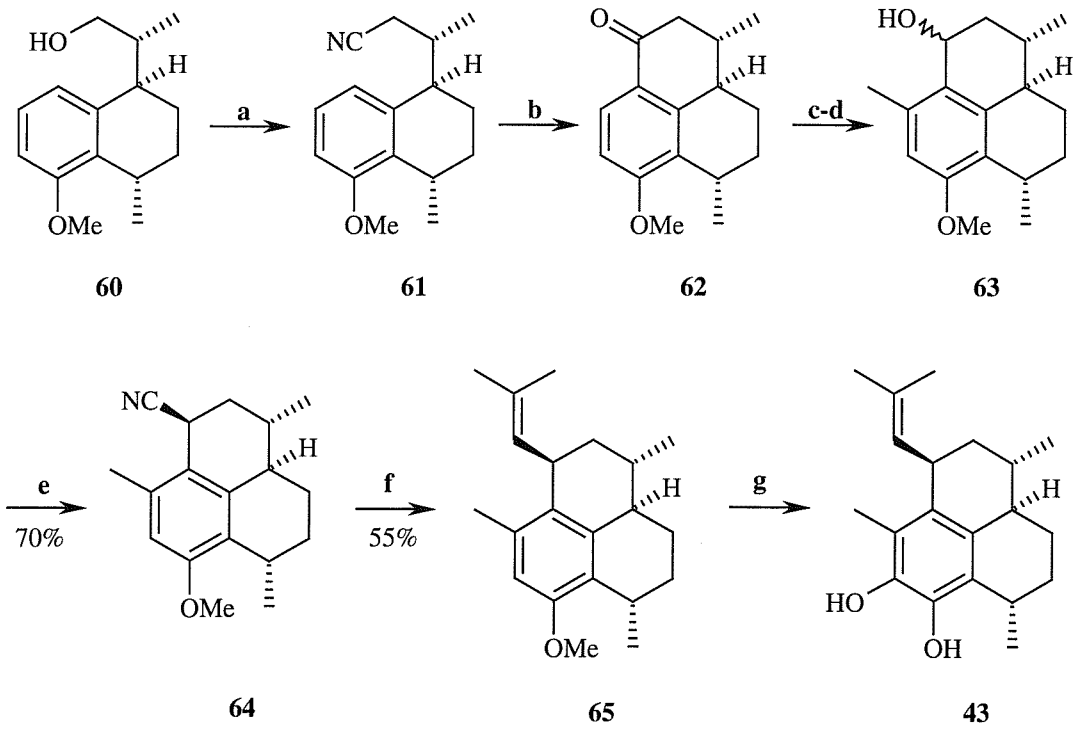
A stereospecific synthesis of the pseudopterosin A-E aglycones reported by McCombie and his co-workers,[19-21] utilised 5-methoxytetralone **53** as a readily availiable starting material. This was converted *via* a Reformatsky reaction to a β-hydroxy ester which upon subsequent dehydration (to **54**) and reduction afforded the olefin **55**. Homogeneous reduction of **55** over Wilkinson catalyst furnished the required diastereoisomer **56** with good selectivity. Protection of the alcohol and sebsequent regioselective benzylic oxidation gave the ketone **57**. Treatment with $MeCeCl_2$ installed the C-1 methyl group and dehydration of the tertiary alcohol then gave **58**. Stereoselective hydrogenation of the olefin **58** to **60** was achieved by intramolecular hydride transfer from the corresponding silane **59** (Scheme 7).




**Reagents & Conditions:** **a.** Zn, $MeCHBrCO_2Et$; **b.** TsOH, $C_2H_4Cl_2$; **c.** Red-Al; **d.** $H_2$, $ClRh(PPh_3)_3$, *t*-BuOK, THF, 3 atm., 48 hr; **e.** *p*-$NO_2PhCOCl$-py; **f.** $K_2S_2O_8$, $CuSO_4$, collidine, aq. MeCN; **g.** PCC, celite, $CH_2Cl_2$; **h.** aq. KOH; **i.** $MeCeCl_2$; **j.** TsOH, RT; **k.** *t*-$Bu_2SiHCl$, imidazole; **l.** TFA, $CH_2Cl_2$; **m.** $Bu_4NF$, 18-24% overall from **53**.

**Scheme 7**

To install the third ring, alcohol **60** was converted into nitrile **61** via a tosylate. A Friedel-Crafts acylation then afforded tricyclic ketone **62**. Reduction of the ketone **62** allowed directed metallation of the resultant alcohol giving the methylated product **63**. Treatment with $Et_2AlCN$ and $SnCl_4$ next afforded the nitrile **64** with good selectivity for the pseudoaxial isomer. Subsequent reduction, hydrolysis and Julia olefination to **65** succeeded in introducing side chain. The second phenolic OH group was then installed by oxidation with Fremy's salt providing the pseudopterosin A-E aglycone **43** (Scheme 8).




**60** **61** **62** **63**

**64** **65** **43**

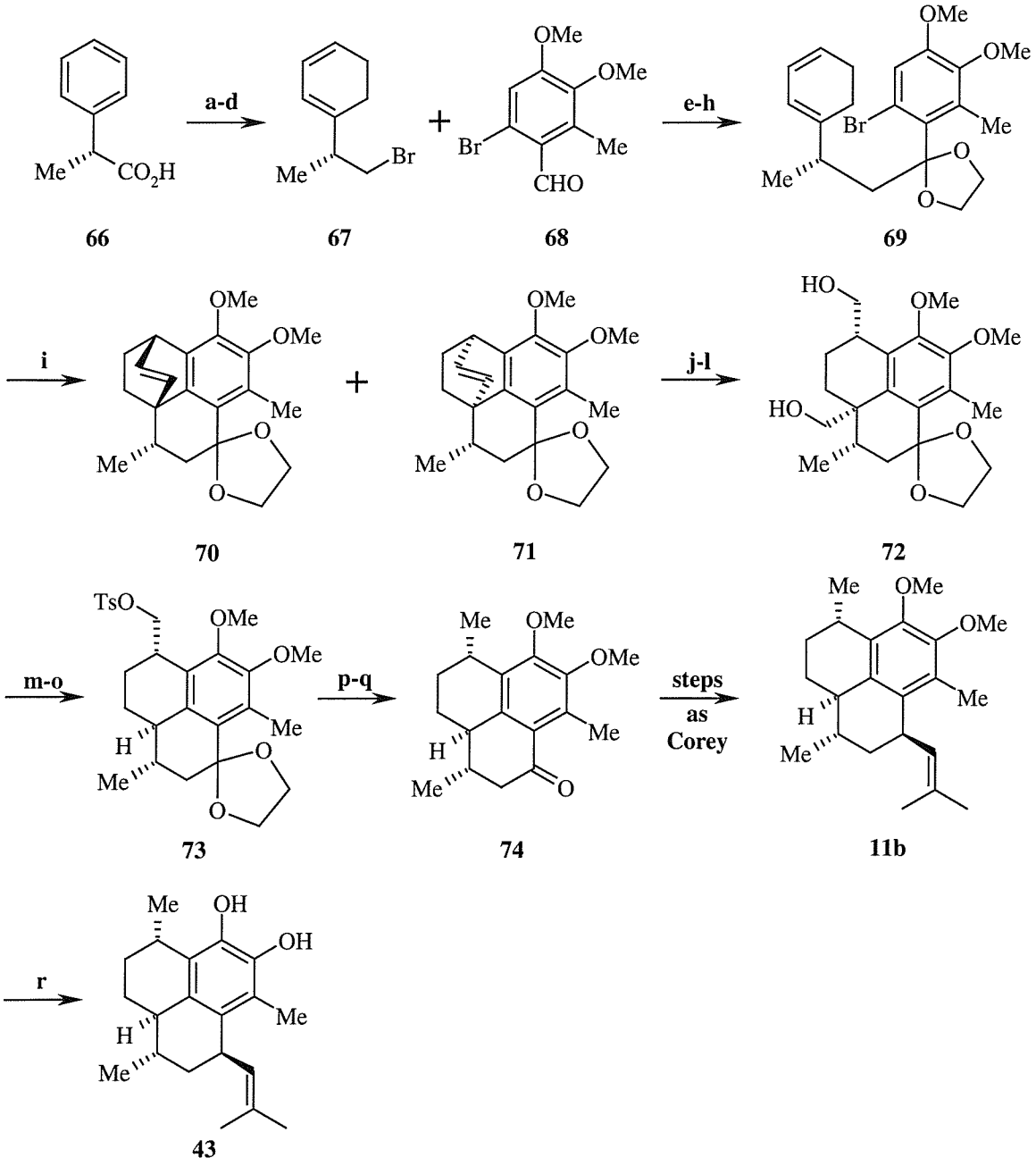
**Reagents & Conditions:** **a.** TsCl, py; MsOH, NaCN, DMSO, 65°C; **b.** MsOH, $(CH_2Cl)_2$, 85°C, 2 hr; NaOAc-$H_2O$, 85°C, 2 hr, 60-70% overall from **60**; **c.** $NaBH_4$; **d.** *t*-BuLi, MeI; **e.** $Et_2AlCN$, $SnCl_4$, 70%; **f.** DIBAL-H; $PhSO_2C(Li)Me_2$; Na-Mg, $K_2HPO_4$, 55%; **g.** $BBr_3$, 2,6-dibutylpyridine; $ON(SO_3K)_2$, $KH_2PO_4$; $Na_2S_2O_4$.

**Scheme 8**

## (V) The Buszek Synthesis

A total synthesis of pseudopterosin A-E aglycone has also been described by Buszek and Bixby in which an intramolecular benzyne Diels-Alder reaction was utilised.[22] Their approach used the readily available starting material (*R*)-(-)-2-phenylpropionic acid **66** which was reduced to the corresponding alcohol with $LiAlH_4$. A subsequent Birch reduction followed by base induced isomerisation and bromination gave the cyclohexadiene **67**. Coupling of the resultant Grignard reagent with the aldehyde **68** gave a mixture of benzylic alcohols. Oxidation to the ketone and protection as its 1,3-dioxolane ketal then gave **69**.

Slow addition of LDA to **69** generated the corresponding benzyne which rapidly underwent the desired intramolecular Diels-Alder reaction giving a 58:42 mixture of diastereoisomers **70** and **71**. Oxidative cleavage of the ethylene bridge in **71** gave the diol **72** after reduction with sodium borohydride. Selective tosylation of the least encumbered alcohol followed by oxidation of the remaining alcohol with Dess-Martin periodinane facilitated a stereospecific decarbonylation with Wilkinson's catalyst giving **73**. The C-19 methyl group was introduced by nucleophilic hydride displacement of the tosylate. Deketalisation afforded the hexahydrophenalene-1-one **74**. The isobutenyl side chain was introduced in accordance with the procedure published by Corey giving **11b**. Deprotection of the two methyl ethers then gave pseudopterosin aglycone **43** (Scheme 9).

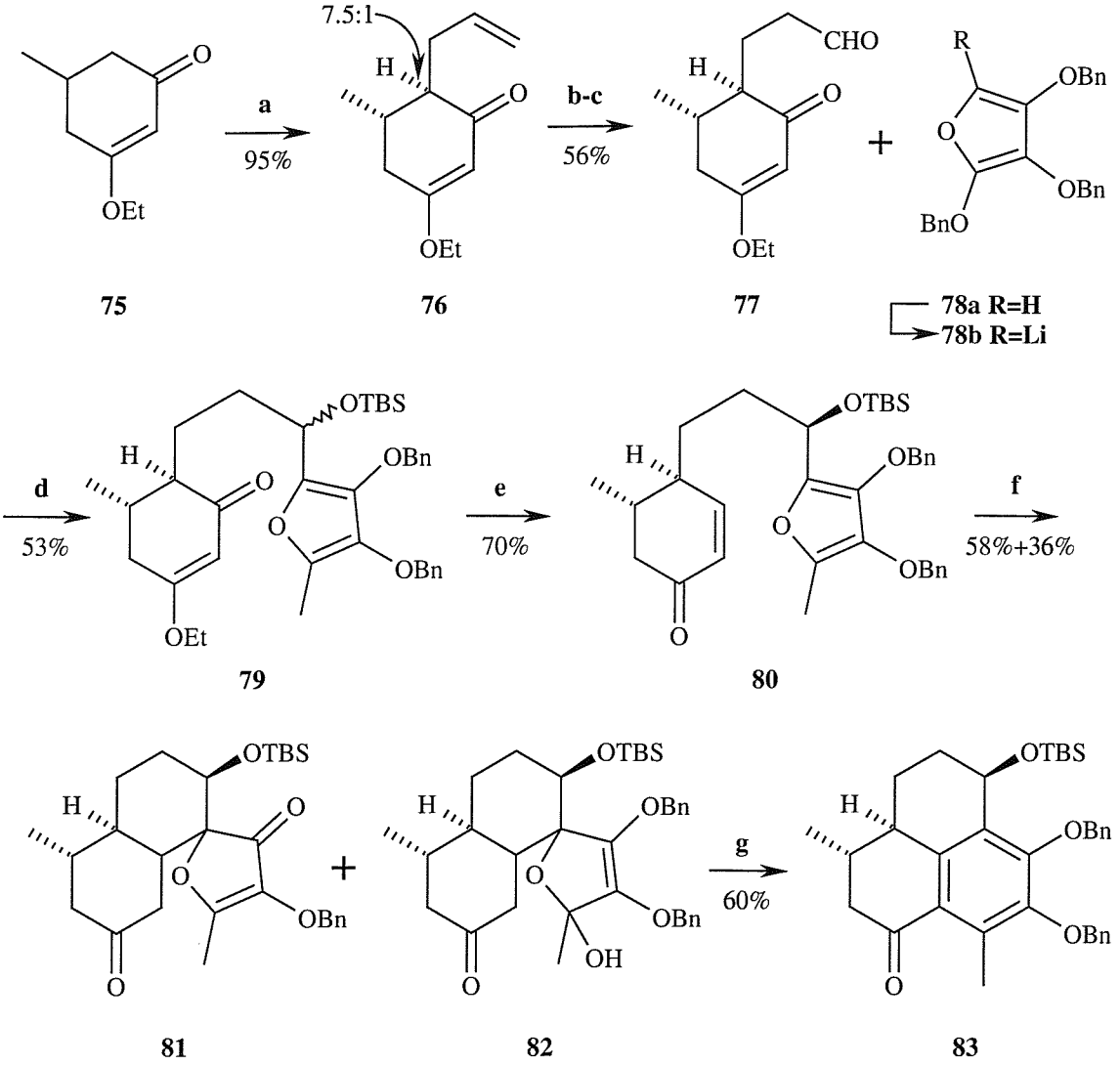



**Reagents & Conditions:** **a.** $LiAlH_4$, THF, 12 hr, 65°C; **b.** Na, $NH_3$, EtOH, 6 hr, -78°C; **c.** *t*-BuOK, DMSO, 2 hr, 65°C, 56% from **66**; **d.** $PPh_3$, NBS, cat. py, $CH_2Cl_2$, RT, 86%; **e.** Mg, THF; **f.** **68**, 0°C, 78%; **g.** $(COCl_2)$, DMSO, $Et_3N$, -78°C to RT; **h.** $TMSOCH_2CH_2OTMS$, cat. TMSOTf, 81% for two steps; **i.** LDA, THF, -78°C to RT, 12 hr, 63-71%; **j.** NMO, cat. $OsO_4$, PhMe/acetone-$H_2O$; **k.** $NaIO_4$; **l.** $NaBH_4$, 85% over three steps; **m.** TsCl, py, 83%; **n.** Dess-Martin periodinane; **o.** $(PPh_3)RhCl$, PhCN, 76%; **p.** $LiAlH_4$, THF, 68%; **q.** PPTS, acetone-$H_2O$, 100%; **r.** TMSI, $CHCl_3$.

**Scheme 9**

## (VI) The Jung Synthesis

Jung *et al.*[23] reported an approach to the pseudopterosins. The synthesis utilised an intramolecular Michael addition of an electron rich furan onto a cyclohexanone as a key step. The synthesis began with the allylation of 5-methyl-3-ethoxycyclohexenone **75** to afford the *trans*-diastereomer **76** as the major component. Conversion to the aldehyde **77** was achieved by sequential hydroboration and oxidation. Union of **77** with the lithium anion **78b** gave a 1:1 diastereotopic mixture of secondary alcohols which were silylated giving **79**. Reduction of the enone with DIBAL-H and elimination on silica gel gave **80**. Exposure of **80** to $SnCl_4$ gave the tetralins **81** and **82**. A second cyclisation was then affected by treatment of **82** with *t*-BuOK in *t*-BuOH giving a mixture of the desired phenalene **83** and the desilylated analogue (Scheme 10).

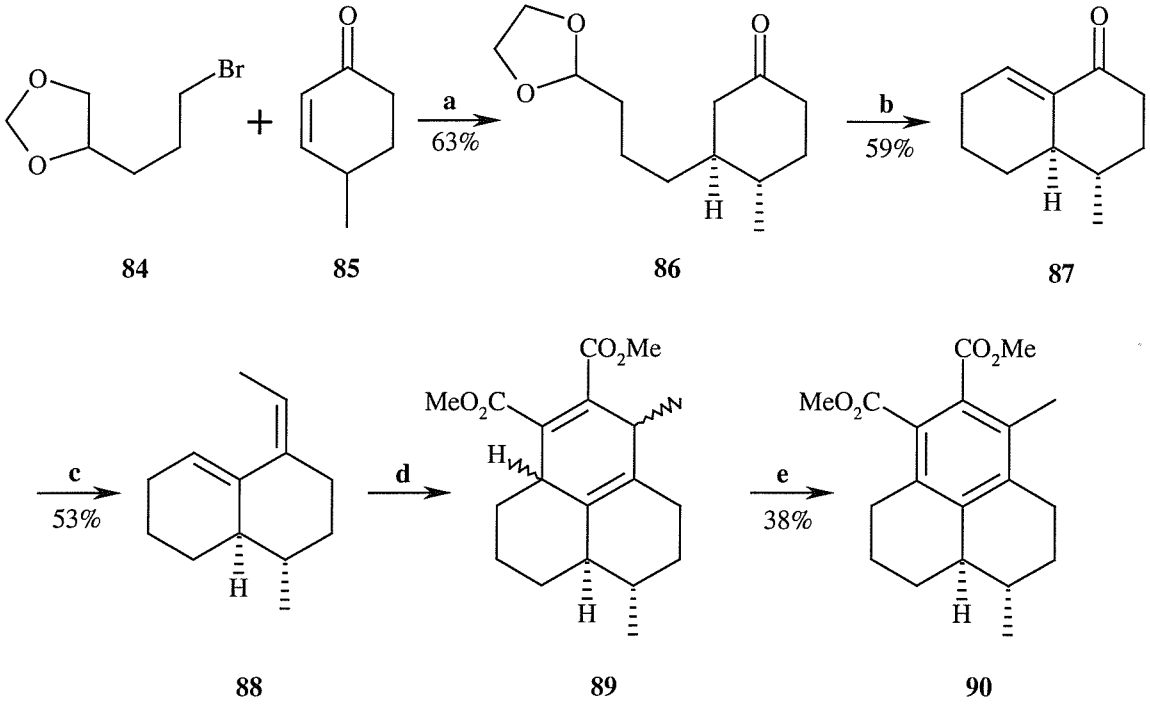



**Reagents & Conditions: a.** LDA, THF/HMPA; allyl bromide, -78°C; **b.** $Sia_2BH$; $H_2O_2$, NaOH; **c.** DMSO, $(COCl)_2$, $Et_3N$; **d.** *n*-BuLi, THF, 0°C; TBSCl, ImH, DMF, THF, -78°C; **e.** DIBAL-H, PhMe, -78°C; **f.** $SnCl_4$; **g.** *t*-BuOK, *t*-BuOH; TBSCl.

## Scheme 10

## (VII) The Frejd Approach

The synthetic strategy adopted by Frejd *et al.*, was based upon a Diels-Alder reaction.[24] The key intermediate in the synthesis was diene **88** which was accessed through a series of straight forward transformations starting from the α,β-unsaturated ketone **85**. A Diels-Alder reaction with DMAD in the presence of a Lewis acid afforded the tricycle **89**. Subsequent aromatisation with DDQ gave hexahydrophenalene **90** (Scheme 11). While this approach provides a rapid entry into the tricyclic skeleton of the pseudopterosins, the key issues of establishing the catchecol and introducing substituents at C-1 and C-7 with the correct stereochemistry have yet to be addressed.




**84** **85** **86** **87**

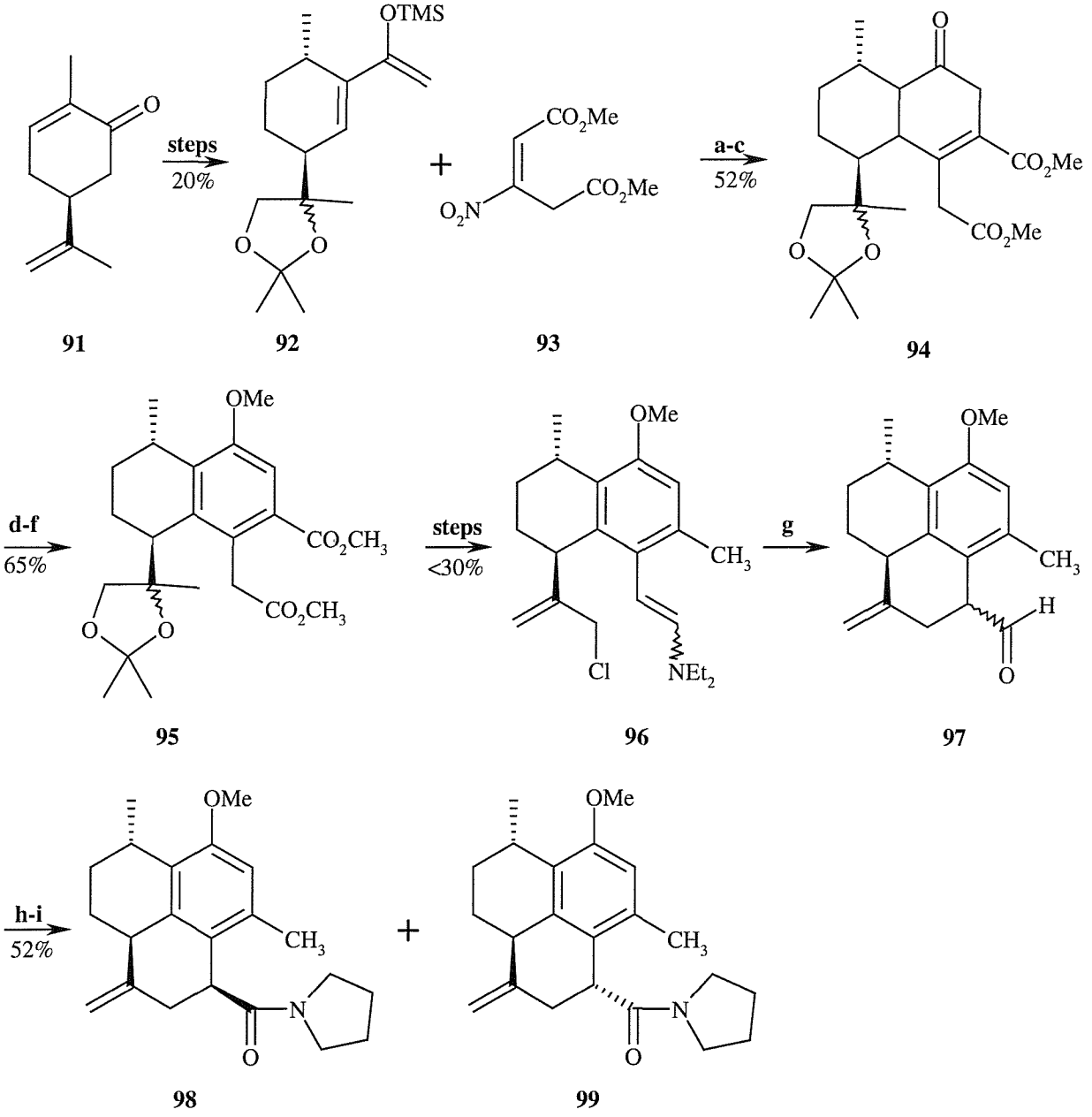
**88** **89** **90**

**Reagents & Conditions:** **a.** Mg, $CuBr.Me_2S$, -78°C, 12 hr; **b.** HCl, THF, 80°C, 6 hr; **c.** $Ph_3P$=CHMe; **d.** DMAD, $AlCl_3$, 0°C; **e.** DDQ, DMF, 140°C, 38% over two steps.

**Scheme 11**

## (VIII) The Kozikowski Approach

An approach to the pseudopterosin skeleton by Kozikowski and Wu[25] began with (*S*)-carvone **91**, which was elaborated to the diene **92** through a series of eight transformations. A Diels-Alder reaction of **92** with dienophile **93** gave the decalin **94** upon hydrolysis and elimination. Aromatisation of **94** to the tetralin **95** was achieved by DDQ oxidation of the silyl enol ether. Numerous transformations then yielded the chloride **96**, which upon cyclisation afforded the tricycle **97** as an inseparable mixture. Conversion to the corresponding amides and subsequent separation by chromatography then gave **98** and **99** (Scheme 12).

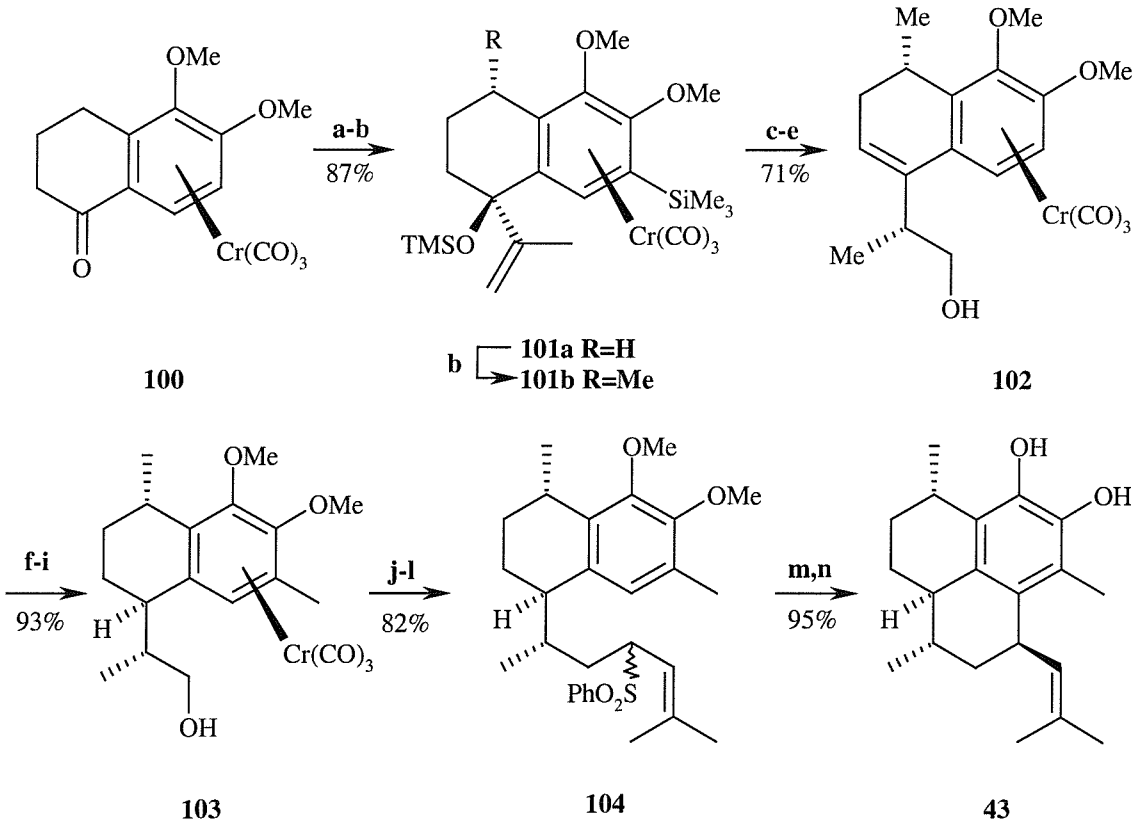



**Reagents & Conditions: a. 93**, 3,5-di-*t*-butylcatechol, 0°C to RT, 15 hr; **b.** 2M HCl, THF, 0°C, 5 min; **c.** DBU, THF, 0°C to RT, 1½ hr; **d.** TMSI, HMDS, $Et_3N$, DCE, -23°C, 2 hr; **e.** DDQ, PhH, RT, 12 hr; **f.** $Me_2SO_4$, $K_2CO_3$, $Bu_4NI$, acetone, dark, reflux, 15 hr; **g.** EtOH, NaI, dark, 85°C, 15 hr; EtOH-$H_2O$, 85°C, 12 hr; **h.** $NaClO_2$, 2-methyl-2-butene, 1M $KH_2PO_4$, *t*-BuOH, RT, 12 hr; **i.** pyrrolidine, $Et_3N$, 2-chloro-1-methylpyridinium iodide, $CH_2Cl_2$, 45°C, 2 hr.

## Scheme 12

## (IX) The Schmalz Approach

Schmalz and co-workers have reported numerous approaches to the pseudopterosins,[26-28] helioporin C-E,[10,29,30] the *seco*-pseudopterosins[31-33] and various analogues. Their synthesis of pseudopterosin A-E aglycone begins with the chiral 1-tetralone-$Cr(CO)_3$ derivative **100** which was converted into the bis-silylated complex **101a**. Metallation and methylation next produced **101b**. Hydroboration followed by desilylation and elimination afforded **102**. Methylation of the aromatic nucleus and reduction with $SmI_2$ gave **103** as a single diastersomer. Subsequent decomplexation and tosylation followed by treatment with lithiated phenylprenylsulfone afforded **104**. Lewis acid cyclisation of **104** and demethylation furnished the pseudopterosin aglycone **43** (Scheme 13).

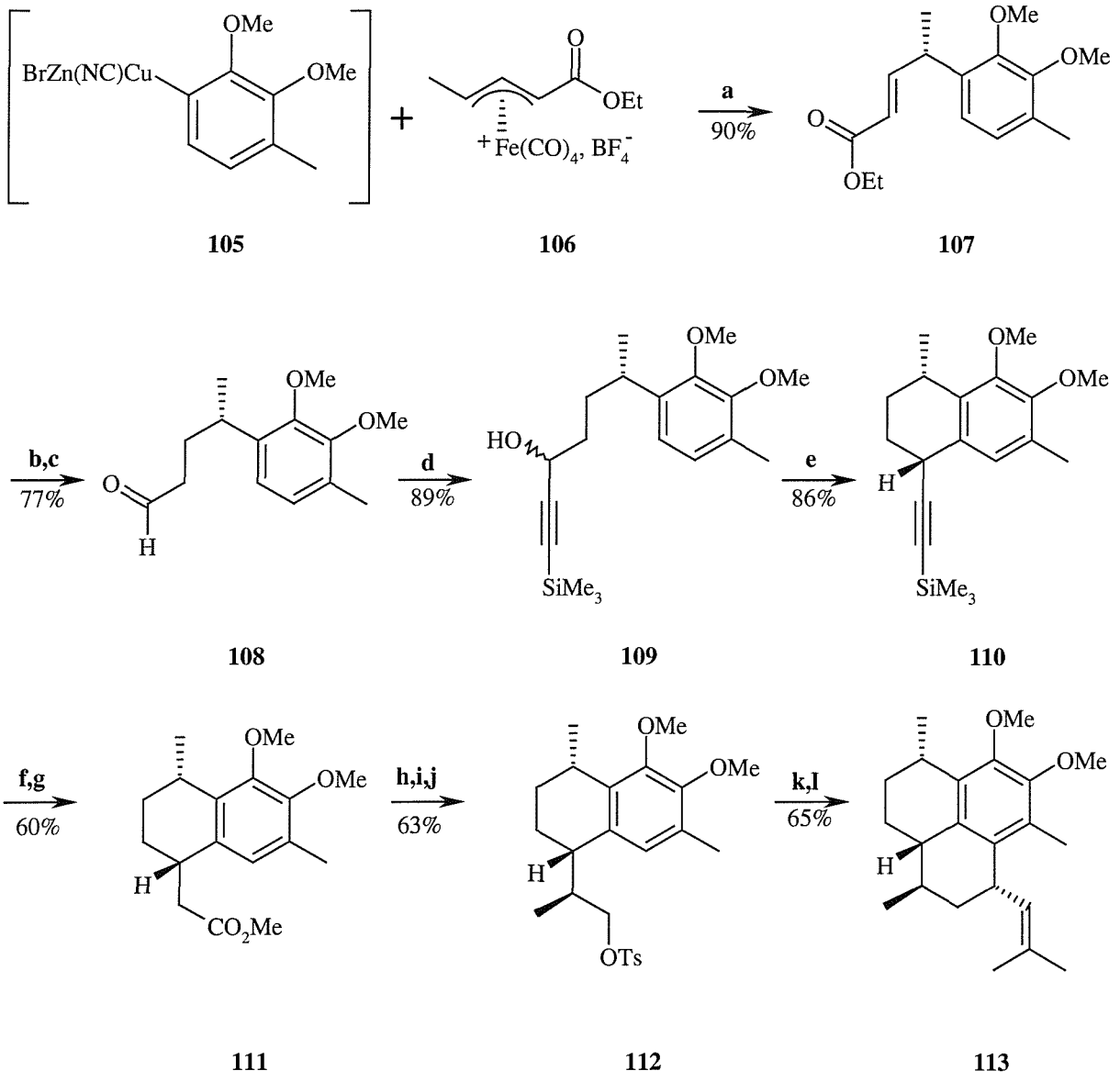



**Reagents & Conditions:** **a.** isopropenyllithium, $Me_3SiCl$; **b.** *n*-BuLi, THF/HMPT, MeI; **c.** $BH_3.SMe_2$, THF, 30°C, $NaOH/H_2O_2$; **d.** TBAF, THF, 0°C; **e.** *p*-TsOH.$SiO_2$, $C_6H_6$, 25°C; **f.** *t*-$BuMe_2SiCl$, imidazole, DMF, 23°C; **g.** *n*-BuLi, THF, -75°C, MeI; **h.** TBAF, THF, 23°C; **i.** $SmI_2$, $H_2O$, THF/HMPT; **j.** $Et_2O$, hν, air; **k.** TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 35°C; **l.** phenylprenylsulfone, *n*-BuLi, -78°C; **m.** $EtAlCl_2$, $CH_2Cl_2$; **n.** LiSEt, DMF.

## Scheme 13

## (X) The Kocienski Approach

Kocienski *et al.* were the first to publish a total synthesis of pseudopterosin K & L aglycone,[34] and in more recent times has reported a synthesis of pseudopterosin G aglycone dimethyl ether.[35] Their synthesis started with the regio- and enantiofacially-selective addition of the zinc-cuprate reagent **105** to the iron(II) complex **106** giving the adduct **107**. Conjugate reduction of the enoate ester followed by reduction of the ester afforded a saturated aldehyde **108**. Subsequent addition of (trimethylsilyl)ethynylmagnesium bromide gave the propargylic alcohols **109**. Cyclisation was achieved via a cobalt stabilised propargylic cation, which after decomplexation afforded the tetrahydronaphthalene **110**. Hydroboration-oxidation gave a carboxylic acid, which upon esterification gave **111**. α-Alkylation followed by reduction and tosylation then gave the toluene-*p*-sulfonate ester **112**. Lewis acid mediated electrophilic cyclisation of the intermediate allylic sulfone then gave the tricycle **113** (Scheme 14).

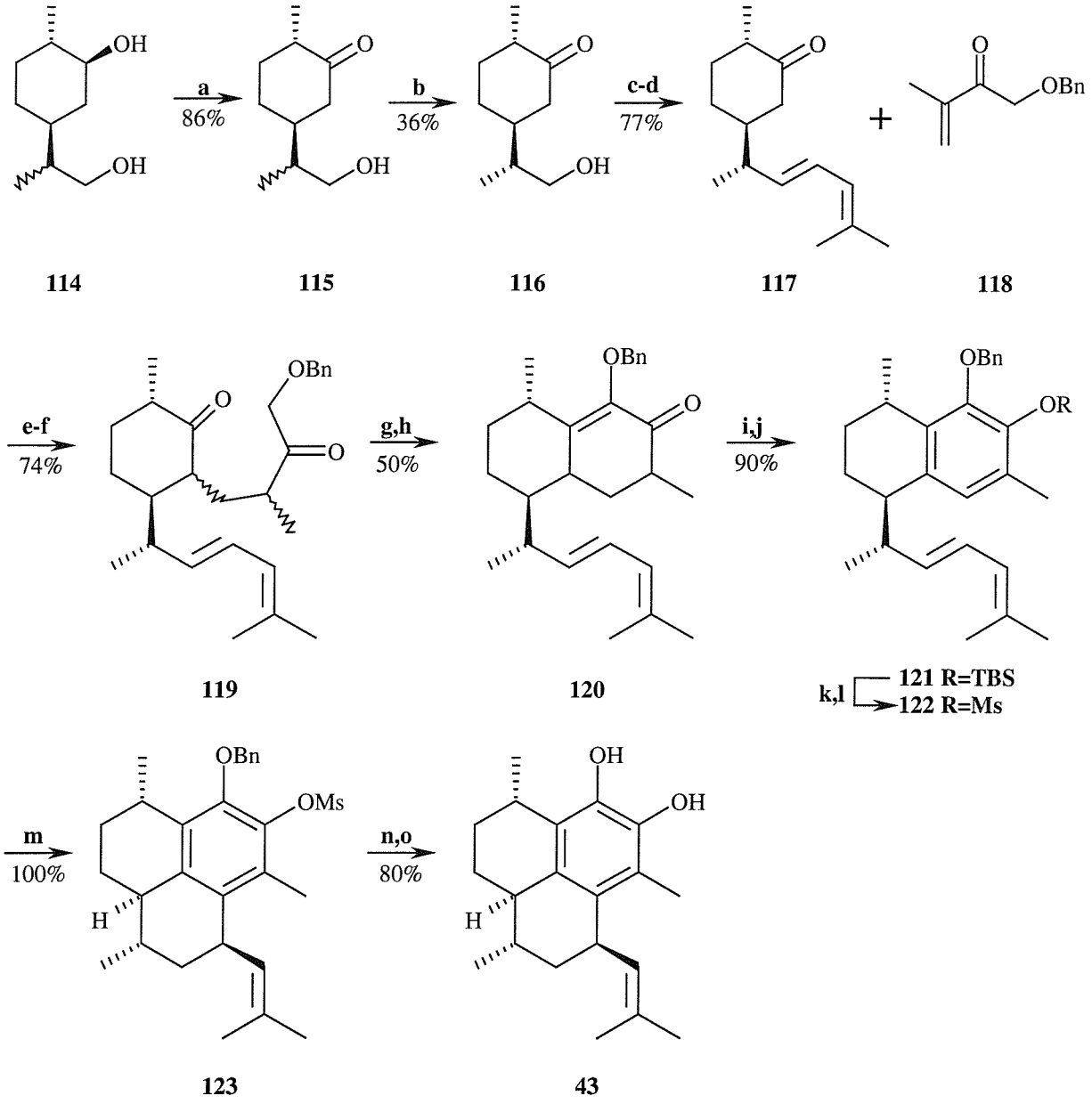



**Reagents & Conditions:** **a.** –70°C to 0°C; **b.** Mg, MeOH, 5°C; **c.** DIBAL-H, $CH_2Cl_2$; **d.** $Me_3SiC{\equiv}C$-MgBr, 0°C; **e i.** $Co_2(CO)_8$, $CH_2Cl_2$, 20°C; **ii.** $BF_3.Et_2O$, -20°C; **iii.** $Fe(NO_3)_3.9H_2O$, MeOH, 20°C; **f i.** $(C_6H_{11})_2BH$, THF, 5°C; **ii.** $H_2O_2$, NaOH, MeOH, 30-50°C; **g.** tetramethylguanidine, MeI, PhMe, 20°C; **h i.** LDA, THF, -40°C; **ii.** MeI; **i.** $LiAlH_4$, THF, 0°; **j.** TsCl, DMAP, $Et_3N$, $CH_2Cl_2$; **k.** $Me_2C{=}CH\text{-}CH(Li)SO_2Ph$, THF; **l.** $EtAlCl_2$, $CH_2Cl_2$, -30°C.

## Scheme 14

## (XI) The Third Corey Approach

Corey and co-workers have recently developed a third route to the pseudopterosins aglycone.[36] The starting material is the diol **114**, available in two steps from (*S*)-(–)-limonene. Selective oxidation at the C-2 position gave a diastereomeric mixture of ketones **115**. Exposure to isopropenyl acetate with Amano PS lipase afforded selective acetylation of the (8*S*)-hydroxy ketone and allowed isolation of the desired (8*R*)-alcohol **116**. Oxidation and selective olefination gave the *E*-diene **117**, which was coupled with the enone **118** to afford diketone **119**. Aldol cyclisation and dehydration next gave enone **120**, which was subsequently aromatized to the tetra-hydronaphthalene **121**. A diasteroeselective cationic cyclisation akin to that developed by Kocienski gave tricycle **123** from the mesylate **122**. Deprotection then afforded the pseudopterosin aglycone **43** (Scheme 15).

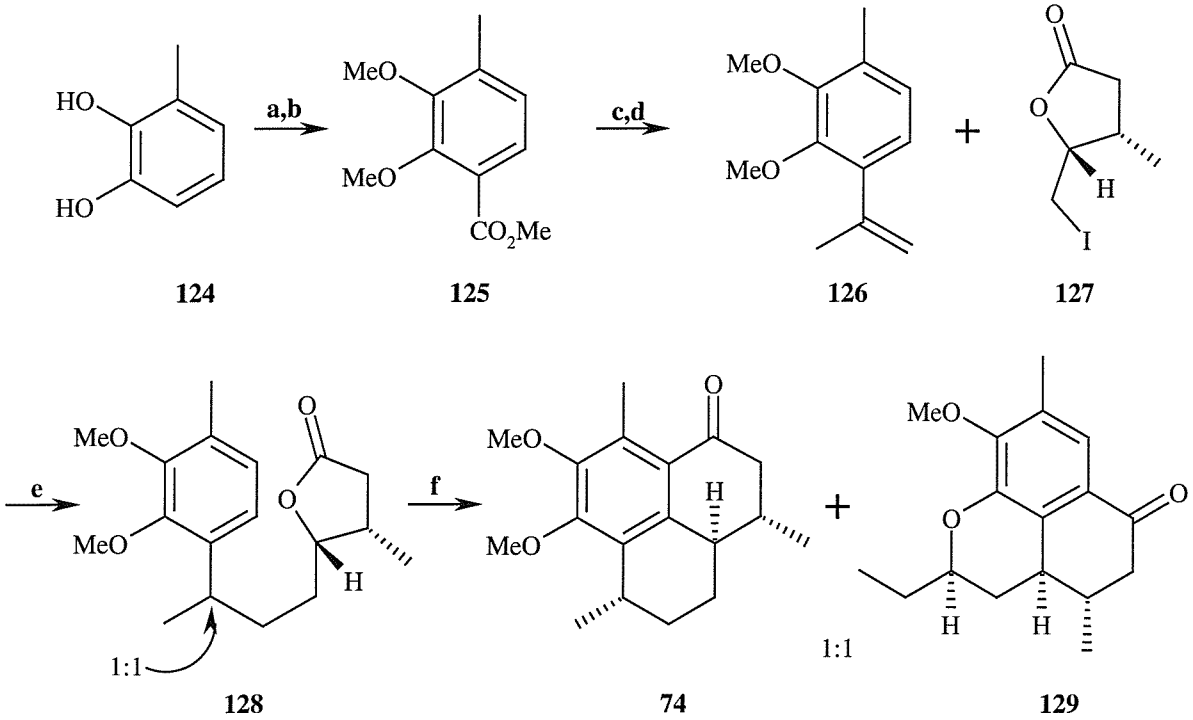



**Reagents & Conditions:** **a.** NaOCl, aq. AcOH; **b.** isopropenyl acetate, *i*-$Pr_2O$, lipase; **c.** NaOCl, TEMPO, $CH_2Cl_2$-$H_2O$; **d.** ylide, DME; **e.** LDA, TMSCl; **f.** $SnCl_4$, $CH_2Cl_2$, -78°C; **g.** KOH, 0°C; **h.** $SOCl_2$-pyr, 23°C; **i.** LDA, TBSOTf; **j.** $MnO_2$; **k.** $BuNF_4$, THF; **l.** $CH_3$-$SOCl_2$-$Et_3N$, $CH_2Cl_2$; **m.** $CH_3SO_3H$, $CH_2Cl_2$, -50°C; **n.** MeMgBr, THF, 0°C; **o.** $BBr_3$, $CH_2Cl_2$, 0°C.

## Scheme 15

## (XII) The Harrowven-Dennison Approach to The Pseudopterosins

A formal total synthesis of the Pseudopterosin aglycone was completed within the group and provided a relatively rapid entry into the pseudopterosins[37] (Scheme 16). The synthesis began with a Kolbe-Schmitt carboxylation of 3-methylcatechol **124**.[38] The resulting acid was then exhaustively methylated with MeI to give the ester **125**. Exposure of **125** to MeLi followed by the distillation of the resultant alcohol from potassium hydrogen sulfate afforded the styrene **126**. Union of **126** with the iodolactone **127** gave the cyclisation precursor **128** as an inseparable 1:1 mixture. Treatment of **128** with PPA gave the tricyclic ketone **74** and the benzochromenone **129** (Scheme 16). Unfortunately the synthesis failed to control the stereogenic center at C-7 and the radical coupling of the styrene and the iodolactone gave rise to large quantities of polymeric material.




**Reagents & Conditions: a.** $CO_2$, $K_2CO_3$, 120°C, 1600psi, 6 hr, 90%; **b.** KOH, MeI, DMSO, RT, 4 hr, 95%; **c.** 2.5 eq MeLi, THF, -78°C, 2 hr; MeOH, 98%; **d.** $KHSO_4$, distil, 97%; **d.** $Bu_3SnH$, AIBN, PhMe, reflux, 16 hr, 23%; **d.** PPA, neat, 90°C, 30 min, 51%.

**Scheme 16**

*Chapter Two*

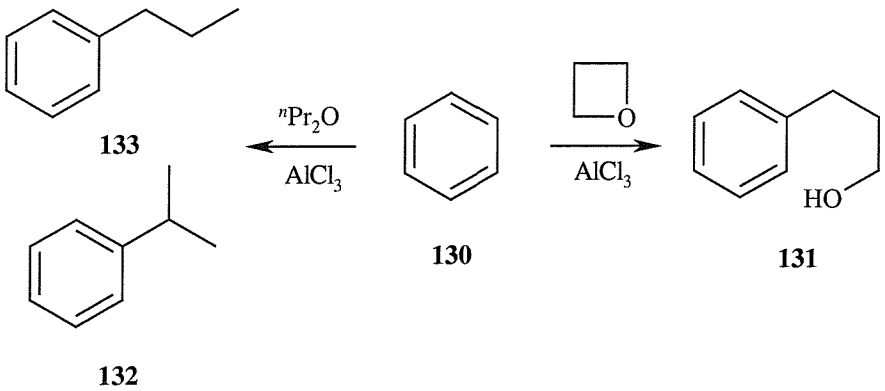
# Cyclic Ethers as Electrophiles in the Friedel-Crafts Reaction

## 2.1 The Friedel-Crafts Reaction

Electrophilic substitution onto aromatic rings were first studied in 1877 by the French alkaloid chemist Charles Friedel and his American partner, James Crafts.[39,40] The Lewis acid mediated alkylation and acylation of aromatic rings is a reaction of very broard scope and numerous reviews on the topic have been published.[41,42] To date there has been limited research into the use of higher cyclic ethers in the Friedel-Crafts reaction and a review of the subject is presented in the following text.

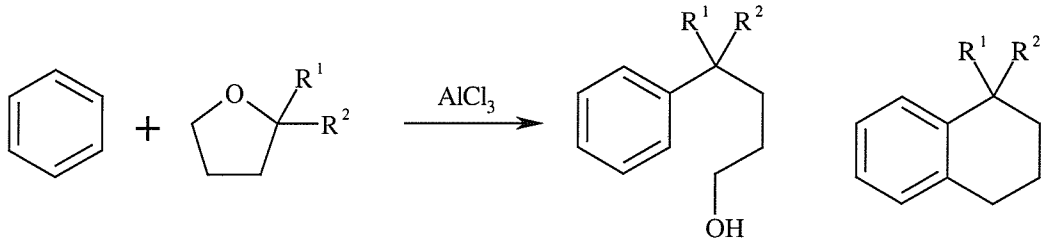
## 2.2 Higher Cyclic Ethers as Electrophiles in the Friedel-Crafts Reaction

Friedel-Crafts alkylation reactions with cyclic ethers are known to give complex mixtures of products due to rearrangement of the intermediate carbocations.[43,44] However this has not always proved to be the case, as shown by Searles.[45] Here an oxirane reacts smoothly with benzene **130** in the presence of aluminium chloride affording the corresponding alcohol **131** whereas the analogous reaction with *n*-propyl ether gives a mixture of *i*-propylbenzene **132** and *n*-propylbenzene **133** due to rearrangement of the intermediate carbocation. The lack of rearrangement in the oxirane reaction suggests that it proceeds via a concerted mechanism (Scheme 17).




**Scheme 17**

In 1959, Kadyrov and Tsukorvanik published a series of papers investigating the reaction of tetrahydrofurans with benzene.[46-48] Their exploration discovered that unsubstituted tetrahydrofurans were unsuitable electrophiles in the Friedel-Crafts reaction. However the reactions proceed smoothly with the introduction of alkyl substituents on the C-2 position. Thus an aluminium chloride mediated reaction of 2-methyltetrahydrofuran with benzene at ambient temperatures gave the alcohol **134** and elevation of the temperature to reflux afforded the tetralin **135**. Increased substitution at the C-2 position lead to an increased yield of the cyclialkylated product **135** (Scheme 18).



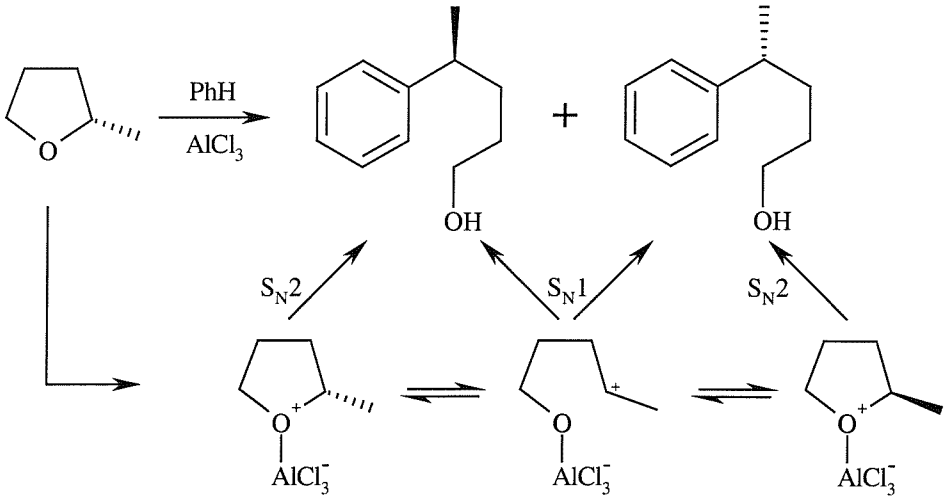

**130** **134** **135**

| $R^1$ | $R^2$ | Temp | 134 | 135 |
|---|---|---|---|---|
| H | H | 80°C | 18% | 7% |
| H | Me | 20°C | 64% | 10% |
| H | Me | 80°C | 10% | 66% |
| Me | Me | 20°C | 5% | 50% |

**Scheme 18**

The stereochemical outcome of Friedel-Crafts reactions has been difficult to predict due to the free carbonium ion mechanism in aromatic alkylation reactions. However Brauman and co-workers[49] reported that the alkylation of benzene with (+)-2-methyltetrahydrofuran in the presence of aluminium chloride proceeded with greater than 35% inversion of configuration in a total yield of 50%. The stereochemical selectivity is thought to result from the cyclic nature of the alkylating reagent or the enforced proximity of the ion pairs produced by the ring opening (Scheme 19). The Friedel-Crafts

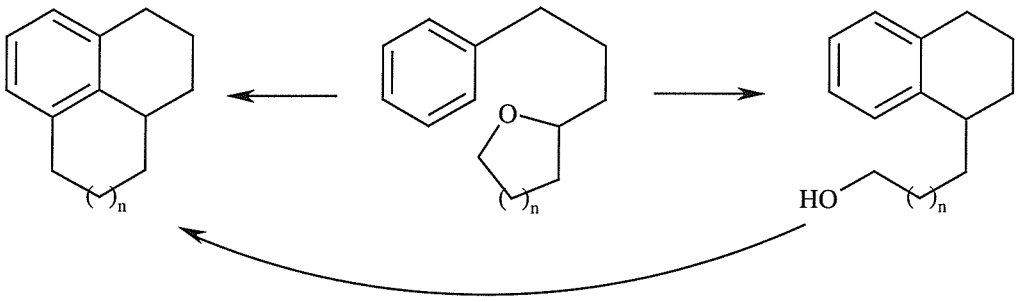
alkylation of benzene with (+)-2-methyloxetane was also reported by Suga[50] and the reaction proceeded with up to 60% inversion. The stereochemistry of Friedel-Crafts reactions with cyclic electrophiles is in marked contrast to the complete racemisation observed with acyclic ethers.[51]




**Scheme 19**

## 2.3 Intramolecular Friedel-Crafts Reactions of Cyclic Ethers

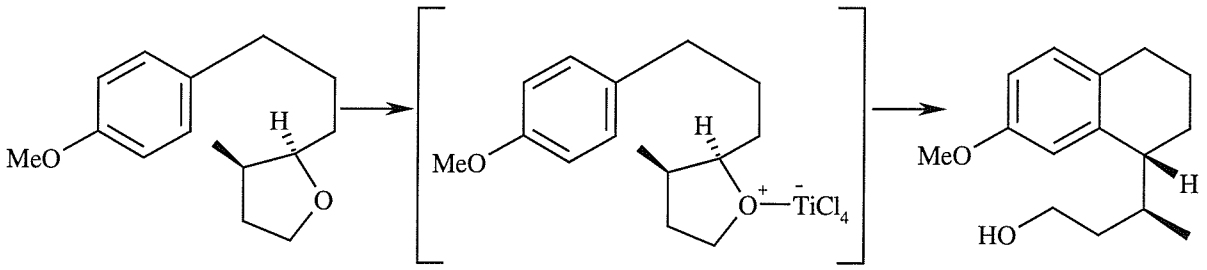
A study into intramolecular cyclisations involving arenes tethered to cyclic ethers as a means of accessing tetrahydronapthalenes and hexahydrophenalenes had been undertaken within the Harrowven group.[52] The arene tethered cyclic ethers **136** were readily accessible via a radical coupling protocol employing the appropriate iodide and styrene fragments. Initial attempts to induce cyclisation of 2-(3-phenylpropyl)-tetrahydrofuran **136** with strong Lewis acids such as aluminium chloride met with failure. However milder Lewis such as titanium(IV) chloride afforded 1,2,3,4-tetrahydronapthalene **138** in reasonable yield. The reaction was also extended to tethered tetrahydropyrans which were also suitable electrophilic counterparts (Scheme 20).




**137** n=1, n=2 **136** n=1, n=2 **138** n=1, n=2

**Scheme 20**

In order to establish the stereochemical course of the ring closure the precursor **139** was synthesised with a variety of diasteromeric ratios. Titanium(IV) chloride mediated ring closure then furnished the alcohols **140** in a ratio identical to that of the starting material. This suggests that the alkylation of the Lewis acid–ether complex occurs via an $S_N2$ mechanism with inversion of stereochemistry (Scheme 21).




**139** **140**

**Scheme 21**

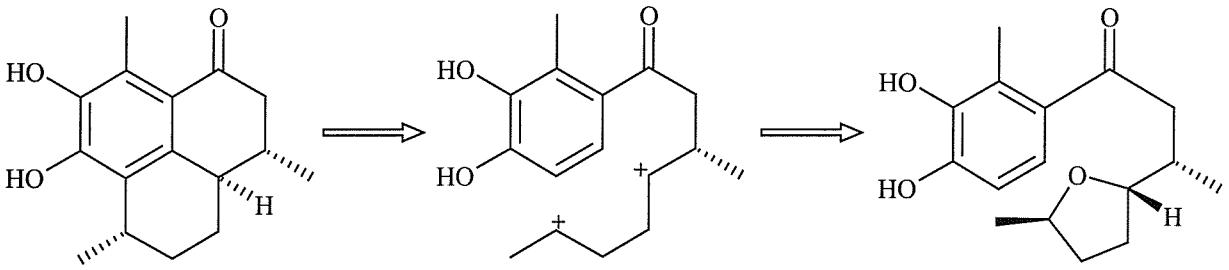
Interestingly the tandem Friedel-Crafts alkylation to the hexahydrophenalene **137** was found to occur upon treatment with zirconium(IV) chloride. However the reaction was found to promote rearrangement of aromatic substituents in some cases. The hexahydrophenalene **137** was also accessed through a stepwise ring closure, first to the tetrahydronapthalene **138** and then to the desired tricycle **137** with PPA.

*Chapter Three*

# The New Synthetic Approach to the Pseudopterosins

## 3.1 Retrosynthetic analysis

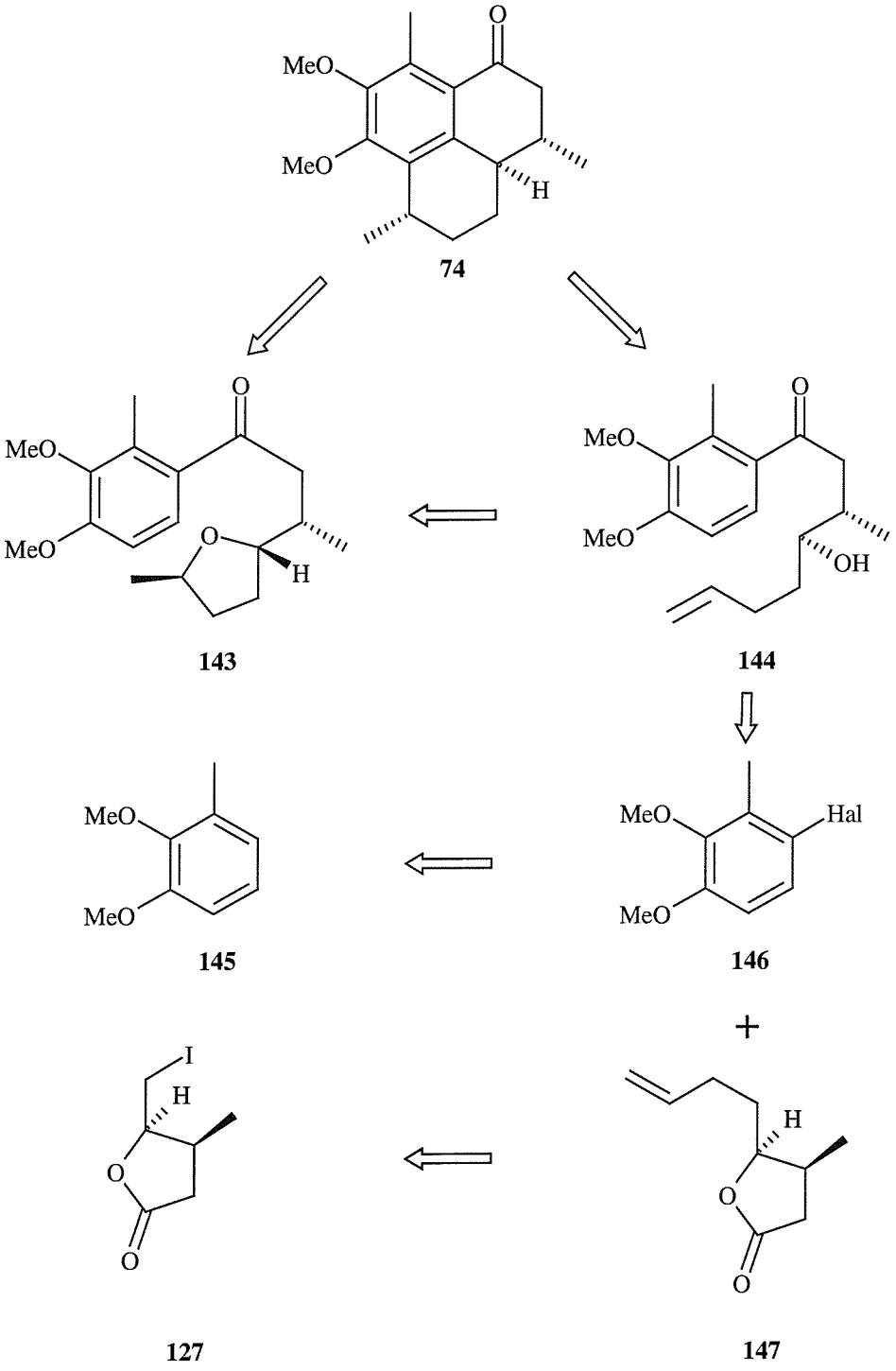
A review of the literature relating to the pseudopterosins revealed several synthetic strategies for the synthesis of the aglycone. The approach by Corey[17,18] utilising the key tricyclic intermediate **40** interested us greatly as we concluded that it may be accessed by a sequential Friedel-Crafts alkylation reaction using the synthon **141** (Scheme 22).




**40** **141** **142**

**Scheme 22**

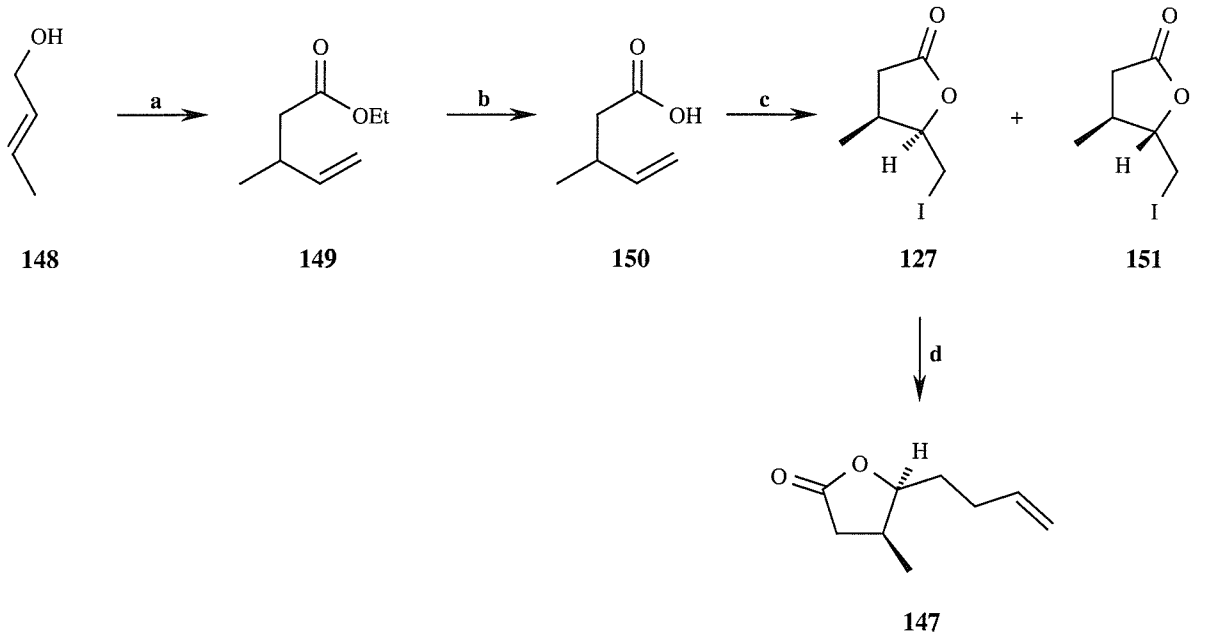
The use of an electrophile such as the tetrahydrofuran **142** provided a means of controlling the stereochemical outcome of the tandem annulation reaction. In addition to this, the use of a catechol substructure gives the correct oxidation level of the aromatic nucleus; which in previous syntheses has proved to be a cause of concern. Initial studies to determine the feasibility of this approach were performed within the group and the tetrahydrofuran was shown to be a suitable candidate for sequential Friedel-Crafts alkylation reactions.[52] The complete retrosynthetic analysis is outlined in Scheme 23.




**Scheme 23**

## 3.2 Our First Approach

The iodolactone **127** was prepared using literature procedures[53] (Scheme 24). Thus, but-2-ene-1-ol **148** underwent a Johnson-Claisen rearrangement when treated with triethyl orthoacetate and *o*-nitrophenol to give the ester **149**.[53] Subsequent saponification of the ester with 15M sodium hydroxide then afforded the corresponding 3-methylpentenoic acid **150**. Iodolactonisation, under kinetic control,[54,55] then gave a 6 : 1 mixture of the *cis* and the *trans* lactones, **127** and **151** respectively, which could be separated by flash column chromatography. Allylation of the iodolactones was then achieved by the reaction of **127** and **151** with allyltributyltin[56] in accordance with the method described by Keck and Yates[57] giving the allyl lactone **147** (Scheme 24).




**148** **149** **150** **127** **151**

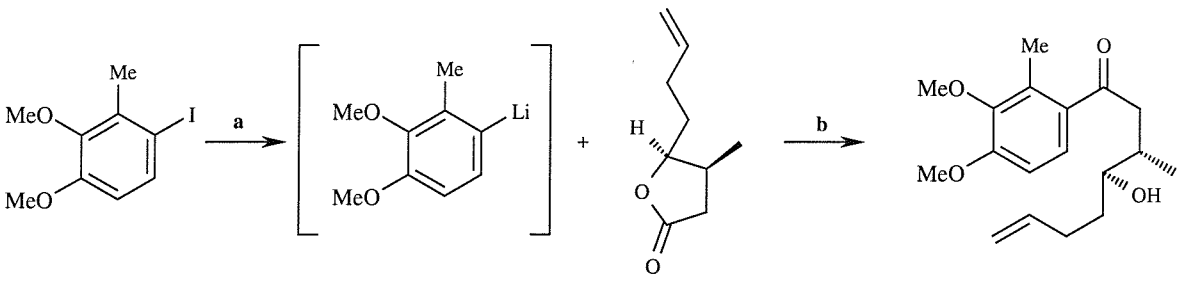
**147**

**Reagents & Conditions: a.** $(EtO)_3CCH_3$, *o*-nitrophenol, Δ, 98%; **b.** 15M NaOH, reflux, 5 hr, 73%; **c.** $NaHCO_3$, $I_2$, $CH_2Cl_2$, $H_2O$, 0°C, 5 hr, 82%; **d.** allyltributyltin, AIBN, PhMe, 60-80°C, 48 hr, 64%.

**Scheme 24**

2,3-Dimethoxy-6-iodotoluene **152** was prepared by the reaction of 2,3-dimethoxytoluene **145** with iodine and mercuric oxide as described by the literature

procedure of McKillop *et al.*[58] Ketone **144** was then accessed by the union of 2,3-dimethoxy-6-iodotoluene **152** and the allyl lactone **147** via transmetallation of **152** with $^{n}$BuLi in THF at −78°C, giving a 20% yield of the desired ketone **144** (Scheme 25).

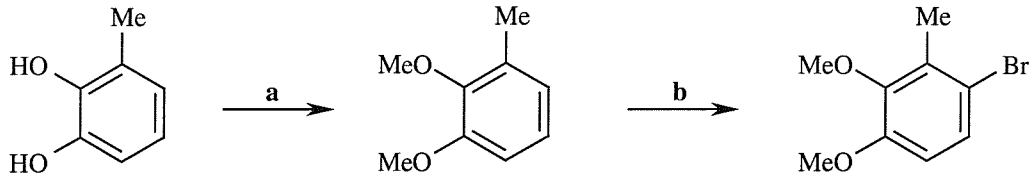



**152** **153** **147** **144**

**Reagents & Conditions: a.** *n*-butyllithium, THF, −78°C, 2½ hr; **b.** −78°C to RT; 1 hr, aq. $NH_4Cl$.

**Scheme 25**

The yield of the coupling reaction was modest and the mass balance of the reaction comprised the recovered starting materials and 3-methylveratrole. In an attempt to improve the yield of the coupling reaction 2,3-dimethoxy-6-bromotoluene **154** was utilises in the hope that this will transmetallate more effectively. The synthesis of **145** was achieved by the reaction of 3-methyl catechol **124** with potassium hydroxide and excess methyl iodide to give the 3-methyl veratrole **145**. The subsequent reaction of **145** with NBS in $CHCl_3$ gave the brominated product **154** (Scheme 26).[59]

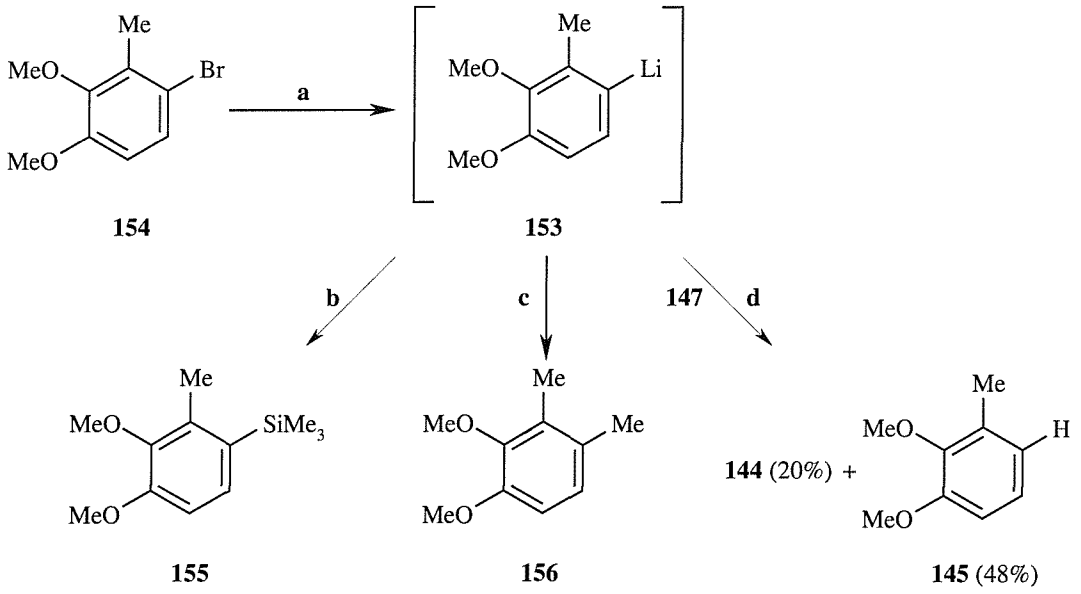



**124** **145** **154**

**Reagents & Conditions: a.** KOH, MeI, DMSO, RT, 24 hr, 74%; **b.** NBS, $CH_3Cl$, reflux, 48 hr, 75%.

**Scheme 26**

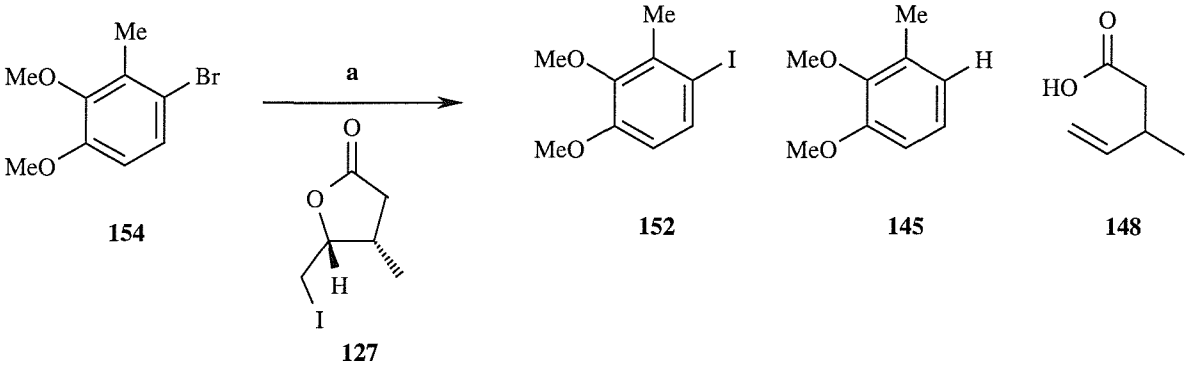
Reaction of 4-bromo-3-methylveratrole **154** with 2 equivalents of *tert*-butyllithium at −78°C, in anhydrous THF, appeared to give the corresponding aryllithium in near quantitative yield as illustrated by the subsequent reaction with suitable electrophiles such as methyl iodide and trimethylsilyl chloride. The products of the reactions were 3,4-dimethylveratrole **156** and 3-methyl-4-trimethylsilyl-veratrole **155** in 88% and quantitative yields respectively (Scheme 27).




**Reagents & Conditions: a.** $^{t}$BuLi, THF, -78°C, 2 hr; **b.** TMSCl, -78°C to RT, 12 hr, 100%; **c.** MeI, -78°C to RT, ½ hr, 88%; **d.** -78°C to RT, 1½ hr.

**Scheme 27**

These results confirm that the halogen-metal exchange reaction proceeded in good yield and that the allyl lactone **147** was therefore an unsuitable electrophile. Interestingly, attempts to couple aryllithium **153** and iodo lactone **127** gave the protonated product **145**, 3-methylpent-4-enoic acid **148** and 4-iodo-3-methylveratrole **152** (Scheme 28). In this case metal-halogen exchange proceeded faster than nucleophilic addition to the carbonyl.

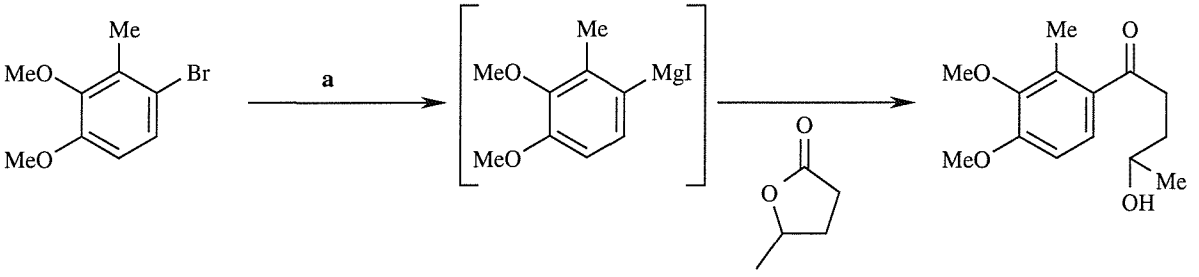



**154** **127** **152** **145** **148**

**Reagents & Conditions: a.** $^{t}$BuLi, THF, -78°C, 2 hr; **127**, -78°C to RT 1 hr.

**Scheme 28**

In an attempt to reduce the basicity of the organometallic nucleophile, the Grignard reagent **157** was generated *in situ* by the transmetallation of the aryl lithium **153** with $MgI_2$.[60] However reaction with γ-valerolactone **158** afforded the desired ketone **159** in a disappointing 22% yield; the major product being the protonated compound **145** (Scheme 29).



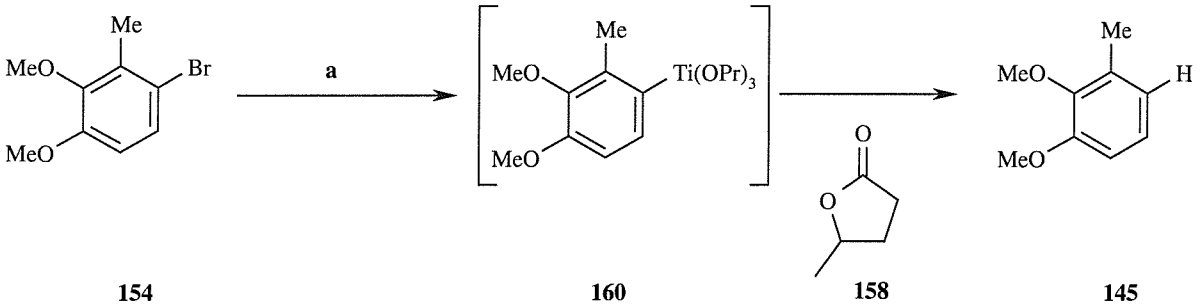

**154** **157** **158** **159**

**Reagents & Conditions: a.** $^{t}$BuLi, THF, -78°C, 3 hr, $MgI_2$, **158**, 0°C, ½ hr, 22%.

**Scheme 29**

Organotitanium reagents,[61,62] which may be formed by the addition of chlorotitanium triisopropoxide to the lithium reagent, are also reported to be highly selective towards nucleophilic attack of carbonyl groups.[63] However, treatment of 4-bromo-3-methyl veratrole **154** with 2 equivalents of $^{t}$BuLi then chlorotitanium

triisopropoxide and γ-valerolactone **158** again afforded the protonated product **145** with recovery of the lactone **158** (Scheme 30).



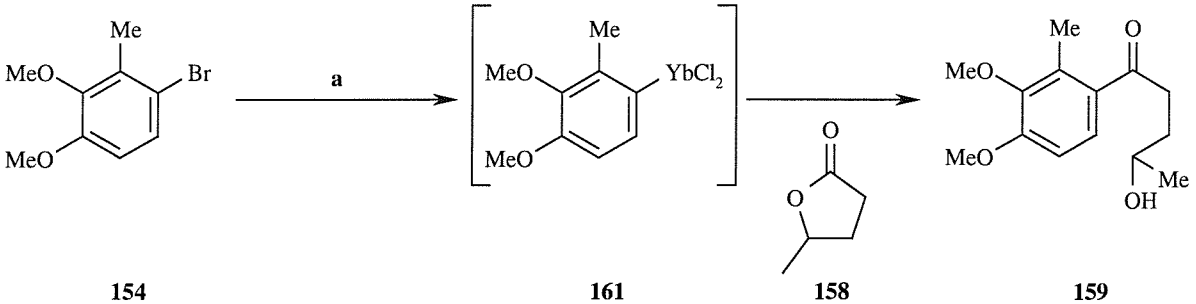

**154** **160** **158** **145**

**Reagents & Conditions: a.** $^t$BuLi, THF, -78°C, 3 hr, $[(CH_3)_2CHO]_3TiCl$, **158**, 0°C, ½ hr, 89%.

**Scheme 30**

The addition of lanthanoid chlorides is also reported to suppress enolization and organoytterbium(III) reagents are conveniently generated by the reaction of organolithiums with ytterbium(III) chloride. Again these reagents are less basic than organolithium and Grignard reagents, and they are reported to react cleanly with various carbonyl compounds to give the addition products in high yields when substrates susceptible to enolisation or metal-halogen exchange are employed.[64,65]

Thus the reaction of 4-bromo-3-methylveratrole **154** with 2 equivalents of $^t$BuLi and subsequent transmetallation with $YbCl_3$ gave the intermediate **161**. Reaction with γ-valerolactone **158** afforded the desired ketone **159** in 17% yield. Again the major by product was the protonated compound **145** (Scheme 31).

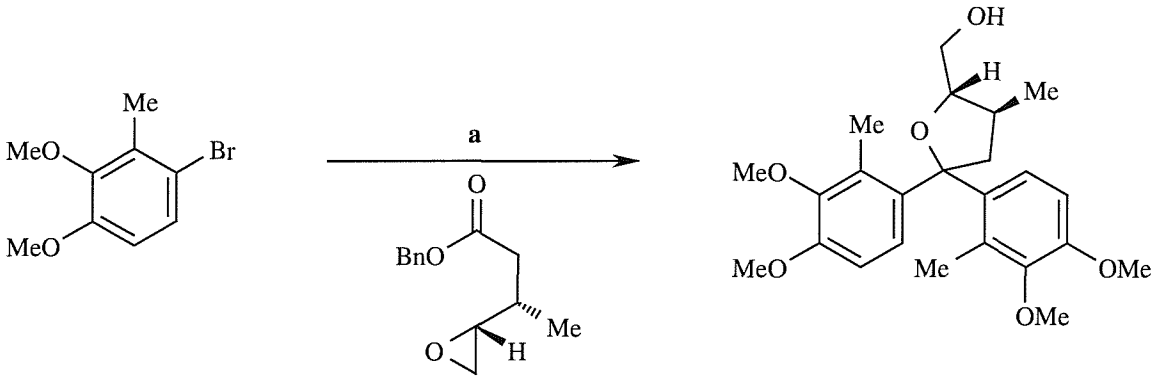



**154** **161** **158** **159**

**Reagents & Conditions: a.** $^t$BuLi, THF, -78°C, 3 hr, $YbCl_3$, **158**, 0°C, ½ hr, 17%.

**Scheme 31**

The iodolactone **127** was readily converted to the benzyl ester[66] **162** in good yield. The reaction of the ester **162** with 4-lithio-3-methylveratrole **153** gave the double addition product, tetrahydrofuran **163**, in 20% yield. Again a significant amount of the protonated product **145** was also recovered (Scheme 32). The *ortho*-methoxy benzyl ester derivative **164** also failed to afford any significant yield of the desired ketone (Figure 6).

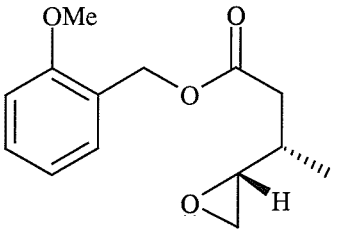



**154** **162** **163**

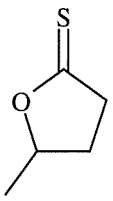
**Reagents & Conditions: a.** $^{t}$BuLi, THF, -78°C, 1 hr, **162**, 0°C, ½ hr, 25%.

**Scheme 32**

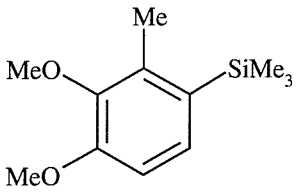
We also attempted to effect coupling of organolithium **153** with thiolactone **165**, prepared from γ-valerolactone by reaction with 2,4-bis(4-methoxyphenyl)1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent).[67] Again this resulted in the formation of the protonated product **145**. Finally, the reaction of aryl silane **155** with γ-valerolactone **158** in the presence of $AlCl_3$ was examined and our failure to induce the desired *ipso*-substitution[68] prompted us to explore an alternative approach (Figure 6).




**164**




**165**




**155**

**Figure 6**

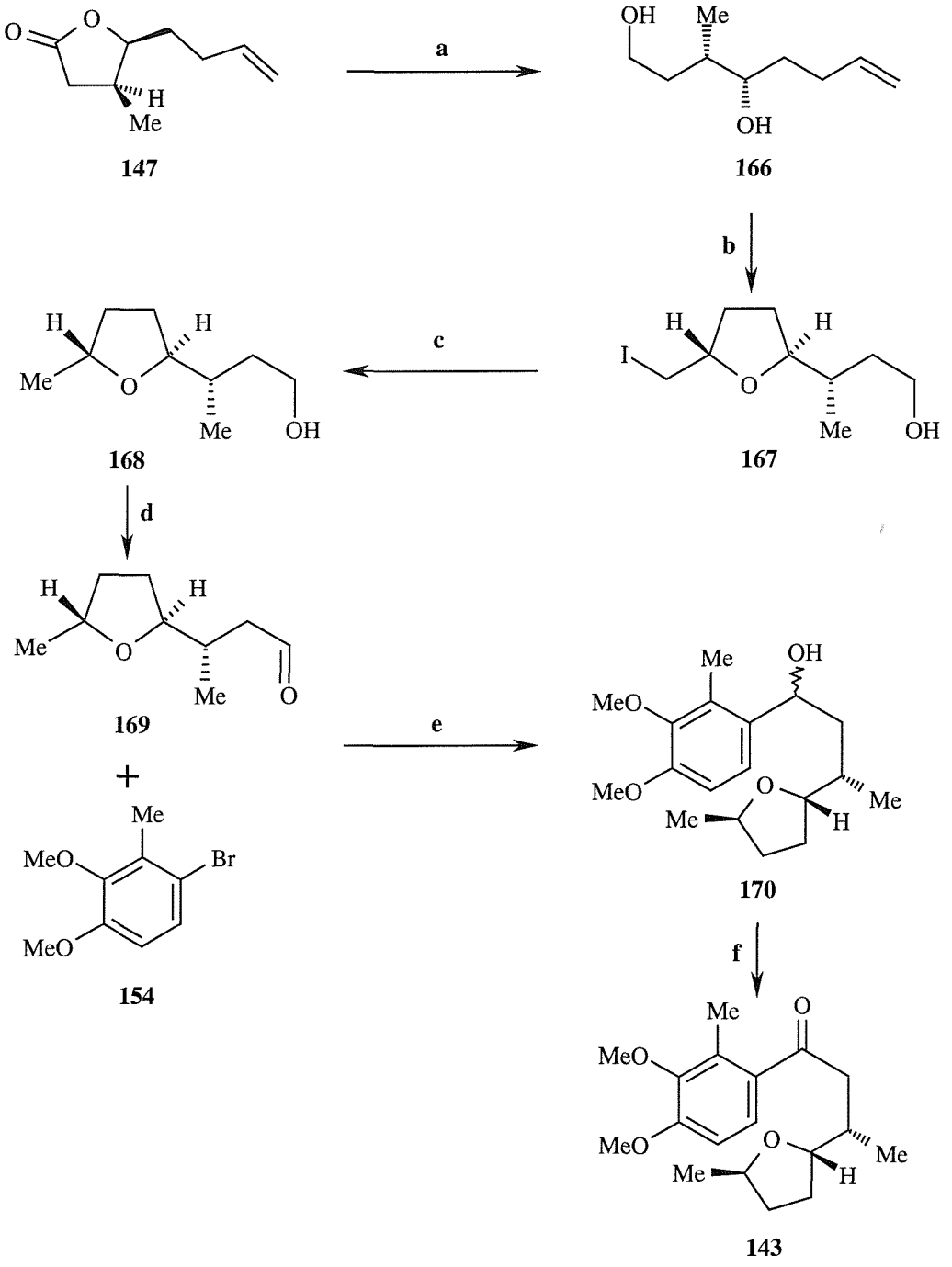
## 3.3 New Synthetic Strategy

As a result of the poor yields from the coupling of the aryl and tetrahydrofuran fragments a new synthetic strategy was adopted. The initial step in the synthesis required the reduction of the allyl lactone **147** to the diol **166**. To achieve this goal several reagents were investigated such as $LiAlH_4$ and $LiBH_4$. However these gave poor yields of the desired diol, presumably due to side reactions such as dehydration or hydroboration of the double bond. Optimal conditions were DIBAL-H in THF, giving the desired diol **166** in 87% yield.

The direct cyclisation of the diol **166** to the tetrahydrofuran derivative **168** failed with reagents such as TsOH in THF, $AlCl_3$ in $CH_2Cl_2$ or HCl (g) bubbled in $CH_2Cl_2$. Therefore an iodoetherication of the γ,δ-unsaturated alcohol **166** with iodine in acetonitrile at 0°C was used and this gave the THF **167** in a 5:1 *cis:trans* ratio in 87% yield.[69]

The subsequent dehalogenation reaction was achieved by reaction of the tetrahydrofuran derivative **167** with tributyltinhydride and AIBN in anh. THF. This affected reduction to **168** in 93% yield.

In order to couple the THF fragment to the aromatic nucleus, the primary alcohol was converted to the aldehyde *via* a Swern oxidation[70] to give **169** in 91% yield. The aldehyde **169** was coupled with 4-bromo-3-methylveratrole **154** via halogen-metal exchange with 1 eq of $^t$BuLi giving the desired alcohol's **170** as a partially separable 1:1 mixture of diastereoisomers in an 82% yield. The alcohol **170** was then oxidised to the unsymmetrical ketone **143** with activated $MnO_2$ in $CH_2Cl_2$ in 73% yield (Scheme 33).

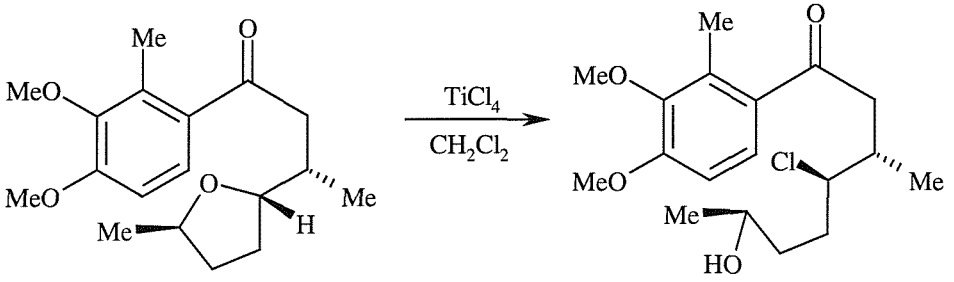



**Reagents & Conditions:** **a.** 3 eq. DIBAL-H, THF, PhMe, RT, 24hr, 87%; **b.** $I_2$, $Na_2CO_3$, $CH_3CN$, 0°C, 5hr, 87%; **c.** $Bu_3SnH$, AIBN, THF, 60°C, 40hr, 93%; **d.** $CO_2Cl_2$, DMSO, $CH_2Cl_2$, -78°C, ½hr; $CH_2Cl_2$, $Et_3N$, -78°C to RT, 2hr, 91%; **e.** $^tBuLi$, THF, -78°C to RT 1hr, 82%, **f.** $MnO_2$, $CH_2Cl_2$, 24hr, 73%.

**Scheme 33**

## 3.4 Friedel-Crafts Cyclialkylation Reactions

In order to investigate the intermolecular Friedel-Crafts cyclisation the ketone **143** was treated with a variety of Lewis acids, which from previous studies within the group had proved successful in achieving the desired transformations.[52] However treatment of the ketone **143** with titanium tetrachloride in dichloromethane failed to effect the desired cyclisation to **74**. Instead a new product that was tentatively assigned as the rearranged material **171** was formed (Scheme 34). A similar result was observed upon treatment with titanium tetrachloride in dichloromethane at RT for 4 days.




**143** **171**

**Scheme 34**

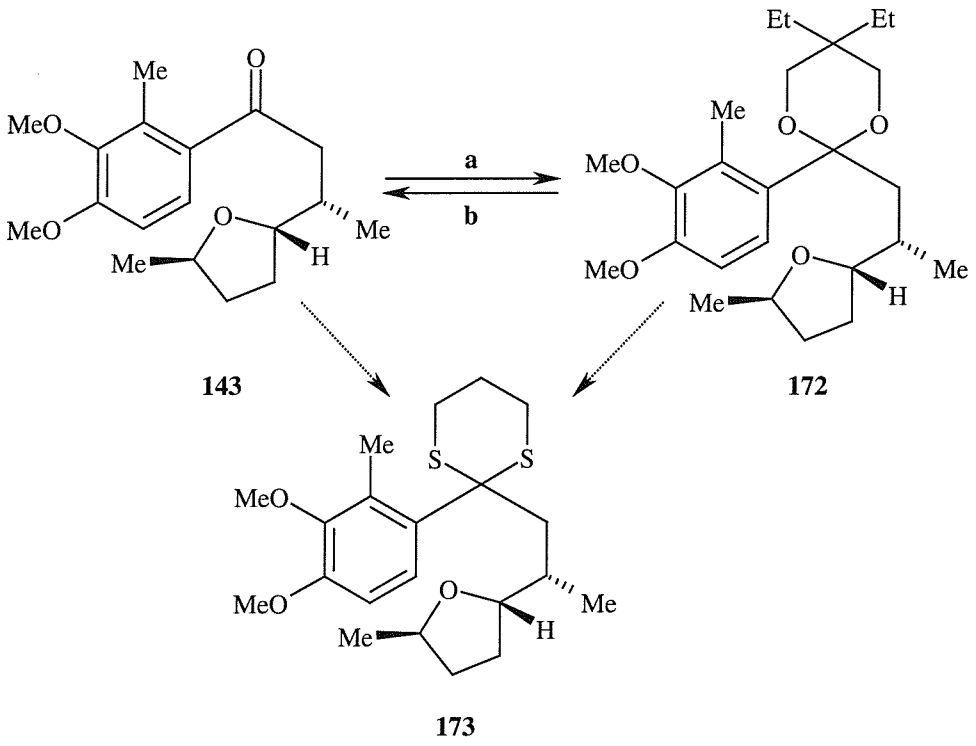
Exposure of **143** to Brønsted acids such as sulfuric and polyphosphoric acid generally resulted in the decomposition of the starting materials while mild Lewis acids such as $BF_3.Et_2O$ and $BCl_3$ failed to induce any reaction. The failure of these reactions was attributed to the presence of the carbonyl group and the low reactivity of the tetrahydrofuran towards Lewis acids.

Attempts to protect the ketone as a thioacetal proved unsuccessful. A summary of the methods employed is presented in Table 1.

| Reagents | Conditions | Products |
|---|---|---|
| 1,3-propanedithiol, *p*TsOH, | RT to reflux, soxhlet | Decomposition |
| 1,2-ethanedithiol, AcOH, *p*TsOH | RT to 60°C, 24hr | Recovered starting materials |
| 1,2-ethanedithiol, $Zn(OTf)_2$, $CH_2Cl_2$ | RT to reflux, 5 days | Recovered starting maetrials |
| 1,2-ethanedithiol, $CH_2Cl_2$, bis(dimethylaluminium), 1,2-ethanedithiolate | -20°C to RT, 5 days | Recovered starting materials |

**Table 1**

Acetalation too proved troublesome but was finally achieved in good yield by treatment of **143** with 2,2-diethyl-1,3-propane diol and PPTS in refluxing toluene for 6 days. However treatment of **172** with 1,3-propanedithiol and $BF_3.Et_2O$ in $CH_2Cl_2$ resulted in deprotection to ketone **143** rather than thioacetalisation to **173** (Scheme 35).



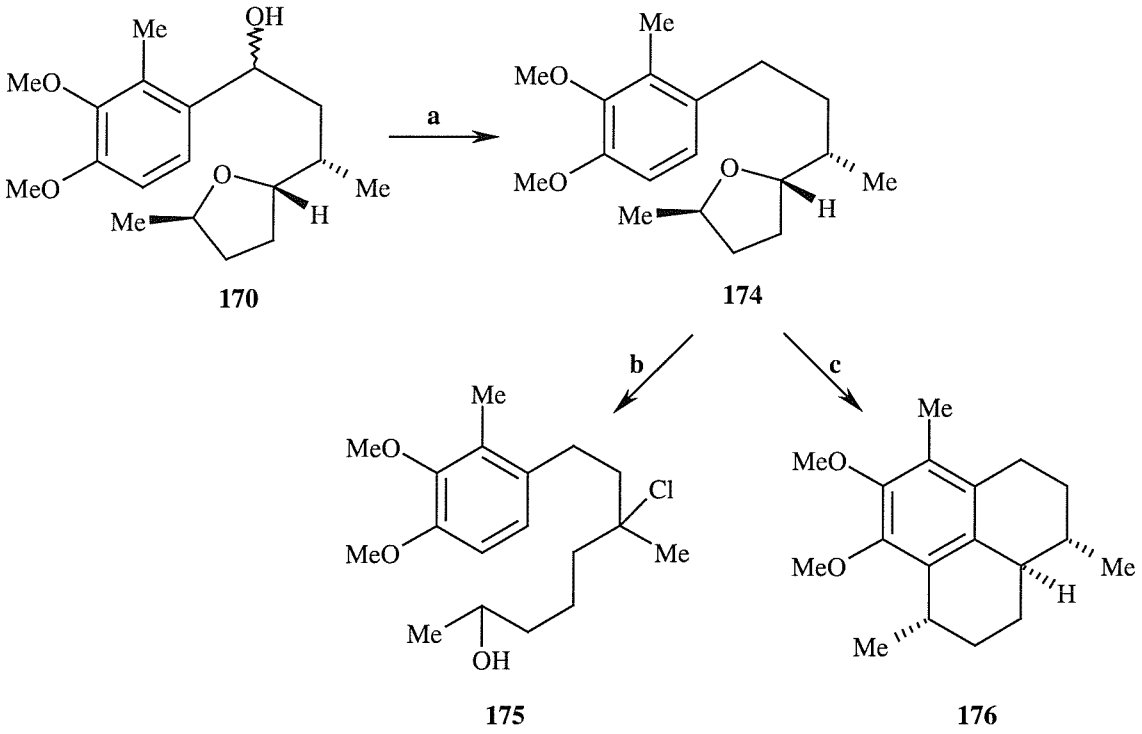

**Reagents & Conditions: a.** $HOCH_2C(C_2H_5)_2CH_2OH$, PPTS, PhMe, reflux, 6 days, 81%; **b.** $BF_3.Et_2O$, $CH_2Cl_2$, RT, 100%.

**Scheme 35**

In view of these results the ketone functionality was removed in order to eliminate its possible interference in the Friedel-Crafts reaction. Thus, catalytic hydrogenolysis of the alcohol **170** gave the reduced derivative **174** in good yield. Unfortunately treatment of **174** with $TICl_4$ in anhydrous $CH_2Cl_2$ failed to effect cyclisation. Instead, fragmentation of the tetrahydrofuran occurred leading to the chloroalcohol **175**. This unexpected product, presumably resulted from a 1,2-hydrogen shift, was formed as a single diastereomer of unknown stereochemistry.

This result was not a complete disappointment since it implicated a Lewis acid-Lewis base interaction between the reagent and the tetrahydrofuran moiety. This provided hope that the desired cyclisation could be achieved under favorable conditions. We therefore surveyed a range of Lewis acids and were delighted to find that treatment of **174** with $BCl_3$ in anhydrous $CH_2Cl_2$ providing the desired tricycle **176** as an 8:1 mixture of diastereoisomers in 42% yield. Interestingly, no deprotection of the aryl methyl ethers was observed, the chloroalcohol **175** being the only identified side product. Switching to

$BF_3.Et_2O$ also proved rewarding. In this case the tricycle **176** was furnished in 81% yield as an 8:1 mixture diastereoisomers (Our assignment of stereochemistry is discussed in detail in chapter five).




**170** **174** **175** **176**

**Reagents & Conditions: a.** Pd-C, $H_2$, EtOH, 24hr, 87%; **b.** $BCl_3$, $CH_2Cl_2$, 0°C to RT, 48 hr, 32%; **c.** $BF_3Et_2O$, $CH_2Cl_2$, O°C to RT, 48 hr, 81%.

**Scheme 36**

## 3.5 Conclusion

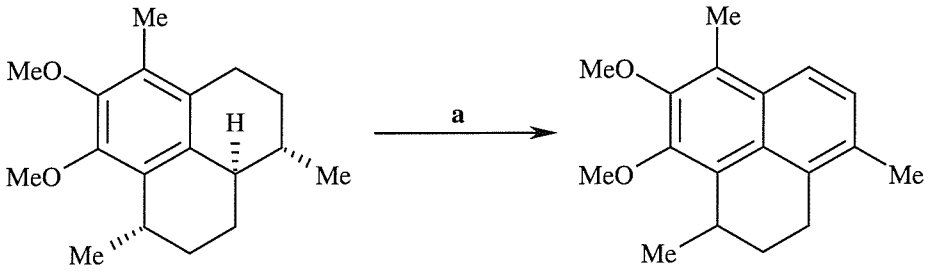
Having achieved a major sub goal, formation of the tricyclic core of the pseudopterosins, we now sought to install the side chain at C-1. These studies are presented in the following chapter.

*Chapter Four*

# Functionalisation of the Hexahydrophenalene Nucleus

## 4.1 Functionalisation of Hexahydrophenalene 176

With hexahydrophenalene **176** in hand we decided to attempt the selective functionalisation at C-1 using a variety of oxidants. Unfortunately this tactic proved unrewarding. Selective oxidations were achieved when **176** was treated with chromium hexacarbonyl and *tert*-butyl hydroperoxide in acetonitrile[71] or selenium dioxide in 1,4-dioxane.[72] However these conditions gave rise to dihydrophenalene **177** which was unsuitable for our purposes (Scheme 37).

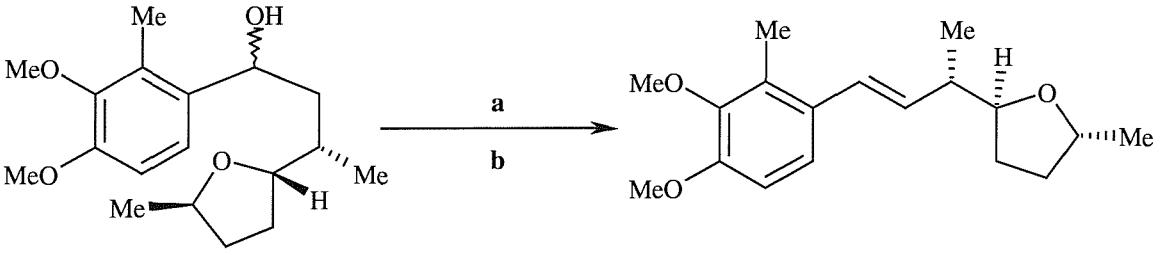



**176** **177**

**Reagents & Conditions: a.** $Se_2O$, 1,4-Dioxane, RT to reflux, 4 days, 75%.

**Scheme 37**

We next sought to introduce functionality at the C-1 centre prior to cyclisation. Unfortunately, treatment of the ketone **143** with $BF_3.Et_2O$ and $BCl_3$ failed to induce cyclisation while similar treatment of the alcohol **170** produced the *trans* alkene **178** (Scheme 38).

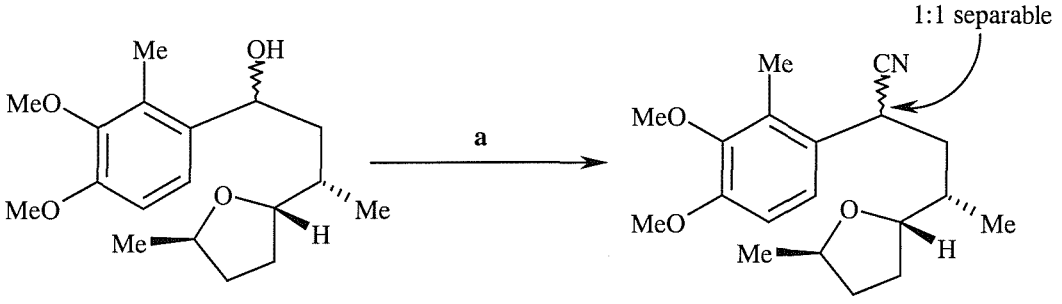



**170** **178**

**Reagents & Conditions: a.** $BCl_3$, $CH_2Cl_2$, 0°C to RT, 24 hr 74%; **b.** TsCl, pyr, DMAP, RT to reflux, 96 hr, 47%.

**Scheme 38**

Elimination of the alcohol also proceeded smoothly when **170** was exposed to TsCl and DMAP in $CH_2Cl_2$. Treatment of **170** with $Et_2AlCN$ and $SnCl_4$, in an attempt to install a nitrile at the C-1 position again led to the formation of the alkene **178**. Fortunately with $Et_2AlCN$ and $BF_3.Et_2O$ in $CH_2Cl_2$ the desired nitrile **179** was produced in 70% yield as a 1:1 mixture of diastereoisomers (Scheme 39). These were separated by recrystalisation from petrol/ether giving **179a** and the stereochemistry established through X-ray spectroscopic analysis (ref appendix). It is worth noting that a 1:1 mixture of nitrile **179** was also produced when a single diastereoisomer of the alcohol **170** was subjected to these reaction conditions.



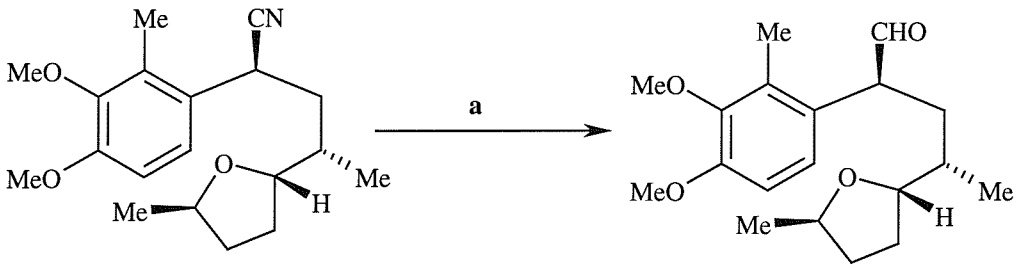

**170** **179**

**Reagents & Conditions: a.** $Et_2AlCN$, $BF_3.Et_2O$, $CH_2Cl_2$, -78°C to RT, 12 hr, 70%.

**Scheme 39**

Unfortunately attempts to achieve cyclisation of the nitrile **179** with $BF_3.Et_2O$, $BCl_3$ and trimethylsilyl trifluoromethanesulfonate afforded none of the desired tricycle. In each case the starting material was returned in good yield. The nitrile **179a** was

therefore converted into the corresponding aldehyde **180** by treatment with DIBAL-H and ethylformate[73] with 5-10% epimerisation at the C-1 stereogenic centre (Scheme 40).

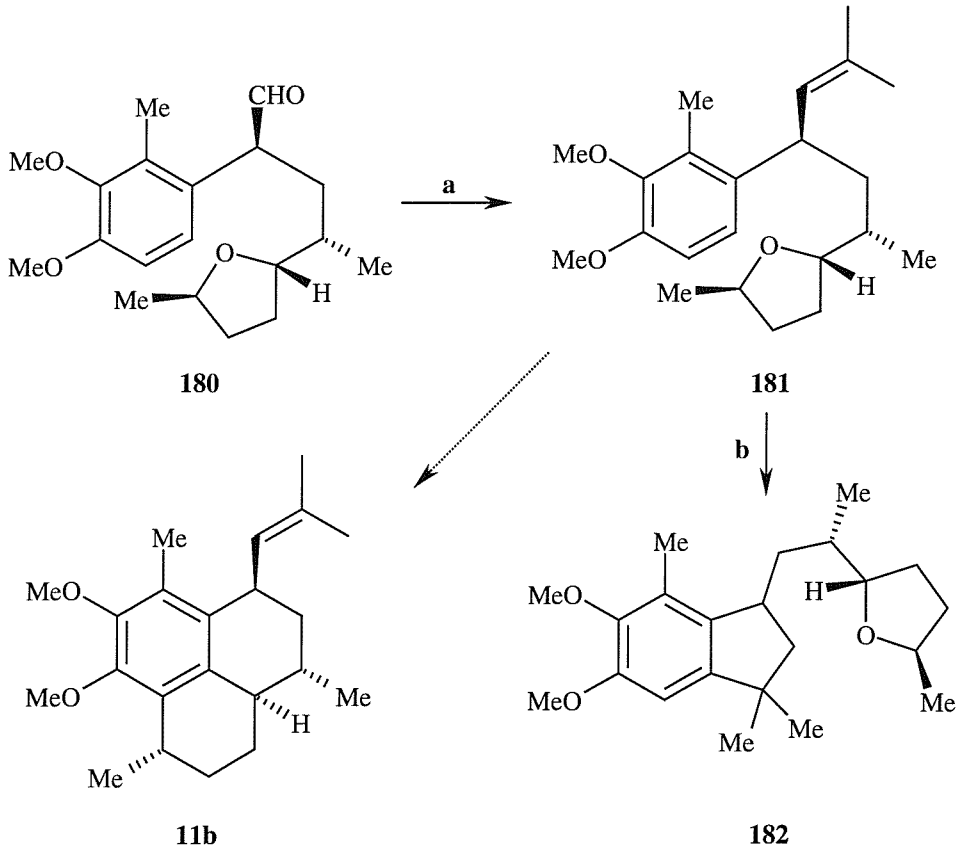



**179a** **180**

**Reagents & Conditions: a.** DIBAL-H, ethyl formate, THF, RT, 12 hr, 64%.

**Scheme 40**

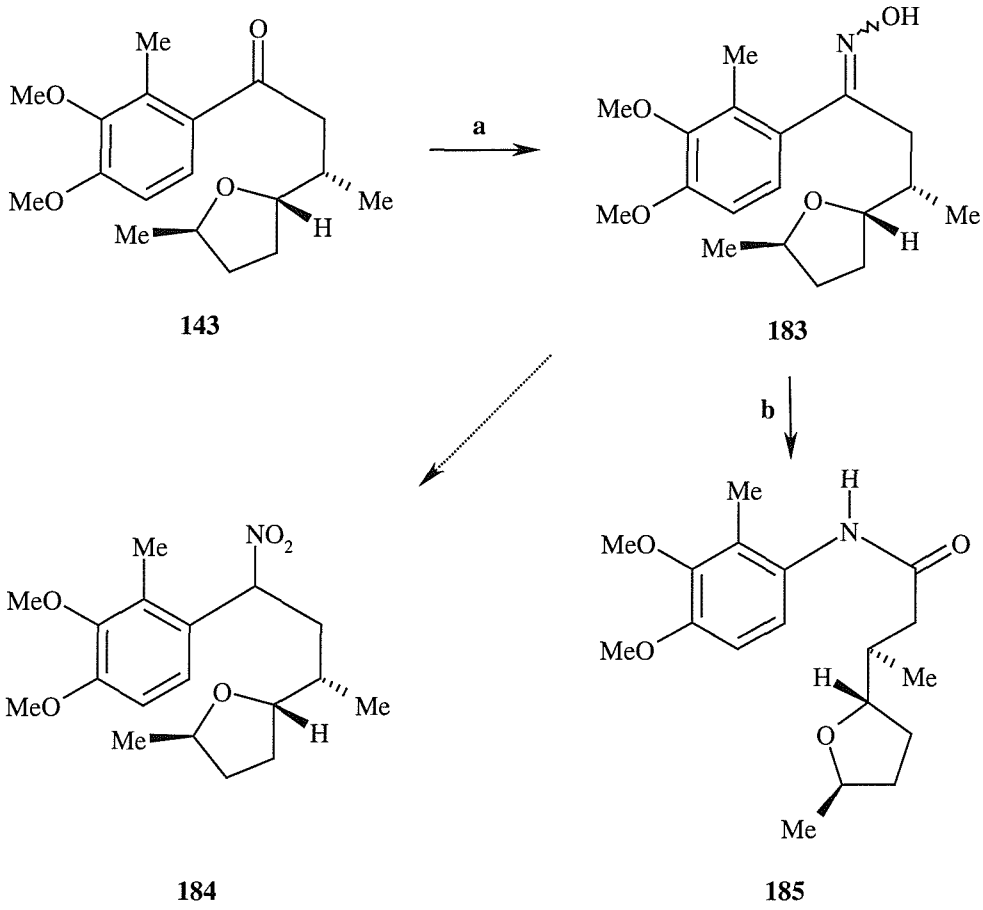
Again attempts to cyclise the aldehyde **180** with Lewis acids proved unsuccessful. The *iso*-butylene side chain was therefore installed *via* a Wittig olefination of the aldehyde **180** with the ylid derived from *iso*-propyl(triphenyl)phosphonium iodide.[74] This gave the alkene **181** in 83% yield. Unfortunately treatment of **181** with $BF_3.Et_2O$ in $CH_2Cl_2$ induced cyclisation to the indane **182** in 54% rather than the desired protected aglycone **11b** (Scheme 41).




**Reagents & Conditions: a.** $^{n}$BuLi, *iso*-propyltriphenylphosponium iodide, THF, 0°C, 2hr, 83%. **b.** $BF_3.Et_2O$, $CH_2Cl_2$, 0°C to reflux, 4 days, 54%.

**Scheme 41**

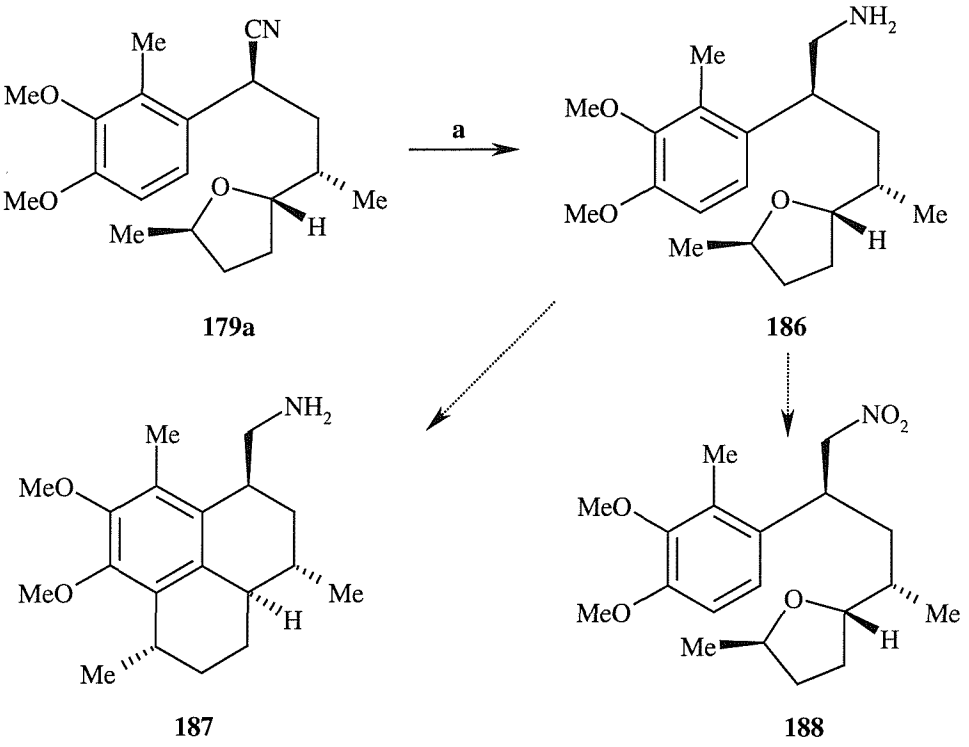
In seeking a functional group that could be tolerated at the C-1 position we attempted to synthesise the nitroalkane **184** *via* the C-1 oxime. While ketone **143** was readily converted to the oxime **183** in good yield,[75] subsequent peracid oxidation[76] gave rise to the Beckmann rearranged product **185** with no discernable formation of the desired nitroalkane **184** (Scheme 42).




**Reagents & Conditions: a.** $NH_2OH.HCl$, pyridine, RT to 80°C, 24hr, 92%. **b.** $CF_3CO_3H$, urea, $Na_2HPO_4$, RT to refflux, 24hr, 47%.

**Scheme 42**

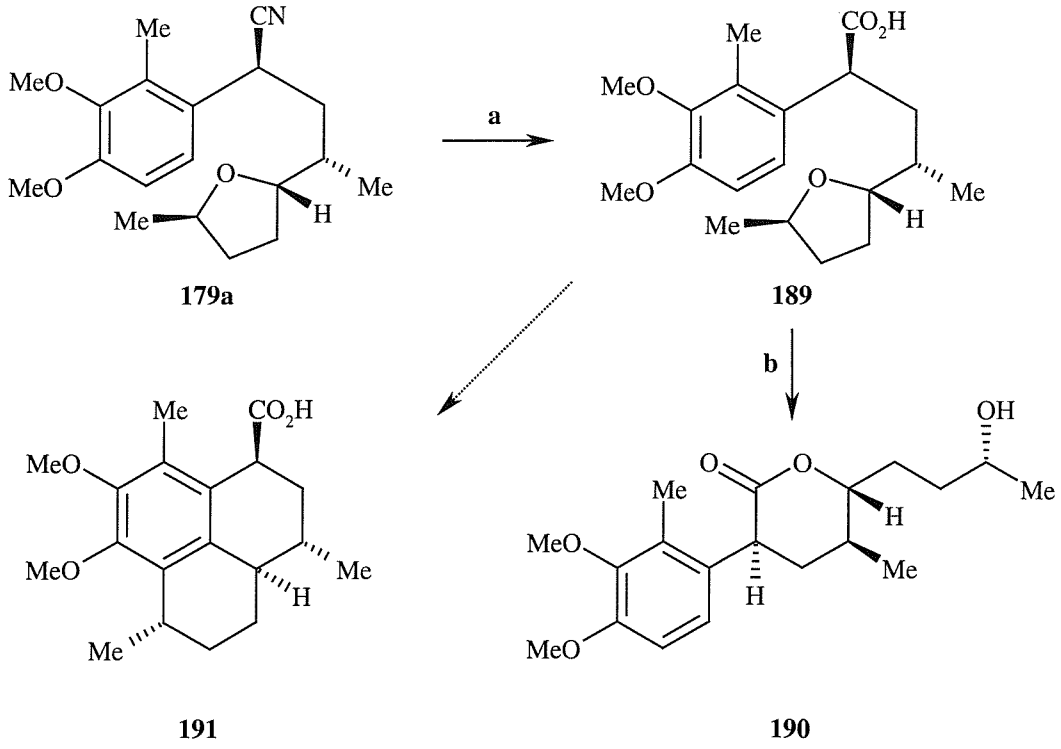
An alternative means of accessing a nitroalkane lay in the conversion of nitrile **179a** into the corresponding amine **186**. A transformation achieved in good yield through the action of $BH_3.Me_2S$.[77] However, oxidation of **186** with a variety of reagents[78-81] failed to access the desired nitroalkene **188** and treatment of **186** with $BF_3.Et_2O$ resulted in no tricyclic product **187** (Scheme 43).




**Reagents & Conditions: a.** $BH_3.Me_2S$, THF, reflux, 4hr, 71%.

**Scheme 43**

The carboxylic acid **189**, which was derived from the corresponding nitrile **179a** *via* a base catalysed hydrolysis,[82] was also investigated. However treatment of **189** with $BF_3.Et_2O$ afforded the lactone **190** as oppose to the desired tricycle **191** (Scheme 44).

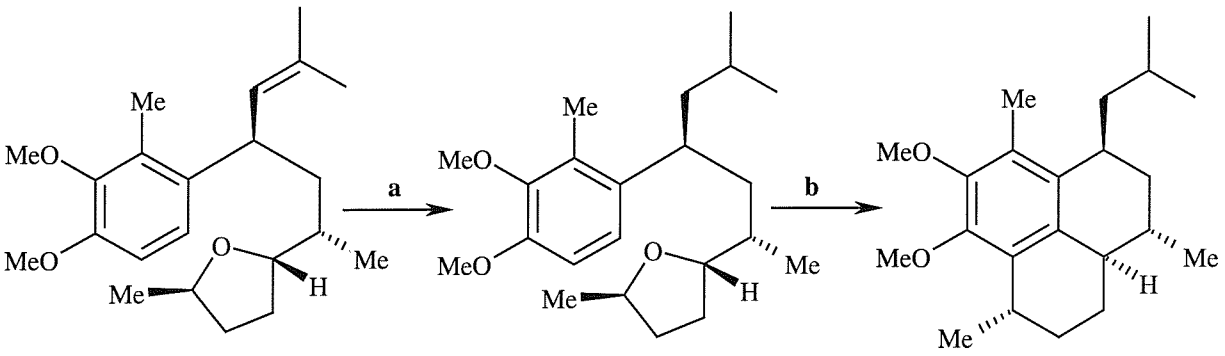



**Reagents & Conditions: a.** aq. NaOH, MeOH, reflux, 24hr, 70%. **b.** $BF_3.Et_2O$, $CH_2Cl_2$, RT to reflux, 24hr, 43%.

**Scheme 44**

Conversion of the ketone **143** into a sterically encumbered alkene was considered as this should not interfere in the Friedel-Crafts alkylation reaction. However, Wittig olefination of **143** with *iso*-propyl(triphenyl)phosphonium iodide failed to give the desired olefin as did the low valent titanium mediated crossed McMurry coupling with acetone.[83-85]

Finally, we decided to target dihydropseudopterosin aglycone dimethylether **193** to establish the validity of the cyclisation with substituents in the C-1 position. Alkene **181** was thus reduced to the corresponding alkane **192** by catalytic hydrogenation. Subsequent treatment with $BF_3.Et_2O$ then gave the desired tricycle **193** in 74% yield (Scheme 45).



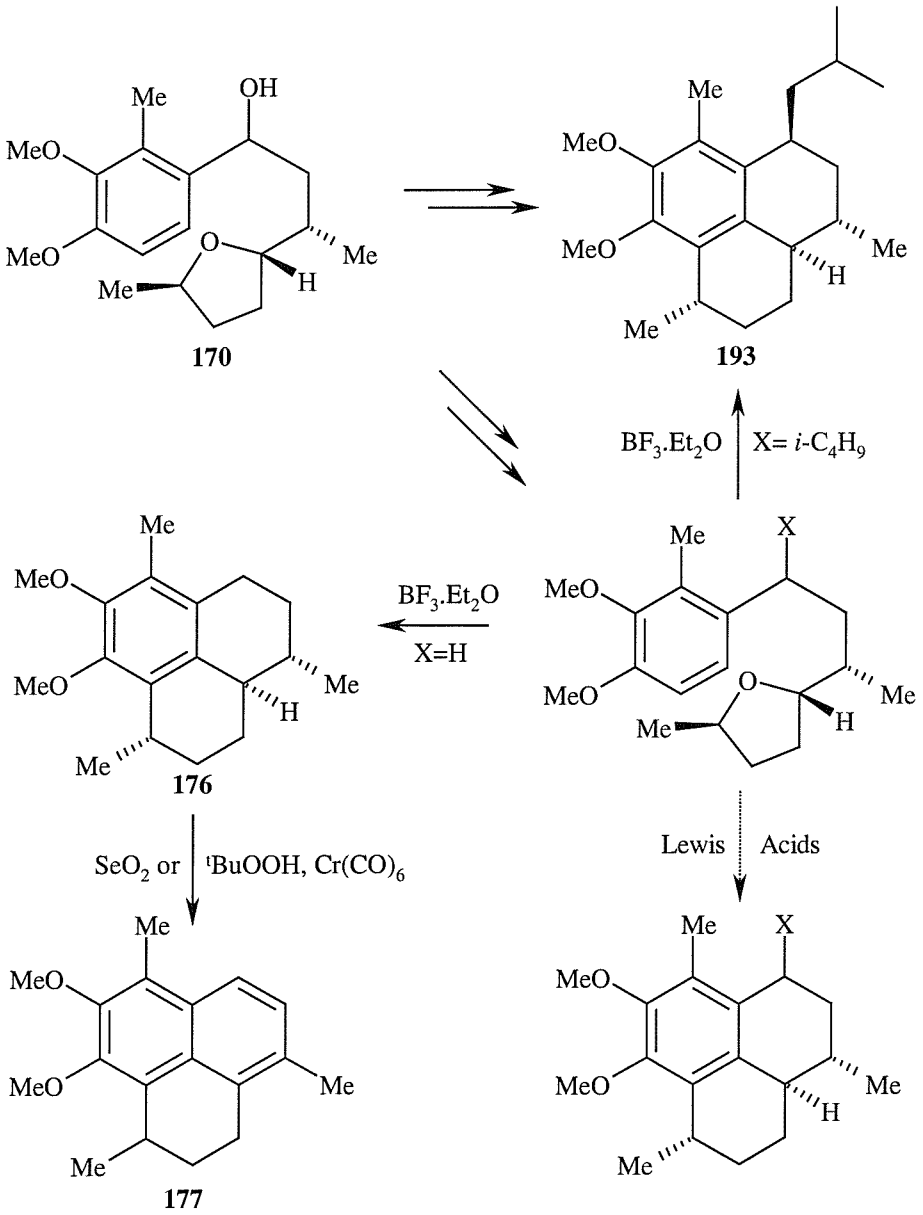

**181** **192** **193**

**Reagents & Conditions: a.** 5% Pd-C, atm $H_2$, EtOH, 24hr, 91%. **b.** $BF_3.Et_2O$, $CH_2Cl_2$, reflux, 3 days, 76%.

**Scheme 45**

## 4.2 Conclusions

Our attempts to effect the synthesis of pseudopterosin through functionalisation of the tricycle **176** were unsuccessful. Likewise, attempts to effect the tandem cyclisation with a range of functionality at the C-1 position met with failure, though the strategy has been extended to the synthesis of dihydropseudopterosin aglycone dimethylether (Scheme 46).



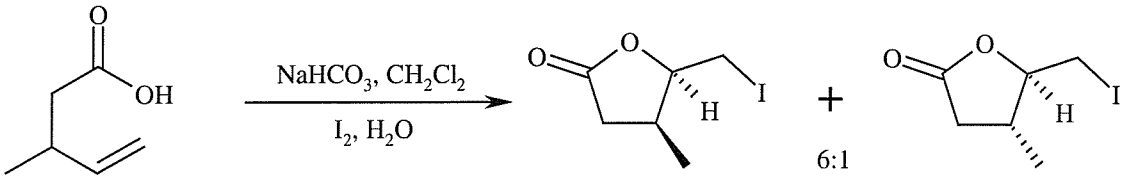

**Scheme 46**

*Chapter Five*

# Stereochemical Discussion

## 5.1 Stereochemical discussion

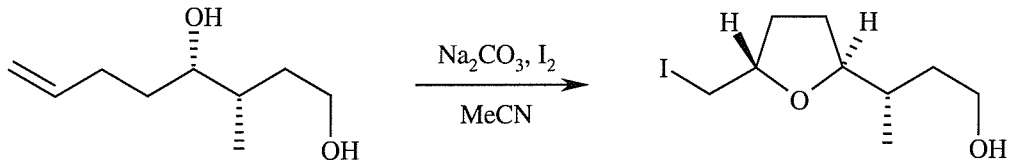
Establishing the stereochemistry of the tricyclic products discussed in the preceding chapters, and the steochemistry of their precursors, was of paramount importance. A variety of techniques were employed to achieve this. The first reaction of stereochemical importance is the iodolactonisation reaction **150** to **127** which is known to favour the *cis* diastereoisomer. As our spectroscopic data was in accord with the literature data of Barlett and Myerson we were confident that the reaction had proceeded in the desired maner (Scheme 48).[55]




**150** **127** **151**

**Scheme 47**

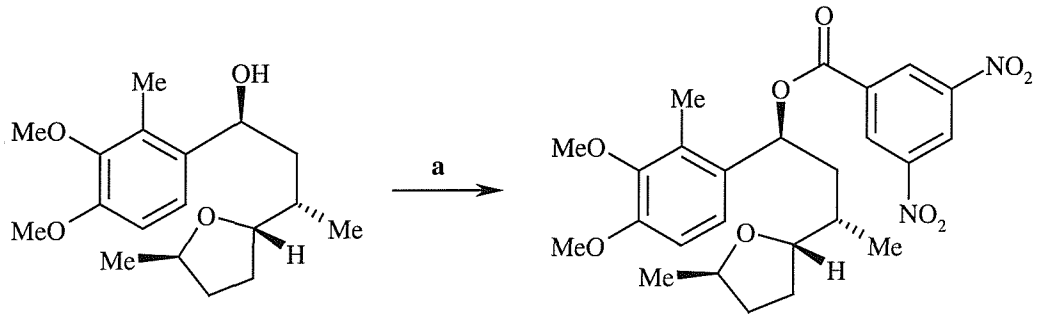
The iodoetherification reaction gave predominately the *trans* diastereomer, which corresponded to the literature observations of Brimble (Scheme 49).[69]




**166** **167**

**Scheme 48**

To confirm this, and to prove that no epimerisation of the lactone had occurred, we sought to obtain a crystalline derivative of a late intermediate. To that end, the alcohol **170a** was separated and the 3,5-dinitrobenzoate ester **194** prepared. Unfortunately the derivative was produced as a viscous oil and attempts to induce crystallisation failed (Scheme 49).




**170a** **195**

**Reagents & Conditions: a.** 3,5-dinitrobenzoyl chloride, $CH_2Cl_2$, pyridine, RT, ½ hr, 60%.

**Scheme 49**

Fortunately the mixture of benzylic alcohols **170** were readily converted into the corresponding nitriles **179**; one of which was crystalline **179a**. The diastereomers were separated by crystallisation and X-ray spectroscopic analysis showed that the solid diastereoisomer had the desired stereochemistry at each of the stereogenic centres. (Ref Appendix). The stereochemistry of the of the dihydro pseudopterosin dimethylether aglycone was difficult to determine. Firstly $^1H$-$^1H$ COSY, $^1H$-$^{13}C$ COSY and 1D GOSEY (n.O.e) experiments were performed to establish the $^1H$ and $^{13}C$ chemical shifts of each hydrogen and saturated carbon centre. N.O.e studies showed that the stereogenic centres at the C-1, C-3 and C-4 positions were as expected. A positive n.O.e was observed between proton $C^1$-H' and $C^2$-H' but not however between proton $C^1$-H' and $C^2$-H" suggesting that the saturated side chain is occupying the axial position. The methyl $Me^{18}$ showed a positive n.O.e in relation to the protons at $C^4$-H', $C^5$-H" but no correlation with the proton $C^5$-H' indicating that this methyl resides in an equatorial position and the stereochemistry of proton $C^4$-H' is correct. Unfortunately the stereochemistry of the methyl at $C^7$ could not be determined from these experiments (Figure 7).

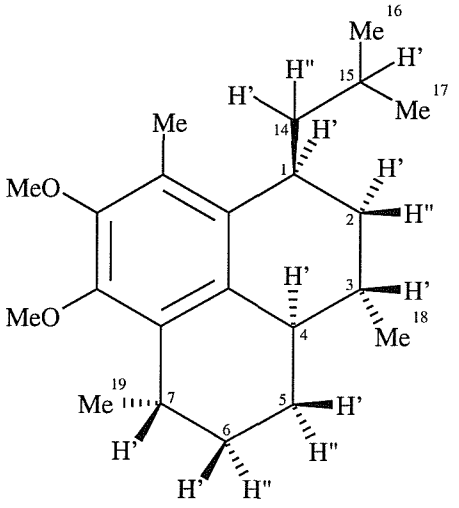
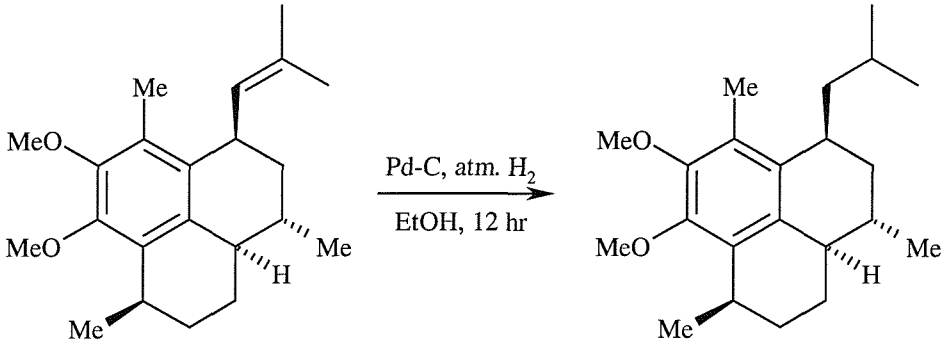



**Figure 7**

In order to determine the C-7 stereochemistry a sample of the pseudopterosin G aglycone dimethylether **195**, generously gifted to us by Professor Kocienski, was catalytically reduced to give the dihydro pseudopterosin G dimethyl aglycone **196** (Scheme 50).




**195** **196**

**Scheme 50**

As expected, a comparison of the NMR data obtained for this material with the data obtained from our synthetic sample showed many minor discrepancies (Figure 7 & Table 2). As these focus around the C-7 stereogenic centre we have concluded that our synthesis provided dihydropseudopterosin A-E aglycone dimethylether.

| Position | Dihydropseudopterosin A aglycone dimethylether 193 $\delta_C$ (300 MHz, $CDCl_3$) | Dihydropseudopterosin G aglycone dimethylether 196 $\delta_C$ (300 MHz, $CDCl_3$) |
|---|---|---|
| 1 | 33.4 | 33.6 |
| 2 | 34.3 | 35.3 |
| 3 | 29.7 | 28.5 |
| 4 | 42.2 | 46.5 |
| 5 | 28.1 | 22.6 |
| 6 | 29.8 | 31.0 |
| 7 | 27.4 | 28.2 |
| 8 | 133.5 | 133.3 |
| 9 | 149.7 | 149.4 |
| 10 | 148.6 | 149.0 |
| 11 | 126.9 | 127.0 |
| 12 | 135.9 | 136.2 |
| 13 | 134.5 | 131.4 |
| 14 | 44.0 | 45.2 |
| 15 | 25.9 | 25.7 |
| 16 | 24.7 | 24.5 |
| 17 | 21.2 | 21.0 |
| 18 | 21.5 | 21.0 |
| 19 | 23.4 | 24.0 |

**Table 2**

*Chapter Six*

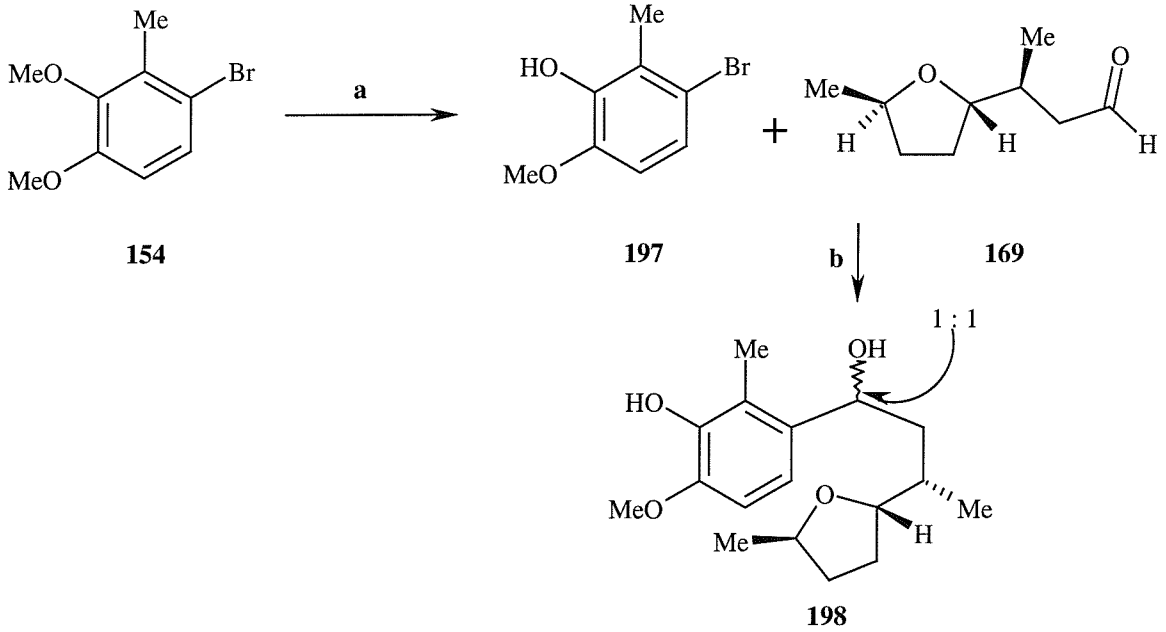
# Pot Pourri

## 6.1 Introduction

During the course of this study a number of different avenues have been explored. Some of these, which could not easily be discussed in the preceding chapters, are collected here. Included in this chapter is a method for differentiating the two hydroxyls on the catechol ring and two further approaches to the pseudopterosin core that were abandoned.

## 6.2 Differential Protection of the Catechol

We decided to seek a method of differentiating the catechol hydroxyls at an early stage in the synthesis, as pseudopterosins A-D and E differ in the point of attachment of the sugar onto the aromatic nucleus. This was readily accomplished by selective demethylation of 4-bromo-3-methylveratrole **154** with $BCl_3$ in $CH_2Cl_2$ to give phenol **197**. Attempts to effect direct coupling of **197** to the aldehyde **169** with 2 eq of $^t$BuLi then gave alcohol **198** in an unacceptable 10% yield.



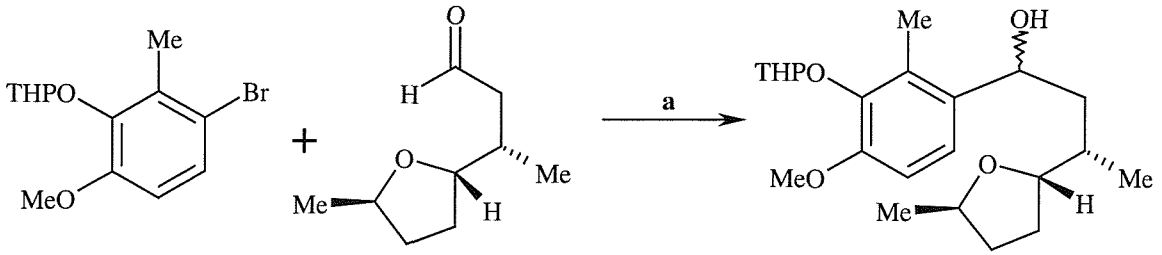

**154** **197** **b** **169**

**198**

**Reagents & Conditions: a.** $BCl_3.Et_2O$, $CH_2Cl_2$, 0°C to RT, 48hr, 79%. **b.** $^t$BuLi, THF, -78°C, 2hr; RT, 14hr.

**Scheme 51**

In order to improve the yield of the coupling reaction phenol **197** was protected as the tetrahydropyran **199** with DHP, using pyridinium toluenesulfonate as the acid catalyst.[86] Coupling of **199** with aldehyde **169** then gave alcohol **200** in an excellent 89% yield with respect to the aldehyde (Scheme 52).

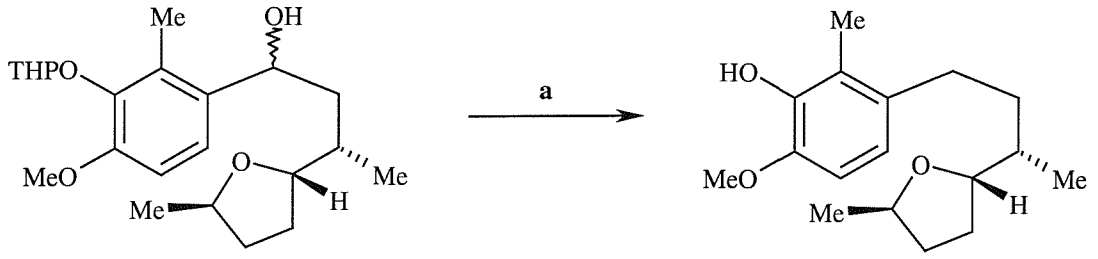



**199** **169** **200**

**Reagents & Conditions: a.** $^{t}$BuLi, THF, -78°C, 2hr, 89%.

**Scheme 52**

Reduction of alcohol **200** to **201** was effected using catalytic hydrogenation. This resulted in partial removal of the THP protecting group so the resultant mixture was treated with 2 M HCl in aqueous THF affording the reduced derivative **201** in 88% yield (Scheme 53).




**200** **201**

**Reagents & Conditions: a.** atm $H_2$, 5% Pd/C, EtOH, 2M HCl, 24hr, 88%.

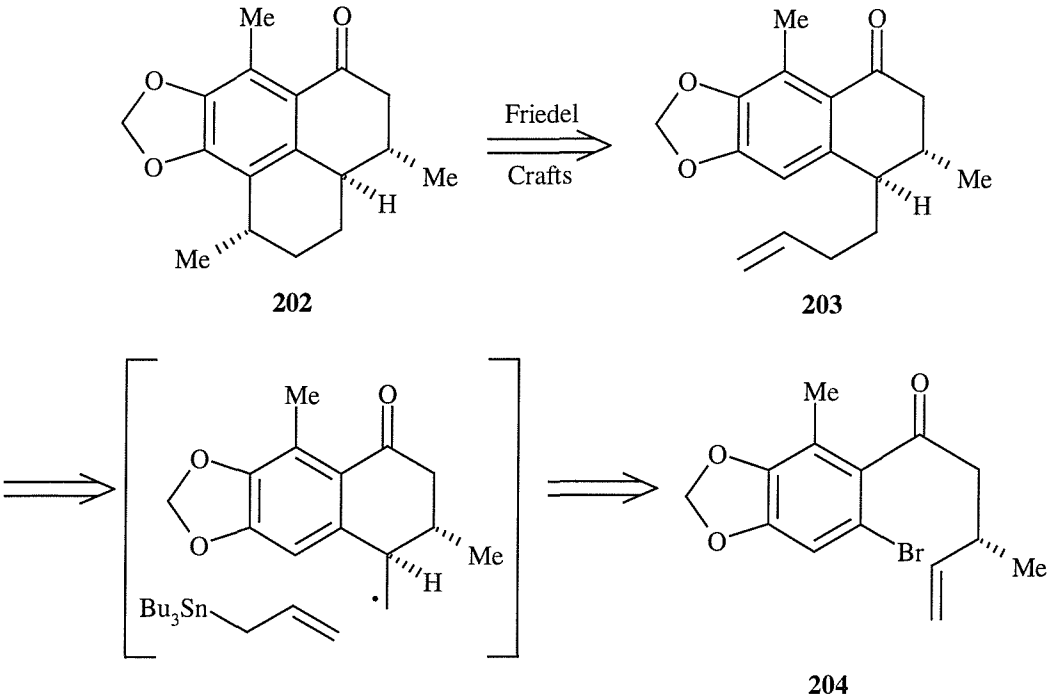
**Scheme 53**

## 6.3 Conclusions

Differentiation of the catechol hydroxyls becomes a key issue when attaching the sugar moieties to the aglycone. Orthogonal protection of the catechol provides a means of distinguishing between them. The preliminary stages of the new synthesis have been repeated with the demethylated analog and this strategy will hopefully provide a convenient route to the pseudopterosins.

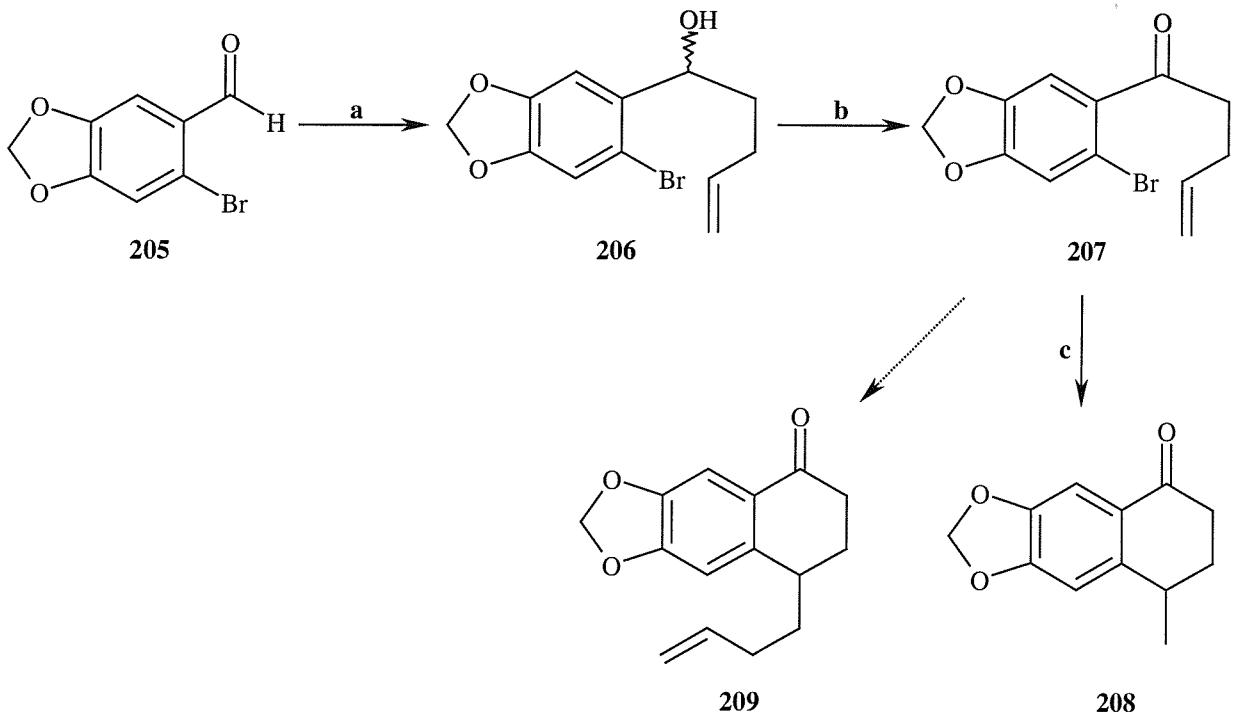
## 6.4 Radical Approach

Alternative approaches to the pseudopterosins are always of keen interest and in promising instances methodology studies are undertaken. Therefore it was envisaged that a radical mediated cyclisation and allylation reaction may lead to the bicyclic structure **203** which in turn could be tranformed into the tricyclic nucleus **202** of the pseudopterosins (Scheme 54).




**Scheme 54**

Thus the model alkene **207** was synthesised by Grignard addition to 6-bromopiperonal **205** giving the alcohol **206** which was subsequently oxidised to the ketone **207** (Scheme 55).




**205** **206** **207** **209** **208**

**Reagents & Conditions: a.** 4-bromo-1-butene, Mg, THF, RT, 12 hr, 60%; **b.** Swern, 41%; **c.** $Bu_3SnH$, AIBN, toluene, 80-90°C, 48 hr, 40%.

**Scheme 55**

Pleasingly the subsequent cyclisation of the alkene **207** with tributyl tin hydride and AIBN gave the corresponding bicycle **208** in 40% yield. Rather than optimise this reaction we immediately sought conditions to effect introduction of the key allyl unit. Alas treatment of **207** with allyltributyltin and AIBN or benzoyl peroxide failed to give the desired allylated bicycle **209** and no product was trapped upon treatment with methyl acrylate, $Bu_3SnH$ and AIBN.

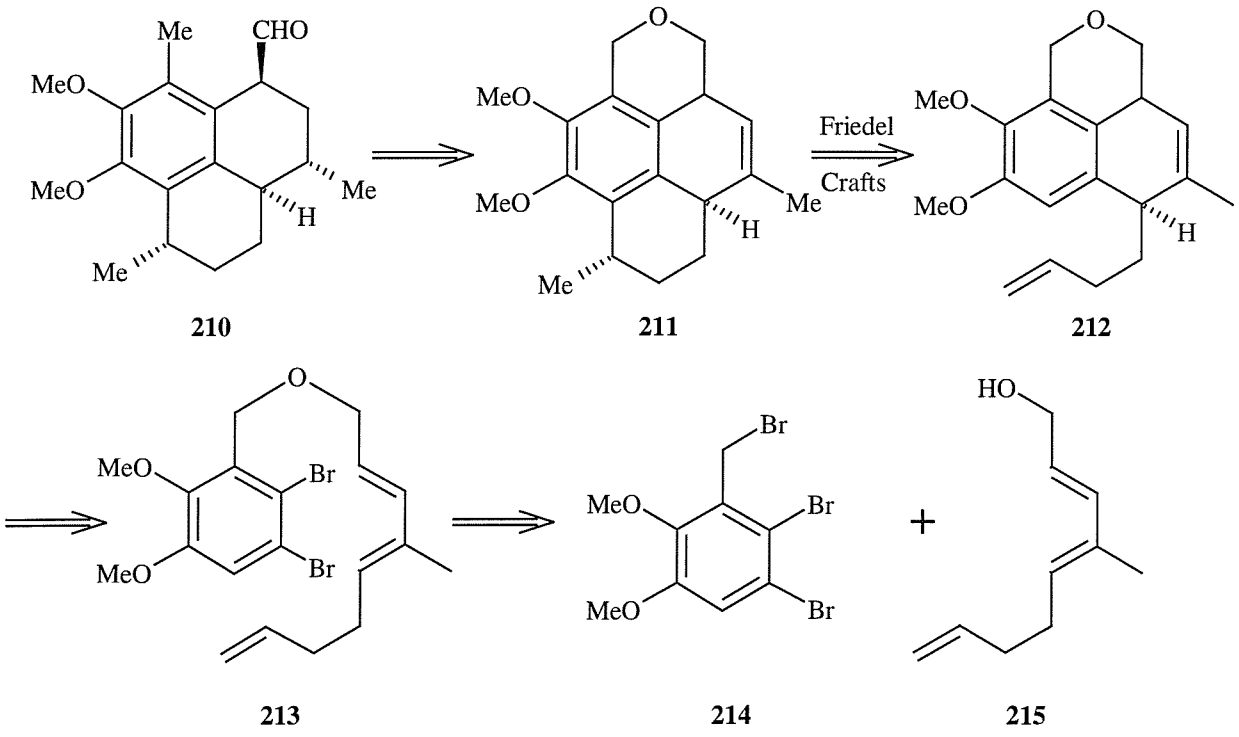
Similarly treatment of **207** with *m*CPBA failed to give the desired epoxide and attempts to carry out a Heck type coupling with $Pd(OAc)_2$, $Et_3N$ and $PPh_3$ proved unsuccessful. In view of these results this alternative strategy was abandoned.

## 6.5 Conclusion

This synthetic strategy allowed the rapid formation of the bicyclic structure. The desired cyclisation allylation reaction failed to give the required allylated bicycle. In light of these results this new synthetic strategy was abandoned.

## 6.6 Intramolecular Diels-Alder Approach

It was envisaged that the tricyclic nucleus **210** of the pseudopterosins may be accessed *via* an intramolecular Diels-Alder reaction of the dibromide **213** which may then be transformed into the tricyclic nucleus **210** (Scheme 56).



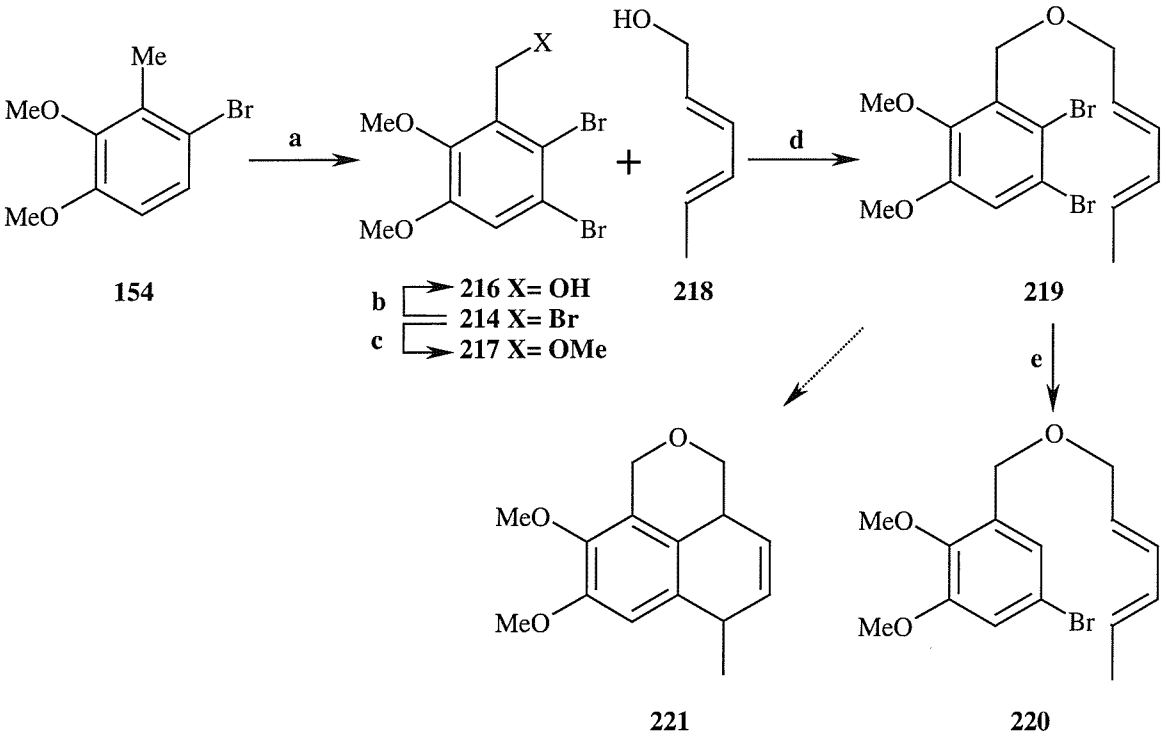

**210** **211** **212**

**213** **214** **215**

**Scheme 56**

The tribromide **214** was obtained by the prolonged exposure of 4-bromo-3-methyl veratrole **154** to NBS in $CHCl_3$ and the substitution around the aromatic nucleus was confirmed by n.O.e studies. The tribromide **214** was readily converted into the

corresponding hydroxy and methoxy derivatives **216** and **217** and therefore the model 1,3-diene **219** was formed in good yield. Unfortunately attempts to carry out the Diels-Alder reaction resulted in the formation of a complex mixture of products which included the monobromide **220**. Similarly treatment with both $Bu_3SnH$ in toluene and photolysis afforded none of the desired bicycle **221** (Scheme 57).




**Reagents & Conditions: a.** NBS, $CHCl_3$, reflux, 24 hr, 82%; **b.** $H_2O$, reflux, 8 hrs, 50%; **c.** MeOH, NaOMe, RT to 70°C, 12 hr, 92%; **d.** NaH, **219**, THF, 0°C to RT, 48 hr, 80%; **e.** $^nBuLi$, THF, -78°C to RT, 1 hr, 8%.

**Scheme 57**

## 6.7 Conclusion

This approach met with limited success and as a result of the failure of the key intramolecular Diels-Alder reaction this approach was abandoned.

*Chapter Seven*

# Experimental

## 7.1 General Experimental

All moisture or air sensitive reactions were conducted in flame-dried apparatus equipped with septum inlets under a positive pressure of argon or nitrogen. Commercial reagents were purified by distillation or recrystallisation were necessary and dry solvents were prepared by standard methods. Organic solvents were evaporated on a Büchi rotary evaporator. Reactions were monitored on thin layer chromatography plates (0.25 mm) impregnated with a 254 nm fluoroscence indicator. The plates were visualized with UV followed by either phosphomolybdic acid reagent (Aldrich) or DNP in sulfuric acid or *p*-anisaldehyde or $KMnO_4$ in aqueous $K_2CO_3$ solution. Flash column chromatography was preformed on Sorbsil C60 40/60H silica gel with slurry packing and running under low pressure. Petrol refers to petroleum ether b.p. 40-60°C and ether refers to diethyl ether.

Melting points were recorded on a stage melting point apparatus and are uncorrected. All samples were recrystallised prior to microanalysis or melting point determination. UV spectra were recorded on a Pye Unicam (PU8800) UV-Vis spectrometer. The solvent the spectra were obtained in is recorded in the parentheses. Maxima are reported as $\lambda_{max}$ (nm) followed in the parentheses by the extinction coefficient, $\varepsilon$ ($dm^3\ mol^{-1}\ cm^{-1}$). The abbreviation inf refers to a point of infection.

The IR spectra were recorded on a Perkin Elmer 1600 series spectrometer using NaCl cells. Details are reported as $\nu_{max}$ ($cm^{-1}$) followed by a description using the following abbreviations : vs = very strong, s = strong, m = medium, w = weak and br = broad.

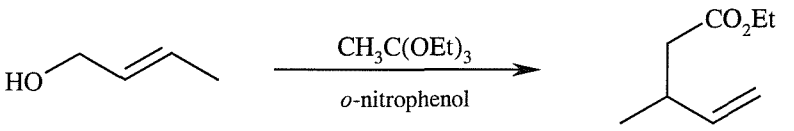
The proton ($^1H$) NMR spectra were recorded in Fourier transform mode on Joel JNM-GX270 (270 MHz), Bruker AC300 (300 MHz), Bruker AM360 (360 MHz) or Bruker DPX400 (400 MHz) spectrometers as stated. The chemical shifts are reported in units of parts per million relative to an internal standard of tetramethylsilane ($\delta_H$ 0.00) or residual $CHCl_3$ ($\delta_H$ 7.27). Multiplicities are described using the following abbreviations :

s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet, obs = obscurred, app = apparent and br = broad.

The carbon ($^{13}C$) NMR spectra were recorded on Joel JNM-GX270 (67.5 MHz), Bruker AC300 (75.5 MHz), Bruker AM360 (90 MHz) or Bruker DPX400 (100 MHz) spectrometers as stated. The chemical shifts are reported in units of parts per million relative to an internal standard of tetramethylsilane ($\delta_C$ 0.00) or the $CDCl_3$ signal ($\delta_C$ 77.2). The muliplicities refer to the signals in the off-resonance spectra as determined by DEPT 135° and DEPT 90° experiments.

The mass spectra and exact mass measurements were recorded on a variety of instruments. The signals are reported in atomic mass units (amu) and are followed by the peak intensity relative to the base peak (100%). Combustion analyses were conducted at University College, London.

**Preparation of 3-methylpent-4-enoic acid ethyl ester 149.**




**148**
$C_4H_7O$ (72)

**149**
$C_8H_{14}O_2$ (142)

Prepared by the method described by Jäger and Günther *et al.*[53]

But-2-ene-1-ol **148** (40.0 g, 560 mmol) was heated with the triethylorthoacetate (90.42 g, 560 mmol) and *o*-nitrophenol (3.9 g, 28 mmol) with stirring until complete distillation of ethanol had occurred. The reaction was allowed to cool and was poured into 2M HCl (75 ml) then extracted with $Et_2O$ (3 × 70 ml). The organic phases were combined, washed with water (3 × 50ml) and brine (2 × 50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **149** as a yellow oil (78.21 g, 551 mmol, 98%).

**FT-IR** $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2966 s, 1736 s, 1641 w, 1458 m, 1375 m, 1281 s, 1182 s, 1032 m, 968 m, 916 m.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 5.78 (1H, ddd, $J$ = 17.2, 10.3, 6.9 Hz, =C**H**), 5.03 (1H, ddd, $J$ = 17.2, 2.6, 1.5 Hz, **H**HC=CH), 4.96 (1H, dt, $J$ = 10.3, 1.5 Hz, H**H**C=CH), 4.14 (2H, q, $J$ = 7.3 Hz, OC**H$_2$**), 2.69 (1H, app. septet, $J$ = 7.0 Hz, C**H**CH$_3$), 2.36 (1H, dd, $J$ = 14.7, 7.0 Hz, O=CC**H**H), 2.26 (1H, dd, $J$ = 14.7, 7.4 Hz, O=CCH**H**), 1.26 (3H, t, $J$ = 7.3 Hz, CH$_2$C**H$_3$**), 1.07 (3H, d, $J$ = 7.0 Hz, CHC**H$_3$**).

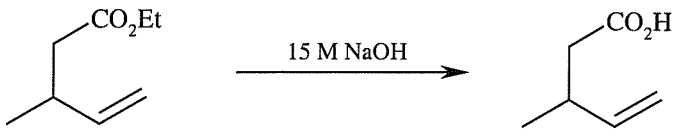
**$^{13}$C NMR** δc (75.5 MHz, $CDCl_3$) 172.5 (s), 142.5 (d), 113.2 (t), 60.2 (t), 41.3 (t), 34.4 (d), 19.7 (q), 14.2 (q).

**LRMS** $^m/_z$ (CI+) 160 ([M+18]$^+$, 30%), 143 ([M+H]$^+$, 19%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 160.1345. $C_8H_{18}O_2N$ requires 160.1338.

These data were fully consistent with those previously reported in the literature.[89]

**Preparation of 3-methylpent-4-enoic acid 150.**




**149**
$C_8H_{14}O_2$ (142)

**150**
$C_6H_{10}O_2$ (114)

Prepared by a method described by Jäger and Günther *et al.*[53]

The ester **149** (78.21 g, 550 mmol) was dissolved in 15M NaOH (74.5 ml) and heated at reflux for 16 hr. Upon cooling the reaction mixture was acidified with conc. HCl until a pH of 3 was achieved. The reaction mixture was extracted $Et_2O$ (3 × 150 ml) and the combined organic phases were washed with $H_2O$ (3 × 100 ml) and brine (2 × 100 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a dark yellow oil. Purification by distillation in vacuum (aspirator pressure, 145 °C) gave **150** as a pale yellow oil (46.05 g, 404 mmol, 73%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3250 vbrs, 2968 s, 1710 s, 1641 w, 1420 m, 1292 m, 1207 m, 994 w, 917 m.

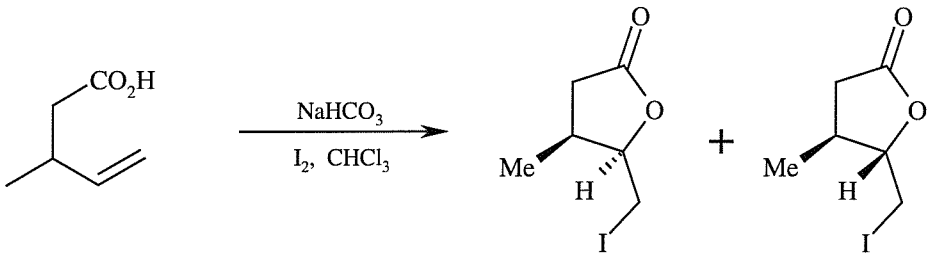
**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 10.88 (1H, br s, $CO_2$**H**), 5.79 (1H, dddt, *J* = 16.9, 10.3, 6.6, 1.5 Hz, C**H**=$CH_2$), 5.05 (1H, dt, *J* = 16.9, 1.5 Hz, CH=CH**H**), 4.99 (1H, dt, *J* = 10.3, 1.5 Hz, CH=CH**H**), 2.70 (1H, app. septet, *J* = 6.9 Hz, C**H**$CH_3$), 2.42 (1H, dd, *J* = 14.7, 7.4 Hz, O=CC**H**H), 2.31 (1H, dd, *J* = 14.7, 7.4 Hz, O=CCH**H**), 1.09 (3H, d, *J* = 6.6 Hz, CH$C$**H**$_3$).

**$^{13}$C NMR** δc (75.5 MHz, $CDCl_3$) 179.2 (s), 142.1 (d), 113.6 (t), 41.1 (t), 34.1 (d), 19.6 (q).

**LRMS** $^{m}/_{z}$ (CI+) 132 ($[M+18]^+$, 100%), 114 ($[M]^+$, 26%).

These data were consistent with those previously reported in the literature.[90]

**Preparation of rel-(4*R*,5*S*)-4-methyl-5-(iodomethyl)-dihydro-2(3*H*)-furan-2-one 127.**




**150** **127** 6:1 **151**

$C_6H_{10}O_2$ (114) $C_6H_9IO_2$ (240)

Prepared by a modified procedure described by Barlett and Myerson.[55]

3-Methyl-4-pentenoic acid **150** (10.0 g, 87.7 mmol) was added to a vigorously stirred solution of $NaHCO_3$ (14.74 g, 175.4 mmol) in $H_2O$ (200 mL) and the reaction was stirred at RT for 1 hr. The reaction was cooled to 0°C and a solution of iodine (44.53 g, 175 mmol) in $CH_2Cl_2$ (200 mL) was added followed by stirring at 0°C for 5 hr. A saturated solution of $Na_2S_2O_3$ (75 mL) was added, the organic phase was then separated, washed with water (3 × 150 mL) and brine (3 × 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark brown oil (17.28 g, 72 mmol, 82%). Analysis of the crude material showed the presence of *cis* and *trans* isomers in a ratio of 6:1 respectively. These were partially separated by flash column chromatography (silica, 50% $Et_2O$ in petrol) to give firstly *cis*-4-methyl-5-(iodomethyl)-dihydro-2(3*H*)-furan-2-one **127**; some mixed fractions, then *trans*-4-methyl-5-(iodomethyl)-dihydro-2(3*H*)-furan-2-one **151**.

Data for the *cis* isomer, *rel-(3S,4S)* **127**.

**FT-IR** $\nu_{Max}$ (neat)/$cm^{-1}$ 2967 s, 1779 s, 1458 w, 1418 m, 1325 m, 1217 m, 1172 s, 1070 m, 970 s, 935 s.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 4.70 (1H, ddd, *J* = 8.8, 5.9, 5.2 Hz, C**H**$CH_2$I), 3.40 (1H, dd, *J* = 10.3, 5.9 Hz, C**H**HI), 3.17 (1H, dd, *J* = 10.3, 8.8 Hz, CH**H**I), 2.80 (1H, m, C**H**$CH_3$), 2.80 (1H, dd, *J* = 20.6, 7.4 Hz, O=CC**H**H), 2.35 (1H, dd, *J* = 20.6, 5.9 Hz, O=CCH**H**), 1.08 (3H, d, *J* = 7.4 Hz, CH$C\mathbf{H}_3$).

**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 175.8 (s), 81.9 (d), 37.9 (t), 32.7 (d), 12.8 (q), 10.3 (t).

**LRMS** $^m/_z$ (CI+) 258 ($[M+18]^+$, 98%), 132 ($[M-108]^+$, 100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 257.9993. $C_6H_{13}O_2NI$ requires 257.9991.

Data for the *trans* isomer, *rel-(3S,4R)* **151**.

**FT-IR** $\nu_{Max}$ (neat)/$cm^{-1}$ 2967 s, 1779 s, 1458 w, 1418 m, 1325 m, 1217 m, 1172 s, 1070 m, 970 s, 935 s.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 4.05 (1H, ddd, *J* = 6.5, 5.2, 4.4 Hz, C**H**$CH_2$I), 3.40 (1H, dd, *J* = 10.9, 5.3 Hz, C**H**HI), 3.17 (1H, dd, *J* = 10.9, 6.5 Hz, CH**H**I), 2.82-2.69 (2H, m, $CH_3$**H** & O=CC**H**H), 2.5-2.21 (1H, m, O=CC**H**H), 1.23 (3H, d, *J* = 6.7 Hz, CH$C\mathbf{H}_3$).

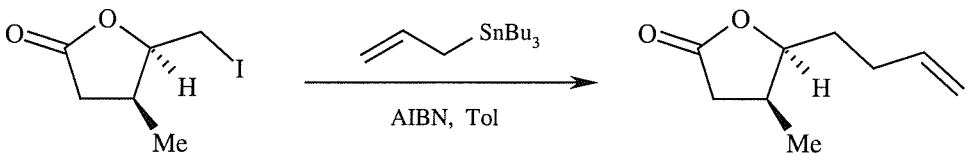
**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 175.2 (s), 84.7 (d), 36.7 (t), 35.9 (d), 18.3 (q), 5.9 (t).

**LRMS** $^m/_z$ (CI+) 258 ($[M+18]^+$, 50%), 132 ($[M-108]^+$, 100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 257.9990. $C_6H_{13}O_2NI$ requires 257.9991.

These data were consistent with those previously reported in the literature.[91]

**Preparation of *rel*-(4*S*,5*S*)-4-methyl-5-(but-3-en-1-yl)-dihydo-2(3*H*)-furanone 147.**




**127**

$C_6H_9IO_2$ (240)

**147**

$C_9H_{14}O_2$ (154)

Prepared using a procedure described by Keck and Yates.[57]

A solution of the *cis* iodolactone **127**, (500 mg, 2.08 mmol) in toluene (10 mL) was degassed by bubbling through $N_2$ gas for 1 hr. AIBN (51 mg, 0.31 mmol) and allyltributyltin (1.29 mL, 4.17 mmol) were added and the reaction was stirred at 80°C for 24 hr. The reaction mixture was then allowed to cool and a saturated solution of KF (30 mL) was added with stirring for 12 hr. The white precipitate formed was removed by filtration and the toluene was removed *in vacuo*. The resultant oil was dissolved in $Et_2O$ (80 mL), washed with water (3 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give two immiscible oils. Purification by flash column chromatography (silica, gradient system 1% $Et_2O$ in petrol to 60% $Et_2O$ in petrol) afforded **147** as a yellow oil (202 mg, 1.31 mmol, 64%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2987 s, 1777 s, 1641s, 1453 m, 1421 m, 1384 m, 1295 m, 1209 s, 1165 s, 998 s, 933 s, 856 w.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 5.81 (1H, ddt, $J$ = 16.9, 10.3, 6.6 Hz, $CH_2$=C**H**$CH_2$), 5.07 (1H, dt, $J$ = 16.9, 1.5 Hz, CH**H**=CH), 5.02 (1H, dt, $J$ =

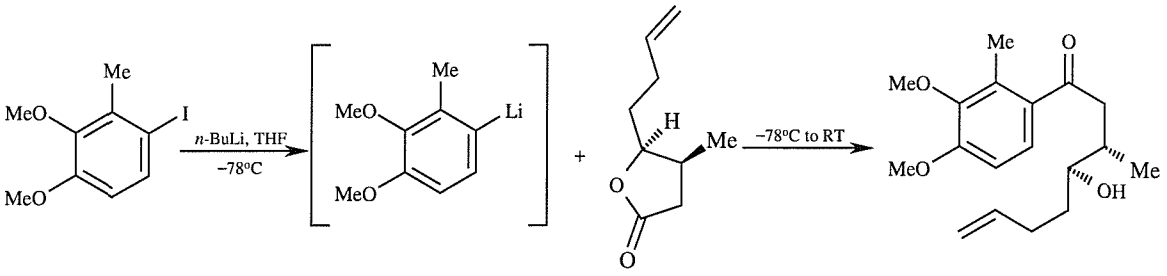
10.3, 1.5 Hz, CHH=CH), 4.47 (1H, ddd, $J$ = 9.6, 5.9, 4.4 Hz, OCH), 2.69 (1H, dd, $J$ = 16.9, 8.1 Hz, O=CCHH), 2.59 (2H, m, $CH_2CH=CH_2$), 2.21 (1H, dd, $J$ = 16.9, 3.7 Hz, O=CCHH), 2.34-2.05 (1H, m, $CH_3CH$), 1.74 (1H, m, OCHCHH), 1.60 (1H, m, OCHCHH), 1.02 (3H, d, $J$ = 7.4 Hz, $CHCH_3$).

**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 176.8 (s), 137.3 (d), 115.9 (t), 82.9 (d), 37.6 (t), 33.1 (d), 30.2 (t), 29.4 (t), 14.1 (q).

**LRMS** $^m/_z$ (CI+) 172 ($[M+18]^+$, 100%), 155 ($[M+H]^+$, 6%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 172.1337. $C_9H_{18}O_2N$ requires 172.1338.

**Preparation of *rel*-(3*S*,4*S*)-1-(1,2-dimethoxy-3-methylphen-4-yl)-4-hydroxy-3-methyloct-7-ene-1-one 144.**




**152** $C_9H_{11}IO_2$ (278)

**153**

**72** $C_9H_{14}O_2$ (154)

**144** $C_{18}H_{26}O_4$ (306)

4-Iodo-3-methylveratrole **152** (310 mg, 1.12 mmol) was dissolved in THF (15 mL) and cooled to −78°C. *n*-BuLi (1.6M in hexane, 0.83 mL, 1.23 mmol) was added over 2 min and the reaction was stirred at −78°C for 4 hr. A solution of the lactone **147** (172 mg, 1.12 mmol) in THF (2 mL) was added and the reaction was stirred at −78°C for a further 1 hr before being allowed to warm to RT over 1 hr. The reaction mixture was quenched with saturated $NH_4Cl$ (10 mL) and extracted into $Et_2O$ (3 × 30 mL). The combined

organic phases were washed with water (3 × 30 mL), brine (2 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark yellow oil. Purification by flash column chromatography (silica, gradient elution, 50% to 70% $Et_2O$ in petrol) gave **144** as a light yellow oil (67 mg, 0.2 mmol, 20%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3477 brw, 3076 w, 2938 s, 1713 s, 1641 m, 1595 s, 1573 m, 1490 s, 1452 s, 1377 m, 1276 s, 1083 s, 1047 s, 1006 s, 912 s, 733 s.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.75 (1H, d, *J* = 8.1 Hz, Ar**H**), 5.85 (1H, ddt, *J* = 17.6, 10.3, 6.6 Hz, $CH_2$=C**H**H), 5.10-4.95 (2H, m, **$H_2$**C=CH), 3.91 (3H, s, ArOC**$H_3$**), 3.78 (3H, s, ArOC**$H_3$**), 3.61 (1H, m, C**H**OH), 3.07 (1H, dd, *J* = 16.2, 6.6 Hz, O=CC**H**H), 2.80 (1H, dd, *J* = 16.2, 6.6 Hz, O=CCH**H**), 2.44 (3H, s, ArC**$H_3$**), 2.35-2.08 (4H, m, =CHC**$H_2$**, C**H**$CH_3$ & CHO**H**), 1.55 (2H, app q, *J* = 8.1 Hz, $CH_2$=$CHCH_2C$**$H_2$**), 0.95 (3H, d, *J* = 7.4 Hz, CHC**$H_3$**).

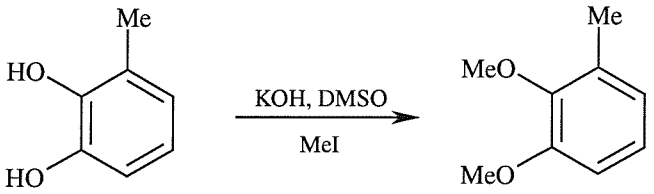
**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 203.6 (s), 155.8 (s), 148.1 (s), 138.9 (d), 133.5 (s), 132.5 (s), 126.0 (s), 115.1 (t), 108.5 (s), 74.2 (d), 60.4 (q), 55.9 (q), 45.2 (t), 35.3 (d), 33.4 (t), 30.8 (t), 14.2 (q), 13.4 (q).

**UV** $\lambda_{max}$ (MeOH) 264 (1020) and 212 (1897).

**LRMS** $^m/_z$ (APCI +ve) 307 ($[MH]^+$, 29%), 289 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (Cl+) Found $[MH]^+$ 307.1916. $C_{18}H_{27}O_4$ requires 307.1909.

**Preparation of 3-methylveratrole 145.**




**124** **145**

$C_7H_8O_2$ (124) $C_9H_{12}O_2$ (152)

Prepared by a modified procedure of Johnston and Rose.[87]

To a vigorously stirred solution of powdered KOH (13.56 g, 242 mmol) in DMSO (130 mL) was added 3-methylcatechol **124** (5.0 g, 40.3 mmol). The reaction was stirred for 20 min and then iodomethane (30.3 mL, 487 mmol) was added followed by continued stirring at RT for 24 hr. The reaction mixture was poured into water (150 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark brown oil. Purification by short path distillation under reduced pressure (aspirator pressure, 75-85°C) gave **145** as a light yellow oil (4.548 g, 29.9 mmol, 74%).

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3065 w, 2936 s, 1587 s, 1485 s, 1305 s, 1095 s, 1011 s, 806 s, 687 s.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.98 (1H, t, $J$ = 7.4 Hz, Ar**H**), 6.80 (2H, app d, $J$ = 7.4 Hz, Ar**H**), 3.88 (3H, s, ArOC**H$_3$**), 3.83 (3H, s, ArOC**H$_3$**), 2.30 (3H, s, ArC**H$_3$**).

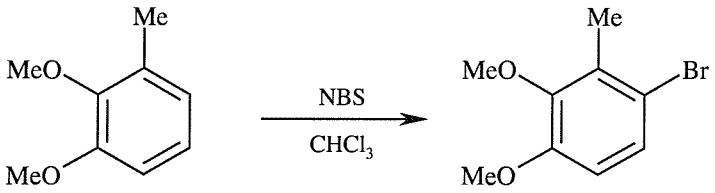
**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.9 (s), 147.5 (s), 132.2 (s), 123.9 (d), 122.9 (d), 110.1 (d), 60.2 (q), 55.8 (q), 15.9 (q).

**UV** $\lambda_{max}$ (MeOH) 270 (142) and 212 (709).

**LRMS** $^{m}/_{z}$ (APCI +ve) 152 ($M^+$, 100%).

These data were consistent with those reported in the literature.[92]

**The preparation of 4-bromo-3-methylveratrole 154.**




**145** **154**

$C_9H_{12}O_2$ (152) $C_9H_{11}BrO_2$ (231)

Prepared by a modified procedure described by McKillop *et al.*[58]

3-Methyl veratrole **145** (4.45 g, 29.2 mmol) was dissolved in $CHCl_3$ (30 mL) and NBS (5.2 g, 29.2 mmol) was added. The reaction was heated at reflux for 2 days and then allowed to cool. Succinimide separated and was removed by filtration. Residual $CHCl_3$ was then removed *in vacuo* giving a yellow oil. Purification by distillation under reduced pressure gave **154** as a cream coloured solid (5.023 g, 21.7 mmol, 75%).

**m.p.** 49-50°C, lit.[59] 51-52°C.

**IR** $\nu_{max}$ (nujol)/$cm^{-1}$ 2920 s, 2848 s, 1573 s, 1456 s, 1406 s, 1377 s, 1294 s, 1225 s, 1169 s, 926 m.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.25 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.68 (1H, d, $J$ = 8.8 Hz, Ar**H**), 3.85 (3H, s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 2.35 (3H, s, $ArCH_3$).

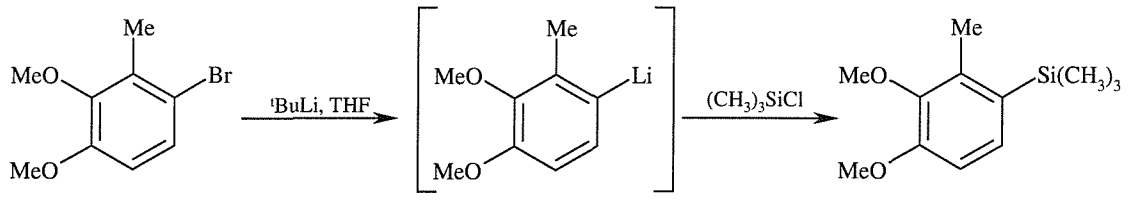
**$^{13}$C NMR** $\delta_H$ (75.5 MHz, $CDCl_3$) 152.3 (s), 148.1 (s), 132.4 (s), 127.5 (d), 116.2 (s), 111.0 (d), 60.6 (q), 56.0 (q), 16.3 (q).

**UV** $\lambda_{max}$ (MeOH) 278 (159), 226 (857) and 213 (924).

**LRMS** $^m/_z$ (APCI +ve) 232 ([M($^{81}$Br)]$^+$, 96%), 230 ([M($^{79}$Br)]$^+$, 100%).

These data were fully consistent with those previously reported in the literature.[59]

**Preparation of trimethyl(2-methyl-3,4-dimethoxy)phenyl)silane 155.**




**154** $C_{12}H_8O_2Br$ (230.9)

**153**

**155** $C_{12}H_{20}O_2Si$ (224)

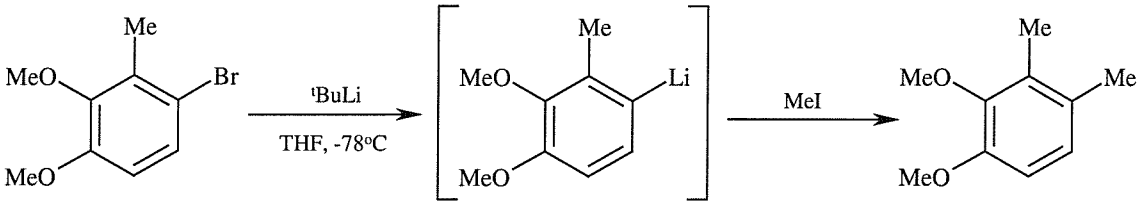
A solution of 4-bromo-3-methyl veratrole **154** (664 mg, 2.86 mmol) in THF (20 mL) was cooled to −78°C under $N_2$. $^t$BuLi (3.83 mL, 1.5M solution in pentane) was added in a dropwise fashion and the reaction was stirred at −78°C for 2 hr giving a yellow solution. TMSCl (0.4 mL, 3.16 mmol) was added and the reaction was allowed to warm to RT over 1 hr then stirred for 14 hr giving a pale yellow solution. The reaction was poured into 1M NaOH (20 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentration *in vacuo* to give **155** as a cream coloured crystalline solid (0.64 g, 2.86 mmol, quantitative).

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.18 (1H, d, $J$ = 8.1 Hz, ArH), 6.79 (1H, d, $J$ = 8.1 Hz, ArH), 3.88 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 2.40 (3H, s, $ArCH_3$), 0.32 (9H, s, $Si(CH_3)_3$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 177.4 (s), 153.5 (s), 147.1 (s), 137.4 (s), 130.2 (d), 109.1 (d), 60.0 (q), 55.5 (q), 15.7 (q), 0.8 (q), 0.1 (q), 0.08 (q).

**LRMS** $^m/_z$ (APCI, +ve) 224 ($M^+$, 100%), 209 ($[M-Me]^+$, 16%).

**Preparation of 3,4-dimethylveratrole 156.**




**154** $C_{12}H_8O_2Br$ (230.9)

**153**

**156** $C_{10}H_{14}O_2$ (166)

4-Bromo-3-methyl veratrole **154** (0.5 g, 2.17 mmol) was dissolved in anh. THF (5 mL) and cooled to −78°C under $N_2$. $^t$BuLi (2.89 mL, 1.5M solution in pentane) was added and the reaction was stirred at −78°C for 2 hr giving a yellow suspension. Methyl iodide (0.14 mL, 2.17 mmol) was added in a dropwise fashion and a pale yellow colour was observed. The reaction mixture was allowed to warm to RT over 30 min before being cooled to −78°C and quenched by the addtion of saturated $NH_4Cl$ (20 mL). The reaction mixture was extracted into $Et_2O$ (3 × 50 mL), washed with water (3 × 50 mL) and brine (3 × 50 mL), dried ($MgSO_4$) and filtered. Concentration *in vacuo* gave **156** as a dark yellow oil (318 mg, 1.92 mmol, 88%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3025 m, 2940 s, 1590 m, 1498 s, 1470 s, 1308 s, 1270 s, 1230 s, 1098 s, 1010 s, 820 m, 780 m, 750 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.89 (1H, d, $J$ = 7.4 Hz, Ar**H**), 6.78 (1H, d, $J$ = 7.4 Hz, Ar**H**), 3.85 (3H, s, ArOC**H**$_3$), 3.78 (3H, s, ArOC**H**$_3$), 2.23 (3H, s, ArC**H**$_3$), 2.20 (3H, s, ArC**H**$_3$).

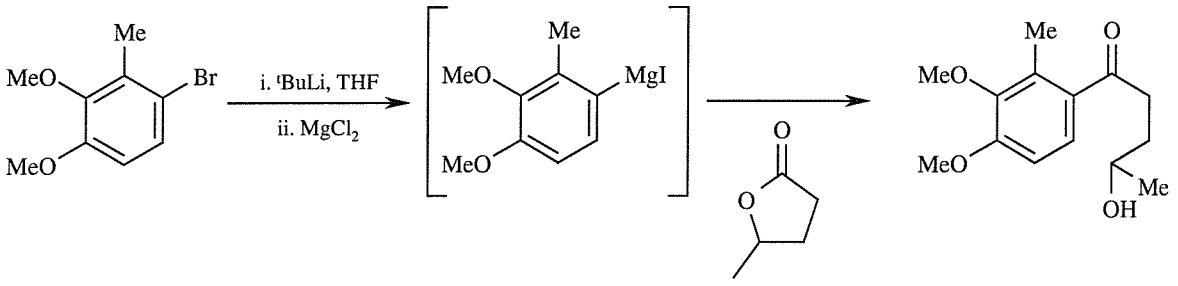
**$^{13}$C-NMR** δ (75.5 MHz, $CDCl_3$) 150.9 (s), 147.3 (s), 130.8 (s), 129.9 (s), 124.8 (d), 109.3 (d), 60.4 (q), 55.9 (q), 19.6 (q), 12.4 (q).

**UV** $\lambda_{max}$ (MeOH) 274 (221) and 216 (952).

**LRMS** $^m/_z$ (APCI +ve) 167 ($[MH]^+$, 100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 184.1345. $C_{10}H_{18}O_2N$ requires 184.1338.

**Preparation of 4-hydroxy-1-(2-methyl-3,4-dimethoxy)phenyl)-1-pentanone 159.**




**154** **157** **158** **159**

$C_{12}H_{11}O_2Br$ (230.9) $C_{14}H_{20}O_4$ (252)

A solution of 4-bromo-3-methyl veratrole **154** (0.5 g, 2.17 mmol) in THF (10 mL) was cooled to −78°C under $N_2$. $^t$BuLi (2.89 mL, 1.5M solution in pentane) was added in a dropwise fashion and the reaction mixture was stirred at −78°C for 3 hr giving a yellow solution. This was transferred via a cannula to a suspension of $MgI_2$ (0.907 g, 3.26 mmol) in THF (7 mL) giving a deep red coloured solution. The reaction mixture was stirred at −78°C for ½ hr and then γ-valerolactone **158** (0.21 mL, 2.17 mmol) was added.

The reaction mixture was stirred at −78°C for 1 hr and then at 0°C for ½ hr giving a pale red coloured solution. A saturated solution of $NH_4Cl$ (30 mL) and water (100 mL) was added and the reaction mixture was extracted into $Et_2O$ (3 × 30 mL). The combined organic phases were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **159** as a pale yellow oil. Purification by flash column chromatography (silica, 70% $Et_2O$ in petrol) gave **159** as a light yellow oil (122 mg, 0.48 mmol, 22%).

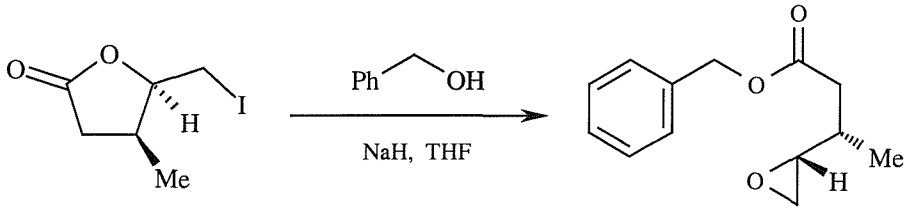
**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3443 br s, 2965 s, 1769 m, 1673 s, 1593 s, 1568 s, 1490 s, 1450 s, 1412 s, 1275 s, 1083 s, 1006 s, 810 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.52 (1H, d, $J$ = 8.1 Hz, Ar**H**), 6.78 (1H, d, $J$ = 8.1 Hz, Ar**H**), 3.91 (3H, s, ArOC**H$_3$**), 3.86 (1H, m, C**H**OH), 3.78 (3H, s, ArOC**H$_3$**), 3.03 (2H, t, $J$ = 7.4 Hz, C**H$_2$**C=O), 2.44 (3H, s, ArC**H$_3$**), 2.04 (1H, br s, CHO**H**), 1.98-1.73 (2H, m, C**H$_2$**CH$_2$C=O), 1.24 (3H, d, $J$ = 5.9 Hz, CHC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 203.5 (s), 155.5 (s), 147.9 (s), 133.5 (s), 131.8 (s), 126.1 (d), 108.5 (d), 67.8 (d), 60.4 (q), 55.9 (q), 37.8 (t), 33.7 (t), 23.9 (q), 13.4 (q).

**LRMS** $^m/_z$ (APCI +ve) 253 ([$MH^+$], 28%), 235 ([MH-$H_2O$], 100%).

**Preparation of benzyl *rel*-(1′*S*,3*R*)-3-oxiran-1′-ylbutanoate 162.**




**127** **162**

$C_6H_9IO_2$ (240) $C_{13}H_{16}O_3$ (220)

NaH (46 mg, 1.15 mmol, 60% dispersion in oil) was dissolved in THF (5 mL) and the benzyl alcohol (0.12 mL, 1.04 mmol) was added with stirring at RT under $N_2$. The reaction mixture was stirred at RT for 1 hr and the iodolactone **127** (250 mg, 1.04 mmol) was added, followed by continued stirring for 24 hr. The THF was removed *in vacuo* and the resultant oil was dissolved in EtOAc (50 mL), washed with water (3 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **162** as a colourless oil. Purification by flash column chromatography (silica, gradient system, 10% $Et_2O$ in petrol to 50% $Et_2O$ in petrol) gave **162** as a colourless oil (166 mg, 0.75 mmol, 73%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2967 s, 1734 s, 1498 w, 1456 s, 1417 w, 1382 m, 1355 m, 1259 brs, 1159 brs, 1097 m, 1001 m, 831 m, 698 s.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.37 (5H, s, Ph), 5.14 (2H, s, Ar**C**$H_2$), 2.81 (1H, ddd, *J* = 6.6, 4.4, 2.9 Hz, O-C**H**), 2.68 (1H, t, *J* = 4.4 Hz, O-C**H**H), 2.52 (1H, dd, *J* = 4.4, 2.9 Hz, OCH**H**), 2.46 (1H, dd, *J* = 15.1, 2.5 Hz, O=CC**H**H), 2.32 (1H, dd, *J* = 15.1, 7.4 Hz, O=CCH**H**), 1.97 (1H, app septet, *J* = 6.6 Hz, $CH_3$C**H**), 1.08 (3H, d, *J* = 6.6 Hz, CH**C**$H_3$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 172.1 (s), 135.9 (s), 128.8 (2 × d), 128.5 (3 × d), 66.5 (t), 55.9 (d), 46.4 (t), 38.1 (t), 33.0 (d), 16.9 (t).

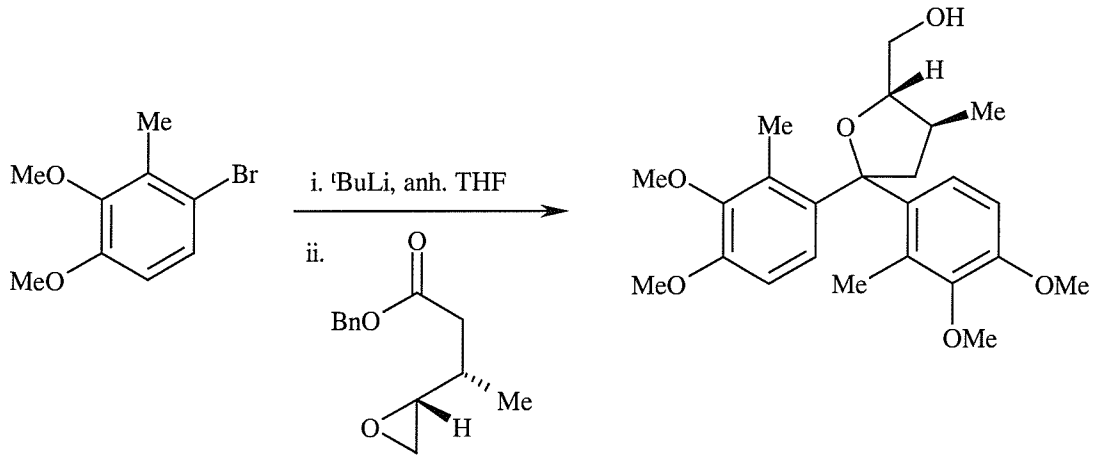
**UV** $\lambda_{max}$ (MeOH) 260 (59) and 214 (477).

**LRMS** $^{m}/_{z}$ (CI+) 238 ($[M+18]^+$, 40%), 221 ($[MH]^+$, 36%), 91 (100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 238.1447. $C_{13}H_{20}O_3N$ requires 238.1443.

These data were consistent with those previously reported in the literature.[66]

**Preparation of *rel*-(2*S*,3*S*)-2-(hydroxymethyl)-3-methyl-5,5-bis(2-methyl-3,4-dimethoxyphenyl)-tetrahydrofuran 163.**




**154** $C_9H_{11}O_2Br$ (231)

**162** $C_{13}H_{16}O_3$ (220)

**163** $C_{24}H_{32}O_6$ (416)

A solution of 4-bromo-3-methylveratrole **154** (0.156 g, 0.68 mmol) in THF (10 mL) was cooled to −78°C under $N_2$. $^t$BuLi (0.9 mL, 1.5M solution in pentane) was added in a dropwise fashion and the reaction mixture was stirred at −78°C for 1 hr giving a yellow solution. A solution of the benzyl ester **162** (0.149 g, 0.68 mmol) in THF (10 mL) was added slowly and upon complete addition the reaction was stirred at −78°C for ½ hr and then at 0°C for a further ½ hr. The reaction mixture was quenched by addition of saturated $NH_4Cl$ (20 mL), diluted with water (100 mL) and extracted into $Et_2O$ (3 × 20 mL). The combined organic phases were washed with water (3 × 75 mL) and brine (3 × 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification

by flash column chromatography (silica, 50% $Et_2O$ in petrol) gave **163** as a pale yellow oil (56 mg, 0.13 mmol, 20%).

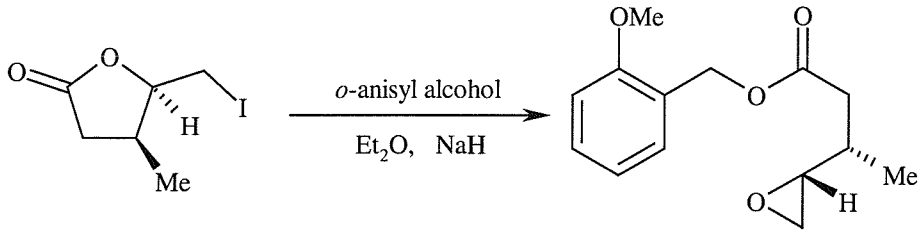
**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3456 br s, 2958 s, 1956 m, 1488 s, 1463 s, 1411 m, 1299 s, 1169 w, 1085 s, 1032 s, 911 s, 732 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.34 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.21 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.72 (2H, d, *J* = 8.8 Hz, Ar**H**), 3.87 (6H, s, ArOC**H$_3$**), 3.71 (3H, s, ArOC**H$_3$**), 3.69 (3H, s, ArOC**H$_3$**), 3.75 (2H, m, C**H$_2$**OH), 3.49 (1H, q, *J* = 6.6 Hz, C**H**CH$_2$OH), 3.14 (1H, dd, *J* = 13.6, 6.6 Hz, Ar$_2$CC**H**H), 2.45 (1H, m, C**H**CH$_3$), 1.90 (6H, s, ArC**H$_3$**), 1.53 (1H, br s, O**H**), 1.23 (1H, dd, *J* = 13.6, 6.6 Hz, Ar$_2$CH**H**), 1.07 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151.8 (s), 151.3 (s), 148.4 (s), 147.8 (s), 138.9 (s), 136.3 (s), 132.1 (s), 129.5 (s), 121.9 (d), 121.6 (d), 108.5 (d), 108.1 (d), 88.4 (s), 86.6 (d), 62.8 (t), 60.3 (2 × q), 55.7 (2 × q), 47.1 (t), 34.6 (d), 30.5 (q), 16.4 (q), 13.2 (q).

**LRMS** $^m/_z$ (APCI, +ve) 417 ($[MH]^+$, 57%), 399 ($[MH\text{-}H_2O]^+$, 55%), 265 ($[MH\text{-}152]^+$, 100%).

**Preparation of 2-methoxybenzyl *rel*-(1′*S*,3*R*)-3-oxiran-1-ylbutanoate 164.**




**127** $C_6H_9O_2I$ (240)

**164** $C_{14}H_{18}O_4$ (250)

NaH (250 mg, 6.25 mmol, 60% dispersion in oil) was added to a solution of the *o*-anisyl alcohol (576 mg, 4.17 mmol) in $Et_2O$ (20 mL) at RT. A solution of the iodolactone **127** (1.0 g, 4.17 mmol) in $Et_2O$ (10 mL) was added in a dropwise fashion over 5 minutes. The reaction mixture was stirred at RT for 24 hrs and then diluted with $H_2O$ (30 mL) and extracted into $Et_2O$ (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a pale yellow oil. Purification by flash column chromatography (silica, 20% $Et_2O$ in petrol) afforded **164** as a colourless oil (765 mg, 3.06 mmol, 78%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2965 s, 1733 s, 1604 m, 1496 s, 1462 s, 1288 s, 1249 s, 1160 s, 1120 w, 1028 m, 756 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.33 (2H, m, Ar**H**), 6.96 (1H, t, *J* = 7.4 Hz, Ar**H**), 6.91 (1H, d, *J* = 8.8 Hz, Ar**H**), 5.19 (2H, s, Ar**CH$_2$**), 3.85 (3H, s, ArO**CH$_3$**), 2.81 (1H, ddd, *J* = 6.6, 4.4, 2.9 Hz, O**CH**), 2.68 (1H, t, *J* = 4.4 Hz, OC**H**HCH), 2.52 (1H, dd, *J* = 4.4, 2.9 Hz, OCH**H**CH), 2.46 (1H, dd, *J* = 15.1, 2.5 Hz, O=CC**H**H), 2.32 (1H, dd, *J* = 15.1, 7.4 Hz, O=CCH**H**), 1.97 (1H, m, CH$_3$C**H**), 1.08 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

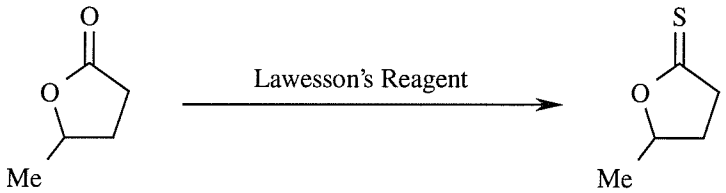
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 172.2 (s), 157.7 (s), 130.1 (d), 129.9 (d), 124.1 (s), 120.6 (d), 110.6 (d), 62.1 (t), 56.0 (d), 55.5 (q), 46.5 (t), 38.3 (t), 33.2 (d), 16.9 (q).

**UV** $\lambda_{max}$ (MeOH) 272 (1250) and 210 (4333).

**LRMS** $^m/_z$ (CI+) 268 ($[H+18]^+$, 40%), 251 ($[H+H]^+$, 4%), 138 ($[M-112]^+$, 100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 268.1560. $C_{14}H_{22}O_4N$ requires 268.1549.

**Preparation of 5-methyldihydro-2(5*H*)-furanthione 165.**




**158** $C_5H_8O_2$ (100)

**165** $C_5H_8OS$ (116)

A solution of γ-valerolactone **158** (1.9 mL, 19.98 mmol) and Lawesson's reagent (8.1 g, 19.98 mmol) in toluene (50 mL) was stirred at reflux under $N_2$ for 48 hr giving an orange coloured solution. The reaction mixture was allowed to cool and the cream coloured suspension was removed by filtration. The mixture was extracted into $Et_2O$ (3 × 50 mL) and the combined organic phases were washed with water (3 × 100 mL) and brine (3 × 100 mL), dried ($MgSO_4$), filtered and concentration *in vacuo* to a dark yellow oil. Purification by flash column chromatography (silica, 40% $Et_2O$ in petrol) gave **165** as an orange/yellow oil (1.782 g, 15.4 mmol, 77%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2978 s, 2932 s, 1455 m, 1348 s, 1291 s, 1236 s., 1162 s, 1088 w, 1077 w, 1038 s, 866 s.

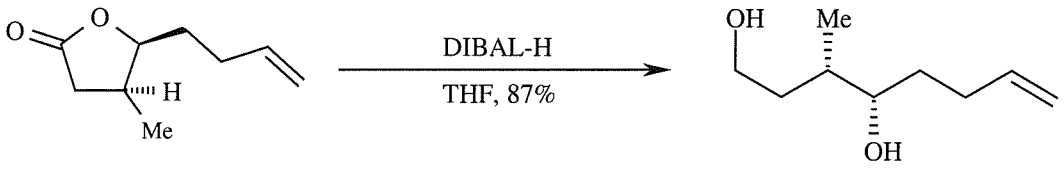
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 5.00 (1H, dqd, *J* = 8.8, 6.6, 5.9 Hz, $CH_3CH$), 3.17 (1H, ddd, *J* = 19.1, 8.8, 5.5 Hz, CHHC=S), 3.02 (1H, ddd, *J* = 19.1, 9.6, 8.8 Hz, CHHC=S), 2.39 (1H, dddd, *J* = 12.5, 8.8, 6.6, 5.5 Hz, $CHHCH_2C$=S), 1.86 (1H, ddt, *J* = 12.5, 9.6, 8.8 Hz, $CHHCH_3C$=S), 1.50 (3H, d, *J* = 6.6 Hz, $CH_3CH$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 222.8 (s), 87.4 (d), 45.3 (t), 31.5 (t), 20.6 (q).

**LRMS** $^m/_z$ (CI+) 134 ($[M+18]^+$, 6%), 117 ($[M+H]^+$, 100%).

These data were consistent with those previously reported in the literature.[88]

**Preparation of (3*S*,4*S*)-3-methyl-7-octene-1,4-diol 166.**




**147**

$C_9H_{14}O_2$ (154)

**166**

$C_9H_{18}O_2$ (158)

DIBAL-H (1M solution in toluene, 13.4 mL, 13.4 mmol) was added dropwise over 10 min to a solution of the lactone **147** (1.03 g, 6.69 mmol) in THF (30 mL). The reaction mixture was stirred at ambient temperature for 48 hr then quenched by addition of 2M HCl (30 mL). The reaction mixture was extracted into EtOAc (3 × 50 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a light yellow oil. Purification by flash colunm chromatography (silica, 1:1 EtOAc in petrol) gave **166** (915 mg, 5.79 mmol, 87%) as a colourless oil.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3300 brs, 2935 s, 1640 m, 1456 s, 1376 m, 1254 m, 1117m, 1054 s, 1002 s, 946 w, 910 s.

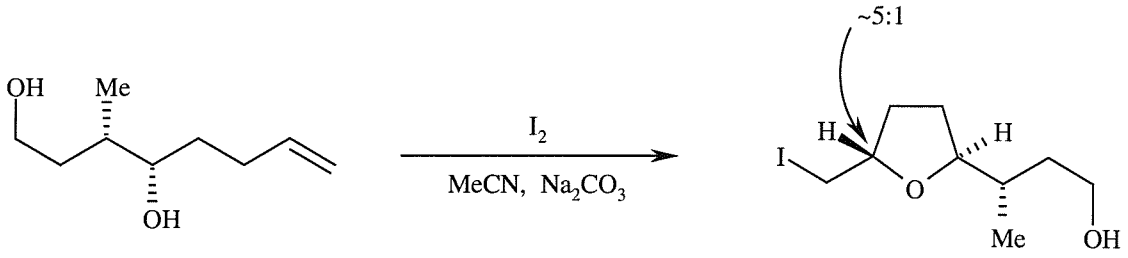
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 5.85 (1H, ddt, $J$ = 16.9, 10.3, 6.6 Hz, $CH_2$=C**H**), 5.06 (1H, dd, $J$ = 16.9, 1.5 Hz, C**H**H=CH), 4.98 (1H, dd, $J$ = 10.3, 1.5 Hz, CH**H**=CH), 3.73 (1H, m, C**H**OH), 3.62 (2H, m, C**H$_2$**OH), 3.08 (2H, br s, O**H**), 2.24 (1H, dt, $J$ = 14.7, 6.6 Hz, C**H**HCH=$CH_2$), 2.11 (1H, dt, $J$ = 14.7, 6.6 Hz, CH**H**CH=$CH_2$), 1.81-1.45 (5H, m, $CH_3$C**H**, $CH_2$O**H** & C**H$_2$**CHOH), 0.90 (3H, d, $J$ = 6.6 Hz, CHC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 138.9 (d), 114.9 (t), 74.5 (d), 60.8 (t), 36.4 (d), 36.2 (t), 32.8 (t), 30.9 (t), 14.2 (q).

**LRMS** $^m/_z$ (APCI +ve) 159 ($[MH]^+$, 3%), 141 ($[MH-H_2O]^+$, 100%).

**HRMS** (EI+) Found $[MH]^+$ 159.1385. $C_9H_{19}O_2$ requires 159.1381.

**Preparation of *rel-(2S,3′S,5S)*-2-(iodomethyl)-5-(1′-hydroxybut-3′-yl)-tetrahydrofuran 167.**




**166**

$C_9H_{18}O_2$ (158)

**167**

$C_9H_{17}O_2I$ (284)

A solution of diol **166** (2.29 g, 14.55 mmol) in freshly distilled MeCN (30 mL) was cooled to 0°C under $N_2$. $Na_2CO_3$ (1.54 g, 14.55 mmol) and iodine (18.47 g, 72.75 mmol) were added and the reaction was stirred at 0°C for 2½ hr then quenched with sat. $Na_2S_2O_3$ (300 mL). The reaction mixture was extracted into EtOAc (3 × 100 mL) and the combined organic phases were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by flash colunm chromatography

(silica, 60% $Et_2O$ in petrol) afforded **167** (3.59 g, 12.64 mmol, 87%) as a yellow oil in a *trans : cis* ratio of 5:1.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3393 brs, 2956 s, 2874 s, 1456 s, 1425 m, 1374 m, 1348 w, 1193 w, 1166 w, 1056 s, 1007 s, 969 m, 948 m, 904 w, 874 w.

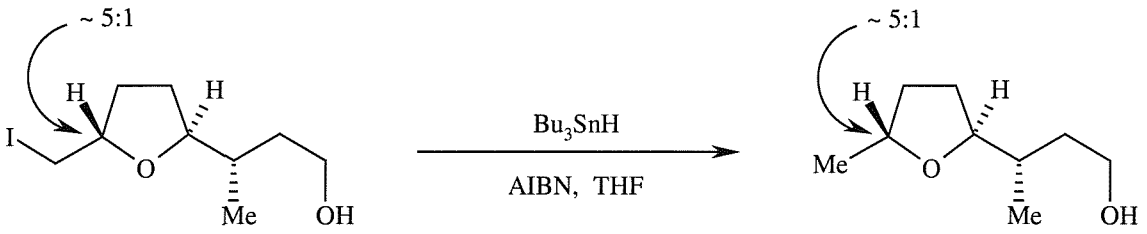
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 4.03 (1H, dtd, *J* = 14.0, 6.6, 2.9 Hz, $ICH_2CH$), 3.81 (1H, dt, *J* = 9.6, 5.1 Hz, $CHCHCH_3$), 3.71 (2H, m, $CH_2OH$), 3.21 (2H, d, *J* = 6.6 Hz, $ICH_2CH$), 2.16 (1H, br s, $CH_2OH$), 2.20-1.31 (7H, m, $CH_3CH$, $CH_2CH_2OH$ & $CHCH_2CH_2CH$), 0.94 (3H, d, *J* = 7.4 Hz, $CH_3CH$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 84.1 (d), 78.6 (d), 60.9 (t), 35.8 (t), 34.4 (d), 32.9 (t), 29.1 (t), 15.6 (q), 11.1 (t). Additional signals for the *rel*-(2*R*,3′*S*,5*S*) diastereoisomer $\delta_C$ 84.7 (d), 78.4 (d), 36.1 (t), 34.3 (d), 31.6 (t), 27.9 (t), 15.5 (q), 10.2 (t).

**LRMS** $^m/_z$ (APCI +ve) 285 ($[MH]^+$, 14%), 267 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (EI+) Found $[MH]^+$ 285.0353. $C_9H_{18}O_2I$ requires 285.0352.

**Preparation of *rel*-(2*S*,3′*S*,5*R*)-2-(1′-hydroxybut-3′-yl)-5-methyltetrahydrofuran 168.**




**167** $C_9H_{17}O_2I$ (284)

**168** $C_9H_{18}O_2$ (158)

AIBN (299 mg, 1.82 mmol) and $Bu_3SnH$ (2.0 mL, 7.28 mmol) were added to a solution of the THF **167** (2.07 g, 7.28 mmol) in THF (30 mL) at RT. The reaction mixture was stirred at 40-45°C for 2 hr and then quenched by the addition of sat. KF (50 mL). After stirring for 6 hr a white solid was removed by filtration and the mother liquor was extracted into EtOAc (4 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a viscous oil. Purification by flash colunm chromatography (silica, 50% $Et_2O$ in petrol) afforded **168** (1.08 g, 6.80 mmol, 93%) as a yellow oil in a *trans : cis* ratio of ~5:1.

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3384 brs, 2966 s, 2873 s, 1458 s, 1376 s, 1192 w, 1066 s, 1014 m, 992 m, 884 w, 818 w.

**$^1$H-NMR** $\delta_H$ (400 MHz, $CDCl_3$) 4.09 (1H, ddq, *J* = 8.4, 6.1, 5.9 Hz, $CH_3CHO$), 3.93 (1H, ddd, *J* = 9.2, 6.0, 5.1 Hz, CHCHO), 3.71 (1H, dt, *J* = 10.9, 6.1 Hz, CHHOH), 3.63 (1H, ddd, *J* = 10.9, 7.3, 5.7 Hz, CHHOH), 2.71 (1H, br s, $CH_2OH$), 2.03 (1H, dddd, *J* = 9.7, 7.3, 6.1, 2.4 Hz, $CH_3CHCH\alpha H$), 1.95-1.40 (6H, m, $CH_3CHCH$, $CHHCH_2CHCHH_2CH_2OH$), 1.23 (3H, d, *J* = 5.9 Hz, $CH_3CHO$), 0.95 (3H, d, *J* = 6.6 Hz, $CH_3CHCH$). These assignments were confirmed by $^1$H-$^1$H COSY.

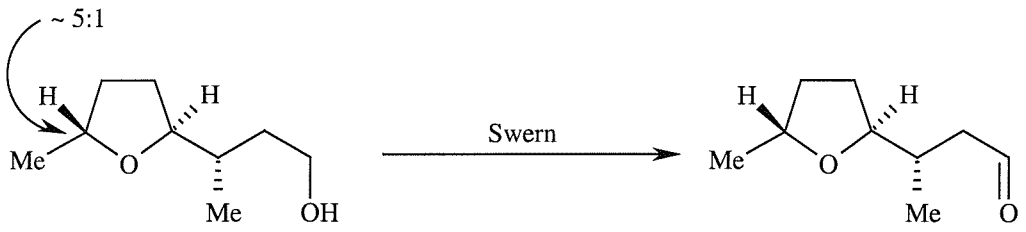
**n.O.e** (400 MHz, $CDCl_3$) irradiation of signal at $\delta_H$ 4.09 ($CH_3$**C**H**O**) caused an n.O.e enhancement at 2.03 ($CH_3$CH**C**H**C**αH), 1.46 (**C**H**C**αHCHCH) and 1.23 (**C**$H_3$CHO).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 82.6 (d), 75.6 (d), 60.9 (t), 36.0 (t), 34.8 (d), 34 2 (t), 29.0 (t), 21.5 (q), 15.7 (q). Additional signals for the minor *rel*-(2*R*,3′*S*,5*S*) diastereoisomer $\delta_C$ 83.3 (d), 33.0 (t), 27.6 (t), 20.9 (q), 15.8 (q).

**LRMS** $^m/_z$ (APCI +ve) 159 ($[MH]^+$, 24%), 141 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (EI+) Found $[MH]^+$ 159.1399. $C_9H_{19}O_2$ requires 159.1399.

**Preparation of *rel*-(2′*S*,3*S*,5′*R*)-3-(5′-methyltetrahydrofuran-2′-yl)-butanal 169.**




**168**

$C_9H_{18}O_2$ (158)

**169**

$C_9H_{16}O_2$ (156)

To a solution of oxalyl chloride (2M in $CH_2Cl_2$, 9.89 mL, 19.79 mmol) in $CH_2Cl_2$ (10 mL) at −78°C was added, in a dropwise fashion over 10 min, a 1M solution of DMSO (34.92 mL, 34.92 mmol) in $CH_2Cl_2$. The reaction mixture was stirred at −78°C for 45 min then a solution of the alcohol **168** (1.84 g, 11.64 mmol) in $CH_2Cl_2$ (30 mL) was added *via* a cannula maintaining the temperature below −60°C. $Et_3N$ (6.49 mL, 46.56 mmol) was added after stirring for 2 hr at −78°C and upon complete addition the reaction mixture was allowed to warm to −30°C over 1 hr. The mixture was poured into 0.5M $NaHSO_4$ (100 mL) and extracted into $CH_2Cl_2$ (3 × 75 mL). The combined organic phases

were washed with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a pale yellow oil. Purification by flash column chromatography (silica, 20% $Et_2O$ in petrol) gave firstly mixed fractions of 1:1 *cis* : *trans* diastereoisomers (309 mg, 1.98 mmol, 17%) as a colourless oil and then the *trans* diastereoisomer **169** (1.35 g, 8.65 mmol, 74%) as a colourless oil.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2965 s, 2878 s, 1724 s, 1456 m, 1377 m, 1189 w, 1083 s, 1023 m, 875 w, 816 w.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 9.71 (1H, t, $J$ = 2.9 Hz, O=C**H**), 3.98 (2H, m, $CH_3$C**H**O & CHC**H**O), 2.47 (2H, dd, $J$ = 8.8, 2.9 Hz, C**H$_2$**C=O), 2.23 (1H, m, C**H**HCH$_2$), 2.02 (1H, m, CH**H**C**H$_2$**), 1.90 (1H, m, CH$_2$C**H**H), 1.60-1.40 (2H, m, CH$_2$CH**H** & CH$_3$C**H**CH), 1.20 (3H, d, $J$ = 5.9 Hz, C**H$_3$**CHO), 0.98 (3H, $J$ = 6.6 Hz, C**H$_3$**CHCH).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 202.1 (d), 81.9 (d), 75.3 (d), 46.7 (t), 34.2 (t), 32.7 (d), 28.2 (t), 21.4 (q), 16.3 (q).

**LRMS** $^m/_z$ (APCl +ve) 157 ($[MH]^+$, 47%), 155 ($[M-H]^+$, 100%).

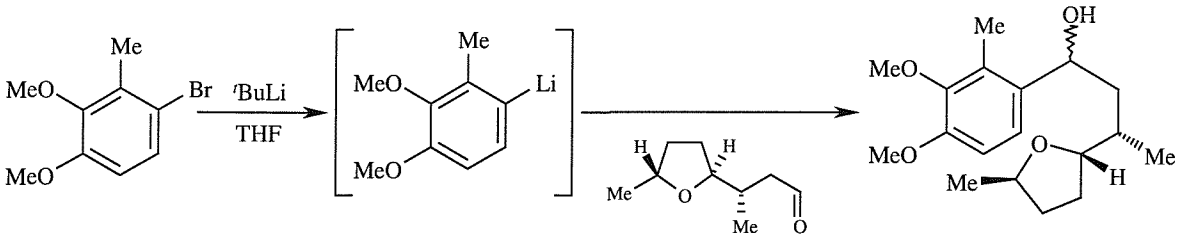
**HRMS** (CI+) Found $[M-H+H_2NOH]^+$ 188.1292. $C_9H_{18}O_3N$ requires 188.1287.

NMR analysis of the mixed fractions revealed additional signals, which are highlighted below:

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 9.74 (1H, t, $J$ = 2.2 Hz, O=C**H**), 3.80 (2H, m, $CH_3$C**H**O & CHC**H**O), 1.21 (3H, d, $J$ = 6.6 Hz, C**H$_3$**CH) and 0.97 (3H, d, $J$ = 6.6 Hz, C**H$_3$**CH).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 202.8 (d), 82.4 (d), 75.6 (d), 46.8 (t), 33.0 (t), 32.2 (d), 27.3 (t), 20.9 (q), 16.6 (q).

**Preparation of *rel*-(1′*RS*,2*S*, 3′*S*,5*R*)-2-(1′-(3″,4″-dimethoxy-2″-methylphenyl)-1′-hydroxybut-3′-yl)-5-methyltetrahydrofuran 170 + 170a.**




**154**
$C_9H_{11}O_2Br$ (231)

**169**
$C_9H_{16}O_2$ (156)

**170 + 170a**
$C_{18}H_{28}O_4$ (308)

4-Bromo-3-methylveratrole **154** (5.92 g, 25.64 mmol) was dissolved in THF (50 mL) and cooled to −78°C. $^t$BuLi (1.46M in pentane, 21.4 mL, 25.64 mmol) was added dropwise over 10 min and the reaction mixture was stirred at −78°C for 1 hr giving a yellow/orange coloured solution. A solution of the aldehyde **169** (2.0 g, 12.82 mmol) in THF (20 mL) was added *via* a cannula maintaining the temperature below −60°C. Upon complete addition the reaction mixture was allowed to warm to RT over 2 hr giving a yellow solution. The reaction mixture was quenched with sat. $NH_4Cl$ (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a yellow oil. Purification by flash column chromatography (silica, gradient elution 20-50% $Et_2O$ in petrol) initially gave **170a** as a single diastereoisomer (887 mg, 2.88 mmol, 23%) and then fractions of mixed diastereoisomers **170** (2.34 g, 7.60 mmol, 59%), both as colourless oils.

Data recorded on single diastereoisomer **170a**:

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3446 brs, 2926 s, 1488 s, 1454 s, 1416 s, 1374 w, 1270 s, 1214 m, 1082 s, 1052 s, 1025 m, 999 m, 871 w, 814 m, 690 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.25 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.80 (1H, d, $J$ = 8.8 Hz, Ar**H**), 5.01 (1H, dd, $J$ = 10.3, 1.5 Hz, ArC**H**OH), 4.15 (1H, app dq, $J$ = 8.8, 5.9 Hz, $CH_3$C**H**O), 4.05 (1H, dt, $J$ = 9.6, 5.1 Hz, CHC**H**O), 3.86 (3H, s, ArOC**H$_3$**), 3.78 (3H, s, ArOC**H$_3$**), 3.63 (1H, br s, CHO**H**), 2.25 (3H, s, ArC**H$_3$**), 2.15-1.35 (7H, m, $CH_3$C**H**, C**H$_2$**C**H$_2$**CHCH**H$_2$**C**H$_2$**OH), 1.25 (3H, d, $J$ = 5.9 Hz, C**H$_3$**CH), 0.98 (3H, d, $J$ = 6.6 Hz, C**H$_3$**CH).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151 5 (s), 147.0 (s), 136.6 (s), 128.9 (s), 121.2 (d), 109.7 (d), 82.4 (d), 75.9 (d), 67.8 (d), 60.4 (q), 55.8 (q), 42.4 (t), 34.3 (d), 34.1 (t), 29.1 (t), 21.6 (q), 15.3 (q), 11.3 (q).

**UV** $\lambda_{max}$ (MeOH) 274 (231), 226 (1155) and 210 (1232).

**LRMS** $^m/_z$ (APCI +ve) 309 ($[MH]^+$, 5%), 291 ($[MH\text{-}H_2O]^+$, 100%).

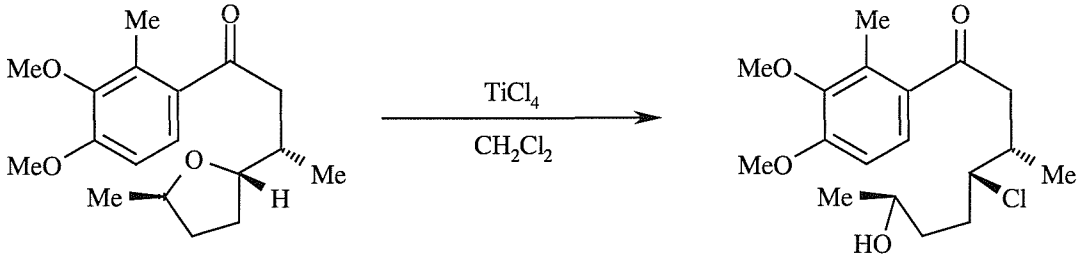
**HRMS** (EI+) Found $[M]^+$ 308.1965. $C_{18}H_{28}O_4$ requires 308.1987.

NMR analysis of the mixed fractions **170** revealed additional signals, which are shown below:

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 4.90 (1H, dd, $J$ = 10.3, 1.5 Hz, ArC**H**OH), 3.88 (1H, m, CHC**H**O), 3.08 (1H, br s, CHO**H**), 2.27 (3H, s, ArC**H$_3$**), 1.04 (3H, d, $J$ = 6.6 Hz, C**H$_3$**CH).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 137.2 (s), 128.7 (s), 120.7 (d), 82.8 (d), 75.5 (d), 69.2 (d), 41.7 (t), 35.3 (d), 28.7 (t), 21.5 (q), 16.9 (q), 11.2 (q).

**Preparation of *rel*-(3*S*,4*R*,7*R*)-1-(1,2dimethoxy-3-methylphen-4-yl)-4-chloro-3-methyloct-7-hydroxy-1-one 171.**




**143**

$C_{18}H_{26}O_4$ (306)

**171**

$C_{18}H_{27}O_4Cl$ (343)

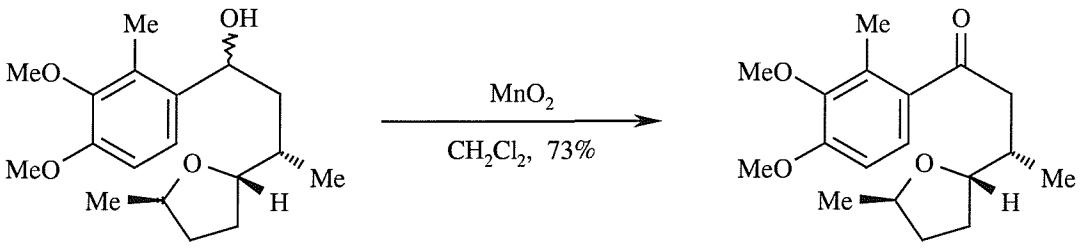
$TiCl_4$ (0.1 mL, 0.91 mmol) was added to a solution of the ketone **143** (100 mg, 0.33 mmol) in $CH_2Cl_2$ (10 mL) at RT under $N_2$. The reaction mixture was stirred at RT for 4 days then quenched with $H_2O$ (10 mL) and extracted into $CH_2Cl_2$ (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown film. Purification by flash column chromatography (silica, gradient elution 20-100% $Et_2O$ in petrol) afforded a colourless film tentatively assigned as **171** (14 mg, 0.04 mmol, 12%).

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.45 (1H, d, $J$ = 8.0, Ar**H**), 6.72 (1H, d, $J$ = 8.0, Ar**H**), 4.15 (2H, m, **CH**Cl & **CH**OH), 3.88 (3H, s, ArOC**H$_3$**), 3.80 (3H, s, ArOC**H$_3$**), 2.54 (2H, m, ArCOC**H$_2$**), 2.40 (3H, s, ArC**H$_3$**), 1.92-1.58 (6H, m, C**H**CH$_3$, C**H$_2$**C**H$_2$** & C**H**CH$_3$), 1.21 (3H, d, $J$ = 6.0, C**H$_3$**CH), 1.17 (3H, d, $J$ = 6.6, CHC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 122.2 (d), 108.3 (d), 86.8 (d), 67.7 (d), 60.1 (q), 55.7 (q), 49.9 (t), 34.7 (d), 34.4 (t), 30.3 (t), 22.8 (q), 19.9 (q), 13.0 (q). Quarternary carbons were not observed.

Further data could not be obtained as this compound deteriorated on standing.

**Preparation of *rel*-(2*S*,3′*S*,5*R*)-2-(1′-(3″,4″-dimethoxy-2″-methylphenyl)-1-oxo-but-3′-yl)-5-methyltetrahydrofuran 143.**




**170**

$C_{18}H_{28}O_4$ (308)

**143**

$C_{18}H_{26}O_4$ (306)

$MnO_2$ (519 mg, 5.97 mmol), activated by azeotroping residual water away with toluene, was added to a stirred solution of the alcohol **170** (92 mg, 0.29 mmol) in $CH_2Cl_2$ (30 mL). The reaction was stirred at RT for 6 hr after which time further $MnO_2$ (519 mg, 5.97 mmol) was added. Continued stirring for 24 hr was followed by filtering through celite. The residual solids were washed with copious amounts of $CHCl_3$ (100 mL) and the mother liquors were concentrated *in vacuo* giving a yellow oil. Purification by flash column chromatography (silica, 30% $Et_2O$ in petrol) gave **143** (64 mg, 0.21 mmol, 73%) as a colourless oil.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2964 s, 2868 s, 1676 s, 1593 s, 1569 s, 1490 s, 1449 s, 1412 s, 1375 m, 1274 s, 1244 s, 1222 s, 1084 s, 887 w, 868 w, 838 w, 804 m, 772 w, 693 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.55 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.75 (1H, d, $J$ = 8.8 Hz, Ar**H**), 4.05 (1H, dquin, $J$ = 8.8, 5.9 Hz, $CH_3CHO$), 3.93 (1H, dt, $J$ = 9.6, 5.1 Hz, CHCHO), 3.90 (3H, s, $ArOCH_3$), 3.77 (3H, s, $ArOCH_3$), 2.99 (1H, dd, $J$ = 15.4, 4.8 Hz, ArCOCHH), 2.65 (1H, dd, $J$ = 15.4, 8.8 Hz, ArCOCHH), 2.42 (3H, s, $ArCH_3$), 2.34 (1H, m), 2.00 (2H, m), 1.68 (1H, m), 1.48 (1H, m), 1.21 (3H, d, $J$ = 5.9 Hz, $CH_3CH$), 0.96 (3H, d, $J$ = 6.6 Hz, $CH_3CH$).

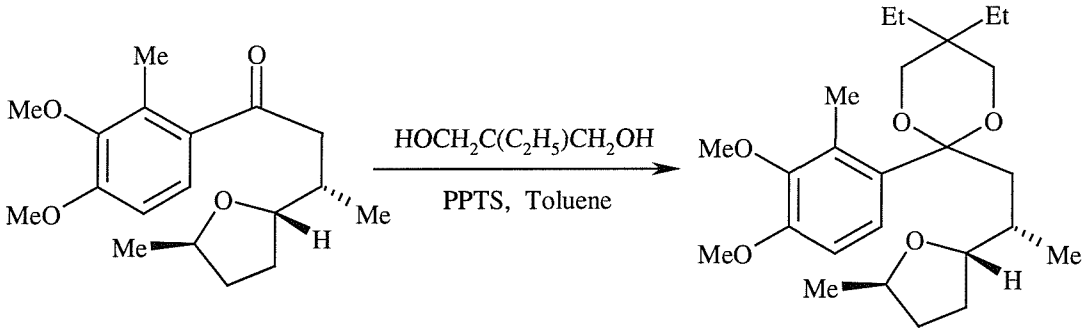
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 202.9 (s), 155.3 (s), 147.9 (s), 133.3 (s), 132.5 (s), 125.9 (d), 108.4 (d), 82.3 (d), 75.5 (d), 60.4 (q), 55.8 (q), 44.8 (t), 34.7 (d), 34.3 (t), 29.2 (t), 21.5 (q), 15.8 (q), 13.3 (q).

**UV** $\lambda_{max}$ (MeOH) 275 (9180) and 225 (6630).

**LRMS** $^m/_z$ (APCI +ve) 307 ($[MH]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 306.1837. $C_{18}H_{26}O_4$ requires 306.1813.

**Preparation of *rel*-(2″*S*,2‴*S*,5‴*R*)-2-(3′,4′-dimethoxy-2′-methylphenyl)-5,5-diethyl-2-(2″-[5‴-methyltetrahydrofuran-2‴-yl]propyl)-1,3-dioxane 172.**




**143**
$C_{18}H_{26}O_4$ (306)

**172**
$C_{25}H_{40}O_5$ (420)

2,2-Diethylpropan-1,2-diol (216 mg, 1.63 mmol) and PPTS (205 mg, 0.82 mmol) was added to a solution of ketone **143** (250 mg, 0.82 mmol) in toluene (50 mL) at RT under $N_2$. The reaction mixture was stirred at reflux under a soxhlet extractor containing 4Å molecular sieves for 6 days and then allowed to cool. The mixture was diluted with $H_2O$ (50 mL), extracted into $Et_2O$ (3 × 40 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a light brown oil. Purification by flash column chromatography (silica, 10% $Et_2O$ in petrol) afforded **172** as colourless oil (280 mg, 0.67 mmol, 81%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2959 s, 1596 s, 1575 m, 1486 s, 1459 s, 1410 s, 1381 s, 1270 s, 1218 s, 1173 s, 1085 s, 814 s.

**$^1$H-NMR** $\delta_H$ (400 MHz, $CDCl_3$) 7.14 (1H, d, $J$ = 8.7 Hz, Ar**H**), 6.72 (1H, d, $J$ = 8.7 Hz, Ar**H**), 3.99-3.70 (2H, m, $CH_3$**CH**O & CH**CH**O), 3.84 (3H, s, ArOC**H$_3$**), 3.75 (3H, s, ArOC**H$_3$**), 3.49 (4H, brs, C**H$_2$**O & C**H$_2$**O), 2.31 (3H, s, ArC**H$_3$**), 1.99-0.95 (7H, m, $CH_3$**CH**, C**H$_2$**C**H$_2$**, ArC$H_2$C**H$_2$**), 1.18 (3H, d, $J$ = 6.0 Hz, CHC**H$_3$**), 0.91 (3H, d, $J$ = 6.6 Hz, CHC**H$_3$**), 0.82 (6H, d, $J$ = 7.5 Hz, 2 × $CH_2$C**H$_3$**), 0.4 (4H, t, $J$ = 7.5 Hz, 2 × C**H$_2$**$CH_3$).

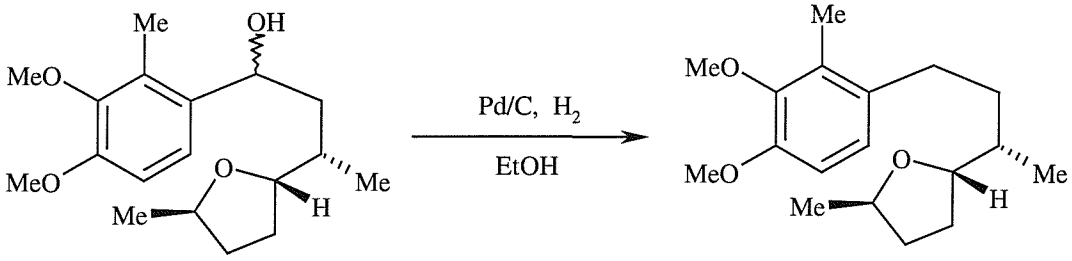
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.0 (s), 148.0 (s), 131.3 (s), 131.0 (s), 124.7 (d), 108.9 (d), 103.5 (s), 83.7 (d), 75.1 (d), 68.7 (t), 68.3 (t), 60.1 (q), 55.6 (q), 45.3 (t), 34.5 (q), 34.2 (t), 33.1 (d), 29.5 (t), 24.4 (t), 22.6 (t), 21.5 (q), 17.9 (q), 12.3 (q), 7.7 (q), 6.5 (q).

**UV** $\lambda_{max}$ (MeOH) 270 (151) and 225 (958).

**LRMS** $^m/_z$ (APCI +ve ) 421 ($[MH]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 420.2875. $C_{25}H_{40}O_5$ requires 420.2899.

**Preparation of *rel*-(2*S*,3′*S*,5*R*)-2-(1′-(3″,4″-dimethoxy-2″-methylphenyl)-but-3′-yl)-5-methyltetrahydrofuran 174.**




**170**

$C_{18}H_{28}O_4$ (308)

**174**

$C_{18}H_{28}O_3$ (292)

A vigorously stirred solution of the alcohol **170** (400 mg, 1.30 mmol) and 5% Pd/C (319 mg, 0.15 mmol) in EtOH (20 mL) was purged three times each with $N_2$ and $H_2$. The reaction mixture was stirred at RT under $H_2$ at atmospheric pressure for 4 days. The reaction mixture was purged with $N_2$, filtered through celite and the resultant filtrate was concentrated *in vacuo* giving **174** as a pale yellow/colourless oil (327 mg, 1.12 mmol, 87%).

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 2962 s, 2870 s, 1603 w, 1578 w, 1489 s, 1456 s, 1417 m, 1374 m, 1270 s, 1224 s, 1085 s, 1005 s, 801 m, 688 w.

**$^1$H NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.87 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.71 (1H, d, $J$ = 8.8 Hz, Ar**H**), 4.05 (1H, app dquin, $J$ = 8.8, 5.9 Hz, $CH_3CHO$), 3.93 (1H, app dt, $J$ = 9.6, 5.1 Hz, CHC**H**O), 3.85 (3H, s, ArOC**H$_3$**), 3.79 (3H, s, ArOC**H$_3$**), 2.66 (1H, ddd, $J$ = 13.3, 11.4, 5.1 Hz, ArCH**H**), 2.48 (1H, ddd, $J$ = 13.3, 11.4, 5.1 Hz, ArC**H**H), 2.24 (3H, s, ArC**H$_3$**), 2.15-1.35 (7H, m, $CH_3$C**H**, C**H$_2$**C**H$_2$**, ArCH$_2$C**H$_2$**), 1.23 (3H, d, $J$ = 5.9 Hz, CHC**H$_3$**), 1.05 (3H, d, $J$ = 6.6 Hz, CHC**H$_3$**).

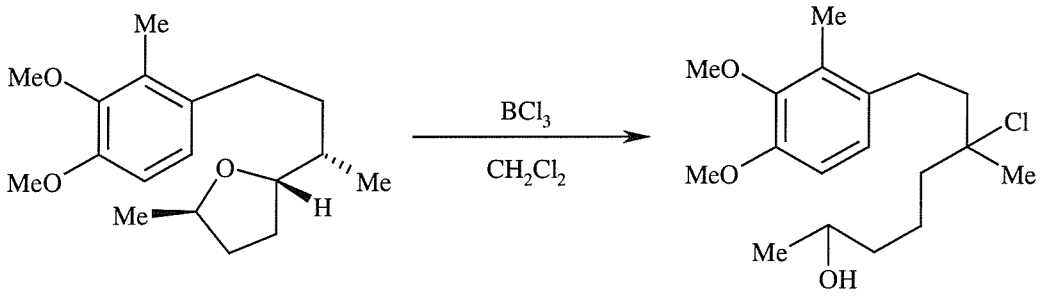
**$^{13}$C NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 150.9 (s), 147.4 (s), 134.6 (s), 130.3 (s), 124.1 (d), 109.5 (d), 83.2 (d), 75.1 (d), 60.3 (q), 55.8 (q), 38.5 (q), 34.4 (t), 33.9 (t), 31.1 (t), 29.8 (t), 21.5 (d), 16.1 (q), 11.8 (q).

**UV** $\lambda_{max}$ (MeOH) 278 (1343) and 230 (1927).

**LRMS** $^m/_z$ (APCI +ve) 293 ($[MH]^+$, 28%), 275 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 292.2033. $C_{18}H_{28}O_3$ requires 292.2038.

**Preparation of 6-chloro-8-(3,4-dimethoxy-2-methylphenyl)-6-methyloctan-2-ol 175.**




**174**

$C_{18}H_{28}O_3$ (292)

**175**

$C_{18}H_{29}O_3Cl$ (328)

A solution of $BCl_3$ (0.8 mL, 0.8 mmol, 1 M solution in heptane) in $CH_2Cl_2$ (10 mL) was added in a dropwise fashion to an ice-cold solution of the tetrahydrofuran **174** (213 mg, 0.73 mmol) in $CH_2Cl_2$ (10 ml) under $N_2$. The reaction mixture was allowed to warm to RT, stirred for 48 hr then quenched with ice/water (20 mL) and extracted into $Et_2O$ (3 x 15 mL). The combined organic phases were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* giving a yellow film. Purification by flash column chromatography (silica, gradient elution in 5-50% $Et_2O$ in petrol) firstly gave the tricycle **176** (83 mg, 0.30 mmol, 42%) and then **175** as a colourless oil (76 mg, 0.23 mmol, 32%) and single, unknown diastereoisomer.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3411 brs, 2941 s, 2837 w, 1490 s, 1455 s, 1418 w, 1378 w, 1271 s, 1224 w, 1084 s, 1004 w, 801 w, 733 m, 668 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.9 (1H, d, $J$ = 8.1 Hz, Ar**H**), 6.7 (1H, d, $J$ = 8.1 Hz, Ar**H**), 3.86 (3H, s, ArOC**H$_3$**), 3.80 (3H, s, ArOC**H$_3$**), 2.75 (2H, m, ArC**H$_2$**), 2.26 (3H, s, ArC**H$_3$**), 2.00-1.4 (8H, m, ArCH$_2$C**H$_2$** & C**H$_2$**C**H$_2$**C**H$_2$**), 1.63 (3H, s, CClC**H$_3$**), 1.23 (3H, d, $J$ = 6.6 Hz, CHOHC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151.1 (s), 147.5 (s), 133.3 (s), 130.4 (s), 124.3 (d), 109.7 (d), 74.6 (s), 68.1 (d), 60.3 (q), 55.8 (q), 45.2 (t), 44.3 (t), 39.4 (t), 27.7 (q), 28.6 (t), 23.8 (q), 21.2 (t), 11.8 (q).

**UV** $\lambda_{max}$ (MeOH) 278 (1554) and 233 (2244).

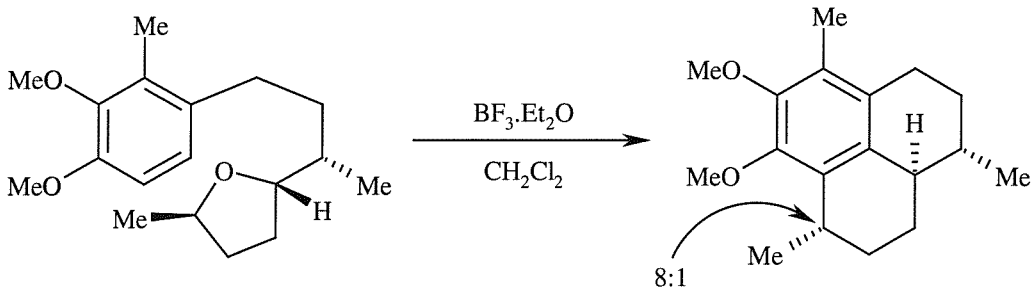
**LRMS** $^m/_z$ (APCI +ve) 329 ($[MH]^+$, 15%), 293 ($[MH\text{-}HCl]^+$, 17%), 275 ($[MH\text{-}HCl\text{-}H_2O]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 328.1804. $C_{18}H_{29}O_3Cl$ requires 328.1805.

**Alternative preparation of 175.**

$TiCl_4$ (0.04 mL, 0.39mmol) was added in a dropwise fashion to a solution of the tetrahydrofuran **174** (38 mg, 0.13 mmol) in $CH_2Cl_2$ (10 mL) at RT under $N_2$. The reaction mixture was stirred at RT for 6 hr and quenched by the careful addition of $H_2O$ (10 mL). The reaction mixture was extracted into $CH_2Cl_2$ (3 × 15 mL) and the combined organic phases were washed with $H_2O$ (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by flash column chromatography (silica, 40% $Et_2O$ in petrol) gave **175** (23 mg, 0.07 mmol, 54%) as a colurless oil.

**Preparation of (1*S*,3a*R*,4*S*)-1,4,7-trimethyl-8,9-dimethoxy)-2,3,3a,4,5,6-hexahydro-(1*H*)-phenalene 176.**




**174** **176**

$C_{18}H_{28}O_3$ (292) $C_{18}H_{26}O_2$ (274)

A solution of $BF_3.Et_2O$ (0.1 mL, 0.75mmol) in $CH_2Cl_2$ (5 mL) was added dropwise over 5 min to an ice-cold solution of the tetrahydrofuran **174** (200 mg, 0.68 mmol) in $CH_2Cl_2$ (10 mL) under $N_2$. The reaction mixture was allowed to warm to RT then stirred for 48 hr. A further 2 eq. of $BF_3.Et_2O$ was added and the reaction was stirred at reflux for 3 days. The reaction mixture was quenched with ice/water (20 mL) and extracted into $Et_2O$ (3 x 15 mL). The combined organic phases were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a yellow film. Purification by flash column chromatrography (silica, gradient elution in 5-50% $Et_2O$ in petrol) gave **176** as a colourless oil (201 mg, 0.73 mmol, 81%) and an inseparable 8:1 mixture of diastereoisomers.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2927 s, 2860 s, 1460 s, 1410 s, 1375 w, 1318 s, 1251 w, 1119 m, 1069 s, 1037 w, 1022 w, 1006 w, 978 w.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 3.88 (3H, s, ArOC**H**$_3$), 3.83 (3H, s, ArOC**H**$_3$), 3.33 (1H, tq, *J* = 7.4, 7.4 Hz, ArC**H**CH$_3$), 2.73 (1H, ddd, *J* = 16.9, 5.9, 2.2 Hz, ArC**H**H), 2.58 (1H, ddd, *J* = 16.9, 11.4, 5.9 Hz, ArCH**H**), 2.15 (3H, s, ArC**H**$_3$), 1.90-1.30 (7H, m, C**H**$_2$C**H**$_2$CHC**H**, & ArCH$_2$C**H**$_2$), 1.26 (3H, d, *J* = 7.4 Hz, CHC**H**$_3$), 1.12 (3H, d, *J* = 6.6 Hz, CHC**H**$_3$), 1.12 (1H, obs m,

ArC**H**). Additional signals for the minor diastereoisomer $\delta_H$ 3.91 (3H, s, ArOC**H**$_3$), 3.82 (3H, s, ArOC**H**$_3$), 3.20 (1H, m, ArC**H**CH$_3$), 1.28 ((3H, d, *J* = 7.4 Hz, CHC**H**$_3$).

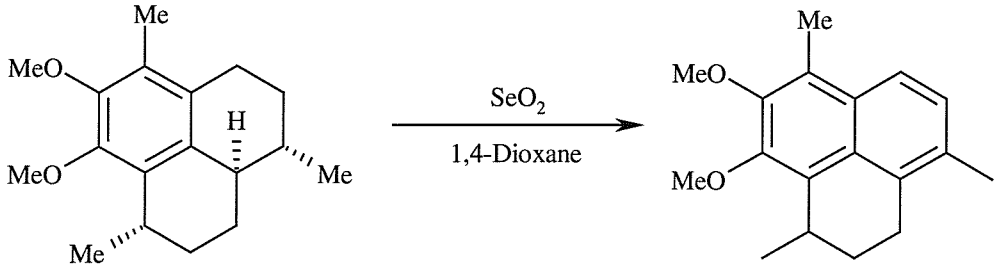
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 149.2 (s), 148.8 (s), 134.3 (s), 133.9 (s), 130.6 (s), 127.3 (s), 60.7 (q), 60.2 (q), 42.9 (d), 34.9 (d), 32.1 (t), 30.7 (t), 27.8 (t), 27.7 (t), 27.6 (d), 24.2 (q), 20.8 (q), 11.7 (q).

**UV** $\lambda_{max}$ (MeOH) 275 (422) and 235 (1475).

**LRMS** $^m/_z$ (APCI +ve) 275 ($[MH]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 274.1919. $C_{18}H_{26}O_2$ requires 274.1932.

**Preparation of 8,9-dimethoxy-1,4,7-trimethyl-2,3-dihydro-1*H*-phenalene 177.**




**176**
$C_{18}H_{26}O_2$ (274)

**177**
$C_{18}H_{22}O_2$ (270)

$SeO_2$ (98 mg, 0.89mmol) was added to a solution of the tricycle **176** (162 mg, 0.59 mmol) in 1,4-dioxane (20 mL) at RT under $N_2$. The reaction mixture was warmed to reflux and stirred for 4 days giving a dark brown/red solution. The reaction mixture was allowed to cool, diluted with $H_2O$ (50 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with $Na_2S_2O_3$ (100 mL) and sat. $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a dark yellow oil.

Purification by flash column chromatography (silica, 2% $Et_2O$ in petrol) afforded **177** as a colourless oil (119 mg, 0.44 mmol, 75%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2928 s, 1738 w, 1595 w, 1504 w, 1455 s, 1391 s, 1353 m, 1319 m, 1261 s, 1099 s, 1066 s, 1018 s, 963 m, 793 m.

**$^1$H-NMR** $\delta_H$ (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.21 (1H, d, *J* = 8.4 Hz, Ar**H**), 3.89 (3H, s, ArOC**H$_3$**), 3.80 (3H, s, ArOC**H$_3$**), 3.57 (1H, dqd, *J* = 11.6, 7.0, 2.5 Hz, ArC**H**CH$_3$), 2.90 (2H, m, ArC**H$_2$**), 2.48 (3H, s, ArC**H$_3$**), 2.33 (3H, s, ArC**H$_3$**), 1.91 (2H, m, C**H$_2$**CH$_2$Ar), 1.19 (3H, d, *J* = 7.0 Hz, C**H$_3$**CH). These assignments were confirmed by $^1$H-$^1$H and $^1$H-$^{13}$C COSY experiments.

**n.O.e** (400 MHz, $CDCl_3$) irradiation of the signal at $\delta_H$ 3.89 (ArOC**H$_3$**) caused an n.O.e enhancement at $\delta_H$ 3.57 (ArC**H**CH$_3$) and 1.19 (ArCHC**H$_3$**).

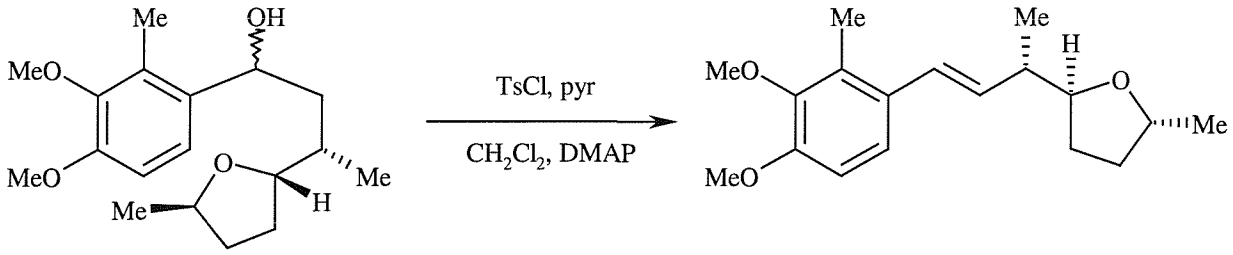
**$^{13}$C-NMR** $\delta_C$ (100 MHz, $CDCl_3$) 149.2 (s), 148.0 (s), 132.6 (s), 130.8 (s), 130.2 (s), 129.5 (s), 127.8 (d), 127.1 (s), 123.8 (s), 121.6 (d), 61.3 (q), 60.8 (q), 28.2 (t), 27.1 (d), 22.4 (t), 20.6 (q), 19.9 (q), 11.3 (q).

**UV** $\lambda_{max}$ (MeOH) 290 (648) and 238 (5022).

**LRMS** $^m/_z$ (APCI +ve) 271 ($[MH]^+$, 84%), 270 ($[M]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 270.1619. $C_{18}H_{22}O_2$ requires 270.1609.

**Preparation of *rel*-(2*S*,3′*S*,5*R*)-2-[1′-(3,4-dimethoxy-2-methylphenyl)-but-1′-en-3′-yl]-5-methyltetrahydrofuran 178.**




**170**

$C_{18}H_{28}O_4$ (308)

**178**

$C_{18}H_{26}O_3$ (290)

A solution of the alcohol **170** (887 mg, 2.88 mmol), TsCl (549 mg, 2.88 mmol), pyridine (0.23 mL, 2.88 mmol) and DMAP (35 mg, 0.29 mmol) in $CH_2Cl_2$ (50 mL) was stirred at RT for 24 hrs and then at reflux for 3 days. A further 2 eq. of TsCl was added and after stirring at reflux for 24 hrs the reaction mixture was diluted with $H_2O$ (30 mL) and extracted into $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 20% $Et_2O$ in Petrol) afforded **178** as a colourless oil (391 mg, 1.35 mmol, 47%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2963 s, 1598 m, 1488 s, 1453 s, 1294 s, 1270 s, 1219 s, 1084 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.14 (1H, d, $J$ = 8.1 Hz, Ar**H**), 6.75 (1H, d, $J$ = 8.1 Hz, Ar**H**), 6.53 (1H, d, $J$ = 16.2 Hz, ArC**H**=CH), 5.90 (1H, dd, $J$ = 16.2, 7.4 Hz, ArCH=C**H**), 4.14-3.90 (2H, m, C**H**OC**H**), 3.86 (3H, s, ArOC**H**$_3$), 3.78 (3H, s, ArOC**H**$_3$), 2.46 (1H, m, CH=CHC**H**), 2.27 (3H, s, ArC**H**$_3$), 2.10-1.92 (2H, m, C**H**$_2$CH$_2$), 1.70-1.45 (2H, m, CH$_2$C**H**$_2$), 1.25 (3H, d, $J$ = 6.6 Hz, CHC**H**$_3$), 1.16 (3H, d, $J$ = 6.6 Hz, CHC**H**$_3$).

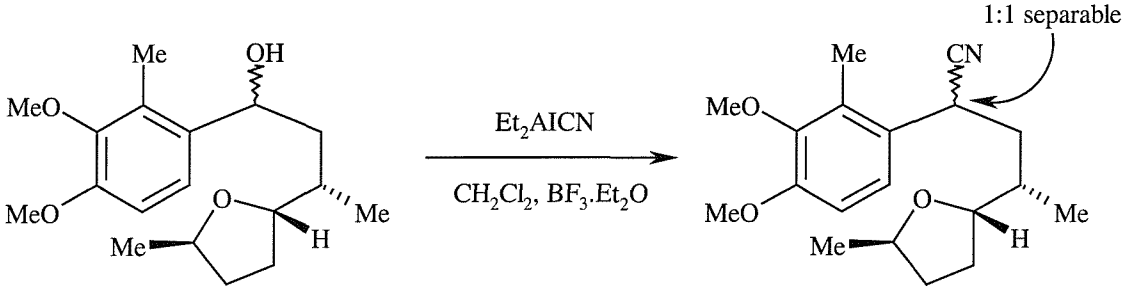
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151.9 (s), 147.2 (s), 132.8 (d), 131.1 (s), 129.7 (s), 127.8 (d), 121.4 (d), 109.7 (d), 82.8 (d), 75.2 (d), 60.4 (q), 55.8 (q), 42.9 (d), 34.2 (t), 29.9 (t), 21.4 (q), 17.3 (q), 12.2 (q).

**UV** $\lambda_{max}$ (MeOH) 262 (1141) and 210 (1778).

**LRMS** $^m/_z$ (APCI +ve) 291 ($[MH]^+$, 100%), 273 ($[MH-H_2O]^+$, 26%).

**HRMS** (CI+) Found $[MH]^+$ 291.1958. $C_{18}H_{27}O_3$ requires 291.1960.

**Preparation of *rel*-(2*RS*,2″*R*,4*S*,5″*S*)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-(5″-methyltetrahydrofuran-2″-yl)-pentyronitrile 179a and 179b.**




**170**

$C_{18}H_{28}O_4$ (308)

**179a + 179b**

$C_{19}H_{27}O_3N$ (317)

A solution of the alcohol **170** (300 mg, 0.97 mmol) in $CH_2Cl_2$ (20 mL) was added to a solution of $Et_2AlCN$ (4.9 mL, 4.87 mmol, 1 M in toluene) in $CH_2Cl_2$ (5 mL) at −78°C. The reaction mixture was stirred at −78°C for 5 minutes and $BF_3.Et_2O$ (0.12 mL, 0.97 mmol) was added over 1 minute. Upon complete addition the reaction was allowed to warm to RT and after stirring for 12 hrs a pale yellow solution had formed. The mixture was quenched with ice water (100 mL) and extracted into $Et_2O$ (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash column chromatography (silica, 20-50% $Et_2O$ in petrol) afforded **179a** and **179b** (215 mg, 0.68 mmol, 70%) as a 1:1 mixture of diastereoisomers which were separated by crystallisation from petrol.

Data for white crystalline solid; *rel-(2S,2″R,4S,5″S)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-(5″-methyltetrahydrofuran-2″-yl)-pentyronitrile* **179a**:

**m.p.** 103-104°C

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2960 s, 1604 w, 1578 w, 1490 s, 1452 s, 1416 m, 1274 s, 1230 m, 1100 s, 1006 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.19 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.78 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.03 (2H, m, **CHOCH**), 3.84 (3H, s, ArO**CH$_3$**), 3.77 (3H, s, ArO**CH$_3$**), 2.28 (3H, s, Ar**CH$_3$**), 2.05-1.40 (8H, m, Ar**CH**(CN)**CH$_2$CH** & **CH$_2$CH$_2$**), 1.08 (3H, d, *J* = 6.6 Hz, CH**CH$_3$**), 0.87 (3H, d, *J* = 6.6 Hz, CH**CH$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.3 (s), 147.6 (s), 129.3 (s), 127.8 (s), 123.1 (d), 121.3 (s), 110.1 (d), 80.6 (d), 75.4 (d), 60.3 (q), 55.7 (q), 39.1 (t), 36.5 (d), 34.2 (t), 32.2 (d), 29.2 (t), 21.6 (q), 15.8 (q), 11.7 (q).

**UV** $\lambda_{max}$ (MeOH) 275 (159), 224 (814) and 210 (888).

**LRMS** $^m/_z$ (APCI +ve, no cone) 318 ($[MH]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 317.1986. $C_{19}H_{27}O_3N$ requires 317.1991.

**CHN** Found: C, 71.70; H, 8.62; N, 4.41. $C_{19}H_{27}O_3N$ requires C, 71.92; H, 8.52; N, 4.42.

Data for colourless oil; *rel-(2R,2″R,4S,5″S)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-(5″-methyltetrahydrofuran-2″-yl)-pentyronitrile* **179b**:

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 2963 s, 1601 w, 1582 w, 1491 s, 1454 s, 1416 m, 1272 s, 1222 s, 1084 s, 1004 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.13 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.78 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.03 (2H, m, **CHOCH**), 3.84 (3H, s, ArOC**H$_3$**), 3.77 (3H, s, ArOC**H$_3$**), 2.26 (3H, s, ArC**H$_3$**), 2.05-1.40 (8H, m, ArC**H**(CN)C**H$_2$**C**H** & C**H$_2$**C**H$_2$**), 1.20 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**), 0.98 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

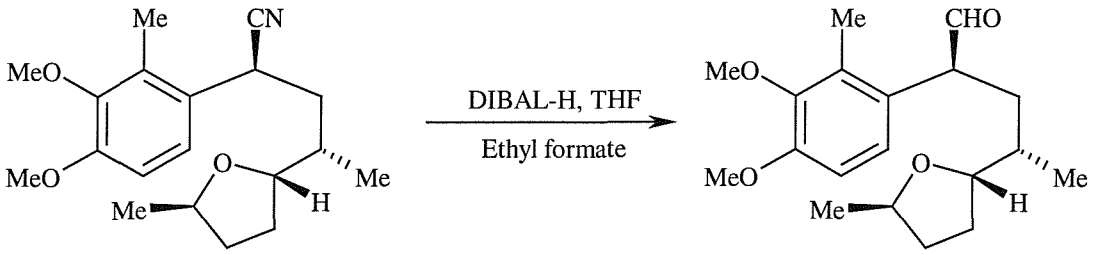
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.3 (s), 147.6 (s), 129.8 (s), 127.7 (s), 122.9 (d), 121.8 (s), 110.1 (d), 80.6 (d), 75.4 (d), 60.3 (q), 55.7 (q), 38.1 (t), 35.1 (d), 34.0 (t), 32.3 (d), 28.8 (t), 21.4 (q), 15.6 (q), 11.6 (q).

**UV** $\lambda_{max}$ (MeOH) 274 (164), 224 (849) and 210 (976).

**LRMS** $^m/_z$ (CI+) 335 ([M+18]$^+$, 100%), 318 ([MH]$^+$, 68%), 300 ([MH-18]$^+$, 46%).

**HRMS** (CI+) Found [M+$NH_4$]$^+$ 335.2343. $C_{19}H_{31}O_3N_2$ requires 335.2335.

**Preparation of *rel*-(2*S*,2″*R*,4*S*,5″*S*)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-(5″-methyltetrahydrofuran-2″-yl)-pentanal 180.**




**179a**

$C_{19}H_{27}O_3N$ (317)

**180**

$C_{19}H_{28}O_4$ (320)

DIBAL-H (20% in hexane, 1.25 mL, 1.12 mmol) was added to a solution of the nitrile **179a** (177 mg, 0.56 mmol) in THF (20 mL) at −78°C and the reaction mixture was stirred at −78°C for ½ hr then warmed to RT and stirred for 12 hr. Ethyl formate (0.1 mL, 1.12 mmol) was added and after stirring for 1 hr the reaction mixture was poured into saturated $NH_4Cl$ (30 mL) and stirred for a further ½ hr before 10% $H_2SO_4$ (20 mL) was added. The reaction mixture was extracted into $Et_2O$ (2 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash column chromatography (silica, 30% $Et_2O$ in petrol) afforded **180** (115 mg, 0.36 mmol, 64%) as a colourless oil with 5-10% of the *rel*-(2*R*,2″*R*,4*S*,5″*S*) diasteroisomer.

**FT-IR** $\nu_{max}$ (neat) 2963 s, 1721 s, 1599 w, 1579 w, 1487 s, 1454 s, 1416 m, 1375 m, 1272 s, 1084 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 9.58 (1H, d, $J$ = 1.5 Hz, CHCHO), 6.80 (2H, m, 2 × ArH), 4.02-3.85 (2H, m, CHOCH), 3.85 (3H, s, $ArOCH_3$), 3.78 (3H, s, $ArOCH_3$), 2.28 (3H, s, $ArCH_3$), 2.00-1.3 (8H, m, ArCH(CHO)$CH_2$CH & $CH_2CH_2$), 0.93 (3H, d, $J$ = 6.6 Hz, $CHCH_3$), 0.86 (3H, d, $J$ = 6.6 Hz, $CHCH_3$).

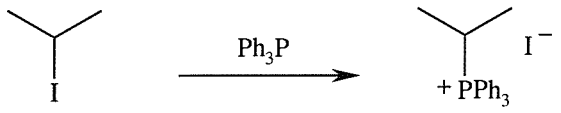
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 200.6 (d), 152.1 (s), 147.8 (s), 131.9 (s), 127.4 (s), 123.7 (d), 109.9 (d), 82.8 (d), 75.2 (d), 60.4 (d), 55.7 (q), 52.4 (d), 36.1 (d), 34.3 (t), 33.5 (t), 29.7 (t), 21.5 (q), 15.9 (q), 12.2 (q). Additional signals for the minor *rel*-(2*R*,2″*R*,4*S*,5″*S*) diastereoisomer $\delta_C$ 200.9 (d), 123.9 (d), 110.1 (d), 83.3 (d), 52.7 (d), 35.2 (d), 32.0 (t), 28.6 (t), 21.2 (q), 12.1 (q).

**UV** $\lambda_{max}$ (MeOH) 270 (171).

**LRMS** $^m/_z$ (APCI +ve) 321 ($[MH]^+$, 79%), 303 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (El+) Found $[M]^+$ 320.1963. $C_{19}H_{28}O_4$ requires 320.1987.

**Preparation of *iso*-propyl(triphenyl)phosphonium iodide 180b.[74]**




**180a** $C_3H_7I$ (170)

**180b** $C_{21}H_{22}PI$ (432)

$Ph_3P$ (4.63 g, 17.7 mmol) was added to 2-iodopropane **180a** (1.17 mL, 11.7 mmol) at RT under $N_2$. The reaction mixture was heated to 100°C giving a pale yellow solution. After 6 hrs a white solid was formed which was removed by filtration, washed with $Et_2O$ (250 mL) and dried *in vacuo* affording the desired ylid **180b** as an off white crystalline solid (4.227 g, 9.78 mmol, 83%).

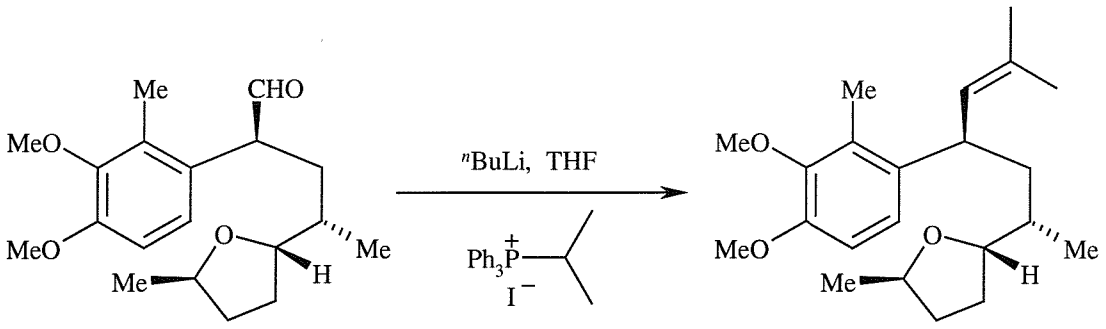
**m.p.** 190-191°C, lit.[74] 191°C.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.86 (6H, m, 6 × Ar**H**), 7.76-7.60 (9H, m, 9 × Ar**H**), 5.10 (1H, dq, $J$ = 17.7, 6.6 Hz, C**H**$(CH_3)_2$), 1.31 (3H, d, $J$ = 6.6 Hz, CHC**H**$_3$), 1.25 (3H, d, $J$ = 6.6 Hz, CHC**H**$_3$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 135.1 (d), 134.0 (d), 130.8 (d), 118.0 (s), 22.2 (q), 21.6 (q), 16.5 (d).

Data consistent with those reported in the literature.[74]

**Preparation of *rel*-(2*S*,4′*S*,5*R*,6′*S*)-2-(4′-[3″,4″-dimethoxy-2″methylphenyl]-2′-methylhept-2′-en-6′-yl)-5-methyltetrahydrofuran 181.**




**180** $C_{19}H_{28}O_4$ (320)

**180b**

**181** $C_{22}H_{34}O_3$ (346)

$^n$BuLi (1.47 M in hexane 1.1 mL, 1.60 mmol) was added in a dropwise fashion to a stirred suspension of *iso*-propyltriphenylphosphonium iodide **180b** (691 mg, 1.60 mmol) in THF (20 mL) at 0°C under $N_2$ giving a deep red solution. A solution of aldehyde **180** (256 mg, 0.80 mmol) in THF (10 mL) was added slowly *via* a dropping funnel and the resultant lighter red solution was stirred at 0°C for 2 hrs. The reaction mixture was quenched with ice/$H_2O$ (100 mL) giving a colourless solution which was extracted into $Et_2O$ (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a colourless oil. Purification by flash column chromatography (silica, 10% $Et_2O$ in Petrol) effected removal of the minor diastereoisomer giving **181** as a colourless oil (230 mg, 0.66 mmol, 83%).

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 2963 s, 2926 s, 1600 w, 1580 w, 1488 s, 1451 s, 1374 m, 1276 s, 1221 m, 1085 s, 1009 m, 799 w.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.96 (1H, d, *J* = 7.4 Hz, Ar**H**), 6.73 (1H, d, *J* = 7.4 Hz, Ar**H**), 5.23 (1H, d, *J* = 9.6 Hz, C**H**=C), 410-3.85 (3H, m, ArC**H**, $CH_3CHO$ & CHC**H**O), 3.84 (3H, s, ArOC**H$_3$**), 3.79 (3H, s, ArOC**H$_3$**), 2.29 (3H, s, ArC**H$_3$**), 2.05-1.20 (7H, m, $CH_3$C**H**, C**H$_2$**C**H$_2$** & ArCHC**H$_2$**), 1.70 (3H, s, CH=CC$H_3$C**H$_3$**), 1.64 (3H, s, CH=CC**H$_3$**C$H_3$), 1.20 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**), 0.98 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

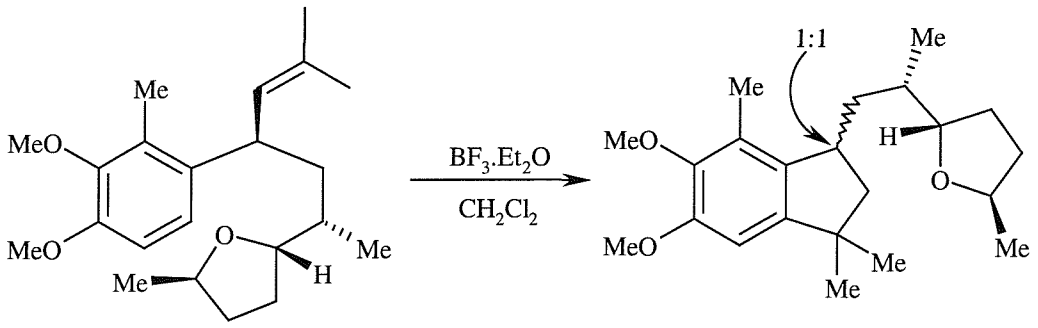
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 150.6 (s), 147.1 (s), 138.9 (s), 131.8 (s), 130.4 (s), 128.6 (d), 121.9 (d), 109.7 (d), 83.5 (d), 75.1 (d), 60.4 (q), 55.8 (q), 40.6 (t), 36.6 (d), 36.1 (d), 34.3 (t) 29.9 (t), 26.1 (q), 21.5 (q), 18.6 (q), 16.1 (q), 11.5 (q).

**UV** $\lambda_{max}$ (MeOH) 274 (139).

**LRMS** $^m/_z$ (APCI +ve) 347 ($[MH]^+$, 6%), 291 ($[M-C_4H_7]^+$, 11%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 364.2886. $C_{22}H_{38}O_3N$ requires 364.2852.

**Preparation of *rel*-(1″*RS*,2*S*,2′*S*,5*R*)-2-[1′-(5″,6″-dimethoxy-3″,3″,7″-trimethyl-2″,3″-dihydro-1″*H*-inden-1″-yl)-prop-2′-yl]-5-tetrahydrofuran 182.**




**181**

$C_{22}H_{34}O_3$ (346)

**182**

$C_{22}H_{34}O_3$ (346)

$BF_3.Et_2O$ (0.05 mL, 0.36 mmol) was added to a solution of alkene **181** (115 mg, 0.33 mmol) in $CH_2Cl_2$ (20 mL) at 0°C under $N_2$. The reaction mixture was allowed to warm to RT and after stirring for 12 hr further $BF_3.Et_2O$ (0.1 mL, 0.72 mmol) was added. The reaction mixture was then stirred at reflux for 4 days then cooled, quenched with $H_2O$ (50 mL) and extracted into $Et_2O$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown film. Purfication by flash column chromatography (silica, 10% $Et_2O$ in Petrol) gave **182** as a light brown oil (62 mg, 0.18 mmol, 54%) and as an inseparable 1:1 mixture of diastereoisomers.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2955 s, 2861 s, 1742 w, 1714 w, 1597 m, 1463 s, 1374 m, 1359 m, 1330 s, 1309 s, 1225 s, 1098 s, 1009 m, 977 m, 837 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.55 (1H, s, Ar**H**), 6.53 (1H, s, Ar**H**), 4.15-3.60 (2H + 2H, m, 2 × $CH_3CHO$ & 2 × CHCHO), 3.85 (3H + 3H, s, 2 × $ArOCH_3$), 3.76 (3H + 3H, s, 2 × $ArOCH_3$), 3.19 (1H + 1H, m, 2 × ArCH), 2.23 (3H, s, $ArCH_3$), 2.22 (3H, s, $ArCH_3$), 2.21-1.33 (9H + 9H, m, 2 × $CH_2CHCH_2$, OCHCH & 2 × $CH_2CH_2$), 1.32 (3H + 3H, s, 2 × $CCH_3$), 1.24 (3H + 3H, s,

2 × $CCH_3$), 1.10 (3H + 3H, d, $J$ = 6.5 Hz, 2 × $CHCH_3$), 1.02 (3H + 3H, d, $J$ = 7.0 Hz, 2 × $CHCH_3$).

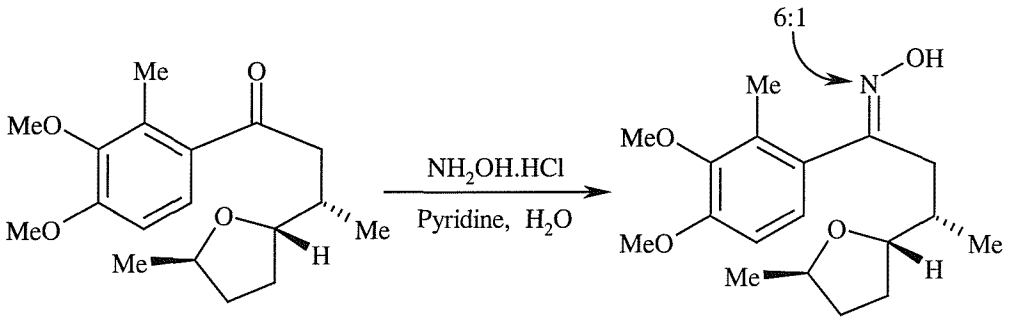
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.1 (2 × s), 147.2 (s), 147.0 (s), 146.4 (2 × s), 138.3 (s), 137.7 (s), 127.7 (s), 127.5 (s), 103.8 (d), 103.7 (d), 83.7 (d), 82.2 (d), 75.0 (2 × d), 60.3 (2 × q), 55.9 (2 × q), 47.4 (t), 45.6 (t), 43.9 (s), 43.8 (s), 41.5 (d), 39.9 (t), 39.8 (d), 38.1 (t), 34.4 (2 × t), 32.2 (d), 31.1 (d), 29.9 (t), 30.2 (t), 21.5 (q), 21.3 (q), 17.6 (2 × q), 17.4 (2 × q), 16.1 (q), 16.0 (q), 12.8 (q), 12.6 (q).

**UV** $\lambda_{max}$ (MeOH) 282 (329).

**LRMS** $^m/_z$ (APCI +ve) 347 ($[M+H]^+$, 9%), 329 ($[M-H_2O]^+$, 14%), 219 ($[M-127]^+$, 100%).

**HRMS** (EI) Found $[M]^+$, 346.2508. $C_{22}H_{34}O_3$ requires 346.2515.

**Preparation of *rel*-(3*S*)-1-(3,4-dimethoxy-2-methylphenyl)-3-[(2*S*,5*R*,)-5-methyltetrahydro-2-furanyl]-butane-1-one oxime 183.**




**143**

$C_{18}H_{26}O_4$ (306)

**183**

$C_{18}H_{27}O_4N$ (321)

Hydroxylamine hydrochloride (140 mg, 2.01 mmol) was added to a solution of ketone **143** (512 mg, 1.67 mmol) in pyridine (20 mL) and $H_2O$ (10 mL) at RT. The mixture was stirred at RT for 12 hr then further hydroxylamine hydrochloride (280 mg, 4.02 mmol) was added and the mixture stirred at 80°C for 24 hr. The reaction mixture was cooled, diluted with brine (150 mL) and extracted into EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a light yellow oil. Purification by flash column chromatography (silica, 30% $Et_2O$ in petrol) gave **183** as a colourless film (495 mg, 1.54 mmol, 92%) as an inseparable 6:1 mixture of diastereoisomers.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3302 br s, 2964 s, 2931 s, 1598 m, 1493 s, 1462 s, 1453 s, 1415 s, 1290 s, 1270 s, 1223 s, 104 s, 1002 m, 732 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.94 (1H, d, $J$ = 8.4 Hz, Ar**H**), 6.9 (1H, br s, NO**H**), 6.73 (1H, d, $J$ = 8.4 Hz, Ar**H**), 4.02-3.85 (2H, m, $CH_3$**CH**O & CH**CH**O), 3.85 (3H, s, ArOC**H**$_3$), 3.80 (3H, s, ArOC**H**$_3$), 2.75 (1H, dd, $J$ = 21.5, 10.5 Hz, ArC(NOH)C**H**H), 2.59 (1H, dd, $J$ = 21.5, 3.8 Hz, ArC(NOH)CH**H**), 2.17 (3H, s, ArC**H**$_3$), 2.00-1.36 (5H, m, $CH_3$**CH** & **CH**$_2$**CH**$_2$), 1.17 (3H, d,

$J$ = 5.9 Hz, $CHCH_3$), 0.98 (3H, d, $J$ = 6.7 Hz, $CHCH_3$). Additional signals due to the minor diastereoisomer $\delta_H$ 3.84 (3H, s, $ArOCH_3$), 3.78 (3H, s, $ArOCH_3$), 2.24 (3H, s, $ArCH_3$), 0.88 (3H, d, $J$ = 6.7 Hz, $CHCH_3$).

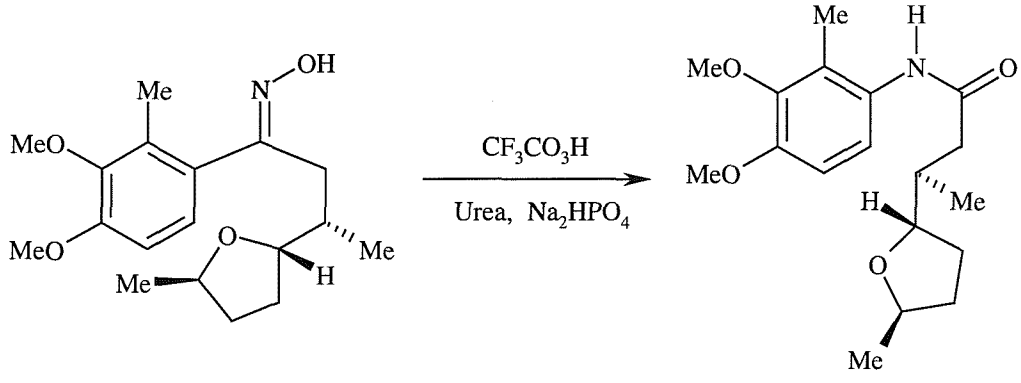
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 158.3 (s), 152.9 (s), 147.5 (s), 130.0 (s), 128.0 (s), 122.3 (d), 109.7 (d), 82.5 (d), 75.4 (d), 60.2 (q), 55.8 (q), 35.7 (d), 34.3 (t), 32.2 (t), 29.6 (t), 21.4 (q), 15.7 (q), 13.4 (q). Additional signals due to minor diastereoisomer $\delta_C$ 124.6 (d), 109.5 (d), 82.9 (d), 75.1 (d), 21.2 (q), 16.2 (q).

**UV** $\lambda_{max}$ (MeOH) 275 (214) and 246 (642).

**LRMS** $^m/_z$ (APCI +ve) 322 ($[MH]^+$, 93%), 304 ($[MH-H_2O]^+$, 100%).

**HRMS** (EI) Found $[M]^+$, 321.1940. $C_{18}H_{27}O_4N$ requires 321.1940.

**Preparation of N1-(3,4-dimethoxy-2-methylphenyl)-(3*R*)-3-[(2*S*,5*R*)-5-methyltetrahydro-2-furanyl]butanamide 185.**




**183**

$C_{18}H_{27}O_4N$ (321)

**185**

$C_{18}H_{27}O_4N$ (321)

A solution of peroxytrifluoroacetic acid was prepared by the addition of 30% $H_2O_2$ (0.15 mL, 1.41 mmol) to a solution of trifluoroacetic anhydride (0.24 mL, 1.70 mmol) in

acetonitrile (10 mL) at RT under $N_2$. This was added over 1 hr to a stirred mixture of urea (2 mg, 0.02 mmol), dibasic sodium phasphate (1.505g, 10.61 mmol) and oxime **183** (227 mg, 0.71 mmol) in MeCN (20 mL) at reflux under $N_2$. The reaction mixture was stirred at reflux for 24 hr then quenched by dilution with $H_2O$ (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 50-100% $Et_2O$ in petrol) afforded **185** as a cream coloured solid. Recrystallation from *n*-pentane/$Et_2O$ gave **185** as a cream solid (107 mg, 0.33 mmol, 47%).

**m.p.** 96-98°C (*n*-pentane-$Et_2O$).

**FT-IR** $\nu_{max}$ (nujol)/$cm^{-1}$ 3471 w, 3271 br m, 2963 s, 1737 w, 1655 s, 1592 w, 1526 s, 1490 s, 1452 s, 1417 m, 1375 m, 1267 s, 1082 s, 1004 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.52 (1H, br s, N**H**), 7.38 (1H, d, *J* = 8.9 Hz, Ar**H**), 6.75 (1H, d, *J* = 8.9 Hz, Ar**H**), 4.10 (2H, m, $CH_3CHOCH$), 3.85 (3H, s, $ArCH_3$), 3.79 (3H, s, $ArCH_3$), 2.30-1.85 (5H, m), 2.18 (3H, s, $ArCH_3$), 1.77-1.45 (2H, m), 1.24 (3H, d, *J* = 5.9 Hz, $CH_3CH$), 1.03 (3H, d, *J* = 6.0 Hz, $CHCH_3$).

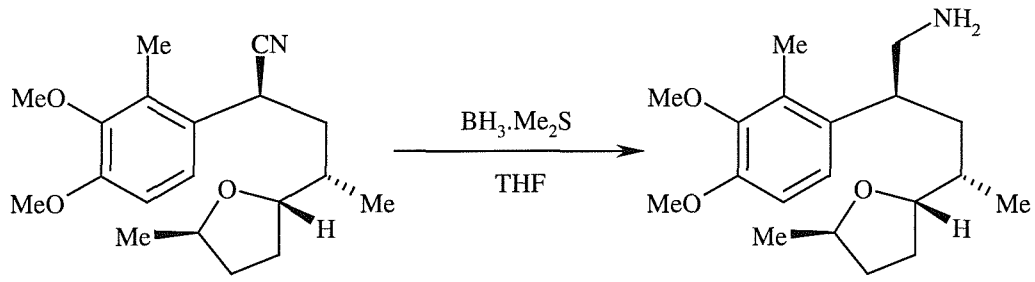
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 171.5 (s), 150.7 (s), 147.5 (s), 129.6 (s), 126.0 (s), 120.4 (d), 109.2 (d), 81.8 (d), 76.0 (d), 60.5 (q), 56.0 (q), 41.3 (t), 35.1 (d), 34.2 (t), 28.9 (t), 21.6 (q), 15.6 (q), 10.9 (q).

**UV** $\lambda_{max}$ (MeOH) 280 (139) and 236 (659).

**LRMS** $^m/_z$ (APCI +ve) 322 ($[MH]^+$, 100%), 304 ($[MH-H_2O]^+$, 14%).

**CHN** Found: C, 66.68; H, 8.60; N, 4.28. $C_{18}H_{27}O_4$ requires C, 67.29; H, 8.41; N, 4.36 %.

**Preparation of *rel*-(2*R*,2″*S*,4*S*,5″*R*)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-[-5″-methyltetrahydrofuran-2″-yl]pentylamine 186.**




**179a**
$C_{19}H_{27}O_3N$ (317)

**186**
$C_{19}H_{31}O_3N$ (321)

A solution of nitrile **179a** (200mg, 0.63 mmol) in THF was warmed to reflux. $BH_3.Me_2S$ (0.34 mL, 0.69 mmol, 2M in THF) was slowly added and the reaction mixture stirred at reflux for 4 hr then cooled. 6M HCl (5 mL) was added in a dropwise fashion resulting in the evolution of hydrogen gas. The reaction mixture was then refluxed for ½ hr, cooled to O°C, neutralised to pH 10 with NaOH and extracted into $Et_2O$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash column chromatography (silica, 10 % MeOH in $CH_2Cl_2$) gave **186** as a colourless film (143 mg, 0.45 mmol, 71 %) which contained 5% of the *rel*-(2*S*,2″*S*,4*S*,5″*R*) diasteroisomer.

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3365 br w, 2961 s, 2944 s, 2866 s, 1599 w, 1572 w, 1490 s, 1453 s, 1415 m, 1375 m, 1270 s, 1084 s, 1006 m, 803 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.84 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.75 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.10-3.85 (2H, m, **CHOCH**), 3.82 (3H, s, $ArOCH_3$), 3.76 (3H, s, $ArOCH_3$), 3.03 (1H, dd, *J* = 14.7, 6.0 Hz, $CHHNH_2$), 2.78 (1H, dd, *J* = 14.7, 8.08 Hz, $CHHNH_2$), 2.26 (3H, s, $ArCH_3$), 1.99-1.22 (8H, m, $ArCHCH_2CH$ & $CH_2CH_2$), 1.75 (2H, br s, $NH_2$), 1.16 (3H, d, *J* = 5.9 Hz,

$CHCH_3$), 0.88 (3H, d, $J$ = 6.6 Hz, $CHCH_3$) + additional signals due to minor diastereoisomer.

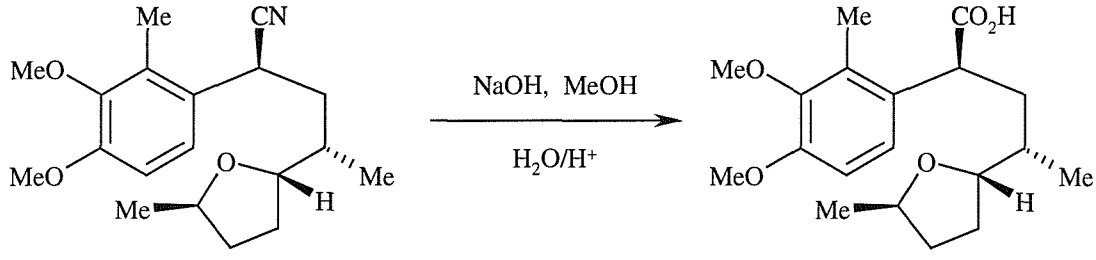
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 150.9 (s), 147.2 (s), 134.1 (s), 131.6 (s), 121.6 (d), 110.0 (d), 83.5 (d), 75.1 (d), 60.4 (q), 55.7 (q), 49.1 (t), 36.7 (t), 36.3 (d), 35.4 (d), 34.3 (t), 30.0 (t), 21.4 (q), 15.8 (q), 12.0 (q) + additional signals due to minor diastereoisomer.

**UV** $\lambda_{max}$ (MeOH) 274 (100).

**LRMS** $^m/_z$ (APCI +ve) 363 ([MH+MeCN]$^+$, 18%), 322 ([MH]$^+$, 100%).

**HRMS** (EI) Found 321.2314. $C_{19}H_{31}O_3N$ requires 321.2304.

**Preparation of *rel*-(2*S*,2″*S*,4*S*,5″*R*)-2-(3′,4′-dimethoxy-2′-methylphenyl)-4-[5″-methyltetrahydro-2″-furanyl]-pentanoic acid 189.**




**179a**
$C_{19}H_{27}O_3N$ (317)

**189**
$C_{19}H_{28}O_5$ (336)

An aqueous solution of NaOH (10 mL, 25%) was added to a solution of the nitrile **179a** (270 mg, 0.85 mmol) in MeOH (25 mL) at RT. The reaction mixture was stirred at reflux for 24 hr then cooled to 0°C, acidified with 2M HCl (pH 2) and extracted into EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash

column chromatography (silica, 60% $Et_2O$ in petrol) afforded **189** as a colourless oil (199 mg, 0.59 mmol, 70%) which contained 15% of the *rel*-(2*R*,2″*S*,4*S*,5″*R*) diasteroisomer.

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3148 br m, 2963 s, 1730 s, 1703 s, 1601 w, 1574 w, 1489 s, 1453 s, 1415 m, 1378 m, 1272 s, 1219 s, 1171 s, 1083 s, 1003 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 10.2 (1H, br s, $CO_2$**H**), 7.04 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.75 (1H, d, *J* = 8.8 Hz, Ar**H**), 4.09-3.85 (2H, m, **CHOCH**), 3.84 (3H, s, ArOC**H$_3$**), 3.78 (3H, s, ArOC**H$_3$**), 2.31 (3H, s, ArC**H$_3$**), 2.26-1.23 (8H, m, **CH$_2$CH$_2$**, **CHCH$_3$CH$_2$CH**), 1.18 (3H, d, *J* = 5.9 Hz, CHC**H$_3$**), 0.91 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

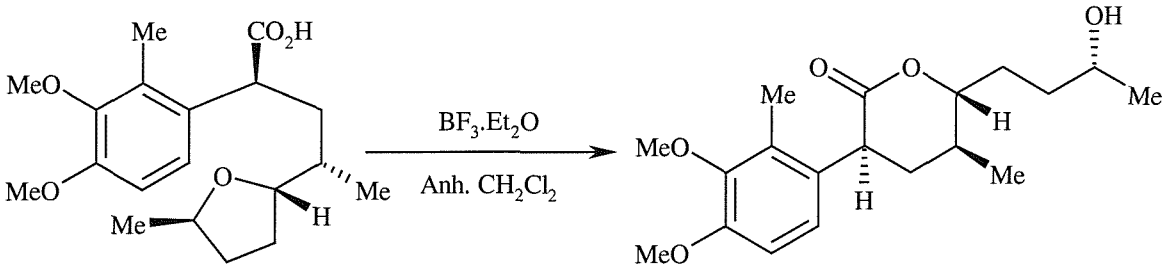
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 180.5 (s), 151.8 (s), 147.2 (s), 131.4 (s), 129.9 (s), 122.9 (d), 109.9 (d), 82.7 (d), 75.3 (d), 60.4 (q), 55.7 (q), 44.1 (d), 35.9 (d), 35.2 (t), 34.2 (t), 29.6 (t), 21.4 (q), 15.9 (q), 12.0 (q). Additional signals due to minor diastereoisomer $\delta_C$ 179.9 (s), 131.3 (s), 122.5 (d), 82.9 (d), 75.1 (d), 44.3 (d), 35.4 (t), 21.2 (q), 15.7 (q).

**UV** $\lambda_{max}$ (MeOH) 274 (134) and 228 (790).

**LRMS** $^m/_z$ (APCl -ve) 337 ($[MH]^+$, 9%), 335 ($[M-H]^+$, 100%), 291 ($[MH-CO_2]^+$, 74%).

**HRMS** (EI) Found $[M]^+$ 336.1941. $C_{19}H_{28}O_5$ requires 336.1937.

**Preparation of *rel*-(3*S*,3″*R*,5*S*,6*R*)-3-(3′,4′-dimethoxy-2′-methylphenyl)-6-[3″-hydroxybutyl]-5-methyltetrahydro-2*H*-2-pyranone 190.**




**189**

$C_{19}H_{28}O_5$ (336)

**190**

$C_{19}H_{28}O_5$ (336)

$BF_3.Et_2O$ (0.05 mL, 0.39 mmol) was added to a solution of acid **189** (132 mg, 0.39 mmol) in $CH_2Cl_2$ (15 mL) at RT under $N_2$ giving a yellow coloured solution. The reaction mixture was stirred at RT for 12 hr then further $BF_3.Et_2O$ (0.2 mL, 1.56 mmol) was added and the reaction was stirred at reflux for 24 hr. The reaction mixture was cooled, quenched with $H_2O$ (30 mL) and extracted into $Et_2O$ (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography (silica, gradient elution 10-50-100% $Et_2O$ in petrol) afforded **190** as a colourless film (57mg, 0.17 mmol, 43%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3416 br s, 2961 s, 1731 s, 1714 s, 1602 w, 1581 w, 1493 s, 1469 s, 1274 s, 1220 s, 1183 s, 1082 s, 1007 s, 754 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.85 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.76 (1H, d, $J$ = 8.8 Hz, Ar**H**), 4.10 (1H, td, $J$ = 8.8, 3.0 Hz, $CO_2$**CH**), 3.97 (1H, t, $J$ = 6.9 Hz, Ar**CH**$CO_2$), 3.88 (3H, s, ArO**CH$_3$**), 3.79 (3H, s, ArO**CH$_3$**), 2.22 (3H, s, Ar**CH$_3$**), 2.11-1.50 (8H, m, **CH$_2$CHCH$_3$** & **CH$_2$CH$_2$CH**), 1.71 (1H, br s, **OH**), 1.25 (3H, d, $J$ = 5.9 Hz, CH**CH$_3$**), 1.04 (3H, d, $J$ = 5.9 Hz, CH**CH$_3$**).

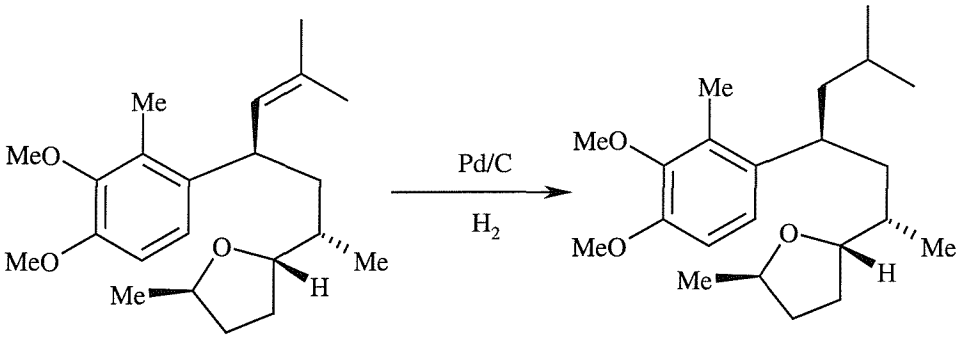
**$^{13}$C-NMR** $\delta_C$ (300 MHz, $CDCl_3$) 173.8 (s), 151.9 (s), 147.5 (s), 130.8 (s), 130.6 (s), 123.5 (d), 109.7 (d), 85.2 (d), 68.3 (d), 60.4 (q), 55.8 (q), 41.6 (d), 35.2 (t), 34.8 (t), 30.8 (d), 30.2 (t), 24.0 (q), 17.8 (q), 12.1 (q).

**UV** $\lambda_{max}$ (MeOH) 270 (134) and 222 (694).

**LRMS** $^m/_z$ (APCI +ve) 337 ($[MH]^+$, 8%), 165 (100%).

**HRMS** (EI) Found $[M]^+$ 336.1925. $C_{19}H_{28}O_5$ requires 336.1936.

**Preparation of *rel*-(2*S*,4′*S*,5*R*,6′*S*)-2-(4′-[3″,4″-dimethoxy-2″-methylphenyl]-2′-methylhept-6′-yl)-5-methyltetrahydrofuran 192.**




**181** $C_{22}H_{34}O_3$ (346)

**192** $C_{22}H_{36}O_3$ (348)

A vigorously stirred solution of alkene **181** (287 mg, 0.83 mmol) and 5% Pd-C (175 mg, 0.08 mmol) in ethanol (20 mL) was purged three times with $N_2$ and $H_2$. The reaction mixture was then stirred under $H_2$ at atmospheric pressure for 24 hr. The reaction was purged three times with $N_2$ and then filtered through celite. The mother liquor was concentrated *in vacuo* giving **192** as colourless film (262 mg, 0.75 mmol, 91%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2958 s, 2866 s, 1600 w, 1580 w, 1489 s, 1463 s, 1453 s, 1415 m, 1374 m, 1292 s, 1270 s, 1085 s, 1008 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.89 (1H,d, *J* = 8.8 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.8 Hz, Ar**H**), 4.04 (1H, dquin, *J* = 8.8, 5.9 Hz, $CH_3CHO$), 3.84 (3H, s, $ArOCH_3$), 3.78 (3H, s, $ArOCH_3$), 3.76 (1H, obs, CHCHO), 2.99 (1H, m, ArC**H**), 2.26 (3H, s, $ArCH_3$), 2.10-1.35 (10H, m, $CH_2CH_2$, $CH_2CHCH_3$ & $CH_2CH$), 1.21 (3H, d, *J* = 5.9 Hz, $OCHCH_3$), 0.94 (3H, d, *J* = 6.6 Hz, $CHCH_3$), 0.85 (3H, d, *J* = 5.9 Hz, $CH_3CHCH_3$), 0.82 (3H, d, *J* = 5.9 Hz, $CH_3CHCH_3$).

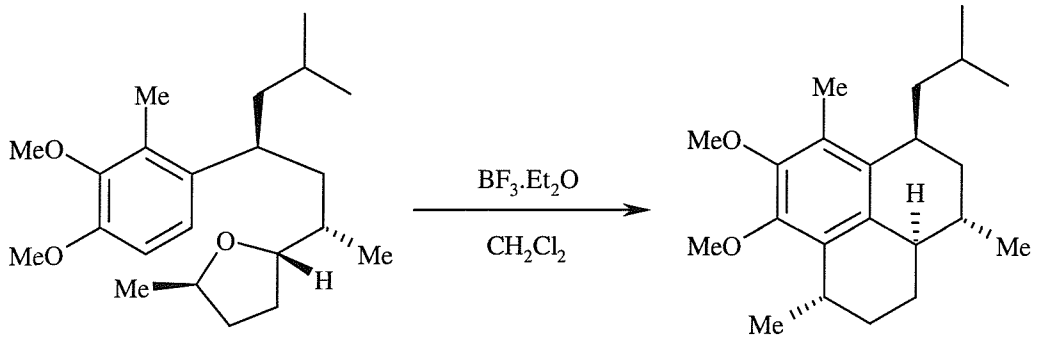
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 150.4 (s), 147.0 (s), 138.5 (s), 130.2 (s), 121.4 (d), 109.7 (d), 83.1 (d), 75.1 (d), 60.3 (q), 55.7 (q), 48.3 (t), 41.1 (t), 36.0 (d), 34.4 (d), 34.3 (t), 29.9 (t), 25.6 (d), 23.3 (q), 22.2 (q), 21.5 (q), 16.1 (q), 11.6 (q).

**UV** $\lambda_{max}$ (MeOH) 272 (191) and 228 inf (1044).

**LRMS** $^m/_z$ (APCI +ve) 349 ($[MH]^+$, 7%), 331 ($[MH\text{-}H_2O]^+$, 100%).

**HRMS** (EI+) Found $[M]^+$ 348.2664. $C_{22}H_{36}O_3$ requires 348.2672.

**Preparation of *rel*-(1*S*,3*S*,3a*R*,6*S*)-1-(2′-methylprop-1-yl)-7,8-dimethoxy-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-phenalene 193.**




**192**
$C_{22}H_{36}O_3$ (348)

**193**
$C_{22}H_{34}O_2$ (330)

$BF_3.Et_2O$ (0.14 mL, 1.07 mmol) was added to a solution of tetrahydrofuran **192** (124 mg, 0.26 mmol) in $CH_2Cl_2$ (10 mL) at RT under $N_2$. The reaction mixture was stirred at reflux for 2 days then $CHCl_3$ (15 mL) and further $BF_3.Et_2O$ (0.14 mL, 1.07 mmol) was added. The mixture was stirred at reflux for a further 24 hr then quenched with $H_2O$ (20 mL) and extracted into $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography (silica, 20% $CH_2Cl_2$ in petrol) afforded **193** as a colourless oil (91mg, 0.28 mmol, 76%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2951 s, 2866 s, 1462 s, 1454 s, 1409 s, 1365 m, 1317s, 1252 w, 1137 w, 1114 w, 1072 s, 1007 m.

**$^1$H-NMR** $\delta_H$ (400 MHz, $CDCl_3$) 3.85 (3H, s, ArOC**H**$_3$), 3.81 (3H, s, ArOC**H**$_3$), 3.39 (1H, dqd, *J* = 8.0, 7.2, 4.1 Hz, $CH_3$C**H**), 2.96 (1H, ddt, *J* = 9.6, 4.6, 2.3 Hz, $CH_2$C**H**Ar), 2.21 (3H, s, ArC**H**$_3$), 2.20 (1H, app ddt, *J* = 14.3, 7.8, 4.7 Hz, $CH_2$CH**H**), 2.11 (1H, td, *J* = 10.5, 5.0 Hz, ArC**H**), 1.98 (1H, dtd, *J* = 13.5, 8.0, 4.6 Hz, C**H**HC$H_2$), 1.86 (1H, dt, *J* = 13.0, 2.3 Hz, CHCH**H**CH), 1.78 (1H, app octet d, *J* = 6.6, 3.7 Hz, C**H**(C$H_3$)$_2$), 1.61 (1H, ddqd, *J* = 13.0, 10.5, 6.3, 2.5 Hz, $CH_3$C**H**), 1.59 (1H, s, ArC**H**$_3$), 1.56 (1H, dddd, *J* = 13.6,

9.0, 7.7, 4.2 Hz, CH**H**$CH_2$), 1.48 (1H, ddd, *J* = 14.0, 3.7, 2.3 Hz, CH**H**$CH(CH_3)_2$), 1.47 (1H, app dt, *J* = 13.0, 4.6 Hz, CHC**H**HCH), 1.21 (3H, d, *J* = 7.2 Hz, $CHCH_3$), 1.17 (1H, ddd, *J* = 14.0, 9.6, 6.6 Hz, C**H**$HCH(CH_3)_2$), 1.17 (1H, dddd, *J* = 14.3, 10.5, 9.0, 8.0 Hz, $CH_2$C**H**H), 1.08 (3H, d, *J* = 6.3 Hz, $CHCH_3$), 1.02 (3H, d, *J* = 6.5 Hz, $CHCH_3$), 0.92 (3H, d, *J* = 6.6 Hz, $CHCH_3$). These assignments were confirmed by $^1$H-$^1$H and $^1$H-$^{13}$C COSY experiments

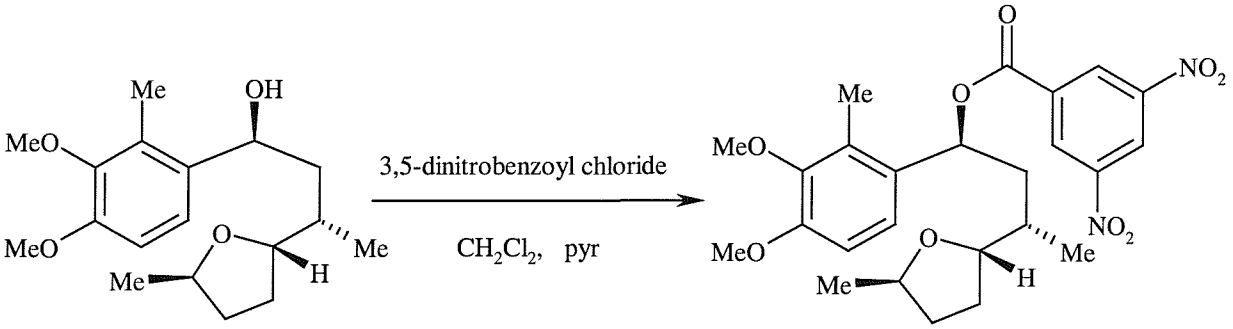
**$^{13}$C-NMR** $\delta_C$ (100 MHz, $CDCl_3$) 149.7 (s), 148.6 (s), 135.9 (s), 134.5 (s), 133.5 (s), 126.9 (s), 60.9 (q), 60.3 (q), 43.9 (t), 42.2 (d), 34.3 (t), 33.4 (d), 29.8 (t), 29.7 (d), 28.1 (t), 27.4 (d), 25.9 (d), 24.7 (q), 23.4 (q), 21.5 (q), 21.2 (q), 11.6 (q).

**UV** $\lambda_{max}$ (MeOH) 276 (250) and 215 (6930).

**LRMS** $^m/_z$ (APCI +ve) 331 ($[MH]^+$, 100%), 330 ($[M]^+$, 20%).

**HRMS** (CI+) Found $[M+18]^+$, 348.2903. $C_{22}H_{38}O_2N$ requires 348.2916.

**Preparation of *rel*-(1*R*,2″*S*,3*R*,5″*R*)-1-(3′,4′-dimethoxy-2′-methylphenyl)-3-(5″-methyltetrahydrofuran-2″-yl)-but-1-yl 3,5-dinitrobenzoate 194.**




**170a**

$C_{18}H_{28}O_3$ (292)

**194**

$C_{25}H_{30}N_2O_9$ (502)

3,5-Dinitrobenzoyl chloride (472 mg, 2.05 mmol) was added to a solution of alcohol **170a** (210 mg, 0.68 mmol) and pyridine (0.12 mL, 1.36 mmol) at RT. The reaction mixture was stirred at RT for ½ hr resulting in the formation of a white suspension. The reaction mixture was diluted with 2M HCl (20 mL) and extracted into $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a yellow solid. Purification by flash column chromatography (silica, 40% $Et_2O$ in petrol) afforded **194** as a viscous yellow oil (203 mg, 0.40 mmol, 60%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3104 w, 2966 s, 1728 s, 1628 w, 1599w, 1546 s, 1492 m, 1456 m, 1344 s, 1272 s, 1167 s, 1082 s, 912 m, 825 w, 807 w.

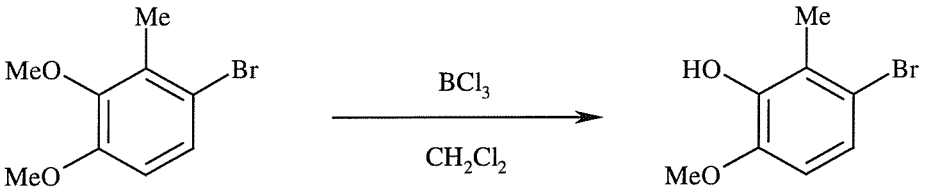
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 9.21 (1H, s, Ar**H**), 9.14 (2H, s, Ar**H**), 7.18 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.80 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.38 (1H, t, *J* = 6.9 Hz, ArC**H**OH), 4.05 (1H, dquin, *J* = 8.8, 5.9 Hz, $CH_3$C**H**O), 3.93 (1H, dt, *J* = 9.6, 5.1 Hz, CHC**H**O), 3.83 (3H, s, ArOC**H$_3$**), 3.78 (3H, s, ArOC**H$_3$**), 2.42 (3H, s, ArC**H$_3$**), 2.20-1.88 (4H, m, CHC**H$_2$**C**H$_2$**CH), 1.71-1.40 (3H, m, CHOHC**H$_2$**C**H**), 1.22 (3H, d, *J* = 5.9 Hz, C**H$_3$**CH), 1.04 (3H, d, *J* = 6.6 Hz, C**H$_3$**CH).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 172.5 (s), 161.8 (s), 152.6 (s), 148.6 (s), 147.0 (s), 134.4 (s), 130.8 (s), 129.4 (d), 122.3 (d), 122.1 (d), 109.9 (d), 82.0 (d), 75.3 (d), 75.2 (d), 60.3 (q), 55.6 (q), 38.8 (t), 34.5 (d), 34.1 (t), 29.2 (t), 21.3 (q), 16.1 (q), 11.5 (q).

**UV** $\lambda_{max}$ (MeOH) 282 inf (2845), 248 (7530).

**LRMS** $^m/_z$ (CI+) 291 ([MH-210]$^+$, 100%).

**Preparation of 3-bromo-6-methoxy-2-methylphenol 197.**




**154**

$C_9H_{12}O_2$ (152)

**197**

$C_8H_9O_2Br$ (217)

A solution of $BCl_3$ (2.2 mL, 2.17 mmol, 1M in heptane) in $CH_2Cl_2$ (10 mL) was added dropwise over 5 min to an ice cold solution of veratrole **154** (500 mg, 2.17 mmol) in $CH_2Cl_2$. The reaction mixture was then allowed to warm to RT and was stirred for 48 hrs giving a brown solution. The reaction mixture was diluted with water (20 mL) and extracted into $Et_2O$ (2 × 20 mL). The ethereal extract was washed with 1M NaOH (2 × 20 mL) giving a red solution which became brown upon acidification with 2M HCl (pH 1-2). The reaction mixture was extracted into $Et_2O$ (3 × 20 mL) and the combined ethereal phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 10% $Et_2O$ in petrol) afforded **197** as a colourless oil which crystallised to a white solid (371 mg, 1.71 mmol, 79%) on standing.

**m.p.** 30-32°C.

**FT-IR** $\nu_{max}$ (neat) /$cm^{-1}$ 3510 s, 3005 w, 2939 m, 2840 m, 1680 m, 1654 m, 1636 m, 1608 m, 1586 m, 1475 s, 1438 s, 1396 m, 1387 m, 1333 m, 1279 s, 1248 s, 1230 s, 1201 s, 1183 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.06 (1H, d, *J* = 8.8 Hz, Ar**H**), 6.62 (1H, d, *J* = 8.8 Hz, Ar**H**), 5.85 (1H, s, ArO**H**), 3.88 (3H, br s, ArOC**H$_3$**), 2.34 (3H, s, ArC**H$_3$**).

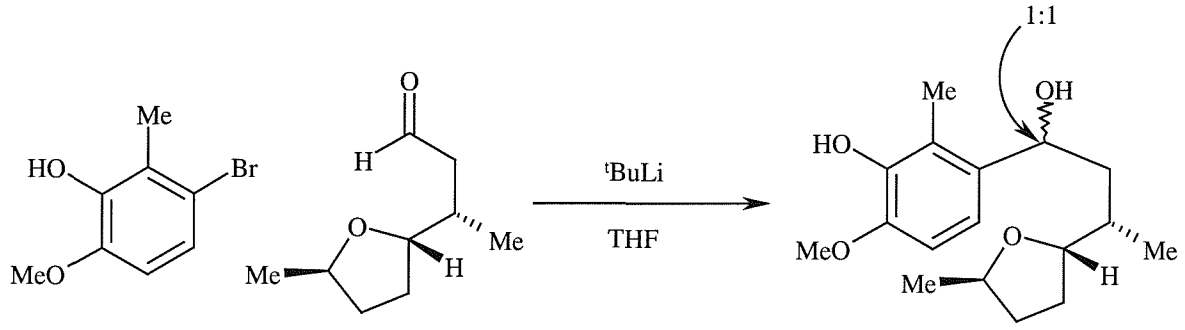
**n.O.e** (400 MHz, $CDCl_3$) irradiation of the signal at $\delta_H$ 6.62 (Ar**H**) caused an n.O.e enhancement at $\delta_H$ 7.06 (Ar**H**) and 3.88 (ArOC**H$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 145.6 (s), 144.6 (s), 124.1 (s), 122.7 (d), 117.1 (s), 109.2 (d), 56.3 (q), 15.6 (q).

**UV** (MeOH) $\lambda_{max}$ 283 (2020) and 242 (1800).

**LRMS** $^m/_z$ (APCI +ve) 218 ([M($^{81}$Br)]$^+$, 100%), 216 ([M($^{79}$Br)]$^+$, 86%).

**Preparation of rel-(1′*RS*,2*R*,3′*S*,5′*S*)-2-(1-(3″-hydroxy-4″-methoxy-2″-methylphenyl)-1′-hydroxybut-3′-yl)-5-methyltetrahydrofuran 198.**




**197** **169** **198**

$C_8H_9O_2Br$ (216.9) $C_9H_{16}O_2$ (156) $C_{17}H_{26}O_4$ (294)

$^t$BuLi (2.4 mL, 3.14 mmol, 1.3M in pentane) was added dropwise over 5 min to a solution of phenol **197** (340 mg, 1.57 mmol) in THF (15 mL) at −78°C and the reaction mixture was stirred for 1 hr. A solution of the aldehyde **169** (245 mg, 1.57 mmol) in THF (10 mL) was added over 10 min via a cannula and the reaction mixture was stirred at −78°C for 2 hrs then warmed to RT. After a further 14 hr the reaction mixture was diluted with sat. aq. $NH_4Cl$ (20 mL) and extracted into EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 10% $Et_2O$ in petrol) afforded **198** as a colourless oil (46 mg, 0.16 mmol, 10%) and an inseparable 1:1 mixture of diastereoisomers.

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3412 br s, 2965 s, 2870 s, 1616 m, 1590 m, 1494 s, 1471 s, 1441 s, 1379 s, 1340 m, 1281 s, 1236 s, 1162 m, 1024 s, 910 m, 879 m, 870 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.02 (1H + 1H, d, $J$ = 8.8 Hz, 2 × Ar**H**), 6.75 (1H + 1H, d, $J$ = 8.8 Hz, 2 × Ar**H**), 5.78 (1H + 1H, br s, 2 × ArO**H**), 5.04 (1H, br m, C**H**OH), 4.93 (1H, br m, C**H**OH) 4.05 (1H + 1H, m, 2 × $CH_3$C**H**O), 3.93 (1H, m, CHC**H**O), 3.87 (3H + 3H, s, 2 × ArOC**H**$_3$), 3.85 (1H, obs m,

CHCHO), 3.60 (1H + 1H, br s, 2 × CHOH), 2.24 (3H + 3H, s, 2 × ArCH$_3$), 2.15-1.40 (7H + 7H, m, 2 × CH$_2$CH$_2$CHCHCH$_2$), 1.27 (3H, d, *J* = 5.9 Hz, CHCH$_3$), 1.24 (3H, d, *J* = 5.9 Hz, CHCH$_3$), 1.03 (3H, d, *J* = 6.6 Hz, CHCH$_3$), 0.98 (3H, d, *J* = 6.6 Hz, CHCH$_3$).

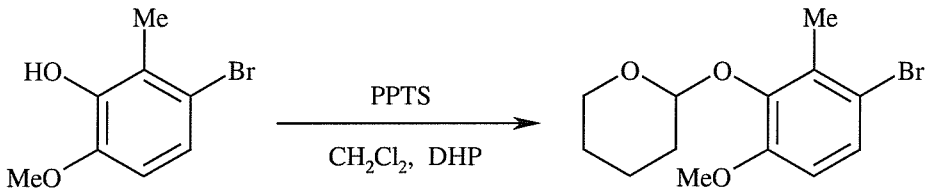
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 145.1 (2 × s), 143.5 (2 × s), 137.6 (s), 136.9 (s), 120.8 (2 × s), 116.5 (d), 116.0 (d), 108.0 (2 × d), 82.5 (2 × d), 75.8 (d), 75.6 (d), 69.4 (d), 68.0 (d), 56.1 (2 × q), 42.3 (t), 42.1 (t) 34.3 (t), 34.2 (2 × d), 33.1 (t), 29.1 (2 × t), 21.6 (q), 21.0 (q), 15.7 (q), 15.4 (q), 11.0 (q), 10.8 (q).

**UV** $\lambda_{max}$ (MeOH) 280 (2313) and 235 (2705).

**LRMS** $^m/_z$ (APCI +ve) 294 ([M]$^+$, 10%), 277 ([MH-$H_2O$]$^+$, 100%).

**HRMS** (CI+) Found [MH-$H_2O$]$^+$ 277.1807. $C_{17}H_{25}O_3$ requires 277.1804.

**Preparation of 2-(3-bromo-6-methoxy-2-methylphenoxy)-tetrahydro-2*H*-pyran 199.**




**197**

$C_8H_9O_2Br$ (217)

**199**

$C_{13}H_{17}O_3Br$ (301)

A solution of phenol **197** (1.016 g, 4.68 mmol), 3,4-dihydro-2*H*-pyran (2.8 mL, 30.42 mmol) and pyridinium *para*-toluenesulfonate (118 mg, 0.47 mmol) in $CH_2Cl_2$ (20 mL) was stirred at RT for 48 hrs. The reaction mixture was diluted with $Et_2O$ (200 mL) and washed with 1M NaOH (3 × 100 mL). The organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a pale yellow oil. Purification by flash column

chromatography (silica, 10% $Et_2O$ in petrol) afforded **199** as a colourless oil (796 mg, 2.65 mmol, 56%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2943 s, 2836 m, 1574 w, 1472 s, 1437 s, 1293 s, 1286 s, 1222 s, 1200 s, 1179 s, 1113 m, 1084 s, 1070 s, 1004 m, 945 s, 929 m, 910 s,

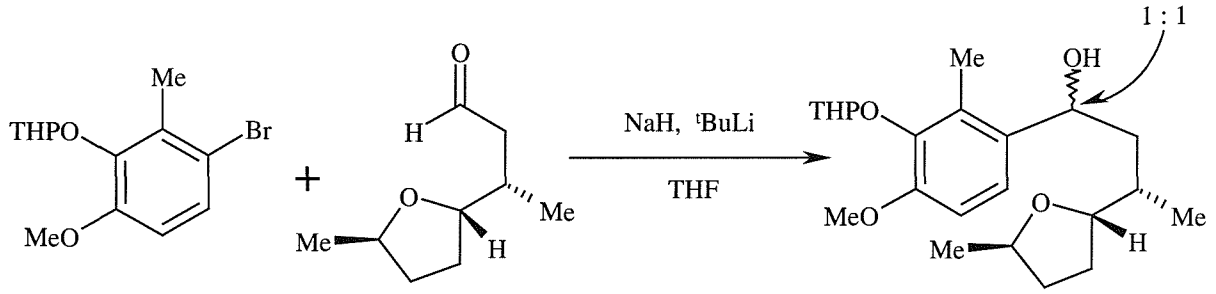
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.20 (1H, d, $J$ = 8.8 Hz, Ar**H**), 6.68 (1H, d, $J$ = 8.8 Hz, Ar**H**), 5.23 (1H, app t, $J$ = 3.3 Hz, OC**H**O), 4.10 (1H, dt, $J$ = 11.8, 5.8 Hz, OC**H**HCH$_2$), 3.82 (3H, s, ArOC**H$_3$**), 3.57 (1H, ddd, $J$ = 11.8, 8.1, 4.4 Hz, OCH**H**CH$_2$), 2.41 (3H, s, ArC**H$_3$**), 2.05-1.85 (3H, m, C**H$_2$**C**H**HCH$_2$), 1.71-1.58 (3H, m, OCH$_2$CH**H**C**H$_2$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151.9 (s), 145.6 (s), 132.8 (s), 127.5 (d), 116.5 (s), 111.1 (d), 101.6 (d), 63.6 (t), 56.1 (q), 30.8 (t), 25.4 (t), 19.6 (t), 17.5 (q).

**UV** $\lambda_{max}$ (MeOH) 281 (1100) and 234 (2900).

**LRMS** $^m/_z$ (APCI –ve) 301 ([MH]$^+$, 2%), 217 ([MH($^{81}$Br)–THP]$^+$, 100%), 215 ([MH($^{79}$Br)–THP]$^+$, 86%).

**Preparation of *rel*-(1′*RS*,2*S*,2‴*RS*,3′*S*,5*R*)-2-(1′-(tetrahydro-2‴*H*-2‴-pyranyloxy)-4″-methoxy-2″-methylphenyl)-1′-hydroxybut-3′-yl)-5-methyltetrahydrofuran 200.**




**199** $C_{13}H_{17}O_3Br$ (301)

**169** $C_9H_{16}O_2$ (156)

**200** $C_{22}H_{34}O_5$ (378)

$^t$BuLi (1.91 mL, 2.87 mmol, 1.5M in pentane) was added dropwise over 5 min to a solution of the bromide **199** (784 mg, 2.61 mmol) in THF (10 mL) at −78°C under $N_2$. The reaction mixture was stirred at −78°C for 1 hr giving a yellow coloured solution. A solution of the aldehyde **169** (203 mg, 1.30 mmol) in THF (10 mL) was added over 5 min and the resultant yellow solution was stirred at −78°C for 1 hr then quenched with sat. aq. $NH_4Cl$ (20 mL) and extracted into EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash column chromatography (silica, 50% $Et_2O$ in petrol) afforded **200** as a colourless viscous oil (439 mg, 1.16 mmol, 89%) and as an inseparable complex mixture of diastereoisomers.

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3428 br s, 2963 s, 2870 s, 2836 m, 1489 s, 1462 s, 1441 s, 1382 s, 1354 s, 1322 m, 1271 s, 1200 s, 1180 s, 1146 m, 1033 s, 950 s, 912 s, 732 s, 668 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.23 (1H + 1H, d, $J$ = 8.8 Hz, 2 × Ar**H**), 6.80 (1H + 1H, d, $J$ = 8.8 Hz, 2 × Ar**H**), 5.16 (1H + 1H, br m, 2 × OC**H**O), 5.02 (1H, dd, $J$ = 10.3, 1.5 Hz, ArC**H**OH), 4.92 (1H, dd, $J$ = 10.3, 1.5 Hz, ArC**H**OH), 4.12 (1H + 1H, dt, $J$ = 11.8, 5.8 Hz, 2 × OC**H**HCH$_2$), 4.05-

3.93 (2H + 2H, m, 2 × $CH_3CHO$, 2 × CHCHO), 3.87 (3H + 3H, s, 2 × $ArOCH_3$), 3.57 (1H + 1H, ddd, $J$ = 11.8, 8.1, 4.4 Hz, 2 × $OCHHCH_2$), 3.06 (1H, br s, ArCHOH), 2.98 (1H, br s, ArCHOH), 2.31 (3H, s, $ArCH_3$), 2.29 (3H, s, $ArCH_3$), 2.10-1.10 (13H + 13H, m, 2 × $CH_2CH_2CH_2$, 2 × $CHCH_2CH_2CH$, 2 × $CHCH_2$) 1.24 (3H + 3H, d, $J$ = 5.9 Hz, 2 × $CHCH_3$), 0.89 (3H, d, $J$ = 6.6 Hz, $CHCH_3$), 0.85 (3H, d, $J$ = 6.6 Hz, $CHCH_3$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 151.2 (2 × s), 144.7 (2 × s), 137.2 (s), 136.6 (s), 129.4 (2 × s), 121.2 (d), 120.7 (d), 109.9 (d), 109.8 (d), 101.8 (d), 101.7 (d), 82.9 (d), 82.4 (d), 75.7 (d), 75.5 (d), 69.1 (d), 68.0 (d), 63.8 (t), 63.6 (t), 55.9 (2 × q), 34.3 (d), 34.2 (d), 34.1 (2 × t), 30.9 (2 × t), 29.2 (t), 29.1 (t), 28.9 (2 × t), 25.5 (2 × t), 21.6 (q), 21.5 (q), 19.9 (2 × t), 16.7 (2 × q), 12.4 (q), 12.3 (q).

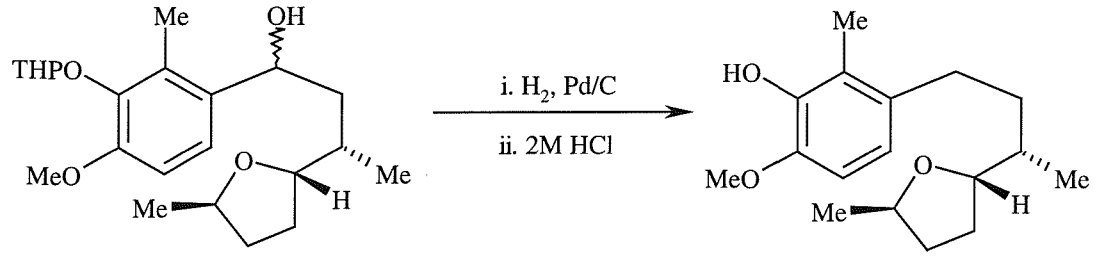
**UV** $\lambda_{max}$ (MeOH) 276 (1280) and 232 (3500).

**LRMS** $^m/_z$ (APCI –ve) 377 ($[M-H]^+$, 22%)

$^m/_z$ (APCI +ve, no cone) 294 ($[MH-THP]^+$, 10%), 277 (100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 396.2747. $C_{22}H_{38}O_5N$ requires 396.2750.

**Preparation of *rel*-(2*S*,3′*R*,5*R*)-2-(1′-(3″-hydroxy-4″-methoxy-2″-methylphenyl)-but-3′-yl)-5-methyltetrahydrofuran 201.**




**200**

$C_{22}H_{34}O_5$ (378)

**201**

$C_{17}H_{26}O_3$ (278)

A vigorously stirred solution of the alcohol **200** (392 mg, 1.04 mmol) and 5% Pd/C (265 mg, 0.12 mmol) in EtOH (20 mL) was purged three times with $N_2$ and three times with $H_2$. The reaction was stirred under $H_2$ at atmospheric pressure for 24 hr then purged three times with $N_2$ and filtered through celite. The mother liquors were concentrated *in vacuo* giving a brown oil which was stirred in a solution of 2M HCl (20 mL) and THF (20 mL) at RT for 24 hrs. The reaction mixture was diluted with 2M HCl (50 mL) and extracted into EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a dark green oil. Purification by flash column chromatography (silica, 20% $Et_2O$ in petrol) afforded **201** as a colourless oil (376 mg, 1.04 mmol, 88%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 3544 br m, 3447 br m, 2963 s, 2870 s, 1748 w, 1723 w, 1621 w, 1587 w, 1493 s, 1463 s, 1441 s, 1376 m, 1344 m, 1280 s, 1232 s, 1160 w, 1082 s, 998 m, 876 m, 795 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 6.67 (2H, s, Ar**H**), 5.75 (1H, br s, ArO**H**), 4.05 (1H, dquin, $J$ = 8.8, 5.9 Hz, $CH_3$C**H**O), 3.93 (1H, app dt, $J$ = 9.6, 5.1 Hz, C**H**CHO), 2.66 (1H, ddd, $J$ = 13.3, 11.4, 5.1 Hz, ArCH**H**), 2.48 (1H, ddd, $J$ = 13.3, 11.4, 5.1 Hz, ArC**H**H), 2.24 (3H, s, Ar**CH$_3$**), 2.15-1.35 (7H, m,

$ArCH_2CH_2CHCHCH_2CH_2$), 1.23 (3H, d, $J$ = 5.9 Hz, $CHCH_3$), 1.05 (3H, d, $J$ = 6.6 Hz, $CHCH_3$).

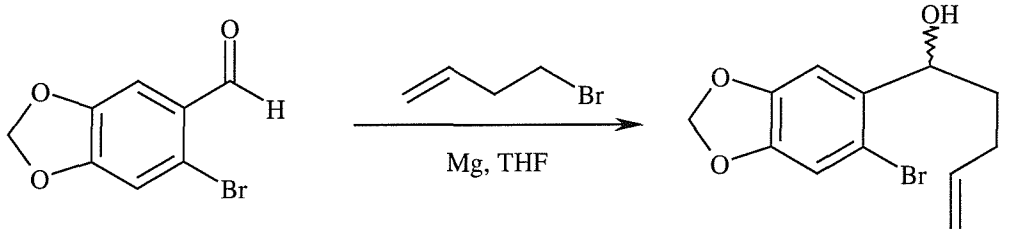
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 144.5 (s), 143.8 (s), 135.0 (s), 122.1 (s), 119.5 (d), 107.8 (d), 83.2 (d), 75.1 (d), 56.1 (q), 38.5 (d), 34.4 (t), 33.9 (t), 31.0 (t), 29.8 (t), 21.5 (q), 16.1 (q), 11.4 (q).

**UV** $\lambda_{max}$ (MeOH) 280 (2500) and 234 (3100).

**LRMS** $^m/_z$ (APCI +ve) 279 ($[MH]^+$, 6%), 229 (100%).

**HRMS** (CI+) Found $[MH]^+$ 279.1966. $C_{17}H_{27}O_3$ requires 279.1960.

**Preparation of 6-bromo-5-(1-hydroxypent-4-en-1-yl)-benz[1,3]dioxole 206.**




**205**

$C_8H_5O_2Br$ (213)

**206**

$C_{12}H_{13}O_3Br$ (285)

A solution of the bromide (5.00 g, 37.06 mmol) in THF (10 mL) was added slowly to a suspension of Mg (890 mg, 37.06 mmol) and iodine (10 mg) in THF (30 mL) at RT. The resultant mixture was heated at reflux for 1 hr and added *via* a cannula to a solution of the aldehyde **205** (13.18 g, 57.60 mmol) in THF (50 mL). The reaction mixture was stirred at RT for 12 hr then quenched with $H_2O$ (50 mL) and extracted into EtOAc (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 10-20% $Et_2O$ in petrol) afforded **206** as a yellow oil (6.31 g, 22.1 mmol, 60%).

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3406 brs, 2914.7 s, 1640 w, 1501 m, 1475 s, 1235 s, 1119 w, 1039 s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.05 (1H, s, Ar**H**), 6.96 (1H, s, Ar**H**), 5.98 (2H, s, O**CH$_2$**O), 5.88 (1H, ddt, *J* = 16.9, 10.3, 6.6 Hz, CH$_2$=**CH**), 5.09 (1H, d, *J* = 16.9 Hz, **CH**H=CH), 5.05 (1H, m, Ar**CH**), 5.01 (1H, d, *J* = 10.3 Hz, **CH**H=CH), 2.22 (2H, m, CH$_2$=CHC**H$_2$**), 2.10 (1H, s, **OH**), 1.77 (2H, m, CH(OH)C**H$_2$**).

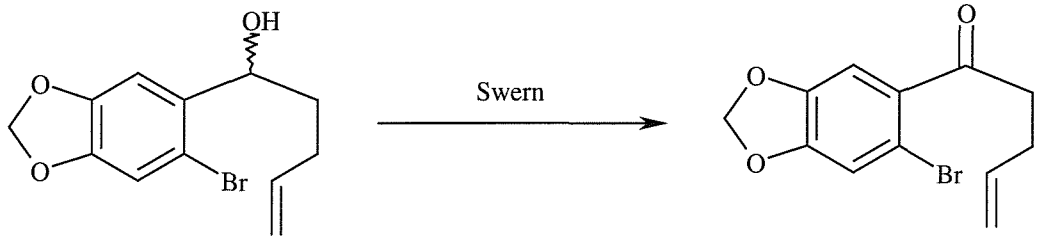
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 147.9 (s), 147.6 (s), 138.2 (d), 137.2 (s), 115.3 (t), 112.5 (d), 112.2 (s), 107.3 (d), 101.9 (t), 72.5 (d), 36.9 (t), 30.2 (t).

**UV** $\lambda_{max}$ (MeOH) 294 (427), 238 (527) and 210 (1139).

**LRMS** $^m/_z$ (CI+) 286 ([M($^{81}$Br)]$^+$, 8%), 284 ([M($^{79}$Br)]$^+$, 8%), 169 ([M-H$_2$O($^{81}$Br)]$^+$, 98%), 267 ([M-H$_2$O($^{79}$Br)]$^+$, 100%).

**HRMS** (CI+) Found [M-H$_2$O($^{79}$Br)]$^+$ 267.0012. $C_{12}H_{12}O_2Br$ requires 267.0020.

**Preparation of 6-bromo-5-(1-oxopent-4-en-1-yl)-benz[1,3]dioxole 207.**




**206** $C_{12}H_{13}O_3Br$ (285)

**207** $C_{12}H_{11}O_3Br$ (283)

To a solution of oxalyl chloride (3.3 mL, 37.63 mmol) in $CH_2Cl_2$ (50 mL) at –78°C was added the DMSO (4.7 mL, 66.41 mmol). The reaction mixture was stirred at –78°C for

30 minutes before addition of a cooled solution of the alcohol **206** (6.31 g, 22.1 mmol) in $CH_2Cl_2$ (20 mL). After 30 minutes a cream precipitate had formed and $Et_3N$ (12.3 mL, 88.4 mmol) was added. The reaction was warmed to RT over 1 hr, 0.5M $NaHSO_4$ (100 mL) added and the product extracted into $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a yellow oil. Purification by flash column chromatography (silica, 10% $Et_2O$ in petrol) afforded **207** as a colourless oil (2.58 g, 7.28 mmol, 41%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2907 s, 1629 s, 1640 m, 1614 m, 1502 s, 1477 s, 1406 s, 1384 s, 1240 s, 1122 s, 1035 s.

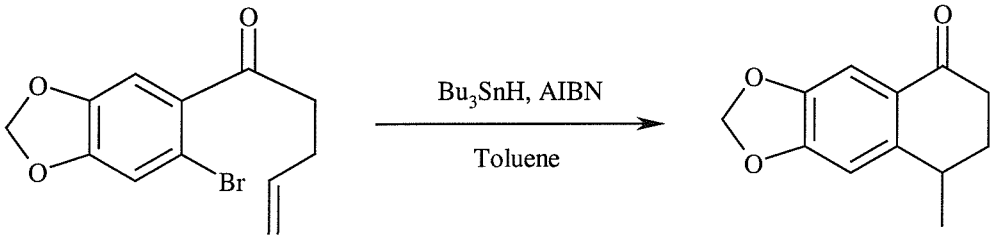
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.04 (1H, s, Ar**H**), 6.93 (1H, s, Ar**H**), 6.04 (2H, s, O**CH$_2$**O), 5.87 (1H, ddt, *J* = 16.9, 10.3, 6.6 Hz, $CH_2$=C**H**), 5.09 (1H, d, *J* = 16.9 Hz, CH**H**=CH), 5.01 (1H, d, *J* = 10.3 Hz, C**H**H=CH), 3.0 (2H, t, *J* = 7.5 Hz, C**H$_2$**$CH_2$), 2.45 (2H, q, *J* = 6.9 Hz, $CH_2$C**H$_2$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 201.9 (s), 150.0 (s), 147.4 (s), 136.9 (d), 134.6 (s), 115.5 (t), 113.7 (d), 111.2 (s), 108.8 (d), 102.4 (t), 41.6 (t), 28.4 (t).

**UV** $\lambda_{max}$ (MeOH) 300 (453), 275 (475) and 220 (1697).

**LRMS** $^m/_z$ (APCI +ve) 285 ([MH($^{81}$Br)]$^+$, 56%), 283 ([MH($^{79}$Br)]$^+$, 68%), 229 ([M-$C_4H_7$($^{81}$Br)]$^+$, 100%), 227 ([M-$C_4H_7$($^{79}$Br)]$^+$, 99%).

**Preparation of 8-methyl-5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxol-5-one 208.**




**207**
$C_{12}H_{11}O_3Br$ (283)

**208**
$C_{12}H_{12}O_3$ (204)

A solution of the alkene **207** (325 mg, 1.15 mmol) in toluene (20 mL) was degassed with $N_2$ for 10 minutes. AIBN (20 mg, 0.12 mmol) was added and the reaction mixture was heated to 80°C. $Bu_3SnH$ (0.3 mL, 1.15 mmol) was added slowly *via* a syringe and the mixture stirred at 80-90°C for 48 hr, cooled and sat. aq. KF (20 mL) added. After 24 hrs the resultant white solid was removed by filtration. The mother liquor was extracted into EtOAc (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a colourless oil. Purification by flash column chromatography (silica, 50-80% $Et_2O$ in petrol) gave **208** as a colourless film (94 mg, 0.46mmol, 40%).

**FT-IR** $\nu_{max}$ (neat)/$cm^{-1}$ 2973 m, 1673 s, 1617 s, 1503 s, 1481 s, 1430 s, 1330 s, 1254 s, 1038 s, 932s.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.42 (1H, s, Ar**H**), 6.70 (1H, s, Ar**H**), 5.97 (2H, s, $OCH_2O$), 2.98 (1H, dq, *J* = 11.8, 6.3 Hz, ArC**H**), 2.70 (1H, ddd, *J* = 17.6, 8.8, 4.6 Hz, C=OCH**H**), 2.50 (1H, ddd, *J* = 17.6, 8.1, 4.4 Hz, CH**H**C=O), 2.19 (1H, ddd, *J* = 17.7, 8.8, 4.6 Hz, $CCH_2CHH$), 1.83 (1H, dddd, *J* = 17.7, 11.8, 8.1, 4.4 Hz, C=$OCH_2CHH$), 1.33 (3H, d, *J* = 6.3 Hz, $CHCH_3$).

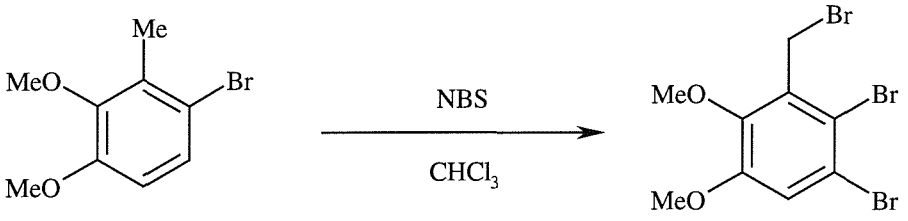
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 196.8 (s), 152.3 (s), 146.8 (s), 146.2 (s), 126.8 (s), 107.0 (d), 106.3 (d), 101.7 (t), 35.9 (t), 33.2 (d), 30.7 (t), 20.9 (q).

**UV** $\lambda_{max}$ (MeOH) 320 (709), 275 (674), 235 (1525) and 210 (1294).

**LRMS** $^{m}/_{z}$ (APCI +ve) 246 ($[MH+MeCN]^+$, 16%), 205 ($[MH]^+$, 100%).

**HRMS** (CI+) Found $[M+NH_4]^+$ 222.1133. $C_{12}H_{16}O_3N$ requires 222.1130.

**Preparation of 2,3-dibromo-5,6-dimethoxybenzyl bromide 214.**




**154**
$C_9H_{11}O_2Br$ (231)

**214**
$C_9H_9O_2Br_3$ (389)

*N*-Bromosuccinimide (385 mg, 2.17 mmol) was added to a stirred solution of the veratrole **154** (500 mg, 2.17 mmol) in $CHCl_3$ (20 mL) then refluxed for 24 hrs. A further 2eq of NBS (770 mg, 4.34 mmol) was added and refluxing continued for24 hr resulting in the formation of a white solid and a deep red solution. Upon cooling, the white crystalline solid was removed by filtration. The filtrate was diluted with water (30 mL) and extracted into $CH_2Cl_2$ (2 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a light brown solid. Purification by flash column chromatography (silica, 10% $Et_2O$ in petrol) afforded **214** as a white solid (550 mg, 1.41 mmol, 82%).

**m.p.** 134-136°C

**FT-IR** $\nu_{max}$ (nujol mull)/$cm^{-1}$ 2923 s, 2853 s, 1570 w, 1460 m, 1420 m, 1376 m, 1236 m, 1176 w, 850 m.

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.20 (1H, s, Ar**H**), 4.78 (2H, s, Ar**CH$_2$**), 3.99 (3H, s, ArO**CH$_3$**), 3.89 (3H, s, ArO**CH$_3$**).

**n.O.e** (400 MHz, $CDCl_3$) Irradiation of the signal at $\delta_H$ 3.89 (ArO**CH$_3$**) caused an n.O.e enhancement of 12.1% at $\delta_H$ 7.20 (Ar**H**).

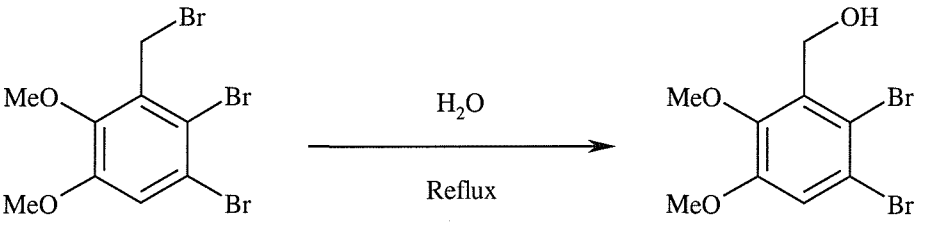
**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.5 (s), 147.8 (s), 143.4 (s), 133.6 (s), 120.1 (s), 117.5 (d), 61.3 (q), 56.3 (q), 29.3 (t).

**UV** $\lambda_{max}$ (MeOH) 306 (3109) and 240 (6374).

**LRMS** $^m/_z$ (APCI +ve) 392 ([M($^{81}$Br$^{81}$Br$^{81}$Br)]$^+$, 8%), 390 ([M($^{81}$Br$^{81}$Br$^{79}$Br)]$^+$, 25%), 388 ([M($^{79}$Br$^{79}$Br$^{81}$Br)]$^+$, 28%), 386 ([M($^{79}$Br$^{79}$Br$^{79}$Br)]$^+$, 12%), 311 ([M($^{81}$Br$^{81}$Br)]$^+$, 50%), 309 ([M($^{79}$Br$^{81}$Br)]$^+$, 100%), 307 ([M($^{79}$Br$^{79}$Br)]$^+$, 56%).

**HRMS** (EI+) Found [M($^{79}$Br$^{79}$Br$^{79}$Br)]$^+$ 385.8161. $C_9H_9O_2Br_3$ requires 385.8153.

**Preparation of 2,3-dibromo-5,6-dimethoxybenzylalcohol 216.**




**214**
$C_9H_9O_2Br_3$ (389)

**216**
$C_9H_{10}O_3Br_2$ (326)

A suspension of the tribromide **214** (500 mg, 1.29 mmol) in $H_2O$ (20 mL) was stirred at reflux for 8 hrs. The reaction mixture was cooled, extracted into $Et_2O$ (2 × 25 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*

giving a pale yellow oil. Purification by flash column chromatography (silica, 50% $Et_2O$ in petrol) afforded **216** as a white solid (216 mg, 0.66 mmol, 51%).

**m.p.** 71-72°C.

**FT-IR** $\nu_{max}$ (nujol mull)/$cm^{-1}$ 2923 s, 2854 s, 1461 s, 1375 w, 1298 w, 1269 w, 1226 w, 1016 w.

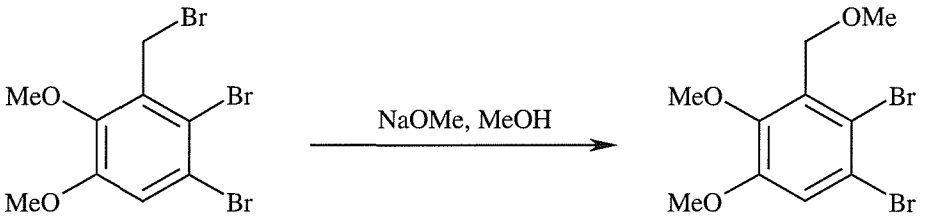
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.18 (1H, s, Ar**H**), 4.89 (2H, d, $J$ = 6.6 Hz, Ar**C**$\mathbf{H_2}$), 3.89 (3H, s, ArOC$\mathbf{H_3}$), 3.87 (3H, s, ArOC$\mathbf{H_3}$), 2.44 (1H, t, $J$ = 6.6 Hz, **O**H).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.6 (s), 147.8 (s), 135.8 (s), 120.1 (s), 117.5 (s), 117.1 (d), 62.0 (t), 61.5 (q), 56.3 (q).

**UV** $\lambda_{max}$ (MeOH) 285 (1813), 226 (7907) and 210 (9302).

**LRMS** $^m/_z$ (APCI +ve) 328 ([M($^{81}$Br$^{81}$Br)]$^+$, 25%), 326 ([M($^{79}$Br$^{81}$Br)]$^+$, 56%), 324 ([M($^{79}$Br$^{79}$Br)]$^+$, 31%), 311 ([MH-$H_2O$($^{81}$Br$^{81}$Br)]$^+$, 53%), 309 ([MH-$H_2O$($^{81}$Br$^{79}$Br)]$^+$, 100%), 307 ([MH-$H_2O$($^{79}$Br$^{79}$Br)]$^+$, 55%).

**Preparation of 2,3-dibromo-5,6-dimethoxybenzyl methyl ether 217.**




**214** $C_9H_9O_2Br_3$ (389)

**217** $C_{10}H_{12}O_3Br_2$ (340)

A suspension of the tribromide **214** (500 mg, 1.29 mmol) in MeOH (5 mL) was added slowly to a solution of sodium methoxide [prepared by addition of Na (44 mg, 1.93 mmol) to MeOH (10 mL)] at RT giving a white suspension which was stirred at RT for 1 hr before heating to 70°C for 12 hr. The reaction mixture was allowed to cool and the methanol was removed *in vacuo* giving a white solid which was partitioned between water (50 mL) and $Et_2O$ (25 mL). The aqueous phase was extracted with $Et_2O$ (2 × 25 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving **217** as a colourless oil which solidified upon standing (404 mg, 1.19 mmol, 92%).

**m.p.** 35-36°C.

**FT-IR** $\nu_{max}$ (nujol mull)/$cm^{-1}$ 2923 s, 2854 s, 1461 s, 1421 m, 1372 w, 1295 w, 1228 w, 1172 w, 1082 m, 940 w.

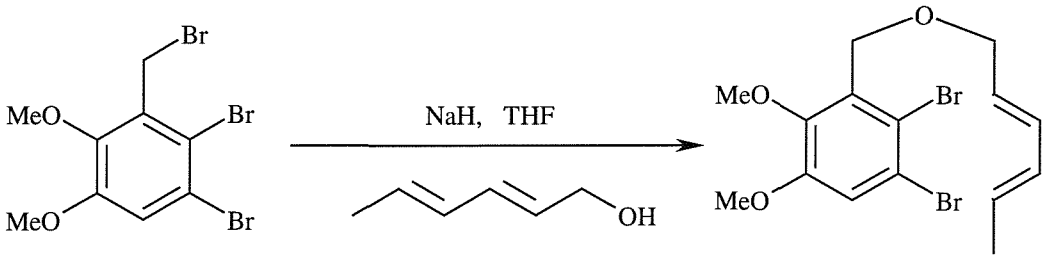
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.19 (1H, s, Ar**H**), 4.66 (2H, s, Ar**CH$_2$**), 3.88 (6H, br s, ArO**CH$_3$**), 3.45 (3H, s, O**CH$_3$**).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.6 (s), 148.4 (s), 133.4 (s), 120.2 (s), 118.9 (s), 117.3 (d), 69.7 (t), 62.1 (q), 58.6 (q), 56.3 (q).

**UV** $\lambda_{max}$ (MeOH) 292 (3398), 228 inf (1472), 212 (2106).

**LRMS** $^{m}/_{z}$ (APCI +ve) 342 ([M($^{81}$Br$^{81}$Br)]$^{+}$, 26%), 340 ([M($^{79}$Br$^{81}$Br)]$^{+}$, 55%), 338 ([M($^{79}$Br$^{79}$Br)]$^{+}$, 30%), 311 ([MH-MeOH($^{81}$Br$^{81}$Br)]$^{+}$, 57%), 309 ([MH-MeOH($^{81}$Br$^{79}$Br)]$^{+}$, 100%), 307 ([MH-MeOH($^{79}$Br$^{79}$Br)]$^{+}$, 48%).

**Preparation 2,3-dibromo-5,6-dimethoxybenzyl 2*E*,4*E*-hexadienyl ether 219.**




**214** **218** **219**

$C_9H_9O_2Br_3$ (389) $C_{15}H_{18}O_3Br_2$ (406)

Sodium hydride (168 mg, 4.91 mmol, 60% dispersion in oil) was added to a solution of the alcohol **218** (482 mg, 4.91 mmol) in THF (20 mL) at 0°C under nitrogen. The reaction mixture was stirred at RT for ½ hr giving a pale brown suspension. A solution of the tribromide **214** (955 mg, 2.46 mmol) in THF (10 mL) was added slowly over 5 minutes giving a dark brown solution which was stirred at RT for 48 hrs. The reaction was diluted with $H_2O$ (30 mL) and extracted into $Et_2O$ (3 × 30 mL). The combined organic phases were washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* affording a pale yellow oil. Purification by flash colunm chromatography (silica, 10% $Et_2O$ in petrol) gave **219** as a white solid (797 mg, 1.96 mmol, 80%).

**m.p.** 48-50°C.

**FT-IR** $\nu_{max}$ (neat)/cm$^{-1}$ 3017 s, 2935 s, 2838 s, 1660 m, 1573 s, 1489 s, 1423 s, 1357 s, 1296 s, 1270 s, 1231 s, 1177 s, 1077 s, 988 s, 837 m, 765 m.

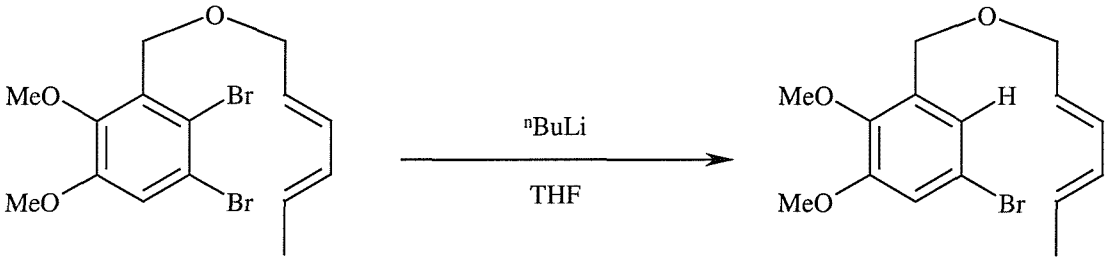
**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.39 (1H, s, Ar**H**), 6.27 (1H, dd, *J* = 15.4, 10.7 Hz, CH=C**H**CH=CH), 6.08 (1H, dd, *J* = 14.7, 10.7 Hz, CH=CHC**H**=CH), 5.80-5.64 (2H, m, C**H**=CHCH=C**H**), 4.69 (2H, s, Ar$CH_2$), 4.12 (2H, d, *J* = 5.9 Hz, O$CH_2$CH), 3.86 (6H, s, O$CH_3$), 1.78 (3H, d, *J* = 6.6 Hz, CH$CH_3$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.6 (s), 148.4 (s), 134.5 (s), 133.7 (d), 131.0 (d), 130.2 (d), 126.8 (d), 120.2 (s), 118.9 (s), 117.2 (d), 71.4 (t), 67.4 (t), 62.1 (q), 56.3 (q), 18.3 (q).

**UV** $\lambda_{max}$ (MeOH) 395 (1406) and 244 (2353).

**LRMS** $^m/_z$ (APCI +ve) 311 (52%), 309 (100%), 307 (47%).

**Preparation of 3-bromo-5,6-dimethoxybenzyl 2*E*,4*E*-hexadienyl ether 220.**




**219**

$C_{15}H_{18}O_3Br_2$ (406)

**220**

$C_{15}H_{19}O_3Br$ (327)

$^n$BuLi (1.42 M in hexane 0.89 mL, 1.27 mmol) was added slowly over 5 min to a solution of the dibromide **219** (514 mg, 1.27 mmol) in THF (20 mL) at –78°C under nitrogen. The reaction was stirred at –78°C for 1 hr before being allowed to warm to RT and diluted with sat. aq. $NH_4Cl$ (20 mL). The mixture was extracted into $Et_2O$ (2 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* giving a pale yellow oil. Purification by flash column chromatography (silica, 20% $Et_2O$ in petrol) afforded a colourless oil tentatively assigned as **220** (33 mg, 0.10 mmol, 8%).

**$^1$H-NMR** $\delta_H$ (300 MHz, $CDCl_3$) 7.19 (1H, s, Ar**H**), 7.05 (1H, s, Ar**H**), 6.27 (1H, dd, *J* = 15.4, 10.7 Hz, CH=C**H**CH=CH), 6.08 (1H, dd, *J* = 14.7, 10.7 Hz, CH=CHC**H**=CH), 5.80-5.64 (2H, m, C**H**=CHCH=C**H**), 4.69 (2H, s, ArC$\mathbf{H_2}$), 4.12 (2H, d, *J* = 5.9 Hz, OC$\mathbf{H_2}$CH), 3.86 (6H, s, OC$\mathbf{H_3}$), 1.78 (3H, d, *J* = 6.6 Hz, CHC$\mathbf{H_3}$).

**$^{13}$C-NMR** $\delta_C$ (75.5 MHz, $CDCl_3$) 152.8 (s), 146.7 (s), 137.4 (s), 133.4 (d), 132.5 (s), 131.0 (d), 130.1 (d), 126.9 (d), 120.2 (d), 111.1 (d), 71.0 (t), 67.0 (t), 61.3 (q), 56.1 (q), 18.3 (q).

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# Appendix

**Table 1.** Crystal data and structure refinement.

| | |
|---|---|
| Identification code | **98mbh098** |
| Empirical formula | $C_{19}H_{27}NO_3$ |
| Formula weight | 317.42 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1/n$ |
| Unit cell dimensions | $a$ = 5.3992(8) Å |
| | $b$ = 14.709(4) Å $\beta$ = 95.704(15)° |
| | $c$ = 22.023(5) Å |
| Volume | 1740.4(6) Å$^3$ |
| $Z$ | 4 |
| Density (calculated) | 1.211 Mg / m$^3$ |
| Absorption coefficient | 0.081 mm$^{-1}$ |
| *F(000)* | 688 |
| Crystal | colourless needle |
| Crystal size | 0.50 × 0.02 × 0.02 mm$^3$ |
| $\theta$ range for data collection | 2.92 – 25.01° |
| Index ranges | $-6 \le h \le 6, -17 \le k \le 17, -23 \le l \le 26$ |
| Reflections collected | 9159 |
| Independent reflections | 2964 [$R_{int}$ = 0.1898] |
| Completeness to $\theta$ = 25.01° | 92.3 % |
| Max. and min. transmission | 0.9984 and 0.9606 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2964 / 0 / 313 |
| Goodness-of-fit on $F^2$ | 0.908 |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0673, $wR2$ = 0.1256 |
| $R$ indices (all data) | $R1$ = 0.2113, $wR2$ = 0.1741 |
| Extinction coefficient | 0.008(2) |
| Largest diff. peak and hole | 0.356 and –0.272 e Å$^{-3}$ |

**Diffractometer:** *Enraf Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *Ewald* sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure:** *SHELXS86* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

**Further information:** http://www.soton.ac.uk/~xservice/strat.htm

**Special details:**

**Table 2.** Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| O3 | 4034(5) | 8449(2) | 599(1) | 39(1) | 1 |
| O2 | 1321(5) | 8271(2) | 1530(1) | 38(1) | 1 |
| O1 | 10217(6) | 14228(2) | 863(2) | 54(1) | 1 |
| C15 | 4413(8) | 9059(3) | 1076(2) | 33(1) | 1 |
| C13 | 3320(9) | 9584(3) | 2043(2) | 40(1) | 1 |
| C16 | 6203(7) | 9733(3) | 1055(2) | 32(1) | 1 |
| C14 | 2990(8) | 8979(3) | 1568(2) | 34(1) | 1 |
| C11 | 6524(7) | 10349(3) | 1542(2) | 34(1) | 1 |
| C12 | 5085(8) | 10269(4) | 2023(2) | 38(1) | 1 |
| N1 | 10219(7) | 11596(3) | 2640(2) | 53(1) | 1 |
| C10 | 9458(8) | 11375(3) | 2162(2) | 39(1) | 1 |
| C9 | 8427(8) | 11115(3) | 1540(2) | 37(1) | 1 |
| C5 | 8224(9) | 13590(3) | 940(2) | 46(1) | 1 |
| C18 | 5374(11) | 7610(4) | 723(3) | 44(1) | 1 |
| C6 | 9400(8) | 12674(3) | 1092(2) | 38(1) | 1 |
| C19 | 7739(9) | 9781(4) | 524(2) | 40(1) | 1 |
| C3 | 7079(10) | 15031(4) | 1299(3) | 57(2) | 1 |
| C8 | 7393(9) | 11976(4) | 1203(2) | 41(1) | 1 |
| C7 | 10967(10) | 12371(4) | 583(3) | 48(1) | 1 |
| C4 | 6780(12) | 14020(4) | 1421(3) | 51(2) | 1 |
| C2 | 9721(10) | 15089(4) | 1127(3) | 65(2) | 1 |
| C1 | 10360(14) | 15852(5) | 747(4) | 68(2) | 1 |
| C17 | −16(11) | 8124(5) | 2049(2) | 44(1) | 1 |

**Table 3.** Bond lengths [Å] and angles [°]..

| | | | |
|---|---|---|---|
| O3–C15 | 1.382(5) | C11–C12 | 1.381(6) |
| O3–C18 | 1.443(6) | C11–C9 | 1.525(6) |
| O2–C14 | 1.375(5) | N1–C10 | 1.139(5) |
| O2–C17 | 1.429(6) | C10–C9 | 1.476(6) |
| O1–C2 | 1.430(6) | C9–C8 | 1.544(6) |
| O1–C5 | 1.450(5) | C5–C6 | 1.512(7) |
| C15–C16 | 1.388(6) | C5–C4 | 1.514(6) |
| C15–C14 | 1.394(6) | C6–C8 | 1.530(6) |
| C13–C14 | 1.372(6) | C6–C7 | 1.535(6) |
| C13–C12 | 1.391(6) | C3–C2 | 1.514(7) |
| C16–C11 | 1.403(6) | C3–C4 | 1.523(7) |
| C16–C19 | 1.500(6) | C2–C1 | 1.461(8) |

| | | | |
|---|---|---|---|
| C15–O3–C18 | 112.2(3) | N1–C10–C9 | 178.2(5) |
| C14–O2–C17 | 116.5(4) | C10–C9–C11 | 112.4(4) |
| C2–O1–C5 | 110.8(4) | C10–C9–C8 | 108.6(4) |
| O3–C15–C16 | 119.3(4) | C11–C9–C8 | 113.3(4) |
| O3–C15–C14 | 119.0(4) | O1–C5–C6 | 107.6(4) |
| C16–C15–C14 | 121.7(4) | O1–C5–C4 | 104.6(4) |
| C14–C13–C12 | 118.9(4) | C6–C5–C4 | 116.9(4) |
| C15–C16–C11 | 118.0(4) | C5–C6–C8 | 110.2(4) |
| C15–C16–C19 | 120.0(4) | C5–C6–C7 | 110.3(4) |
| C11–C16–C19 | 122.0(4) | C8–C6–C7 | 111.9(4) |
| C13–C14–O2 | 124.9(4) | C2–C3–C4 | 102.6(5) |
| C13–C14–C15 | 119.9(4) | C6–C8–C9 | 113.5(4) |
| O2–C14–C15 | 115.2(4) | C5–C4–C3 | 102.3(4) |
| C12–C11–C16 | 119.7(4) | O1–C2–C1 | 112.6(5) |
| C12–C11–C9 | 119.7(4) | O1–C2–C3 | 105.7(4) |
| C16–C11–C9 | 120.5(4) | C1–C2–C3 | 117.9(6) |
| C11–C12–C13 | 121.7(5) | | |

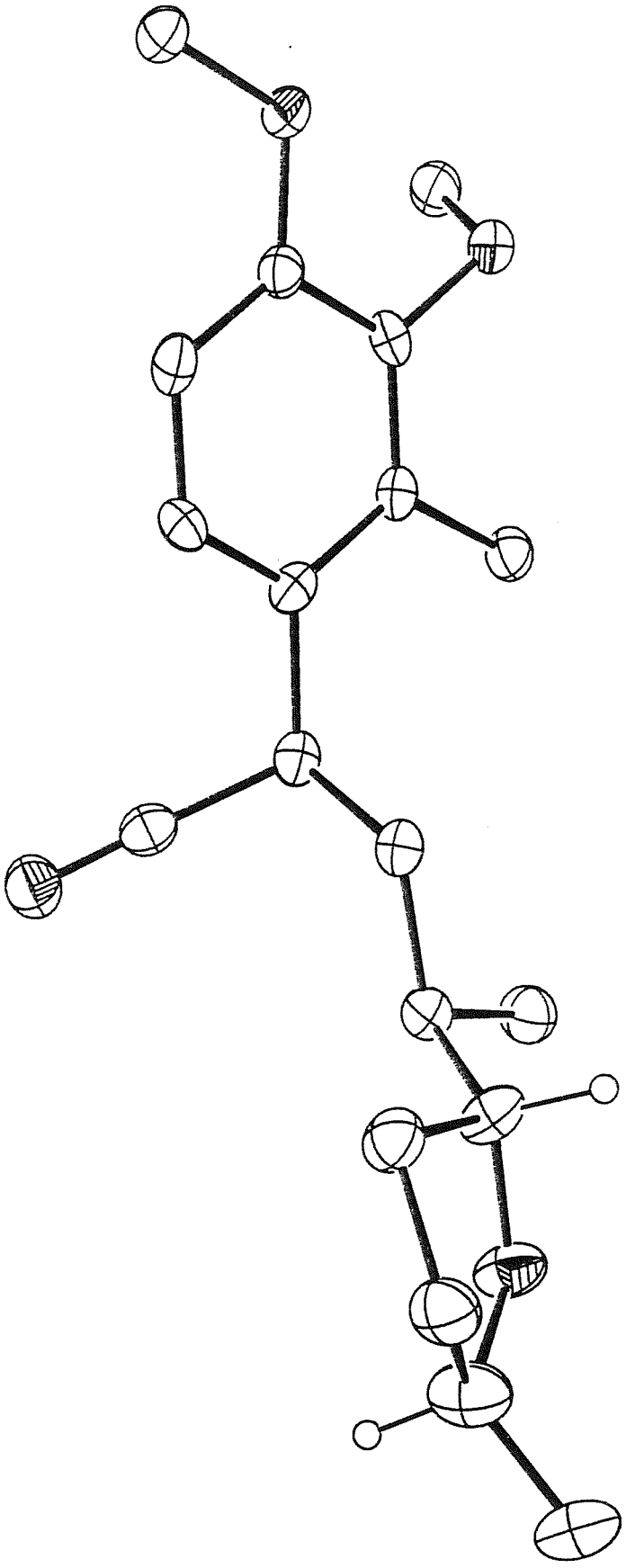
Symmetry transformations used to generate equivalent atoms:

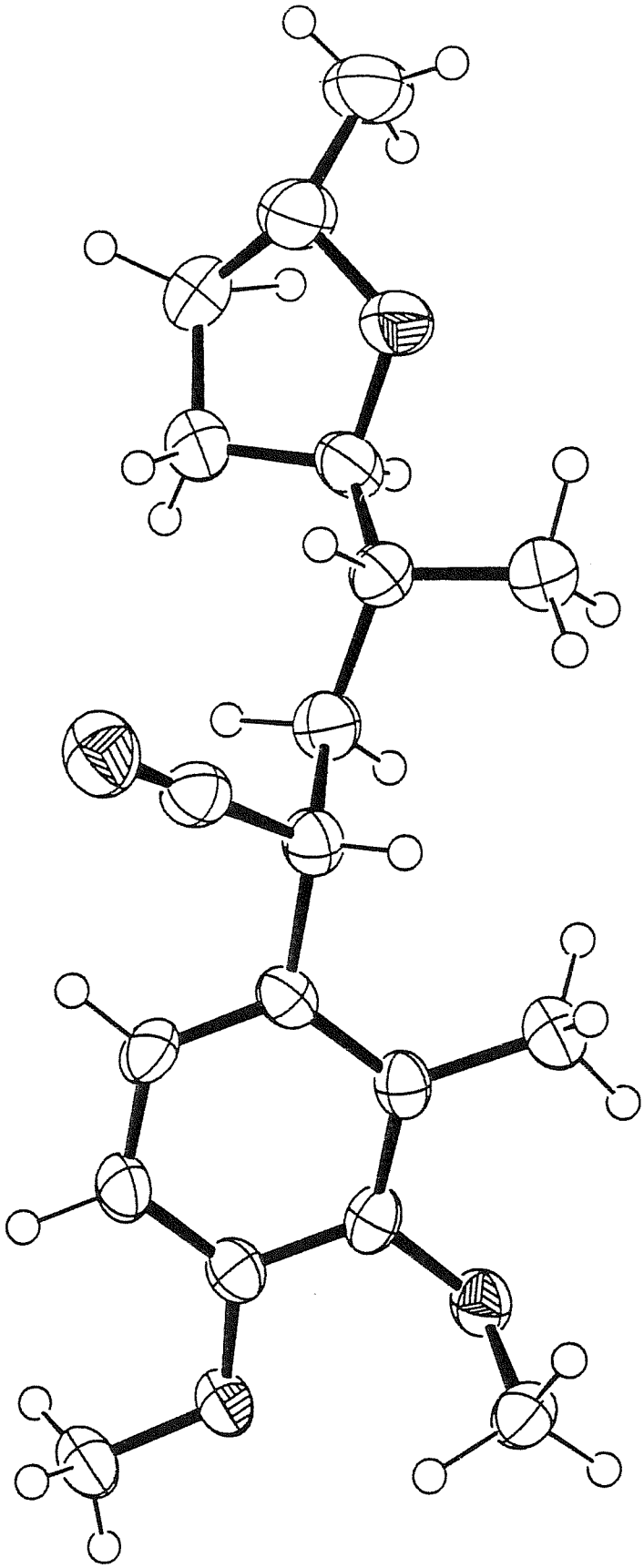
**Table 4.** Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

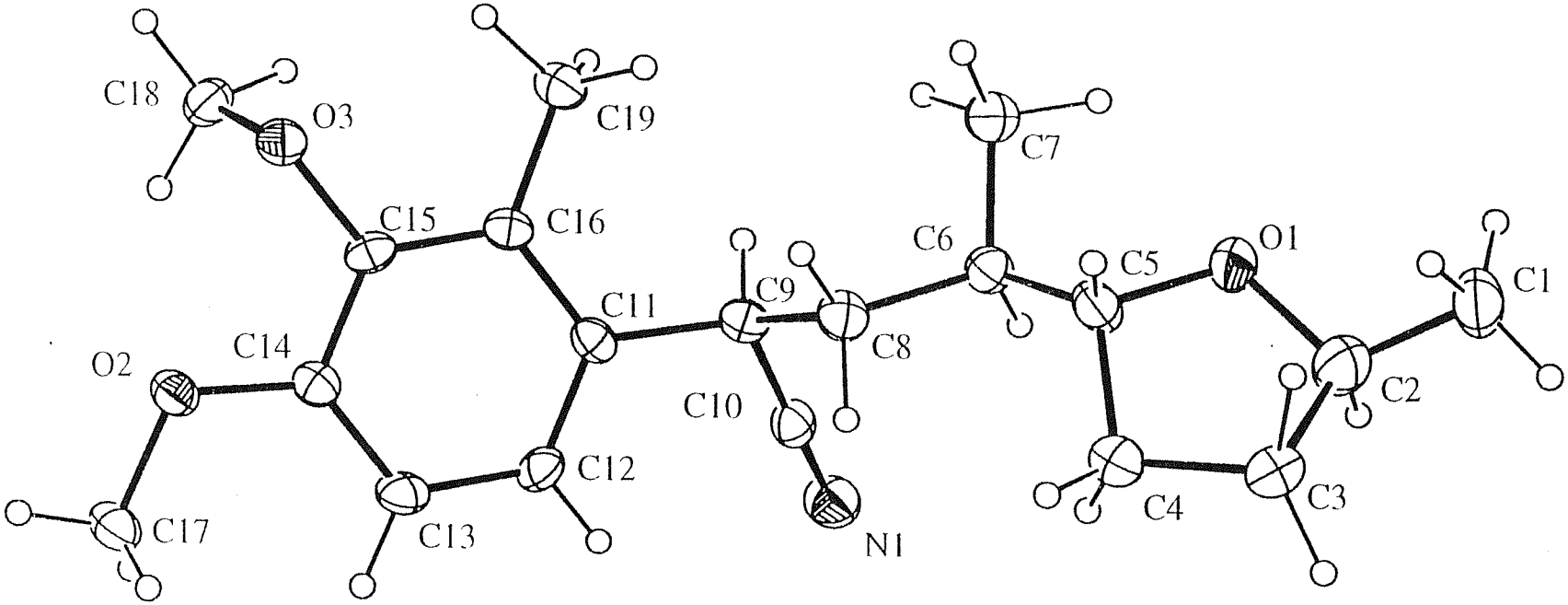
| Atom | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O3 | 45(2) | 42(2) | 30(2) | 1(2) | 3(1) | −3(2) |
| O2 | 37(2) | 43(2) | 33(2) | 4(2) | 7(1) | −5(2) |
| O1 | 63(2) | 33(2) | 68(2) | −2(2) | 23(2) | −2(2) |
| C15 | 33(3) | 39(3) | 25(3) | −5(2) | −4(2) | 5(2) |
| C13 | 49(3) | 44(4) | 26(3) | 4(3) | 7(2) | 3(3) |
| C16 | 33(3) | 38(3) | 26(3) | 3(2) | 1(2) | 4(2) |
| C14 | 32(3) | 39(3) | 30(3) | 3(3) | 2(2) | 0(2) |
| C11 | 33(3) | 34(3) | 34(3) | 8(2) | 6(2) | 1(2) |
| C12 | 47(3) | 36(3) | 30(3) | −9(3) | 0(2) | −5(3) |
| N1 | 52(3) | 64(3) | 44(3) | −2(3) | 3(2) | −7(2) |
| C10 | 40(3) | 32(3) | 45(3) | 3(3) | 6(2) | 2(2) |
| C9 | 40(3) | 41(3) | 31(3) | 2(3) | 5(2) | 0(2) |
| C5 | 48(3) | 39(4) | 54(4) | 10(3) | 19(3) | 1(3) |
| C18 | 61(4) | 35(4) | 38(4) | −4(3) | 6(3) | −1(3) |
| C6 | 38(3) | 39(3) | 37(3) | −1(3) | 3(2) | −2(2) |
| C19 | 34(3) | 52(4) | 33(3) | 2(3) | 4(2) | −4(3) |
| C3 | 67(4) | 49(4) | 56(4) | −12(3) | 18(3) | −2(3) |
| C8 | 46(3) | 42(4) | 34(3) | 5(3) | −1(3) | −1(3) |
| C7 | 48(4) | 50(4) | 46(4) | −4(3) | 8(3) | −3(3) |
| C4 | 60(4) | 47(4) | 47(4) | 1(3) | 16(3) | −1(3) |
| C2 | 62(4) | 53(4) | 85(4) | −13(4) | 25(3) | −3(3) |
| C1 | 72(5) | 41(5) | 92(6) | 7(4) | 23(4) | −6(4) |
| C17 | 42(3) | 56(4) | 34(3) | 6(3) | 8(3) | −9(3) |

**Table 5.** Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| H2 | 10829 | 15134 | 1517 | 78 | 1 |
| H19B | 7000(70) | 9330(30) | 180(20) | 56(14) | 1 |
| H17C | −1110(70) | 7630(30) | 1929(17) | 33(13) | 1 |
| H12 | 5320(60) | 10690(20) | 2343(16) | 16(10) | 1 |
| H13 | 2360(60) | 9500(20) | 2406(16) | 19(10) | 1 |
| H17B | 1130(70) | 7990(30) | 2470(20) | 55(14) | 1 |
| H3A | 6700(90) | 15100(30) | 770(20) | 81(16) | 1 |
| H1A | 10180(80) | 16410(40) | 980(20) | 64(18) | 1 |
| H7A | 11850(70) | 11740(30) | 695(18) | 51(14) | 1 |
| H19A | 9520(80) | 9650(30) | 635(18) | 46(13) | 1 |
| H8A | 6020(80) | 12270(30) | 1479(18) | 54(13) | 1 |
| H18B | 4800(60) | 7370(30) | 1126(17) | 25(11) | 1 |
| H7B | 9980(70) | 12260(30) | 170(20) | 57(15) | 1 |
| H17A | −1040(80) | 8610(40) | 2110(20) | 63(18) | 1 |
| H18A | 7350(100) | 7780(40) | 770(20) | 100(20) | 1 |
| H7C | 12140(80) | 12940(40) | 540(20) | 69(16) | 1 |
| H8B | 6690(60) | 11750(30) | 845(17) | 24(12) | 1 |
| H19C | 7750(80) | 10370(40) | 330(20) | 66(18) | 1 |
| H6 | 10460(60) | 12790(30) | 1493(16) | 24(10) | 1 |
| H9 | 9700(70) | 10860(30) | 1337(17) | 38(13) | 1 |
| H1C | 8920(110) | 15650(40) | 410(30) | 110(20) | 1 |
| H18C | 4920(70) | 7210(30) | 340(20) | 65(15) | 1 |
| H3B | 6760(80) | 15470(30) | 1660(20) | 71(16) | 1 |
| H4B | 5000(120) | 13810(50) | 1380(30) | 130(30) | 1 |
| H4A | 7490(80) | 13780(30) | 1820(20) | 71(18) | 1 |
| H1B | 11930(80) | 15730(30) | 574(19) | 53(15) | 1 |
| H5 | 6950(80) | 13690(30) | 540(20) | 68(15) | 1 |






C18
O3
C19
C7
C15
C16
C6
O1
C1
C9
C5
C11
C8
C14
O2
C10
C2
C12
C4
C3
C17
C13
N1